Delineating the whole brain BOLD response to passive movement kinematics

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***Abstract*—The field of brain-machine interfaces (BMIs) has made great advances in recent years, converting thought to movement, with some of the most successful implementations measuring directly from the motor cortex. However, the ability to record from additional regions of the brain could potentially improve flexibility and robustness of use. In addition, BMIs of the future will benefit from integrating kinesthesia into the control loop. Here, we examine whether changes in passively induced forefinger movement amplitude are represented in different regions than forefinger velocity via a MR compatible robotic manipulandum. Using functional magnetic resonance imaging (fMRI), five healthy participants were exposed to combinations of forefinger movement amplitude and velocity in a factorial design followed by an epoch-based analysis. We found that primary and secondary somatosensory regions were activated, as well as cingulate motor area, putamen and cerebellum, with greater activity from changes in velocity compared to changes in amplitude. This represents the first investigation into whole brain response to parametric changes in passive movement kinematics. In addition to informing BMIs, these results have implications towards neural correlates of robotic rehabilitation.**

I. Introduction

Substantial progress has been achieved in brain-machine interfaces (BMIs) for movement restoration in recent years [1], [2], [3]. A typical interface uses an electrode array inserted into the cortex [4], [2]. Due to constraints such as electrode size and density, surgical complications and other practical factors, these BMIs are relegated to a single area of the brain, typically the primary motor cortex. However, the sensorimotor control system is far more complex than activity in a single region, involving other cortical regions such as the primary and secondary somatosensory cortices (S1 and S2), supplementary motor area (SMA), cingulate motor area (CMA), superior and inferior parietal lobules (SPL and IPL), ventral and dorsal premotor corticies (PMv and PMd), the basal ganglia (BG), thalamus, and cerebellum (CB) [5]. As a result, the prospect of recording from or stimulating multiple brain regions during a movement could improve the performance of BMIs.

There has been a substantial body of work examining whole brain neural correlates of movement parameters, but surprisingly little regarding proprioception through passive movement, an important quantity for developement of more effective BMIs [6], [7]. Some studies have performed tests on passive movement in comparison with those of active movements. In a well-controlled study on forefinger movement at the metacarpophalangeal (MCP) joint, Mima et al. showed increased activity in S1 and S2 using positron emission tomography (PET) during passive movement [8]. An earlier study on elbow flexion using PET found similar results [9]. Francis et al. compared active, passive and electrically-stimulated dorsiflexion of the ankle using fMRI, finding that passive movement elicited activity in the majority of the sensorimotor network [10]. However, these studies simply used arbitrary movement parameters, without specific attention to its kinematics. There has not been an adequate analysis addressing the neural representation behind different passive movement kinematics, specifically the differential contributions of amplitude and velocity.

Current knowledge regarding the neural representation of the kinematics of passive movement is sparse. The bulk of these studies record firing rates from the afferent fibers [11], [12], [13], [14]. Yet since there are different afferent substrates for sensation of kinematics (i.e. muscle spindles, joint capsule receptors and free nerve endings in the skin [5]), it is likely that different regions of the brain represent varying kinematic parameters. As such, the goal of this study was to explore possible alternate central neural representations of variations in amplitude and velocity of passive forefinger movements measured by fMRI over the whole brain. Understanding the neural response behind proprioception will help better target BMI and neurorehabilitation methodologies.

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II. METHODS

A. Experimental Setup

Five healthy right-handed subjects, aged between 23-31 years (1 male), participated in this experiment, conducted according to the requirements of the Zurich Cantonal Ethics Commission. Each subject participated in the experiment in a single session in a Philips Achieva 3.0T magnetic resonance (MR) scanner with a 32 channel receive head coil (Philips, Best, The Netherlands).

