Functional Organization in the Motor Cortex

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By

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Abstract

The representation of reaching movements in the macaque brain has been studied extensively for several decades using electrophysiological methods. Primary motor cortex (M1) neurons have been shown to encode many parameters of arm movements, including movement direction. Lately, the representation of reaching movements has been studied in the human brain as well using different non-invasive methods, including electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI). I continue this trend here by studying directionality of reaching movements in humans using fMRI, and attempt to bridge over the gap between electrophysiological data from monkeys and imaging data from humans.

Hubel and Wiesel have showed in the 1960’s that neurons in the primary visual cortex are organized according to their orientation preference; i.e., neurons that respond most strongly to a certain orientation are most likely to be clustered with neighboring neurons that have a similar preferred orientation. Since then, it has been shown that neurons in the medial temporal cortex (MT) are organized according to their preference for observed motion direction, and primary auditory cortex is organized according to frequency preference. In M1, functional organization has been studied much less extensively, but there is some evidence towards a certain degree of organization according to neuronal preference towards the direction of hand movement in monkeys. In humans, functional organization has yet to be studied.

To that end, a fast event related fMRI paradigm was conducted in which participants used a joystick to move a cursor from a central origin to one of five equidistant targets. The goal was to find directional preference in voxels, at a scale of several millimeters. Since each voxel is thought to encompass about a million neurons, if these neurons are distributed uniformly within the voxel, we would expect a flat tuning curve; i.e., the activation of that voxel would be the same for all directions. On the other hand, a directional preference at such a coarse resolution suggests that the neurons within the voxel are clustered according to their preferred direction (PD). The rationale is that clustering would decrease the number of functional units within a voxel, thus allowing some bias towards one direction over others. This bias could lead to gradual
tuning within a voxel. My findings show that voxels in M1 are directionally tuned, suggesting functional organization. This directional tuning was shown using several analytical tools: (1) I showed directly that when aligning the tuning curve of voxels to their PD (defined as the direction in which activation was highest) there was a gradual decrease in activation, as direction was farther away from that PD. (2) I used multi-voxel pattern analysis to show that spatial patterns of activation across voxels are highly correlated with patterns during trials in the same direction. Moreover, the correlation between two spatial patterns decreases as the distance between the directions increases. (3) I showed that for consecutive trials in the same direction there is suppression in activation level during repeated trials. This effect did not decrease gradually with directional difference between the two consecutive trials, but it suggests that the BOLD signal is in fact sensitive to movement direction. In addition, a model was constructed to estimate cluster size. This model estimated that cluster diameter is several hundreds of microns, which is comparable to the cluster size estimated in other studies in monkey M1.

Given these results, the question of distinguishing between the hand movement component and the visual components of the task remains open. Is the representation of direction actually a representation of hand-movement direction or is there a representation of target location, or of the cursor trajectory? To that end, I ran another experiment with two runs. The first run was standard, as in the first study I described. In the second run, however, the cursor was rotated by 45 degrees with respect to the joystick movements. This allowed dissociation between the visual and movement components of the task, because when aligning the target location in the standard run with the target location in the rotation run, hand movements differ by 45 degrees, and when the two runs are aligned to movement direction, the target location differs by 45 degrees. The same correlation analysis was used as in the previous study, and the correlations between visually aligned directions and motor aligned directions could now be separated. Both motor correlations and visual correlations in M1 were significantly higher than their controls. This led to another experiment in which participants were required to merely observe the cursor moving towards the different targets. The visual elements of the task were the same as before, but the participants were requested not to move their hands during the experiment, and did not have control of the cursor. This experiment was designed to see whether the visual elements of the task were sufficient to cause activation in M1, and moreover, cause the high correlations between same directions. None of the participants in this case show any M1 activation, nor are there any
positive correlations for same direction trials. Thus, the visual elements of the task are represented in M1 only when they carry information that is relevant to movement, such as a cue, or online feedback.

Another open question from the first study is regarding the repetition suppression (RS) I found for movement direction. RS is suggested to reflect the tuning properties of single neurons. Although RS has been shown in neurons in the visual cortex in response to visual stimuli, no such effect has been shown in motor areas. In the next study, electrophysiological data recorded from a macaque was analyzed to find a difference between repeated and non-repeated trials in neuronal firing rate, or in the directional tuning curve at the population level. In addition, since the local field potential (LFP) in visual areas has also been shown to manifest RS and the LFP signal is known as highly correlated with the BOLD signal, we would expect to find some difference between repeated and non-repeated trials. The results show no difference whatsoever between repeated or non-repeated trials either in single units or in LFP. No difference is found even when we limit the dataset to directionally tuned neurons, at their PD or at their least preferred direction (which would imply a change in tuning width). Further research is required to fully answer the question of RS, but the lack of any neuronal repetition effect, could suggest that the RS found in the fMRI signal of the motor cortex does not reflect neuronal responses.
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Introduction

Overview of the motor system

The control of movement is complex and involves many areas of the brain. The main motor areas in the cortex are the primary motor cortex (M1), premotor cortex (PM) and the supplementary motor area (SMA).

M1 is located in front of the central sulcus and its neurons project to many areas in the brain, including PM, SMA, somatosensory areas, the basal ganglia, the cerebellum, the brain stem and the spinal cord. Most of the projections to the spinal cord are to interneurons, and only a small fraction of the projections are directly to motoneurons (Bortoff and Strick, 1993). It receives inputs mainly from PM, SMA and from the primary sensory cortex.

PM is located in the frontal lobe, just anterior to M1. It projects directly to the spinal cord, although not as much as M1, and to the striatum, the cerebellum, M1 and the SMA. PM receives inputs from the prefrontal cortex, which is involved in working memory, and from the posterior parietal cortex (PPC), and is involved in movements triggered by external stimuli (Weinrich and Wise, 1982; Godschalk et al., 1985). The PPC in itself receives many sensory inputs in different modalities as well as motor feedback. It is involved in transforming the sensory information into a common reference frame, and plays a role in planning movement (Andersen et al., 1987). PM can be divided in two: ventral (PMv) and dorsal (PMd). The inputs to the PMd and PMv are via separate paths. PMd inputs go through the medial intraparietal cortex (MIP) and it is involved in reaching (Crammond and Kalaska, 1996; Johnson et al., 1996), mainly in processes related to movement preparation and movement selection (Weinrich and Wise, 1982; Weinrich et al., 1984; Wise and Mauritz, 1985; Kurata and Tanji, 1986; Mauritz and Wise, 1986; Kurata and Wise, 1988; Passingham, 1988; Riehle and Requin, 1989; Mushiake et al., 1991; Boussaoud and Wise, 1993a; Boussaoud and Wise, 1993b; di Pellegrino and Wise, 1993; Crammond and Kalaska, 1994; Kurata and Hoffman, 1994), while PMv inputs go through the anterior intraparietal cortex (AIP) and it is involved mainly in grasping objects (Jeannerod et al., 1995;
Raos et al., 2006), though in contrary to these classic roles, it has been shown that PMd is also involved in grasping (Raos et al., 2006).

PMv is divided into a caudal area (F4) and a rostral area (F5). F5 is involved more in grasping, (distal arm control) (Rizzolatti et al., 1988), while F4 is thought to be involved in proximal arm control (Fogassi et al., 1996). F5 neurons also respond to the visual perception of an action made by someone else. Often, only observed movements identical to those controlled by a given neuron are able to activate it ("mirror neurons") (Pellegrino et al., 1992; Gallese et al., 1996).

The SMA is located mostly in the medial surface of the hemisphere and is anterior to the leg area of M1. SMA proper, the caudal part of the SMA, projects mainly to M1 and directly to the spinal cord (He et al., 1993; He et al., 1995), and receives inputs from pre-SMA (the rostral part of the traditionally defined SMA) and from the contralateral SMA. It is involved in internally generated movements (Roland et al., 1980; Matsuzaka et al., 1992; Halsband et al., 1994), bimanual movement (Brinkman, 1981; Serrien et al., 2002), and temporal sequences of movement, such as finger tapping (Roland et al., 1980; Gaymard et al., 1990; Mushiake et al., 1990; Jenkins et al., 1994; Gerloff et al., 1997; Shima and Tanji, 1998; Lee and Quessy, 2003).

All cortical motor areas are also connected with the cerebellum and the basal ganglia via the thalamus. Damage to these structures provides evidence of their important role in modulation of movement, online corrections and motor learning.

A topographic map of the body in M1

At the end of the nineteenth century Gustav Fritsch and Eduard Hitzig discovered that electrical stimulation of the motor cortex produces movements on the contralateral side of the body (Fritsch and Hitzig, 1870). They showed that stimulating different parts of the cortex activated different groups of muscles. The excitable sites formed a topographical map of movements on the surface of the brain. These results were soon replicated by Ferrier (1873). However, he used stimuli with a longer duration, which were found to evoke coordinated, purposive movements, rather than just twitches. In 1905 a detailed map of the human M1 was described by Campbell (1905). These findings were expanded to several species of monkeys (Leyton and Sherrington,
In the 1930s Penfield found a topographically organized representation of the entire body in human M1 ("homunculus"), where the lips and tongue, thumb and hand receive a disproportionately large representation (Penfield and Boldrey, 1937). A homologous map was found in monkeys (Woolsey et al., 1952). The different joints of the arm are represented in concentric rings in the arm area of M1, such that proximal joints are surrounding distal ones (Murphy et al., 1978). Somatotopic maps in M1 were also generated using functional MRI (fMRI) (Rao et al., 1995).

This topographic map may imply that each body part is represented in an orderly fashion and occupies non-overlapping cortical space. Asanuma suggested that each cortical column in M1 controls a specific muscle, or a set of muscles (Asanuma and Ward, 1971; Asanuma and Rosen, 1972; Asanuma, 1975). However, even the maps of Penfield and Woolsey showed great overlap. Lemon found that single neurons receive afferent input from different fingers (Lemon, 1981). Spike-triggered averaging has shown that neurons activate more than one forelimb muscle (Fetz and Cheney, 1980; Cheney and Fetz, 1985; Cheney et al., 1985; Buys et al., 1986; Lemon et al., 1986; Fetz et al., 1989). In fact, neighboring neurons seem to activate similar muscle fields. It was suggested that M1 neurons activate a functional set of muscles. Filling single corticospinal neurons with horseradish peroxidase (HRP) led to terminal ramifications in more than one spinal motor nucleus (Shinoda et al., 1981). This provided an anatomical basis for this divergence. Later, Schieber & Hibbard (1993) found extensive overlap between fingers in the hand area, suggesting that the control of each finger utilizes a population of neurons distributed throughout the hand area rather than a somatotopically segregated population. Evidence of overlap in the arm subregion was also found in neuroimaging studies in humans with positron emission tomography (PET) (Colebatch et al., 1991; Grafton et al., 1991) and fMRI (Rao et al., 1995; Sanes et al., 1995; Beisteiner et al., 2001; Dechent and Frahm, 2003; Kleinschmidt et al., 2006; Meier et al., 2008). Meier (2008) also showed that the wrist and the forearm were relatively emphasized both ventrally and dorsally to the finger representation, violating the traditional somatotopic order. In addition, M1 arm sub-region has vast horizontal interconnectivity without an obvious topographic plan for fingers, wrist, or other parts of the arm (Huntley and Jones, 1991). Magnetoencephalography in humans likewise has shown that the dipole sources of the neuromagnetic fields generated during movements of different digits are not arrayed in somatotopic order, either in a single subject or averaged across multiple subjects (Cheyne et al.,
1991; Salenius et al., 1997). Taken together, this body of experimental data reviles a pattern of organization which has the richness and the flexibility to execute the complex movements we make.

