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BOLD correlations to force in precision grip: An event-related study

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Abstract—**The introduction of functional neuroimaging has resulted in a profusion of knowledge on various topics, including how blood oxygenation level dependent (BOLD) signal in the brain is related to force. To date, studies that have explicitly examined this relationship have used block designs. To gain a better understanding of the networks involved in human motor control, analyses sensitive to temporal relationships, such as Granger Causality or Dynamic Causal Modeling, require event-related designs. Therefore the goal of this experiment was to examine whether similar or even better relationships between BOLD and force during precision grip could be determined with an event-related design. Five healthy subjects exerted forces at 10%, 20% and 30% of maximum voluntary force, along with an observation condition. We report that the BOLD signal was linearly correlated with precision grip force in primary sensorimotor cortex and cerebellum, showing slightly better correlations than previous work. The results provide a clearer picture regarding the sensitivity of BOLD signal to force and show that event-related designs can be more appropriate than block designs in motor tasks.**

I. Introduction

THE advent of functional neuroimaging has produced great strides in fields such as neuroscience, brain-machine interfaces, and rehabilitation sciences. The most influential neuroimaging method has been functional magnetic resonance imaging (fMRI), which measures the changes in the ratio of oxyhemoglobin to deoxyhemoglobin concentration, known as the blood oxygenation level dependent (BOLD) signal [1]. BOLD has been shown to correlate with local field potentials and represents the mean dendritic input in a given area, also known as postsynaptic activity [2]. Currently, fMRI has the greatest spatial resolution of any non-invasive neuroimaging method, with voxel resolutions of up to 1 mm [3], is also capable of measuring from superficial and deep brain structures, is noninvasive and widely available. These advantages make it attractive for applications that require neural network analysis or local analysis of functionally specific brain areas.

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Our group is interested in how sensitive BOLD signal is to precision grip force under controlled conditions. There has been some relevant work discussing the relationship between BOLD and force in the fingers. Dettmers et al. [4] measured regional cerebral blood flow (rCBF) during a 1 Hz finger flexion task in a positron emission tomography (PET) scanner. They reported logarithmic increases in rCBF, which is closely related to BOLD, with the generated force. Thickbroom et al. [5] reported significant activity above 25% maximum voluntary force (MVF) during static isometric finger flexion force. A later paper by the same group found greater sensitivity to force using dynamic forces, but no significant changes between 5% and 10% MVF [6]. Another study by Cramer et al. in power grip showed increases in BOLD in sensorimotor cortex and supplementary motor area over a wide range of forces [7]. Keisker et al. [8] examined power grip force at 10%, 20% and 30% MVF, finding a linear increase in primary motor cortex (M1) and bilateral cerebellum (CB), but not as much linearity in the primary sensory cortex (S1) and other non-primary motor regions. Van Duinen et al., using a finger abduction paradigm, found similar results in a larger force range between 5 and 70% MVF [9].

All of the aforementioned studies used block designs, yet event-related designs are now increasingly useful due to their ability to investigate causal relationships [10]. While there have been motivational studies that have measured hand-grip force in an event-related design [11], no study has yet explicitly determined the relationship between BOLD and force in such designs. Therefore, the goal of this study was to investigate whether similar or even better relationships between BOLD and force could be disclosed using event-related experimental designs. We found that our data agreed with previous studies and that the force-BOLD relationship linearly increased in sensorimotor cortex and cerebellum from 10% to 20% and 30% of maximum voluntary force.

II. Methods

A. Experimental Setup

Five healthy, right-handed [12] subjects (four male) aged 27-32, participated in this study, approved by the Zurich Cantonal Ethics Committee. Outside the scanner, each subject was familiarized with the MR-compatible precision grip force sensor (Figure 1). The force sensor, developed previously by our group, has a maximum force of 50 N, a resolution of 0.5 N and uses 10 m of optical fibers to

transmit its signal [13]. The force sensor signal was acquired using a 14-bit data acquisition card (NI DAQ USB-6009, National Instruments, Austin, TX, USA) that interfaced with a Windows PC running custom-made code developed in C++ and OpenGL graphics running at a 400 Hz sampling rate. To synchronize the code with the scanner, a TTL pulse from the scanner was passed through a custom-made analog circuit in order to be detected by the data acquisition card. Each subject's maximum voluntary pinch force (MVF) was measured using a separate custom-made force sensor.