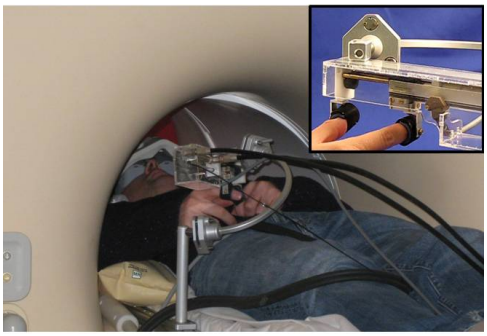

Fig. 1. Experimental setup. The forefinger manipulator was anchored to the scanner bed via an adjustable mount. In the inset, a close-up of the manipulator is shown.

Subjects right forefinger and thumb were then inserted into a MR-compatible forefinger manipulator (Figure 1) capable of smooth, position-controlled movement along a linear track equivalent to a typical forefinger range of motion (60 mm). The device was actuated by a DC motor (Maxon RE40, Switzerland) which remotely controlled the slave piston through a hydrostatic transmission [15]. The slave was equipped with custom-made force transducers (maximum force 32 N), whose signals were transmitted by optic fibers (Baumer, Switzerland) to the control room. In addition to the force sensors, a linear encoder (LM 12CPMM, Dynapar, IL, USA, resolution = 0.125 mm) was used to measure position of the end effector. Further details of the design can be found in previous work [16]. The manipulator was anchored to the scanner with an adjustable mount, allowing comfortable placement of the hand to rest on the right hip, with 0°wrist flexion.

The motor was controlled using a digital position controller (EPOS S2 24/5 (Maxon motors, Switzerland) and LabVIEW software (National Instruments, TX, USA), which also stored the kinematic and force data of the device. We used a proportional derivative (PD) position controller with slave position feedback in a virtual differential damper in order to compensate for the nonlinearities in the hydrostatic transmission. Resistance of the subject to passively induced movement was monitored by the experimenter using the slave force sensors to ensure compliance with experimental instructions. Control and data sampling were performed at 200 Hz.

B. Task

Subjects were instructed to lie supine in the scanner with eyes closed for the duration of the experiment. The right arm and hand rested on a cushion on the side of the body with the wrist in a neutral position. During the acquisition of functional volumes, the manipulator moved the right forefinger at various movement amplitudes and mean velocities. The forefinger was offset at a position of 15 mm from full closure, representing approximately 0°extension of the metacarpophalangeal (MCP) joint. We used a 3x3 factorial design which parametrically varied amplitude and velocity at specific amplitude difference from offset (10, 20 and 40 mm) and velocities (10, 20, and 40 mm/s), as shown in Figure 2. Due to reduced finger extension range of motion of two of the subjects, the maximum amplitude and velocities for these subjects were altered to 30 mm and 30 mm/s, respectively. Finger trajectories were composed of two sequential minimum-jerk trajectories, one in the opening and one in the closing direction.

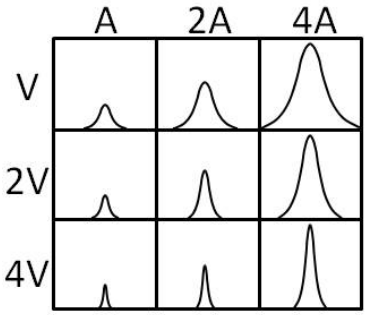

Fig. 2. Experimental protocol. Forefinger amplitude *A* and average velocity *V* were manipulated in a 3x3 factorial design. The total width of each box represents four seconds. The height of each box represents 40 mm displacement.

C. Scanning Parameters

Functional data were acquired in 30 ascending transverse plane slices using a gradient-echo T2*-weighted echo-planar image sequence over the whole brain. Acquired in-plane resolution was 3 x 3 mm^2, 3 mm slice thickness and 1.1 mm gap width over a field of view of 240 x 240 mm^2, a repetition time (TR) of 2.0 s, echo time of 35 ms and a flip angle of 75 deg. Two runs were acquired, each with 465 functional volumes. The total time of the session was approximately 35 minutes.