The role of the arm area of M1

M1 plays a fundamental role on the control of arm movements. What exactly that role is has been the subject of a longstanding debate. In the late 1960’s, Evarts (1968) showed that neurons in the arm area of M1 of the macaque co-vary with muscle force. Thach (1978) showed that neurons in M1 code different parameters of movement: muscle force, joint torque and intended direction. But these motor studies were always to one of two directions. To that end, Georgopoulos and colleagues (1982) studied movements to eight different directions. They found that neurons in the arm area of M1 encode movement direction in space, and that the activity of these neurons can predict the actual direction of movement (Georgopoulos et al., 1986; Georgopoulos et al., 1988). In 1990 directionally tuned neurons were shown to change their preferred direction (PD) while arm movements were made in different parts of extrapersonal space, although the population vector still pointed at the correct direction (Caminiti et al., 1990). This suggests that coding is not entirely extrinsic. Similar results were also found by Scott and Kalaska (1995, 1997), who used different arm postures, and by Sergio and Kalaska (1997, 2003), who used an isometric force in different locations in the workspace. In 1999 Kakei and colleagues (Kakei et al., 1999) designed an experiment in which they differentiated between muscle activity, wrist joint direction, and direction in space. Interestingly, they found both a group of neurons co-varying with muscle activity and a group of neurons co-varying with movement direction in space, which did not change their preferred direction for different muscle activity. Thus, both extrinsic and intrinsic parameters are coded in M1. If M1 encodes both intrinsic and extrinsic parameters, perhaps the transformation between the goal and the execution of the task is done in M1, at least to some extent. Therefore, M1 could be involved in a much more complex process during movement than previously thought, which includes planning, execution, and online correction.

At what point does M1 come into play and becomes involved in the planning? Is it only after we know the required movement vector, or is the movement vector itself planned in M1 as well? To
answer this question we need to know which parameters of the goal are represented in M1. There is evidence towards a representation of the visual cue in human (Saleh et al., 2010) and in non-human primates (Martin and Ghez, 1985; Alexander and Crutcher, 1990; Lurito et al., 1991; Shen and Alexander, 1997). Some studies have even shown neuronal sensitivity to specific features of the visual cue, such as its location or color (Zhang et al., 1997a; Zach et al., 2008).

**Columnar organization in M1**

The primary visual cortex (V1) has long been known to be organized in vertical columns perpendicular to the cortical surface according to the preferred orientation of neurons (Hubel and Wiesel, 1962). These columns were shown, using in-vivo optical imaging, to be arranged in pinwheel-like patterns (Bonhoeffer and Grinvald, 1991). Since then, similar clustering according to the functional properties of neurons has been shown in several other primary sensory areas of the brain, such as somatosensory cortex (Powell and Mountcastle, 1959), primary auditory cortex (A1) (Imig and Adrian, 1977) and middle temporal cortex (MT) (Albright et al., 1984). This has been shown even more convincingly with voltage sensitive dye (Blasdel and Salama, 1986) and with calcium imaging in V1 (Ohki et al., 2005) and later in A1 (Rothschild et al., 2010). Are neurons in M1 also organized according to their functional properties? This has been a longstanding question. M1 has a similar anatomical structure as these other cortical areas. Therefore, we would expect the same general rules that govern the primary sensory areas to govern M1 as well. But according to which parameters do we expect M1 to be organized? Earlier work investigated columnar organization in M1 according to different muscles (Asanuma, 1975) using intracortical microstimulation. Later work focused mostly on movement direction.

Clearly, the picture is not as clear cut in V1, but there is accumulating indirect evidence to support some clustering according to the neurons’ PD. The firing rates of neighboring neurons in M1 have been shown to be correlated (Murphy et al., 1985; Kwan et al., 1987; Vaadia et al., 1995), suggesting that neighboring neurons share common inputs. Georgopoulos and colleagues (1993) estimated the synaptic strength between pairs of neurons using an analysis based on waiting time probability density function, and found that the synaptic strength was negatively correlated with the difference between the neurons’ PDs. This was strengthened by the results of
Hatsopoulos (1998), who used cross-correlation techniques to show that fine temporal synchrony carries information regarding movement direction and contributes to coding beyond the information available from the changes in firing rate. In addition, pairs of neurons with a similar directional preference were found to show higher noise correlation (Lee et al., 1998; Maynard et al., 1999). Later, Ben-Shaul et al. (2003) found that neurons recorded from the same electrode have more similar PDs than neurons recorded from distant electrodes. Amirikian and Georgopoulos (2003) showed that cells with similar PDs tended to segregate into vertically oriented minicolumns 50-100 µm wide and at least 500 µm high. Such minicolumns aggregated across the horizontal dimension in a secondary structure of higher order. In this structure, minicolumns with similar PDs were approximately 200 µm apart and were interleaved with minicolumns representing nearly orthogonal PDs.

Finally, directional tuning has been shown in signals with a larger scale than single neurons, such as multi-unit activity (MUA) (Stark et al., 2009), in which PDs were similar to those of single units recorded from the same electrodes, and LFP (figure 1) (Mehring et al., 2003; Rickert et al., 2005), which represents populations at the resolution of between 250 microns and several millimeters (Mitzdorf, 1987; Victor et al., 1994; Kruse and Eckhorn, 1996; Gail et al., 2003; Kreiman et al., 2006; Liu and Newsome, 2006; Logothetis et al., 2007; Berens et al., 2008; Gieselmann and Thiele, 2008; Katzner et al., 2009; Rasch et al., 2009; Xing et al., 2009). These data suggest some level of clustering of neurons in monkey M1 according to the neurons’ PD; otherwise we would expect the tuning curves at large resolutions to be flat, with no bias towards any one direction over others.

Despite the evidence of functional clustering, it is difficult to reconcile the results of these studies with a strict columnar structure, since the difference between PDs of neurons recorded by a single electrode was relatively large (Ben-Shaul et al., 2003; Stark et al., 2009), and nearby neurons frequently encoded different kinematic parameters (Stark et al., 2009). Since M1 neuronal activity has been found to encode many different parameters, the functional architecture could also be more complex than that found in sensory cortex (Hatsopoulos, 2010).
Figure 1: Directional tuning of a sample movement evoked potential (mEP) obtained from a single electrode in M1 during execution of contralateral movements. Trial averaged LFP activity is shown separately for each movement direction. Time zero indicates movement onset. Note that this mEP is strongly tuned, with the highest amplitude for movement to the left (180 degrees). Rickert et al. 2005

Many studies in humans show a body map in M1, where the size of each area is several millimeters (Zoharia et al., 2012). However, there are practically no studies showing clustering in M1 at a finer resolution. We will further discuss the ability to explore such small structures using functional imaging, despite its relatively coarse resolution.

**FMRI and neuronal coding**

FMRI is widely used to study the brain, but what exactly is the nature of the BOLD fMRI signal, and how exactly is it related to neuronal electrical activity? In 2000, Heeger and colleagues showed that the BOLD signal in MT increases linearly with motion coherence, with a slope comparable to that of the firing rate of single neurons (Heeger et al., 2000). Simultaneously scanning anesthetized monkeys and recording electrical signals revealed that the BOLD signal is much more correlated with the mid gamma range of the LFP signal (i.e. temporal frequencies 40-
130Hz) than MUA or single unit activity (SUA) in visual cortex of monkeys (Logothetis et al., 2001). This suggests that the BOLD signal reflects the inputs rather than spiking outputs, since LFP is known to reflect synchronized input signals of the neural population within up to several millimeters around the electrode tip (Mitzdorf, 1987). Rauch and colleagues (2008) were able to dissociate between the MUA and the LFP signals by using a serotonin receptor agonist, which reduces the MUA without affecting the LFP. Under these conditions, they found that the BOLD signal was also not affected by the serotonin receptor agonist, and was better predicted by the LFP signal.

Mukamel et al. (2005) recorded SUA and LFP from two neurosurgical patients and compared them with the BOLD signal from healthy subjects during presentation of an identical movie segment. Their findings show that the BOLD signal was highly correlated with the signal predicted according to the SUA. Adding to these findings is the work of Shmuel et al. (2006), who showed that the negative fMRI response was actually correlated with the decrease in firing rate in V1. Additionally, Nir and colleagues (2007) reported data from simultaneous recordings of SUA and fMRI. They found that the BOLD signal was correlated not only with the gamma band LFP in the human auditory cortex, but it was also predicted by the correlation between firing rates of neighboring well-isolated single neurons, suggesting that the BOLD signal may reflect the overall local neuronal activity.

On the other hand, this link between brain hemodynamics and local neuronal activity was challenged by the finding of a component of the hemodynamic signal that precedes the onset of a periodic stimulus and that is independent of standard predictors based on LFP and MUA. This trial-locked haemodynamic signal could be due to an arterial pumping mechanism. However, this dissociation was only observed in the absence of visual stimulus. Stimulus-evoked hemodynamic activity was highly predictable by LFP and MUA (Sirotin and Das, 2009).

Recently, electrocorticographic (ECoG) recordings from epileptic humans showed that beta and mid gamma range LFP explain different components of the BOLD signal and that the LFP signal in different cortical regions is differentially correlated with the BOLD response (Conner et al., 2011). The best (pre-stimulus) baseline correlation of beta and gamma power with the BOLD signal was found in the occipital and parietal lobes while the worst correlations were found in the
frontal lobe. Thus, caution should be taken when applying methods that were established in the occipital and parietal lobes to frontal areas.

**Multi-voxel pattern analysis (MVPA)**

Traditionally, fMRI analysis methods have focused on cognitive variables and individual voxels. Since the majority of fMRI studies focused on finding the anatomical loci of these cognitive variables, these analysis methods were extremely productive. However, there are limits to examining voxels in isolation. Haxby and colleagues (2001) were the first to introduce the analysis of MVPA. In this method of analysis, spatially distributed patterns of activation are compared across voxels. Conventional analysis methods were discarding a large amount of information contained in these patterns. MVPA can pick up on much more subtle differences because the spatial distribution of activation in response to two different stimuli can be different even when the average response of the ROI is the same. In Haxby’s study, they compared spatial patterns of visual stimuli between categories and within categories (e.g., faces, houses, chairs, etc.), and found areas where correlation coefficients between pairs of stimuli from the same category were higher than between stimuli from different categories, thereby discriminating between the different perceptual states.

This principal was later utilized to decode grating orientation from the BOLD pattern of activation in early visual areas in single trials (Haynes and Rees, 2005; Kamitani and Tong, 2005). It has been suggested that the reproducible yet specific patterns to the different orientations could reflect sub-voxel tuning. The patterns may arise from variability in the distribution of cortical feature columns, or their vascular supply (see figure 1; Boynton, 2005). The weak biases in the voxels' fMRI responses can be used to distinguish between different stimuli, or different types of movement.