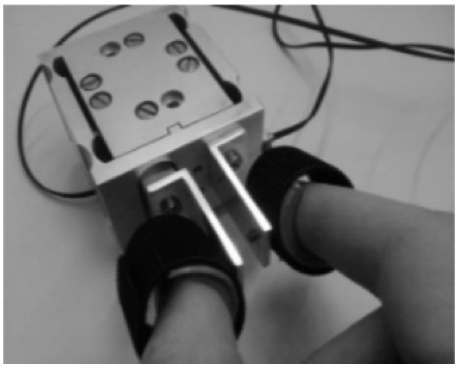

Figure 1: MR-compatible force sensor.

B. Task

Subjects were presented with visual feedback that included a target circle and a vertical bar representing exerted pinch force (Figure 2). Instructions to the subject were to exert force on the sensor in order to reach the target circle, the height of which was proportional to the required force, either 10%, 20% or 30% MVF. The subjects were asked to reach the target as quickly and accurately as possible. The target was presented for 2 s and followed by a written command to "Release" for 3.5 s ± 0.5 s (Figure 2). Occasionally, a fourth condition, observation, was cued during the Release period, requesting the subject to "Remain still for the following trial and look". During this trial, a target was presented at a level corresponding to 25% MVF and the vertical bar automatically reached the target in a smooth trajectory. The three force conditions and one observation condition were presented in pseudorandom order. Each of the conditions was presented 30 times, resulting in 120 trials per run. The subjects performed during two runs.

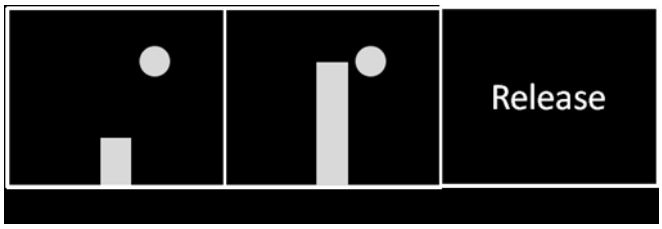

Figure 2: Visual feedback during the task. The circle represents the force target. Exerted force is represented by the height of the bar.

C. Functional Neuroimaging

Scans were performed on a whole body, 3.0-T MR scanner (Philips Medical Systems, Eindhoven, The Netherlands) with an 8-channel SENSE™ head coil. We collected single-shot echo-planar T2*-weighted images of the whole brain (TR/TE = 2000 ms/ 35 ms, FOV = 22 cm x 22 cm, acquisition matrix 128 x 128, slice thickness 3 mm, slice gap 1 mm, 30 slices) with a SENSE factor of 2. Slices were oriented axially with a 20° elevation from the anterior-posterior commissure. For each of the two runs, 340 volumes were recorded following five unrecorded dummy scans, lasting 11.33 minutes per run.

D. Data Analysis and Image Processing

Data were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Preprocessed images were slice time corrected, realigned, normalized to a standard EPI template and then smoothed with a Gaussian filter of 8 mm full-width at half-maximum.

In first-level analysis, the observation condition and three force conditions were separated into four different categories and compared to baseline condition (release). Regressors of no interest included motion-specific realignment parameters and mean activity. Each run was separated into multiple sessions in SPM. A 1/128 Hz high-pass filter eliminated low-frequency drifts. Second level analysis consisted of a t-test based on subject-specific contrasts. All functional statistics were performed using uncorrected t-tests with 20 mm spherical small volume correction based on hypothesized regions of interest (motor network). Anatomical localization was confirmed using the xjView SPM Extension (Cui & Li, Human Neuroimaging Lab, Baylor College of Medicine).

Percent signal change in anatomical locations was determined using the SPM Anatomy toolbox [14]. This toolbox examines BOLD changes in predefined anatomical regions. We examined percent signal change in all the assigned voxels within the predefined regions of the hypothesized Brodmann (BA) areas. Significant differences in percent signal change were determined using a two-way repeated measures ANOVA ($P<0.05$), with force level as one factor, and brain area as the second factor. Post-hoc tests of significant differences were performed using Tukey's Honestly Significant Difference (THSD) and paired t-tests with Bonferroni correction. Linearity of force levels was determined from Pearson's product-moment correlation coefficient.