D. Data Preprocessing

Functional volumes were preprocessed using SPM8 (Wellcome Department of Imaging Neuroscience, London, United Kingdom). Acquired volumes were slice-time corrected, realigned (estimate and rewrite), normalized to a canonical EPI template and then smoothed with a Gaussian kernel of 8 mm full-width at half-maximum. A standard general linear model analysis (GLM) was then performed for each subject. The first nine regressors of interest in the design matrix corresponded to the nine conditions of the experiment. Each condition included the individual movement duration, resulting in epoch-based regressors. Six head movement regressors of no interest were used to correct for head movement. A constant regressor for mean intensity correction completed the design matrix. Second level random effects full factorial analysis was performed

based on the nine separate conditions. Voxel-wise statistics were corrected for multiple comparisons using family-wise error (FWE) correction at $p<0.05$. All coordinates are reported in Montreal Neurological Institute (MNI) space.

III. Results

Full factorial analysis revealed different extent of activations between changes in amplitude and velocity. Figure 3 shows the regions that changed activity with amplitude, and Figure 4 shows those that changed activity with velocity. Amplitude changes were found bilaterally in S2 and the contralateral putamen. Activation changes with velocity were also found in the aforementioned regions, and in contralateral S1/M1, CMA, and ipsilateral cerebellum. There was no significant interaction found between amplitude and velocity. Table I summarizes the results.

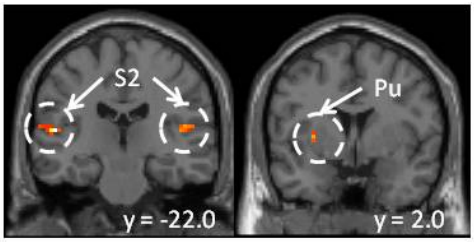

Fig. 3. Peak voxels in main effect of amplitude. On left, the bilateral posterior insula (S2), on the right, the contralateral putamen (Pu). All data are FWE corrected at $p<0.05$.

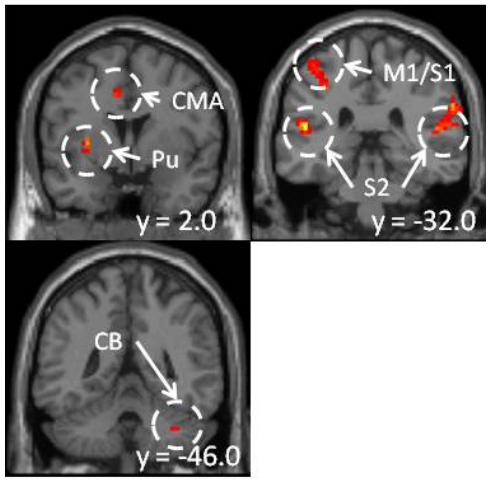

Fig. 4. Peak voxels in main effect of velocity. Top left: contralateral cingulate motor area (CMA) and putamen (Pu). Top right: contralateral postcentral and precentral gyri (S1/M1) and bilateral S2. Bottom left: ipsilateral cerebellar lobule VI (CB). All data are FWE corrected at $p<0.05$.

IV. Discussion

The purpose of this study was to identify whether precisely controlled kinematic changes in the forefinger were differentially represented in the brain. To the authors' knowledge, this is the first pilot evidence specifically aiming to decipher how blood oxygenation level dependent (BOLD) response changes with passive movement kinematics. Full factorial analysis showed significant changes within expected somatosensory brain regions with both amplitude and velocity. Data show more regions activated from changes in velocity compared to changes in amplitude.