Op de Beeck (2010) disputed this point, showing that these patterns did not diminish with smoothing. He claimed that if the patterns were created by the distribution of orientation columns, the decoding ability should have decreased with smoothing, as there are many more columns in a larger, smoothed, unit. Kamitani and Sawahata (2010) responded that spatial smoothing does not prove that the source of MVPA isn’t at the sub-voxel level by showing
analytically that no information is lost by spatial smoothing. Swisher and colleagues (2010) scanned a cat using high-field high-resolution fMRI to show that the majority of the information in multi-voxel patterns about orientation is at a spatial scale of up to a millimeter, which is also the scale of the diameter of a column. This confirms the hypothesis that the origin of multi-voxel patterns is the distribution of orientation columns, and not just large-scale biases. These results were replicated by Freeman et al (2011). However, Freeman was also able to achieve similar results for angular position (retinotopic location), a parameter which is known to be mapped at a large scale rather than fine-scale columnar architecture. This demonstrates that spatial filtering does not distinguish well between maps and columns. Moreover, they show a coarse-level topographic map of orientations, which was both sufficient and necessary for decoding.

The latest paper on the subject examined the scale of organization for object selectivity in the ventral visual cortex, both by investigating the effect of spatial smoothing on MVPA reliability and by comparing the relative weight of higher and lower spatial frequencies. The differential activation for category comparisons was found to be organized at a larger spatial scale than for the within-category comparison. This finding confirms the existence of multiple scales of organization in the ventral visual cortex (Brants et al., 2011).

An intriguing possibility was suggested by Gardner (2010): It is possible that the vasculature system is organized around columnar architecture in a way that could amplify weak signals and make them more easily measurable by fMRI. Cortical columns that share the same tuning properties may often be active together and thus require oxygen and metabolic nutrients together. A single artery could provide oxygenated blood to a number of columns. Thus, the ability of classifiers to work at low spatial resolutions may be the consequence of a well-structured vasculature aligned to the functional architecture of the cortex.
Figure 2: Patterns of orientation-selective responses measured with fMRI. The colored arrows represent the preferred directions of neurons. Top right: synthetic orientation tuning data generated by band-pass filtering random orientation values, assuming neurons are clustered according to their preferred direction. The black squares represent 3 x 3 mm$^2$ fMRI voxels. Bottom right: histograms showing the proportion of selectivity inside each voxel to each of the eight orientations shown below. This shows how different stimulus orientations produce slightly different patterns of responses in V1. Top left: synthetic data, assuming neurons are uniformly distributed. Bottom left: histograms showing flat tuning curves at the voxel level. Adapted from Boynton, 2005.

**FMRI repetition suppression (RS)**

Repetition of the same stimulus has been shown to cause a decrease in activation compared to a novel stimulus (e.g., Buckner et al., 1998). RS, or adaptation, was first introduced as a method for providing information at a sub-voxel resolution by Grill-Spector and Malach (2001). The rationale behind this technique is that a voxel’s activation is the average responses of about a million neurons, while RS enables tagging specific neuronal populations with a certain property. Thus, we can differentiate between a situation in which a neuronal population has the property, and where there are several populations with different properties that are all activated a little to a certain stimulus. An example is given by Malach (2012): if an imaged voxel contains a
heterogeneous and balanced mix of highly selective neurons, for example neurons narrowly tuned to image size, the BOLD response, which pools all these selective responses together, will consequently appear to be “size invariant”. The same will be true, of course, if the neurons in the voxel are individually size invariant. Thus, it is impossible to decide, by observing the BOLD response alone, what are the functional properties of the neurons. Repeated presentations of an identical image in the same size may cause signal reduction in both cases. However, presenting a sequence of varied sizes of the image will cause signal reduction only in the voxel containing invariant neurons, since they are "blind" to the size change, while for the size selective neurons each size change appears as a novel stimulus.

A decrease in activation has been shown in single neurons (Movshon and Lennie, 1979), but the relationship between the neuronal signal and the RS phenomenon is not fully understood. Grill Spector and colleagues (2006) proposed three possible models to explain the RS: (1) “fatigue”, according to which all neurons show a proportionally equivalent decrease in activation in response to a repeated stimulus. The neural mechanism in this case could either be firing rate adaptation or synaptic depression (short term or long term) (Miller and Desimone, 1994; Grill-Spector and Malach, 2001), (2) “sharpening”, where we expect fewer responsive neurons following stimulus repetition (Li et al., 1993; Desimone, 1996; Wiggs and Martin, 1998) and (3) “facilitation”, which predicts that repetition facilitates faster processing of the stimulus and therefore shorter duration of neuronal firing (Sobotka and Ringo, 1996; Henson and Rugg, 2003; James and Gauthier, 2006).

The interpretation of fMRI RS was complicated by Sawamura and colleagues (2006). They showed that neurons in the macaque inferior temporal cortex (IT) adapt to a stimulus that they were responsive to. However, when two stimuli which evoke a similar response were shown one after the other (ABAB…), there was less adaptation to the second stimulus, than when the stimuli were identical (AAAA, or BBBB). This indicates that the level of adaptation shows greater stimulus selectivity than the magnitude of the neuronal response. These results are inconsistent with the fatigue model, in which case adaptation would transfer across stimuli and be purely response dependent. Therefore, the source of adaptation is probably input specific. This hypothesis was later strengthened by De Baene and Vogels (2010), and is consistent with evidence from V1 (Movshon and Lennie, 1979; Müller et al., 1999), but in MT for example,
Kohn and Movshon (2004) found sharpening of the neurons’ tuning curves, which could imply different mechanisms in different areas, different types of stimuli, or different time scales. Further interpretations of RS will be discussed in chapter 3 of the results, about RS in the motor cortex.

MVPA and RS were recently compared in the visual cortex (Sapountzis et al., 2010). The estimates of orientation selectivity obtained with the two methods of analysis were highly correlated across visual areas. However, the MVPA approach was more sensitive to stimulus orientations (i.e., distinguished stimuli with a smaller separation than RS).

**Research goals**

**Functional organization in human M1**

There are many studies about the functional organization in V1 (according to stimulus orientation), in MT (according to observed motion of the stimulus) and in A1 (according to frequency of auditory stimuli). M1 neurons are known to be tuned to movement direction, but there is little evidence of functional organization of these neurons, and none in human M1.

Are neurons in human M1 clustered according to their PDs, or are these neurons uniformly distributed? If neurons with similar PDs are organized in clusters, what size are these clusters? In the first chapter, I answer these questions in two steps. First I show, using several different methods, that voxels, encompassing about a million neurons each, are directionally tuned. I claim that this tuning at such a coarse resolution could not have been found had the neurons been uniformly distributed. Next, I constructed a model to estimate cluster size based on the level of average directional tuning in M1 voxels.

**Visual and motor representations in human M1**

Each trial in our reaching task began with a target appearing on the screen. Then Participants had to wait for the go signal (change of color of the cursor at the center of the screen) and then use the joystick to move the cursor towards the target, while gaining visual feedback of the cursor throughout the trial. The temporal resolution of the BOLD signal is not high enough to separate
the different epochs. This brings up the question, whether human M1 holds information only about movement direction, or is there also a representation of a higher level of the task, such as the visual target or online visual feedback? In the second chapter I dissociate between motor and visual elements of the task in order to address this question by introducing a 45 degree visuomotor rotation. My results show that the activation pattern in M1 is sensitive to the visual components of the task, as well as to the motor components. This sensitivity to visual components disappears in the absence of a motor task. Therefore, the visual representation in M1 is task related, and probably has to do either with the goal of the task, or with the online feedback.

**RS in M1**

In the first chapter I show that the BOLD response in M1 to a repeated movement in the same direction is reduced compared to the response during a non-repeated movement. This was also shown in two other studies (Dinstein et al., 2007; Fabbri et al., 2010), and is added to the many studies that show RS of the BOLD signal for repeated visual stimuli in visual areas. This raises the question, what is the neuronal mechanism for the RS found in fMRI for movements? Is it the same as for visual stimuli? I started by looking for either a decrease in firing rate in M1 neurons for repeated movements, or a change in their tuning curve width (since a decrease in the BOLD signal could reflect a decrease in either the PD and therefore, widening of the tuning curve or in the directions near the PD and therefore, sharpening of the tuning curve). In addition, I look at the LFP, which has been shown to be more correlated with fMRI activation, trying to find some effect of repetition.
Methods

Rapid event related fMRI and deconvolution

Event-related fMRI vs. Block design

Event related fMRI is the use of fMRI to detect responses to individual trials rather than in the more traditional block design, where the same condition is repeated for an entire block with a much longer duration (typically ~10-30 seconds). The advantage of the event related design is that the different conditions can be randomized and unpredictable, and the signal is less sensitive to temporal drift (e.g. due to head motion).

Rapid vs. slow event-related design

When subjects participate in an fMRI experiment, they have to lie on their backs without moving their heads; they are subjected to many stimuli and sometimes have to respond by pushing a button or, as in our example, moving a joystick. In order to gain enough statistical power, there are usually many repetitions. On top of that, because it takes the fMRI signal at least 12 seconds to decay and go back to baseline, the original (slow-event related) fMRI paradigm required a long waiting time until the next trial. This can be very boring. Many have reported falling asleep at some point during the experiment. This is one of the reasons we use a rapid event-related design, in which a new trial begins every 4 seconds (in our case). This allows many more trials in a given session, allowing stronger statistical power. However, necessarily this causes an overlap between the responses to subsequent trials: the BOLD response to a given trial peaks when the participant is usually already performing the next movement. In order to analyze such data, there are prerequisites in designing the task: 1) Eliminating the effects of recent trial history as much as possible by using first-order counterbalancing. I.e., after each of the 5 trial conditions, there is an even distribution of these conditions in the next trial (e.g., ~20% of trials after movement in 0° will be in the same direction, ~20% will be 45°, etc.). This condition is important for ensuring that the response to a trial type is not biased by context or by the history of preceding trial-types. 2) Null trials of various lengths are embedded in the experiment. These null trials provide jitter.
in the inter-trial intervals, and thereby improve the statistical efficiency, i.e., the accuracy with which the hemodynamic responses are estimated. The different sequential trials are averaged out, and the response to a certain condition, movement direction in our case, can be distinguished despite the overlap. This differential overlap provides a more efficient estimation than slow event-related designs (Dale, 1999).

**Deconvolution vs. GLM**

To analyze the data, we use the deconvolution method. Deconvolving the overlapping Hemodynamic Response Function (HRF) is possible according to reasonable assumptions, such that the response to multiple stimuli is the linear sum of the response to the individual stimuli (linear superposition assumption (Glover, 1999)).