III. Results

A. Areas increasing with force

Areas which increase with pinch force (30% vs. 10%) are shown in Figures 3 and 4. A number of regions are active in the sensorimotor cortex, including Brodmann area 1, 2, 3, and 4. We also observed bilateral activity in the cerebellum

(Lobule VI). Table 1 lists these areas and their respective T-values. All areas in the table were significant at $p < 0.05$ (FWE) after small volume of interest correction.

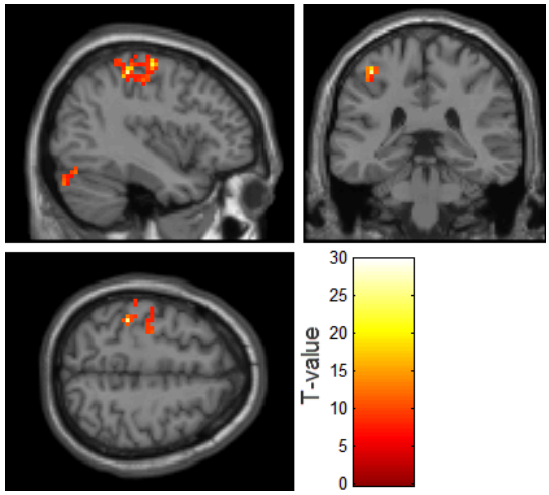

Figure 3: Group results showing areas of increase in sensorimotor cortex with force ($p < 0.001$, extent threshold = 20 voxels, uncorrected). Section centered at (-39, -34, 55).

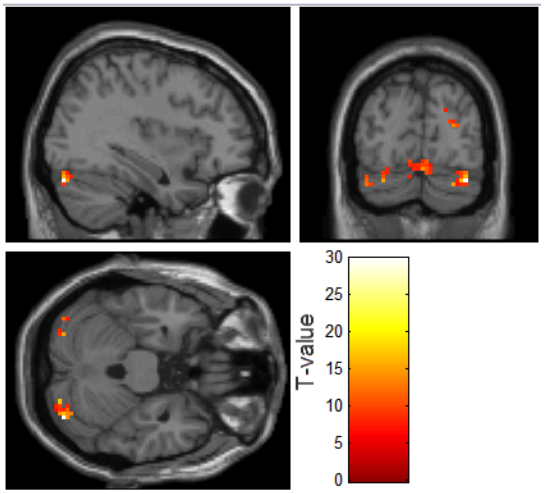

Figure 4: Group results showing areas of increase in bilateral posterior cerebellum with force ($p < 0.001$, extent threshold = 20 voxels, uncorrected). Section centered at (-36, -82,-26).

B. *Percent Signal Change*

Analysis of percent signal changes revealed linearly increasing relationships in the activated regions. Figures 5 and 6 show the percent signal changes in activated Brodmann areas.

Using a two-way, repeated measures ANOVA, we compared the force levels. We found significant differences between the force levels ($F_{(4,2,5)} = 31.26$, $p < 0.0001$), with THSD post-hoc tests revealing significant differences amongst all Brodmann areas between the 10% and 30% level, as well as the 20% and 30% level ($p < 0.05$). Paired t-tests with Bonferroni correction ($p < 0.05/12$) showed which relationships within anatomical areas were significant, as illustrated in Figures 5 and 6.

Table 1: Areas with increasing BOLD signal with force in hypothesized regions. "Region" indicates the estimated anatomical region corresponding to the MNI (Montreal Neurological Institute) coordinates. "Hemi" refers to the hemisphere of the brain. "BA" corresponds to the Brodmann area assigned to the coordinates.