TABLE I. Results of Random Effects Full Factorial Analysis (FWE Corrected, $p<0.05$)

		Main Effect of Amplitude		Main Effect of Velocity	
Region	Side	X/Y/Z	F-value	X/Y/Z	F-value
Postcentral Gyrus	C			-33/-31/43	44.8
Precentral Gyrus	C			-36/-25/58	39.6
CMA	C			-6/-7/49	49.7
S2	C	-51/-22/10	76.5	-51/-22/10	128
S2	I	57/-28/16	46.9	57/-28/16	74.8
Putamen	C	-30/2/4	38.3	-30/2/4	60.8
Cerebellum L6	I			36/-46/-38	24.1
White Matter	C			-39/-10/-14	24.9

The regions primarily responding to parametric modulations of amplitude and velocity are the bilateral S2 and the contralateral Pu, whereas velocity changes are additionally represented in S1/M1, CMA and ipsilateral CB. Given the small subject pool, it is not clear whether this difference is physiological or due to low statistical power. However, since muscle spindle afferents may contribute to proprioception more than cutaneous receptors or joint capsule receptors [17], and are more sensitive to velocity than position [18], the finding that more brain regions respond to velocity input is reasonable.

The results of this study are consistent with previous studies examining neural response to arbitrary, constant movement parameters. Earlier PET studies by Mima et al. [8] (finger) and Weiller et al. [9] (elbow), found activation in S1 and S2 with passive movement. Using magnetoencephalography (MEG), Lange et al. found activation in S1 [19] during passive finger movement, whereas Alary et al. found that S2 was dominant [20]. Studies using fMRI have provided more spatial information. For instance, experiments examining passive movements identified activity in sensorimotor areas with hand opening/closing [21], and forefinger movements [22]. In passive ankle dorsiflexion movements, Ciccarelli et al. [23] and Francis et al. [10] revealed activation in contralateral S1/M1, S2, contralateral Pu, ipsilateral CB, and SMA.

Our present results are largely consistent with experiments examining whole brain correlates of active movement kinematics. Using PET, in separate studies Sadato et al. [24] (precision grip) and Turner et al. [25] (shoulder internal rotation) had subjects perform movements at increasing frequencies. The former study found changes in primary sensorimotor cortex and SMA, whereas the latter included basal ganglia and cerebellum, all regions activated with changes in passive movement velocity in the current work. In contrast to the active movement, one study using passive ankle dorsiflexion could not find any relation between amplitude and BOLD response [23]. This result, inconsistent with our findings, may be due to a suboptimal experimental design that did not explicitly control amplitude.

It should be noted that most previous studies may be counfounded by uncontrolled movement parameters, such as duration, quantity, extent and frequency [26]. In our study, the movements varied not only in amplitude and velocity, but also duration. However, we specifically modeled movement duration by using an epoch-based analysis. Turner et al. [27] used a

reaching paradigm to separate the effects of active movement extent and speed. The authors found that movement extent was most represented in the basal ganglia and cerebellum. In our study, we did not find increased cerebellar activity in amplitude, but we did find changes with movement velocity, in agreement with previous knowledge in animal models [28].

One confounding factor in this study emerges from the endpoint control of the finger. While linear displacement of the finger more closely resembles natural precision grip movement than movement at the MCP, the linear movement causes different displacement of the forefinger joints. As a result, we cannot determine how much of the BOLD response is due to MCP displacement as opposed to the proximal or distal interphalangeal joint displacements. Since we did not anesthetize the forefinger, some of the BOLD response may also be due to stimulation of the mechanoreceptors on the fingertip. While at least one study has attempted to separate the effects of tactile and proprioceptive information [29], there is no information regarding how they contribute to the BOLD response.

Another limitation of this study was the ranges of velocity and amplitude chosen which were based on the robot capabilities as well as physiological constraints. As noted in the methods, a 40 mm amplitude change from initial aperture, totaling 55 mm of forefinger displacement, was too much for two of the subjects. As a result, we reduced the maximum displacement and velocity by 10 mm and 10 mm/s, respectively. It is not clear how this difference has affected the data. Future experiments will address this problem.