An advantage of this method is that it's model free. Generally, it's accepted that the BOLD response to an event, usually a stimulus, is shaped as a single- or two-gamma function. The BOLD signal we measure (i.e., the raw signal) is this HRF convolved with the sequence of events (plus noise). We know the sequence of events and the HRF, and all that is left for us to find is the response amplitude (β) that minimizes the noise, according to the formula: $Y=bX+e$, where $Y$ is the raw data, $X$ is the design matrix, $e$ is the Gaussian noise, and $b$ is the vector of response amplitudes to the different stimuli used in the experiment. This is the General Linear Model (Friston et al., 1994). In the deconvolution method, instead of having to assume a predefined shape of the BOLD response, we model the entire response function (in the temporal domain), without any assumptions about its underlying shape. In this analysis, each condition is represented by several β weights, 10 in our case, causing vector $b$ to be 10 times longer. As a result we don't have to assume that the response to movement in the motor cortex is necessarily shaped the same as the hemodynamic response function (HRF) typically found in primary sensory areas. It has been shown that different areas in the brain show a different response function (Schacter et al., 1997). In addition, the BOLD response appeared to vary considerably across different people (Aguirre et al., 1998). The deconvolution approach allows different response functions for different participants, for different areas of the brain, and even for the different behavioral conditions (i.e., the different movement directions). With that being said, we still expect to see the same general shape of the HRF in the deconvolution kernel.
Experimental paradigm

Each trial lasted 4 s. The trial began with presentation of a red circle in the center of the screen (“origin,” radius of 0.7°). Initially, the participants had to hold an MRI-compatible joystick still, and make no hand movement. After an interval of 500 ms, five circles (targets, radius of 1°) appeared at the upper half of the screen, spread around the center at equal distances, between 0° and 180°, 45° apart. Their distance from the origin was 4.5° of visual angle. Four of the circles were blue and one circle was green, signaling the required future direction of movement. The participants had to keep their hand still until the “go” signal, in which the red “origin” circle turned into a white cursor, which occurred 2 s later. They were instructed to respond by moving the cursor toward the green target, using the joystick. Participants had 1.5 s to reach the target. Upon reaching the target, all circles disappeared. This served as a cue for the participants to release the joystick (thereby relaxing the spring), which resulted in the joystick returning to its starting position at the center. There was no explicit failure signal. If the participants did not reach the target within the 1.5 s time limit, all circles disappeared and the next trial began (participants failed to reach the target in 10.6% of the trials).

Participants were instructed to try and make quick and accurate movements towards the targets. They were not instructed as to how to move their arms towards the target. However, the joystick was relatively small, and in order to make quick and accurate movements towards the target, movements were generally limited to the wrist and hand. The verb "reach" here refers to attaining the target by a movement, even though participants are not actually reaching with their whole arm.

The length of the joystick is 11.5cm, and the angular range of the joystick is +/-15 degrees. Thus, given that participants used the full extent of the joystick range, the size of the movement required to displace the cursor from the origin to the targets was ~3 cm.

The red origin and all five blue targets appeared on the screen for 2–8 s during intermittent null trials, in which the participants were instructed not to move the joystick until the next trial began.
This rapid event-related fMRI study consisted of 250 trials, 50 in each direction. The trial order was counterbalanced (first order). Null trials were pseudorandomly embedded between movement trials. Our constraint was that the total length of all null trials would equal the total length of each of the five movement conditions (200 s). The trial sequences were built using optseq software, which chooses the most efficient sequence (most variable history before each condition) out of 10,000 random sequences sampled. The experiment began and ended with 16 s of a null event.

The fMRI acquisition, preprocessing and defining the regions of interest will be described in the specific methods section of the results chapters 1 and 2.

**Data Analysis**

**Coefficient of variation analysis**

We used a bootstrap analysis, to test whether the coefficient of variation (CV =SD/mean) of each voxel's average response to the five directions of movement is significantly higher than expected by mere chance (e.g., had there been no directional selectivity). In this analysis, we randomly reassigned conditions (directions of movement) to the trials, while maintaining the original proportions of hand movements (each condition was assigned to 20% of the trials). The null conditions were not replaced. We created a new regression matrix, estimated the β values for the different directions, and assessed the CV, separately for each assignment. This procedure was repeated 10,000 times, resulting in a distribution of expected CVs merely due to noise. Next, for each voxel, we assessed its p value: the fraction of CV values obtained by the bootstrap method that were greater than the actual CV of that voxel. Finally, a χ² test was used to show that the distribution of p values across voxels was significantly skewed to low values (differing from a uniform distribution, which would be expected by chance).

The CV analysis was used also for the estimation of cluster size. For this purpose, since each voxel is expected to show some variation in its response by chance (as there were limited repetitions of each direction of movement), we also corrected each voxel's CV by subtracting from its actual variance in response (for the various directions) the mean variance of the
bootstrapped activation (XBS) across iterations: 
\[ CV = \frac{\sqrt{\text{Var}(B) - \text{mean}(\text{Var}(B_{BS}))}}{\text{mean}(B)}. \]

In addition to calculating voxel CV, we also calculated the CV as a measure of the directionality of the LFPs in monkey M1, when monkeys performed the same center-out task [courtesy of S. Cardoso de Oliveira (Cardoso de Oliveira et al., 2001)]. To that end, we used the peak-to-peak distance (the distance between maximum and minimum) of the mean evoked potential, per direction of movement. CVs of LFPs were calculated without subtracting bootstrapped variance. Consequently, the CV is slightly overestimated.

**Analysis of spatial patterns of fMRI response**

To detect directional selectivity of voxel population spatial patterns, each individual's data were split into two datasets, such that each of the 50 trials in each direction was randomly assigned to one of the datasets. For each voxel, we estimated the \( \beta \) values and defined the activation for each direction (i.e., activation value) as the average of the \( \beta \) values measured 6 and 8 s after the beginning of the trial (~4–6 s after movement initiation; normally at the peak activation). Then, in each dataset and for each voxel, we subtracted the voxel's mean activation level (across all directions) to remove activation differences between voxels that are unrelated to movement direction. Without such a normalization procedure, one would get high correlations between the multivoxel spatial patterns from all comparisons, simply because some voxels are more active than others, regardless of the direction of movement.

The above analysis resulted in two matrices, one for each dataset. Each matrix consisted of 5 columns (one for each direction) with length \( N \) equal to the number of voxels in the ROI. The entries of each row of the matrix were the 5 activation values of a single voxel for all 5 directions of movement.

Next, we calculated the correlation coefficient (CC) between the columns of the first and the second datasets (each corresponding to the pattern of activation across all voxels, for a given condition). If the activation values contain information about the direction of movement, one should get a higher CC for movements to the same direction (in the two datasets) than the CC calculated for movements to two different directions. To ensure that the results reflect a reliable
trend, and are not merely due to some arbitrary division of the trials into the two datasets, we repeated this analysis 100 times for each participant; in each iteration, the data were split differently into two random datasets. The results shown are the mean CC values across all 11 participants. The resulting dependence of the CC on the angular difference between the two directions of movements matched a normal distribution: $y_i = h \times e^{-\frac{(x_i - \mu)^2}{2\sigma^2}} - b$.

**Movement repetition analysis**

The purpose of the repetition analysis was to find a decrease in activation when the same movement is made twice in a row. This would provide additional evidence that M1 fMRI activation is sensitive to movement direction. In this analysis, the various conditions were split according to the angular difference between the direction of movement in the current trial and the movement direction in the previous trial. Thus, a condition of 0° means that the movement was to the same direction as in the previous trial. Beta values were estimated in the same way as in the previous analyses.

To test whether a voxel's PD (direction eliciting the greatest response) is the same direction that elicits the greatest repetition suppression (RS), we divided the trials into 10 conditions. First we divided the trials into repeated and nonrepeated trials, and then we divided each set of trials into five conditions according to the current direction of movement. The repetition index for each voxel ($v$) and each direction ($d$) was defined as $\beta_{v,d}(\text{nonrepeated})/\beta_{v,d}(\text{repeated})$.

Both repetition index and activation index (of nonrepeated trials) were normalized by subtracting the mean and dividing by the SD across directions in each voxel (to bring the two different signals to a common scale) and then correlated. Pairwise Student's $t$ test was used to test whether the CCs in the “same direction” and “different direction” conditions were significantly different.

**Estimating the size of a cluster of neurons with similar PDs**

Cluster size was calculated based on the estimated number of clusters in each voxel. In order to estimate the number of clusters within each voxel, we modeled the voxels as having anywhere
between 5 and 1500 clusters. Each cluster was presumed to be a cluster of neurons with similar neuronal properties, including the same PD, which was one of 8 directions, between 0 and 315 degrees, with 45 degree decrements. For each cluster, the PD was randomly chosen from a uniform distribution of the 8 directions (see figure 1). After assigning a PD to each cluster, we can now get a voxel histogram by summing up the clusters with each of the PDs. The voxel histogram is then convolved with the average neuronal tuning function (cosine tuning), to obtain the estimated “tuning curve” of the voxel. Because of the assumed uniformity of the distribution of PDs (Georgopoulos et al., 1988), the more clusters per voxel (i.e., smaller clusters), the flatter the voxel's tuning curve. The voxels' CV is then calculated over 5 consecutive directions (of the 8 possible directions, mimicking our sampling in the fMRI experiment).

![Figure 1](image)

**Figure 1:** An example voxel with 16 clusters. Each of the 16 squares represents a cluster with a PD according to the direction of the arrow. The PD of the entire voxel is the vector sum of the cluster PDs.

This procedure was repeated 1542 times (an average of 140 voxels in each of the 11 participants) with varying number of clusters per voxel (range: 5-1500 clusters), so that the average CV could be calculated per cluster size. The average was calculated across voxels for each participant separately, and then across participants, as was done for the real data. We then plotted the average CV as a function of the number of simulated clusters per voxel. As can be seen in figure 7 of chapter 1 of the results, the smaller the cluster size (i.e., larger number of clusters per voxel), the lower the average CV.

It is possible that neuronal tuning is in fact sharper than a cosine waveform (Amirikian and Georgopoulos, 2000). To find the lower bound on cluster size, the average voxel CV was similarly
calculated for various cluster sizes under the assumption that the average neuronal tuning curve was narrower than 45° (thereby avoiding the smoothing effect imposed by the convolution kernel).

Our goal was to find the cluster size that best corresponds to the mean CV of the actual data.

**Rotation – experimental paradigm and data analysis**

In the second study, after the first run of center-out reaching movements, the participants practiced for ~10 min (inside the scanner) on the visuomotor rotation task, in which the cursor was rotated by 45° CCW with respect to the hand movement. Thus, for the cursor to move towards the target, participants had to move the joystick toward the neighboring (clockwise) target without seeing their hand. The participants had adapted to this new mapping rule implicitly. After the participants reached the targets successfully, they were scanned again while carrying out another 250 “rotation” trials.

After data preprocessing (as described in the methods of results - chapter 2), we calculated the correlation coefficient (CC) between the columns of the baseline and the rotation run (each corresponding to the pattern of activation across all voxels for a given condition). If the estimated β weights contained information about the direction of movement, we expected to find a higher CC for vectors that represent movements to the same direction (in the two datasets) compared with the CC calculated for two different directions. Because the CCs were between baseline movements and rotated cursor movements, we could distinguish between conditions that shared the same hand movement (but differed in their visual aspects, i.e., target location and cursor trajectory) and conditions that shared the same visual aspects (but differed in their hand movement).

When the movements are aligned according to the direction of joystick movement (“movement alignment”), the baseline and rotation run share the motor component but differ in their visual components (target position and cursor direction). Similarly, during “target alignment”, the two conditions share the same visual components but differ in their motor aspects (by 45°).
Now we need to find a control group of CCs to compare these correlations to, in order to find out if they are significant. However, the angular difference between movement directions for the same target alignment is small (45°). As I have shown in the first results chapter, the CCs between compared movements typically drop gradually with increased angular difference (see results chapter 1, figure 4). Therefore, a 45° angle between the two movement directions could produce significant CCs when compared to greater angular differences, such as 90° or 135°, where CCs are typically negative, even if there is no "target" effect.