			MNI coordinates			
Region	Hemi	BA	x	y	z	T-value
M1	L	4	-39	-16	51	21.81
S1	L	3,2,1	-39	-34	55	25.47
Post CB	R	VI	36	-82	-26	26.83
Post CB	L	VI	-36	-73	-20	16.96

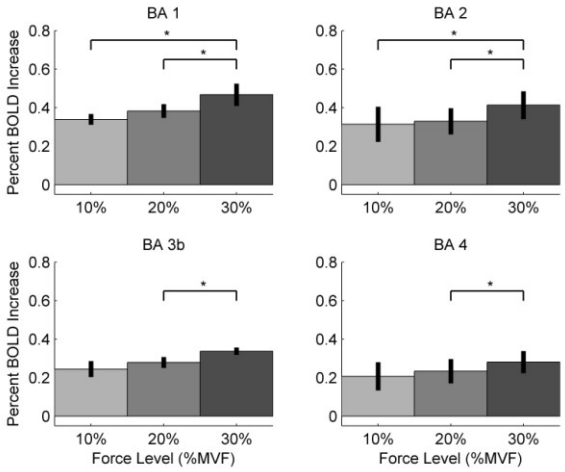

Figure 5: Percent BOLD signal change in sensorimotor cortex. Stars indicate significant differences between levels.

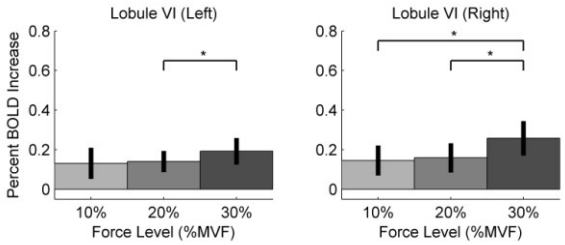

Figure 6: Percent BOLD signal change in cerebellum.

The increase in BOLD signal with force level within the force range is linear. We assessed the degree of linearity using Pearson's correlation. Table 2 shows the relationships between force level and percent BOLD increase with each Brodmann area.

Table 2: Pearson's correlations in BA areas and Cerebellum

BA	R^2
1	0.97
2	0.86
3	0.98
4	0.98
R Lobule VI	0.84
L Lobule VI	0.86

IV. Discussion

The purpose of these experiments was to confirm whether an event-related design would be consistent with previous knowledge of the relationship between brain activity and generated force. As expected, the results are consistent with previous studies. The results indicate that BOLD-force relationships with force levels between 10% and 30% MVF are linear in hypothesized areas using an event-related design and thus are suited for experiments investigating causal effects and stimuli.

We found linear increases in most of the expected sensorimotor areas, i.e. in motor cortex, somatosensory areas, and bilateral posterior cerebellum [8, 15-16]. We did not observe increases in ventral premotor cortex, however, despite the region's known role in control of grip force [17-18]. This is consistent with the results of Kuhtz-Buschbeck et al. [19]. Keisker et al. also showed activation in ventral premotor cortex for power grip, but no linear increase with force [8]. In an experiment on power grip, Ward et al. exhibited increases in the same areas except for a linear increase in the supplementary motor area [16]. This may be due to higher force levels (45% MVF) or greater concentration required to reach the target force.

A number of studies have shown greater sensitivity of BOLD signal or rCBF at lower forces than at higher ones. Dettmers et al. found that during 1 Hz finger flexion, greater increases of rCBF occurred at very low force in sensorimotor cortex [4]. In their study on power grip force, Keisker et al. also described increased sensitivity at low forces [8], attributing this to the increased attention demands. Our results showed that indeed a larger increase occurred below 10% MVF compared to rest than changes between 10% and 20% or 30% MVF in sensorimotor cortex.

According to Keisker et al., in power grip, M1 and cerebellum BOLD signal become linear at forces above 10% MVF [8]. Our results, for all force related regions, are consistent with these findings. In addition, we did not find significant differences between the 10% and 20% force levels as in the aforementioned study in M1. This is probably related to increased sensitivity in the very low force range but may also be due to the lack of statistical power in only five subjects.

V. Conclusion

All studies to date specifically investigating the BOLD signal correlates of force in precision grip have used block designs, which do not offer the possibility to investigate causal relationships and single trials. The goal of this study was to confirm that similar relationships between BOLD signal and force, found in block designs of previous studies, would hold also for precision grip in an event-related design. Our results on five subjects are in concordance with previous work and further provided stronger evidence of linearity of the BOLD-force relationship in S1, M1 and cerebellum. This strongly suggests that event-related experimental approaches may be more appropriate for investigating brain activation during motor tasks.

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