V. Conclusions

Using repeatable and well-controlled robotic passive movements of the index finger in an MR environment, we recorded the response of the brain to parametrically modulated kinematic inputs. We found that velocity elicited responses with greater extent than amplitude. These results will help identify salient brain regions for proprioceptive monitoring, with applications to brain-machine interfaces and rehabilitation.

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References

[1] L. Hochberg, D. Bacher, B. Jarosiewicz, N. Masse, J. Simeral, J. Vogel, S. Haddadin, J. Liu, S. Cash, P. van der Smagt *et al.*, "Reach and grasp by people with tetraplegia using a neurally controlled robotic arm," *Nature*, vol. 485, no. 7398, pp. 372–375, 2012.

[2] C. Moritz and E. Fetz, "Volitional control of single cortical neurons in a brain–machine interface," *Journal of Neural Engineering*, vol. 8, no. 2, p. 025017, 2011.

[3] M. Nicolelis and M. Lebedev, "Principles of neural ensemble physiology underlying the operation of brain–machine interfaces," *Nature Reviews Neuroscience*, vol. 10, no. 7, pp. 530–540, 2009.

[4] S. Chase, R. Kass, and A. Schwartz, "Behavioral and neural correlates of visuomotor adaptation observed through a brain-computer interface in primary motor cortex," *Journal of Neurophysiology*, vol. 108, no. 2, pp. 624–644, 2012.

[5] E. Kandel, J. Schwartz, T. Jessell *et al.*, *Principles of Neural Science*. McGraw-Hill New York, 2000, vol. 4.

[6] D. Weber, R. Friesen, and L. Miller, "Interfacing the somatosensory system to restore touch and proprioception: Essential considerations," *Journal of Motor Behavior*, vol. 44, no. 6, pp. 403–418, 2012.

[7] N. Hatsopoulos and A. Suminski, "Sensing with the motor cortex," *Neuron*, vol. 72, no. 3, pp. 477–487, 2011.

[8] T. Mima, N. Sadato, S. Yazawa, T. Hanakawa, H. Fukuyama, Y. Yonekura, and H. Shibasaki, "Brain structures related to active and passive finger movements in man," *Brain*, vol. 122, no. 10, pp. 1989–1997, 1999.

[9] C. Weiller, M. Jüptner, S. Fellows, M. Rijntjes, G. Leonhardt, S. Kiebel, S. Müller, H. Diener, A. Thilmann *et al.*, "Brain representation of active and passive movements," *NeuroImage*, vol. 4, no. 2, pp. 105–110, 1996.

[10] S. Francis, X. Lin, S. Aboushoushah, T. White, M. Phillips, R. Bowtell, and C. Constantinescu, "fmri analysis of active, passive and electrically stimulated ankle dorsiflexion," *NeuroImage*, vol. 44, no. 2, pp. 469–479, 2009.

[11] R. Stein, D. Weber, Y. Aoyagi, A. Prochazka, J. Wagenaar, S. Shoham, and R. Normann, "Coding of position by simultaneously recorded sensory neurones in the cat dorsal root ganglion," *The Journal of Physiology*, vol. 560, no. 3, pp. 883–896, 2004.

[12] J. Wagenaar, V. Ventura, and D. Weber, "State-space decoding of primary afferent neuron firing rates," *Journal of Neural Engineering*, vol. 8, no. 1, p. 016002, 2011.

[13] G. Bosco and R. Poppele, "Proprioception from a spinocerebellar perspective," *Physiological Reviews*, vol. 81, no. 2, pp. 539–568, 2001.

[14] R. Johansson and Å. Vallbo, "Detection of tactile stimuli. thresholds of afferent units related to psychophysical thresholds in the human hand." *The Journal of Physiology*, vol. 297, no. 1, pp. 405–422, 1979.