To that end, instead of comparing the alignment of same target directions to all other comparisons (the rest of the CC matrix, see results chapter 2, figure 2), we compare that alignment (blue diagonal in the CC matrix) only to the other CCs with the same absolute angular difference (45°, red diagonal). These other CCs serve as the "target control" group. Although the movement directions in this group are 45 degrees apart, just as in the "same target" group, the targets are 90 degrees apart. Thus, we dissociate the effect of having the same target and the effect of having the same, or close, movement directions.

Similarly (although highly unlikely), a positive CC between same hand movements could result from the fact that the two movements have small angular differences between target locations (separated by only 45°). To that end, we compare these CCs (green diagonal in the CC matrix) to a control group of comparisons where the target directions are 45° apart, but movement directions are 90° apart (purple diagonal).

The methods of analysis of the electrophysiological data will be described in the methods section of chapter 3 of the results.
Results I:

Functional Organization of Human Motor Cortex: Directional Selectivity for Movement
Behavioral/Systems/Cognitive

Functional Organization of Human Motor Cortex: Directional Selectivity for Movement

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In monkeys, neurons in the hand representation of the primary motor cortex (M1) are often tuned to the direction of hand movement, and there is evidence that these neurons are clustered according to their “preferred” direction of movement. However, this organizational principle has yet to be demonstrated in M1 of humans. We conducted a functional magnetic resonance imaging (fMRI) study in which participants used a joystick to move a cursor from a central origin to one of five equidistant targets. The fMRI signal of individual voxels was sensitive to the directional aspects of the reaching task and manifested direction-specific adaptation. Furthermore, the correlation between multivoxel patterns of responses for different movement directions depended on the angular distance between them. We conclude that M1 neurons are likely to be organized in clusters according to their preferred direction, since only such a coarse-grained representation can lead to directional selectivity of voxels, encompassing millions of neurons. A simple model that estimates cluster size suggests that the diameter of these clusters is on the order of a few hundred micrometers.

Introduction

Neurons in the primary motor cortex (M1) of monkeys are tuned to the direction of limb movement (Georgopoulos et al., 1982). Single-cell recordings from M1 suggest that these neurons are organized according to their preferred directions (PDs) (Asanuma and Rosén, 1972; Amirikian and Georgopoulos, 2003; Ben-Shaul et al., 2003; Georgopoulos et al., 2007). Directional tuning has also been found in the multiunit activity recorded from M1 (Stark et al., 2009), as well as from local field potentials (LFPs) (Mehring et al., 2003; Rickert et al., 2005), which represent populations at a resolution of ~1 mm (Berens et al., 2008; Rasch et al., 2009). Together these data suggest that in monkeys, M1 neurons are clustered, to some extent, according to their PDs. This organizational feature resembles the columnar organization characteristic of somatosensory cortex (Powell and Mountcastle, 1959), primary visual cortex (V1) (Hubel and Wiesel, 1962), middle temporal cortex (MT) (Albright et al., 1984), and primary auditory cortex (Imig and Adrian, 1977).

Obviously, little is known about the properties of neurons in the homologous area (M1) of humans. A recent study, performed for clinical purposes, showed that human M1 neurons are also often directionally tuned (Truccolo et al., 2008). It is less clear, however, whether the neurons are organized in functionally related clusters, such that neighboring neurons share similar tuning properties. To address these issues, we used functional imaging techniques coupled with multivoxel pattern analysis. This approach seems, at first, unlikely to reveal functional clustering in M1, if only because the spatial resolution of functional magnetic resonance imaging (fMRI) (several millimeters) is much larger than the size of functional units in the cortex. For example, the typical diameter of a cortical column in primary visual cortex, defined on the basis of orientation selectivity, measures hundreds of micrometers in diameter (Berman et al., 1987). Nevertheless, recent applications of multivoxel pattern analysis in imaging studies allowed the detection of columnar organization in visual areas such as V1 (Kamitani and Tong, 2005) and MT (Kamitani and Tong, 2006). In this study, we use these analysis methods to test the hypothesis that neurons cluster according to their directional preferences in the human M1 cortex. We reasoned that examination of directional preferences at the voxel level could support this hypothesis, provided that the number of clusters within a voxel is small. In this case, random fluctuations in the number of clusters with preference for a specific direction, together with the natural tuning characteristics of the neurons, might determine the directional preference of the voxel as a whole.

To that end, our participants performed a “center-out task,” similar to the one performed by monkeys in studies of M1 (Georgopoulos et al., 1982). During an event-related fMRI scan, our participants repeatedly moved a cursor from the center of a screen toward various targets in the periphery by moving a joystick in the corresponding direction. We found (1) that M1 voxels were selective for the directional aspects of the reaching task, (2) that the patterns of activation across M1 voxels became less correlated as the angular difference between movements in-
informed consent was obtained from each participant, and the experimental procedure was approved. Hadassah Ein Kerem Medical Center Ethics Committee approved the experimental procedure. Written informed consent was obtained from each participant.

**Materials and Methods**

**Participants.** Eleven right-handed volunteers with normal or corrected-to-normal visual acuity and no neurological or psychiatric history (3 women and 6 men, aged 18–35) participated in the present experiments. Hadassah Ein Kerem Medical Center Ethics Committee approved the experimental procedure. Written informed consent was obtained from each participant.

**MRI acquisition.** The blood oxygenation level-dependent (BOLD) MRI measurements were performed in a whole-body 3T Trio Siemens scanner. The functional MRI protocols were based on a multislice gradient echo-planar imaging and a standard head coil. The functional data were obtained under the optimal timing parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, imaging matrix = 80 × 80, voxel size: 2.75 × 2.75 × 3.1 mm. The 30 slices (with a gap of 0.3 mm) were oriented in the axial direction. The scan covered the whole brain. Each participant was scanned in one run lasting 20.5 min. The run was comprised of an acquisition of 616 volumes and contained 250 trials.

**Experimental paradigm.** Each trial lasted 4 s. The trial began with presentation of a red circle in the center of the screen ("origin," radius of 0.7°). Initially, the participants had to hold an MRI-compatible joystick still, and make no hand movement. After an interval of 500 ms, five circles (targets, radius of 1°) appeared at the upper half of the screen, spread around the center at equal distances, between 0° and 180°, 45° apart. Their distance from the origin was 4.5° of visual angle (Fig. 1). Four of the circles were blue and one circle was green, signaling the required future direction of movement. The participants had to keep their hand still until the "go" signal, in which the blue "origin" circle turned into a white cursor, which occurred 2 s later. They were instructed to respond by moving the cursor toward the green target, using the joystick (Fig. 1a). Participants had 1.5 s to reach the target. Upon reaching the target, all circles disappeared. This served as a cue for the participants to release the joystick (thereby relaxing the spring), which resulted in the joystick returning to its starting position at the center. There was no explicit failure signal. If the participants did not reach the target within the 1.5 s time limit, all circles disappeared and the next trial began (participants failed to reach the target in 10.6% of the trials). There were also intermittent null trials in which the red origin and all five blue targets appeared on the screen for 2–8 s (thus no target was distinctly marked for movement). These trials were obviously not followed by a "go" signal. During these null trials, the participants were instructed not to move the joystick until the next trial began. The task was programmed with MATLAB version 7.1 (MathWorks), using Psychtoolbox (Brainard, 1997; Pelli, 1997).

This rapid event-related fMRI study consisted of 250 trials, 50 in each direction. The trial order was counterbalanced (first order) and embedded with null trials of various lengths (2, 4, 6, or 8 s). The different lengths of the null trials were used to randomize the timing of the movement trials, which allow a more efficient estimation of activation (Dale, 1999).

Null trials were pseudorandomly embedded between movement trials. Our constraint was that the total length of all null trials would equal the total length of each of the five movement conditions (200 s). The trial sequences were built using optseq software, which chooses the most efficient sequence (most variable history before each condition) out of 10,000 random sequences sampled. The experiment began and ended with 16 s of a null event.

We used only five directions of movement, covering only half of the plane, instead of eight targets covering the entire plane, to achieve as many trials as possible for each condition to obtain a reliable signal. We also chose to use targets with rather small angular differences (45°) rather than spanning the entire plane with larger differences (72°). This was done to allow us to assess not only the selectivity for a specific direction of movement, but also the relationship between voxel representations for similar movements (to neighboring targets).

**Data analysis.** Preprocessing and defining regions of interest (ROIs) was done using Brain Voyager QX (Brain Innovation).

The functional images were superimposed on two-dimensional anatomical images and incorporated into the three-dimensional datasets through trilinear interpolation. Before statistical analysis, head motion correction and high-pass temporal filtering in the frequency domain (3 cycles/total scan time) were applied to remove drifts and to improve the signal-to-noise ratio. The complete dataset was transformed into three-dimensional Talairach space with a resolution of 3 × 3 × 3 mm³.

The left M1 ROI was individually defined for each participant as a cluster within the central sulcus, which showed higher activation during movement than during rest (general linear model, p < 10⁻⁴, Bonferroni corrected, p < 0.01). The average size of M1 was 140 ± 40 functional voxels (see supplemental Table 1, available at www.jneurosci.org as supplemental material).

Further analysis was done using Matlab R2007b (MathWorks). We used linear regression to estimate response amplitudes (β values) for each functional voxel in each condition, solving an equation of the form \( y = Xβ + e \), where the vector \( y \) is the measured voxel time course, the vector \( β \) contains a sequence of the estimated response amplitudes for each of the five conditions, \( X \) is the convolution matrix determined by the sequence of events, and \( e \) is the error (Gaussian noise). The convolution matrix, \( X \), was designed with predictors of onset times for each trial and has the dimensions of 614 × 51. \( X \) contains a row for each time point (TR) in the experiment (totaling 614) and 10 columns for each of the 5 conditions (or conditions in the correlation analyses) plus a column of...
ones for the offset predictor (thus 51 columns). This leads to an independent estimation of the response amplitude, for each condition at each time point (the first point out of the 10 points for each condition is the time of the beginning of a trial). The vector of response amplitudes, $b_i$, is estimated using the equation $b_i = (X^T X)^{-1} X^T y$ and is respectively comprised of 10 values (estimated $\beta$ values) for each condition (one for each time point between 0 and 18 s after the beginning of the trial). The first value of $b_i$ is the mean activation over the entire time course. Importantly, since we estimated the BOLD activation for each time point separately, no assumptions were made about the shape of the hemodynamic response. Linear regression was significant in >99% of voxels. On average, the variance explained by the model accounted for 37% of the total variance.

Coefficient of variation analysis. We used a bootstrap analysis, to test whether the coefficient of variation (CV) (SD/mean) of the five directions of movement in each voxel is significantly higher than expected by mere chance (e.g., had there been no directional selectivity). In this analysis, we randomly realigned conditions (directions of movement) to the trials, while maintaining the original proportions of hand movements (each condition was assigned to 20% of the trials). The null conditions were not replaced. We created a new regression matrix, estimated the $\beta$ values for the different directions, and assessed the CV, separately for each assignment. This procedure was repeated 10,000 times, resulting in a distribution of expected CV's merely due to noise. Next, for each voxel, we assessed its $p$ value: the fraction of CV values obtained by the bootstrap method that were greater than the actual CV of that voxel. Finally, a $\chi^2$ test was used to show that the distribution of $p$ values across voxels (shown in supplemental Fig. 3, available at www.jneurosci.org as supplemental material) was significantly skewed to low values (differing from a uniform distribution, which would be expected by chance).

The CV analysis was used also for the estimation of cluster size (see Discussion and Fig. 7). For this purpose, since each voxel is expected to show some variation in its response by chance (as there were limited repetitions of each direction of movement), we also corrected each voxel's CV by subtracting from its actual variance in response (for the various directions) the mean variance of the bootstrapped activation ($X_{BS}$) across iterations:

$$CV = \frac{\left(\frac{\text{Var}B - \text{mean(Var}B_{BS})}{\text{mean}(B)}\right)}{\text{mean}(B)}$$

In addition to calculating voxel CV, we also calculated the CV as a measure of the directionality of the LFPs in monkey M1, when monkeys performed the same center-out task (courtesy of S. Cardoso de Oliveira (Cardoso de Oliveira et al., 2001)). To that end, we used the peak-to-peak distance (the distance between maximum and minimum of the mean evoked potential, per direction of movement. CV's of LFPs were calculated without subtracting bootstrapped variance. Consequently, the CV is slightly overestimated.

Analysis of spatial patterns of fMRI response. To detect directional selectivity of voxel population spatial patterns, each individual’s data were split into two datasets, such that each of the 50 trials in each direction was randomly assigned to one of the datasets. For each voxel, we estimated the $\beta$ values and defined the activation for each direction (i.e., activation value) as the average of the $\beta$ values measured 6 and 8 s after the beginning of the trial (−4−6 s after movement initiation; normally at the peak activation) (see Fig. 2b). Then, in each dataset and for each voxel, we subtracted the voxel’s mean activation level (across all directions) to remove activation differences between voxels that are unrelated to movement direction. Without such a correction procedure, one would get high correlations between the multivoxel spatial patterns from all comparisons, simply because some voxels are more active than others, regardless of the direction of movement.

The above analysis resulted in two matrices, one for each dataset. Each matrix consisted of 5 columns (one for each direction) with length $N$ equal to the number of voxels in the ROI. The entries of each row of the matrix were the 5 activation values of a single voxel for all 5 directions of movement.

Next, we calculated the correlation coefficient (CC) between the columns of the first and the second datasets (each corresponding to the pattern of activation across all voxels, for a given condition). If the activation values contain information about the direction of movement, one should get a higher CC for movements to the same direction (in the two datasets) than the CC calculated for movements to two different directions. To address the concern of low-frequency temporal trends in our data, we repeated this analysis 100 times for each participant; in each iteration, the data were split differently into two random datasets. The results shown are the mean CC values across all 11 participants. The resulting dependence of the CC on the angular difference between the two directions of movements matched a normal distribution:

$$y_i = h \times e^{-\frac{(x_i - \mu)^2}{\sigma^2}} - b.$$
velocity and the direct trajectory to the center of the target. The mean absolute angular deviation was 10.4° (Fig. 1b).

We defined cortical regions involved in the visuomotor reaching task by identifying voxel clusters that exhibited significant enhanced activity during the task compared with null trials (p < 10^{-8}; Bonferroni corrected, at least p < 0.01). Several ROIs were defined for each participant, but here we focus on the results from left M1 (Fig. 2c).

The resulting time course of activation for each voxel, acquired during the scan, was further analyzed using linear regression to estimate the profile of activation generated by each of the five directions of movements. An example of a voxel’s time course of activation and the extracted convolution kernels (hemodynamic response) to the different directions are shown in Figure 2. For each voxel, the average of the estimated β values measured 6 and 8 s after the beginning of the trial (which were usually the time points of peak activation) served as the extracted parameter of activation level, for each direction.

Voxel tuning analysis
We began by inspecting the degree of directional tuning in each voxel. Note that reaching movements were made only to targets in the upper half of the screen (corresponding to forward joystick movements). Therefore, we could not use the classical estimation of tuning, i.e., cosine fits (Georgopoulos et al., 1982), and had to use other measures instead. For each voxel, we computed the CV, which is the SD of the voxel’s activation level (across different directions), divided by its mean activation level (across those directions). Next, we assessed the probability that each of the voxels would exhibit directional specificity simply by chance, by conducting a bootstrap test in which the direction of each movement was randomly reassigned (in the regression matrix). This analysis revealed that 28% of the voxels in M1 were directionally selective (i.e., they had a CV greater than 95% of the CV values obtained by the bootstrap method). A χ² test showed that the distribution of p values across voxels (supplemental Fig. 3, available at www.jneurosci.org as supplemental material) was significantly skewed to lower values from those expected by chance (χ²(9) = 1386; n = 1542; p < 0.001). Note also that since not all directions of movement were tested, this percentage is likely to be a lower bound on the percentage of voxels sensitive to movement direction.

Next, we aligned all the voxels’ activation tuning curves according to their PD to obtain an average voxel tuning curve (Fig. 3). This computation allowed us to assess whether the average voxel’s preference is only for a single, specific PD or whether there is instead gradual tuning at the voxel level. In the latter case, movement in directions close to the PD, in angular terms, should elicit a greater BOLD response than movements far from the PD. Figure 3b shows that the BOLD signal decreases with angular distance from the voxel’s PD. A one-way repeated-measures ANOVA with direction difference as the relevant factor, taking into account only the BOLD signal for movements with an angular difference of 45°, 90°, and 135° apart, indicated that this factor was marginally significant (F(2,20) = 3.29, p < 0.058) (movements with a 0° difference were discarded from this analysis be-
cause, due to our alignment procedure, their BOLD signal is necessarily greater than the other angular distances; movements with a difference of 180° from PD were discarded as well because there were considerably fewer cases than other directions).

**Multivoxel pattern analysis**

A different approach to study the tuning properties of voxels in a given region is to calculate the correlation between the multivoxel spatial patterns of activation for the different directions. Having shown that voxels show some directional tuning, one may expect to find greater correlation between multivoxel spatial patterns of activations during movements with a smaller angular difference.

To that end, two non-overlapping datasets were created by randomly assigning each of the 50 trials in each direction into one of the two categories. Next, we used linear regression to estimate the level of activation of each voxel in each movement direction separately for each dataset. Finally, to eliminate differences in activation between voxels, in each dataset we subtracted the mean response of each voxel (across the various directions). This resulted in two vectors of activation (across voxels) for each direction of movement, corresponding to the two datasets (see PD maps in supplemental Fig. 1, available at www.jneurosci.org as supplemental material). We then calculated the correlation coefficient ($r$) between the activation vectors for each pair of directions from the two sets (for example, we calculated the correlation between activation elicited by movements toward the 90° target in the first set and movements toward the 180° target in the second set, or by movements elicited in the same direction; see examples in Fig. 4).

This resulted in a matrix of correlation coefficients for all possible comparisons (Fig. 4b). Next, we averaged across conditions having the same angular difference (diagonals of the matrix in Fig. 4b) to obtain the mean correlation (between patterns) as a function of the angular distance between the trajectories: the average correlation tuning curve (Fig. 4c).

As the distance between the directions of movement increased, the correlation decreased (Gaussian fit, $r = 0.999$).

It is possible that the directional selectivity at the level of representation of voxel populations could simply be a side effect of an uneven distribution of PDs across voxels. To test this, we ran the correlation

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**Figure 3.** M1 voxels show directional tuning. 
(a) Example of individual voxel “tuning curves” showing the BOLD activation of 3 voxels as a function of movement direction. Each tuning curve was normalized such that the mean activation of each voxel across all directions was zero. In each participant, the “tuning curves” of all individual voxels from M1 were aligned according to their PD, to generate a “voxel population tuning curve.” This population tuning curve was averaged across participants. 
(b) The resulting “average voxel” activation as a function of the angular distance from the PD. The peak at the PD is a direct result of the alignment procedure, but note the smooth tuning preference as the angular distance between directions of movement increases. Error bars denote SEM across participants.

**Figure 4.** Multivoxel spatial patterns of activation are more similar for closer movements. 
(a) Example of the patterns of M1 activation in one subject for movements in 90° (top) and 180° (bottom), in the two datasets. These examples (shown mainly for illustrative purposes) are taken from the axial plane (Talairach coordinates: $z = 50$) from one of the participants. Blue arrows denote correlations between movements in the same directions ($0.33$ and $0.56$ for this participant), whereas red arrows denote correlations between movement in the different directions ($-0.43$ and $-0.31$). 
(b) Matrix of the average CCs between the multivoxel patterns in the two datasets (across all participants), for all possible direction combinations. The main diagonal corresponds to CCs between same directions; the next diagonals (in gray) correspond to the CC between directions 45° apart, etc (in lighter colors). Red and blue values correspond to the average value (across participants) for the directions in the example (a). 
(c) The similarity between patterns of voxel activations (measured by the CC) decreases as a function of the angular distance between the two directions of movements. The grayscale of each data point (diamonds) indicates the appropriate diagonal in (b) whose average value is depicted. Error bars denote SEM across participants. The black curve denotes the Gaussian fit to the CCs.
analysis using simulated data that preserved the original uneven distribution across voxels. We found no tuning of the correlation coefficients of the patterns of activation for the simulated data (supplemental Fig. 2, available at www.jneurosci.org as supplemental material). We conclude that our results reflect information based on the direction tuning at the voxel level, rather than a global bias in preference toward some directions over others.

**Effect of movement RS**

Another way to study the selectivity of BOLD activation to the direction of movement is to examine the effect of movement repetition. RS, the reduction in the BOLD signal following repeated presentation of the same stimulus, was initially reported in visual cortex (Grill-Spector and Malach, 2001). It was recently documented for motor actions as well (Dinstein et al., 2008). One might therefore expect to find greater reduction of the BOLD signal in M1 when the same movement is repeated across trials. To test this, we categorized the trials according to their similarity to the previous trial. Figure 5 shows the average time course of activation across M1 voxels (Fig. 5a) and the mean BOLD activation (Fig. 5b) as a function of the angular difference from the previous trial. The BOLD activation is lower when the participant made a movement toward the same target as in the previous trial (one-way repeated-measures ANOVA, $F_{(4,40)} = 5.58, p < 0.005$, Tukey–Kramer post hoc test, $p < 0.005$). This phenomenon seems to be limited to the same direction, and does not generalize to near targets (i.e., there is no statistical difference in the BOLD activation for the current movement when the previous movement diverged from it by 45°, 90°, or 135°, $F_{(3,30)} = 0.4, p = 0.75$).

Is the preferred direction of the voxel (eliciting the greatest response) also the direction that elicits the greatest RS? If so, repeated movements toward the voxel’s PD (direction with maximum activation) should lead to greater RS than repeated movements to other directions. To that end, we assessed the correlation between the pattern of multivoxel activation for a given direction and the pattern of multivoxel RS for that direction, as well as for all other directions (see example for the 45° and 90° movement cases in Fig. 6a). This resulted in a matrix of correlation coefficients between the repetition suppression and activation level for all possible movement pairs. Our findings show that the level of activation and RS are positively correlated for same directions (mean CC = 0.29, SD = 0.09), and significantly greater than different directions (mean CC = −0.07, SD = 0.02; $t_{(10)} = 10.12, p < 5 \times 10^{-6}$). To verify that our results did not stem merely from use of the same data for computation of both measures, the nonrepeated trials were divided into two separate groups: one for computing the repetition index and the other for the activation index. Our results remained significant ($t_{(10)} = 5.01, p < 0.001$).