[15] R. Gassert, L. Dovat, O. Lambercy, Y. Ruffieux, D. Chapuis, G. Ganesh, E. Burdet, and H. Bleuler, "A 2-DOF fMRI compatible haptic interface to investigate the neural control of arm movements," in *Robotics and Automation, 2006. ICRA 2006. Proceedings 2006 IEEE International Conference on*. IEEE, 2006, pp. 3825–3831.

[16] R. Gassert, R. Moser, E. Burdet, and H. Bleuler, "MRI/fMRI-compatible robotic system with force feedback for interaction with human motion," *Mechatronics, IEEE/ASME Transactions on*, vol. 11, no. 2, pp. 216–224, 2006.

[17] D. Burke, S. Gandevia, and G. Macefield, "Responses to passive movement of receptors in joint, skin and muscle of the human hand." *The Journal of Physiology*, vol. 402, no. 1, pp. 347–361, 1988.

[18] J. Houk, W. Rymer, and P. Crago, "Dependence of dynamic response of spindle receptors on muscle length and velocity," *Journal of Neurophysiology*, vol. 46, no. 1, pp. 143–166, 1981.

[19] R. Lange, H. Nowak, J. Haueisen, and C. Weiller, "Passive finger movement evoked fields in magnetoencephalography," *Experimental Brain Research*, vol. 136, no. 2, pp. 194–199, 2001.

[20] F. Alary, C. Simoes, V. Jousmäki, N. Forss, and R. Hari, "Cortical activation associated with passive movements of the human index finger: an meg study," *NeuroImage*, vol. 15, no. 3, pp. 691–696, 2002.

[21] A. Guzzetta, M. Staudt, E. Petacchi, J. Ehlers, M. Erb, M. Wilke, I. Krägeloh-Mann, and G. Cioni, "Brain representation of active and passive hand movements in children," *Pediatric Research*, vol. 61, no. 4, pp. 485–490, 2007.

[22] G. Thickbroom, M. Byrnes, and F. Mastaglia, "Dual representation of the hand in the cerebellum: activation with voluntary and passive finger movement," *NeuroImage*, vol. 18, no. 3, pp. 670–674, 2003.

[23] O. Ciccarelli, A. Toosy, J. Marsden, C. Wheeler-Kingshott, C. Sahyoun, P. Matthews, D. Miller, and A. Thompson, "Identifying brain regions for integrative sensorimotor processing with ankle movements," *Experimental Brain Research*, vol. 166, no. 1, pp. 31–42, 2005.

[24] N. Sadato, V. Ibañez, M. Deiber, G. Campbell, M. Leonardo, and M. Hallett, "Frequency-dependent changes of regional cerebral blood flow during finger movements," *Journal of Cerebral Blood Flow & Metabolism*, vol. 16, no. 1, pp. 23–33, 1996.

[25] R. Turner, S. Grafton, J. Votaw, M. Delong, and J. Hoffman, "Motor subcircuits mediating the control of movement velocity: a pet study," *Journal of Neurophysiology*, vol. 80, no. 4, pp. 2162–2176, 1998.

[26] J. Kim, J. Eliassen, and J. Sanes, "Movement quantity and frequency coding in human motor areas," *Journal of Neurophysiology*, vol. 94, no. 4, pp. 2504–2511, 2005.

[27] R. Turner, M. Desmurget, J. Grethe, M. Crutcher, and S. Grafton, "Motor subcircuits mediating the control of movement extent and speed," *Journal of Neurophysiology*, vol. 90, no. 6, pp. 3958–3966, 2003.

[28] T. Ebner, "A role for the cerebellum in the control of limb movement velocity," *Current Opinion in Neurobiology*, vol. 8, no. 6, pp. 762–769, 1998.

[29] K. Druschky, M. Kaltenhäuser, C. Hummel, A. Druschky, W. Huk, B. Neundörfer, and H. Stefan, "Somatosensory evoked magnetic fields following passive movement compared with tactile stimulation of the index finger," *Experimental Brain Research*, vol. 148, no. 2, pp. 186–195, 2003.