We further tried to assess, on a voxel-by-voxel basis, whether the direction of movement similarly affected both the voxel’s level of activation and its repetition index. Had the two measures been uncorrelated, one might expect that 20% of the voxels would show that...

**Figure 5.** RS of the fMRI response in primary motor cortex. *a*, The various colors denote the mean time course of activation in the M1 ROI (across participants) for a movement in a given direction when preceded by a movement in the same direction in the previous trial (blue line) or a different direction (green, red, and cyan denote cases in which the previous trial was 45°, 90°, and 135° apart from the current trial, respectively). Suppression is seen only for cases of repetition of the same movement. *b*, The mean level of activation (measured at time points 6 and 8 s and then normalized such that the mean of each voxel across directions was 0) as a function of the absolute angular difference between the current movement and the movement in the previous trial. Colors correspond to the conditions shown in a. Error bars denote SEM between participants.

**Figure 6.** RS multivoxel patterns are correlated with the activation patterns. *a*, Example of the patterns of activation (left) and the repetition index across voxels (right) for movement at 45° (top) and 90° (bottom). These examples are taken from the axial plane (Talairach coordinates: $z = 50$) of one of the participants. Blue arrows denote correlations between the two measures for the same movement (0.59 and 0.61, respectively for this participant). Isolated red arrows denote correlations between the two measures for different movements ($< 0.26$ and $< 0.09$ for this participant). *b*, The resulting matrix of CCs when comparing the patterns of activation and the repetition index in all possible directions of movement. The main diagonal corresponds to CCs between same directions.
the repetition index was maximal at the voxel’s PD. We found that this was the case in 30% of the voxels, significantly more than that expected by chance ($t_{110} = 4.52, p < 0.0005$).

**Discussion**

In this study, we show that M1 voxels are directionally tuned. This finding, at first, seems puzzling: based on an estimation of ~50,000 neurons in 1 mm$^3$ of cortex (Beaulieu and Colonnier, 1983), there are on the order of 1,000,000 neurons in each voxel. If neuronal PDs are uniformly distributed across the population, one would expect that any fluctuations in firing rates would average out, and the overall activity during different movements would be the same. Thus, no directional preference should be seen at the voxel level.

The finding that voxels do show selectivity to direction of movement suggests that the spatial distribution of the neuronal PDs is not random. If neurons sharing the same PD are clustered in a columnar fashion, a voxel should contain many fewer independent elements. Under such circumstances, directional preference at the voxel level may not be that surprising. A similar preference of voxels in the human cortex has been seen in areas with known columnar organization in the monkey, such as V1 (for orientation) (Kamitani and Tong, 2005) and MT (for direction of motion) (Kamitani and Tong, 2006). Our results are also consistent with electrophysiological evidence in monkeys suggesting some degree of clustering of neurons in M1, based on their direction selectivity (Amirikian and Georgopoulos, 2003; Ben-Shaul et al., 2003; Stark et al., 2009).

**RS**

We find clear evidence for RS in human M1. This finding provides indirect evidence that the direction of movement is a key factor determining the response of neurons in the human motor cortex. A voxel’s direction tuning is determined by two factors: the distribution of PDs across neuronal populations within the voxel and the average neuronal tuning width. Anisotropy of the distribution of PDs (due to the coarse-grained clustering of neuronal populations with similar PDs within a voxel) would result in direction preference at the voxel level. The most prevalent neuronal PD within the voxel’s population of neurons will determine the voxel’s PD. The voxel’s tuning width, however, is affected both by the average neuronal tuning width and, possibly, by spatial correlations (i.e., greater tendency of a voxel to contain more neurons with PDs close to the most prevalent PD than neurons with far PDs).

In principle, RS may be helpful in distinguishing between the neuronal tuning characteristics of the voxel population and the spatial distribution of clusters, as the degree of RS is thought to be related to the average properties of single neurons (Grill-Spector and Malach, 2001). We find that the repetition effect is narrower than 45°; a decrease in activation is seen only for a movement with the same direction as in the previous trial, while a movement 45° away from the previous one does not lead to any significant activation suppression. In this case, we would conclude that the tuning width of the voxel is determined mostly by spatial correlations. However, this finding is at odds with the broad tuning of neurons in macaque M1, which are well fit by a cosine waveform. It is possible that in human M1 the average neuronal tuning curves are narrower than in primates, as has been recently found for frequency tuning in auditory cortex (Bitterman et al., 2008). However, an alternative interpretation is that the relationship between RS and single-cell properties for actions is more complicated than the models so far proposed for sensory inputs (Grill-Spector and Malach, 2001). It is also possible that the RS could reflect the tuning properties of the inputs from other areas (Sawamura et al., 2006), and that the narrower width of the RS effect is a reflection of the narrower tuning curves in visual or parietal areas or their limited receptive field size (Heggeland and Albus, 1978; Andersen et al., 1985).

**Estimating cluster size**

One central goal in this paper was to roughly estimate the size of the average direction-selective cluster in M1 from our data. Consequently, we constructed a model with some simplifying assumptions. We assumed that M1 neurons have preference for one of eight discrete directions (which differ by 45°), and the...
direction tuning curve can be approximated by a cosine function [in which the mean baseline activity and modulation index were taken from Georgopoulos et al. (1982)]. These neuronal parameters were used to describe the tuning properties of an entire cluster, since a cluster was assumed to contain only neurons with the same PD. We also assumed that the PDs of the different clusters are uniformly distributed. However, as the number of clusters per voxel becomes smaller, random picks from this uniform distribution are likely to generate an uneven number of clusters tuned to each of the eight possible directions (Fig. 7a). This would lead to a preference for a specific direction at the voxel level, which would be smoothed to an extent by the characteristic tuning function of the neurons. One can therefore calculate the mean CV of each voxel as a function of the number of clusters within that voxel. The CV thus provides a measure of the modulation in the voxel’s activation for the different directions, as depicted in Figure 7a for the cases in which there were 10 or 100 clusters in a voxel.

Note that the average voxel’s CV drops sharply as the number of direction-tuned clusters increases (Fig. 7b, blue and red curves). The voxel’s CV, however, also depends on the average neuronal tuning width. If tuning is wide (e.g., cosine tuning, blue curve), the neurons also respond to other directions besides the PD. This will obviously dampen variation in firing rates caused by a nonhomogeneous distribution of PDs. When the average neuronal tuning width was taken to follow a cosine fit, the value closest to the mean CV obtained in our experiment was ~40 clusters per voxel.

It is possible that neuronal tuning is in fact sharper than a cosine waveform (Amirikian and Georgopoulos, 2000). To find the lower bound on cluster size, we recalculated the expected voxel CV as a function of the cluster number assuming an extremely narrow neuronal tuning (<45°) (Fig. 7b, red curve). In this case, ~1200 direction-selective clusters within a voxel are necessary to account for the variation observed in our fMRI data.

It should be taken into consideration that our model assumes no correlation between the tuning curves of neighboring clusters. Accounting for such correlations might lead to an estimation of a smaller cluster size. Notwithstanding these limitations, our estimates offer an upper and lower bound (at least in terms of orders of magnitude) on the size of an individual direction-selective cluster within human M1. If we further assume that the same PD is represented across all cortical layers (Hubel and Wiesel, 1962) and that the human cortex is ~2.5 mm thick, one can ignore the third (depth) dimension of our 3 × 3 × 3 mm³ voxels. Thus, in the 3 × 3 mm² of voxel surface area, there are ~40 clusters per voxel, which translate to a cluster diameter of ~470 μm. On the other hand, 1200 clusters per voxel (assuming a narrow tuning curve) would indicate that cluster diameter is ~85 μm.

Interestingly, a similar estimation is found when using tuning curves of the average LFP elicited by movements in eight directions in monkey M1 (de Oliveira et al., 2001) (see Materials and Methods). The CV in this case was 0.2, which corresponded to 78 or 185 clusters per voxel [assuming cosine or narrow (<45°) neuronal tuning width, respectively]. Assuming the LFP covers a surface area of 1 mm² (Berens et al., 2008; Rasch et al., 2009), cluster diameter is estimated to be ~75–380 μm. Our estimation of the human M1 cluster diameter, in the range of 85–470 μm, nicely concurs with the order of magnitude of cluster size in the monkey estimated here (using the above LFP measures) as well as others (Amirikian and Georgopoulos, 2003; Stark et al., 2009).

Finally, it is important to remember that other components in this study, besides the direction of hand movement, could have influenced our results. These include the visual effects of target location, eye movements (which are likely to vary according to the target position), or visual aspects of the cursor movement. Therefore, from our current results we cannot unequivocally ascertain whether the neuronal selectivity is due to limb movement direction per se, or perhaps visual (or oculomotor) aspects of directionality. We shall refer to these important issues, in depth, elsewhere. It is also impossible to distinguish whether the reported activation is due mostly to neuronal activity during movement preparation (“Hold” period) or during the movement itself. This issue requires further investigation.

Conclusions

We show that the fMRI signal of individual voxels in human M1 is sensitive to the directional aspects of the reaching task and manifests direction-specific adaptation. Furthermore, the spatial patterns of the fMRI response are more correlated as movement directions are closer. We conclude that human M1 neurons are organized in clusters according to their PD. The model we constructed to estimate cluster size suggests that cluster diameter is likely to be of the order of a few hundred micrometers, which resembles the diameter estimated in monkeys.

References

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Results II:

The Representation of Visual and Motor Aspects of Reaching Movements in the Motor Cortex
Behavioral/Systems/Cognitive

The Representation of Visual and Motor Aspects of Reaching Movements in the Human Motor Cortex

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The human primary motor cortex (M1) is robustly activated during visually guided hand movements. M1 multivoxel patterns of functional MRI activation are more correlated during repeated hand movements to the same targets than to greatly differing ones, and therefore potentially contain information about movement direction. It is unclear, however, whether direction specificity is due to the motor command, as implicitly assumed, or to the visual aspects of the task, such as the target location and the direction of the cursor’s trajectory. To disambiguate the visual and motor components, different visual-to-motor transformations were applied during an fMRI scan, in which participants made visually guided hand movements in various directions. The first run was the “baseline” (i.e., visual and motor mappings were matched); in the second run (“rotation”), the cursor movement was rotated by 45° with respect to the joystick movement. As expected, positive correlations were seen between the M1 multivoxel patterns evoked by the baseline run and by the rotation run, when the two movements were matched in their movement direction but the visual aspects differed. Importantly, similar correlations were observed when the visual elements were matched but the direction of hand movement differed. This indicates that M1 is sensitive to both motor and visual components of the task. However, repeated observation of the cursor movement without concurrent joystick control did not elicit significant activation in M1 or any correlated patterns of activation. Thus, visual aspects of movement are encoded in M1 only when they are coupled with motor consequences.

Introduction

Which parameters are encoded in the primary motor cortex (M1)? The initial findings in awake behaving monkeys (Evarts, 1968) suggested that M1 is mainly involved in encoding muscle force, that is, intrinsic parameters of movement. The seminal work of Georgopoulos and colleagues (1982) in later years indicated that M1 neurons are often tuned to the direction of limb movement in space and, therefore, encode extrinsic parameters. Since then, accumulating evidence has suggested that M1 encodes both intrinsic and extrinsic parameters of movement (Scott and Kalaska, 1997; Sergio and Kalaska, 1997, 2003; Kakei et al., 1999), and therefore is likely to be involved in a sensorimotor transformation. For example, using a visuomotor rotation task, which introduces a constant angular difference between the motor trajectory of the hand and its viewed trajectory on the screen, Alexander and colleagues showed that M1 neurons are sensitive to the target position on the screen (Alexander and Crutcher, 1990; Shen and Alexander, 1997a). Furthermore, the sensitivity of neurons in M1 to sensory stimuli often depends on their functional relevance: when the color of a visual cue carried crucial information to indicate the required hand movement, a considerable fraction of M1 neurons (20%) displayed color sensitivity (Zach et al., 2008).

We have previously shown, using event-related functional magnetic resonance imaging, that the multivoxel pattern of activation in human M1 conveys information about the direction of hand movement (Eisenberg et al., 2010). In that experiment, participants performed a “center–out” task in which they had moved a cursor to equidistant targets on the screen, using a joystick. The resulting multivoxel activation patterns in M1 were more correlated during similar direction movements than dissimilar ones. Note, however, that this sensitivity to the direction of movement may stem from the motor command to the hand, but it could also be due to the covarying visual (and attentive) aspects of the task, such as the target location or the cursor trajectory. To that end, following Shen and Alexander (1997a), we designed an fMRI experiment that allowed separation of the visual elements of the task from its motor aspects. First, participants completed a “baseline” center–out run, in which the visual and motor components matched. Next, they were introduced with a rotation perturbation, in which the observed cursor trajectory was consistently rotated 45° counterclockwise (CCW) with respect to the hand movement. After practicing the task for a few minutes, participants completed a full rotation run while being scanned. We then compared the
elicited multivoxel pattern activations in M1 during the baseline run and the rotation run. We found that similar hand movements elicited positive correlations between the evoked multivoxel patterns, as expected. More important, conditions that shared the same cursor trajectory and target location but differed in their hand movements also elicited similar positive correlations. On the other hand, there was no evidence for sensitivity to cursor direction in M1 when participants passively viewed all visual aspects of the task (in the absence of joystick control). This suggests that the visual aspects of hand movement are encoded in M1 only when they are tightly coupled with motor consequences.

**Materials and Methods**

**Participants.** Twenty-three right-handed volunteers with normal or corrected-to-normal visual acuity and no neurological or psychiatric history (13 women and 10 men, aged 18–35 years) participated in the present experiments. Five of the participants were excluded from further analysis for various reasons (see below). The experimental procedure was approved by the Hadassah Ein Kerem Medical Center Ethics Committee. Written informed consent was obtained from each participant before the scan.

**MRI acquisition.** The BOLD fMRI measurements were performed in a whole-body 3T TRIO SIEMENS scanner. The fMRI protocols were based on a multislice gradient echo-planar imaging and a baseline head coil. The functional data were obtained using the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, imaging matrix = 64 × 64, voxel size = 2.75 × 2.75 × 3.1 mm. The 30–35 slices (with gap of 0.3 mm) were oriented in the axial position. The scan covered the whole brain. Each of the two functional runs comprised 616 volumes and contained 250 trials.

**Experimental paradigm.** The experimental design is the same as described in our previous study (Eisenberg et al., 2010). Seventeen participants were scanned while carrying out a center–out reaching task. Using an MRI-compatible joystick, they moved a cursor from the center toward five different targets located in the periphery. The baseline center–out reaching task was composed of 250 trials. Next, the participants practiced for ~10 min (inside the scanner) on the visuomotor rotation task, in which the cursor was rotated by 45° CCW with respect to the hand movement. Thus, for the cursor to move toward the target, participants had to move the joystick toward the neighboring (clockwise) target without seeing their hand. The participants had adapted to this new mapping rule implicitly. After the participants reached the targets successfully, they were scanned again while carrying out another 250 “rotation” trials (Fig. 1). Each of the five movement directions (i.e., 0, 45, 90, 135, and 180°) was performed 50 times in each run during the course of two 20 min rapid event-related fMRI scans.

Each trial lasted 4 s. The trial began with a red circle at the center of the screen (“origin”) (Fig. 1). At this stage, the participants had to hold the MRI-compatible joystick still and make no hand movement. After an interval of 500 ms, five circles appeared at the upper half of the screen, spread around the center at equal distances, between 0° and 180°, at steps of 45°. Four of the circles were blue and one circle was green, signaling the required future direction of movement. The participants had to keep their hand still for 2 s until the red “origin” circle turned into a white cursor. They were instructed to respond by moving the cursor toward the green target using the joystick. Participants had 1.5 s to reach the target. Upon reaching the target, all circles disappeared. This served as a cue for the participants to release the joystick (by relaxing the spring), which resulted in the joystick returning to its starting position at the center. There was no explicit failure signal. If the participants did not reach the target within the 1.5 s time limit, all circles disappeared and the next trial began. There were also intermittent null trials (2–8 s long), in which the red origin and all five blue circles appeared on the screen (thus no target was distinctly marked for movement). These trials were obviously not followed by a “go” signal. During these null trials, the participants were instructed not to move the joystick until the next trial began.

The order of the movement trials in each run was counterbalanced (first order) and embedded with null trials of various lengths using OptSeq software. The different lengths of the null trials were used as jittered intertrial intervals to allow a more efficient estimation of activation (Dale, 1999). The total length of all null trials was equal to the total length of each of the five movement conditions (50 trials × 4 s each = 200 s). Each run began and ended with 16 s of a null event. The task was programmed with MATLAB version 7.1 (MathWorks), using Psychtoolbox (Brainard, 1997; Pelli, 1997).

Throughout the session, participants were lying in the supine position inside the scanner, holding the joystick with their right hand while the targets and cursor were projected onto a screen in front of them using a projector (Epson MP 7200). The screen was made visible to the participants through a tilted mirror above their faces. Due to their posture, participants were not able to see their hand or the joystick during the experiment. Note that in this setting, participants were moving the joystick in the horizontal plane, and the targets and the cursor were observed on the screen in the vertical plane. Therefore, the observed cursor movement was in a different location than the actual hand movement, even in the “baseline” condition. However, learning this mapping is almost immediate, as it is similar to our everyday experience, for example, moving the cursor on the computer screen using a mouse.

**Observation paradigm.** We ran a control study on six naive participants, in which they only observed the cursor movements of a center–out task. The cursor movements toward the target were a recording of earlier joystick-induced movements made by the experimenter. During this task, participants were instructed not to move their hands, so that any BOLD activation would be due to mere observation. Participants were instructed to covertly rate the accuracy of the cursor movement on each trial (between 1 and 3, where 3 was most accurate) to require them to pay attention to the cursor movement while avoiding any motor actions. To ensure that they performed the task correctly and were indeed paying attention, two of the participants were scanned for an extra 4 min run, in which they performed the ranking by pushing buttons of an MRI-compatible response box. The two participants rated the accuracy of movement almost identically (r = 0.91, p < 0.0001), and their ratings were significantly negatively correlated with the angular error of movement trajectory (the angle between the actual movement direction at peak velocity and the required one; r(subject 1) = −0.47, r(subject 2) = −0.48, p < 0.005). The session was composed of one observation run (125 trials), then a baseline run with the joystick (250 trials), followed by another observation run (125 trials).

**MT locator.** Three of the six control participants were scanned during an MT localization task. The scan included “stationary” condition blocks, in which stationary concentric white rings were shown at a low contrast,
and “motion” blocks, during which rings were alternately expanding and contracting (in 4 s cycles). The task began with a 33 s stationary block, followed by 12 interleaved “motion” and “stationary” blocks, each lasting 12 s. The scan ended with a 15 s stationary block. In total, the length of the scan was 5:24 min. Participants were instructed to maintain fixation on a red dot in the center of the screen throughout the scan.

Data analysis. Preprocessing and defining regions of interest (ROIs) were done using Brain Voyager QX (Brain Innovation). The first two functional images of each run were discarded to allow for stabilization of the signal. The images were transformed into two-dimensional anatomical images and incorporated into the three-dimensional datasets through trilinear interpolation. Before statistical analysis, head motion correction and high-pass temporal filtering in the frequency domain (three cycles/total scan time) were applied to remove drifts and to improve the signal-to-noise ratio. The complete dataset was transformed into Talairach space and Z-normalized.

Next, we applied the deconvolution method to extract the underlying BOLD response function (the deconvolution kernel, consisting of 10 β weights) for each condition from the acquired signal. This method is described in detail in our previous study (Eisenberg et al., 2010). Note that this method makes no a priori assumptions about the shape of the hemodynamic response function. This analysis resulted in an estimate of the kernel response amplitudes for 10 independent time points (2 before the trial, 2 during the trial, and 6 after each condition).

Regions of interest. Cortical regions involved in the visuomotor reaching task were individually defined based on joint functional and anatomical criteria, applied separately in each participant. The functional criterion for each M1 voxel was the presence of significantly higher BOLD activation during the movement trials (regardless of direction) than during null trials [p < 0.01, false discovery rate (FDR) correction] in the baseline run for all participants (including both test and control groups) according to deconvolution analysis. Active voxels were included in the M1 ROI if they were within a spatially contiguous cluster in the anterior side of the central sulcus of the contralateral (left) hemisphere.

Voxels putatively belonging to the human medial temporal ROI (hMT+) were defined in the control group based on the “observation” run (GLM, observed cursor movements in all directions > rest; p < 0.01, FDR correction). The location of hMT+ was verified in three of the six participants by running an independent MT localizer, using a direct contrast between “movement” and “stationary” conditions (GLM, p < 0.01, FDR correction). The average Talairach coordinates of hMT+ ROI in the observation runs (across three participants) were as follows: X = 42, Y = 66, Z = −3. This corresponded well with its location during the hMT+ localizer scan in the same participants: X = 40, Y = −67, Z = −1.

Analysis of spatial patterns of fMRI response. The criteria for inclusion of directional information in further analysis were that they successfully reached the target in at least 80% of the trials and that the fMRI activation elicited in M1 was above threshold (p < 0.01 after FDR correction) in at least 50 functional voxels. Five of the participants were excluded from further analysis on these grounds (three failed to reach the target in >20% of the trials, and two elicited insufficient fMRI activation).

Further analysis was done using MATLAB R2007b (MathWorks). We applied the deconvolution method on each of the two runs separately and estimated the hemodynamic response (β weights) for each movement direction in each voxel separately. The activation level (per direction) was defined by the mean of the β weights 6 and 8 s after the beginning of the trials (4–6 s after movement initiation, which generally corresponded to the peak activation). Then, to remove activation differences between voxels that were unrelated to movement direction, in each dataset and for each voxel, we centered the extracted activation level for each direction by subtracting the voxel’s mean activation level (across all directions). This analysis resulted in two matrices, one for each run. Each matrix consisted of five columns, one for each direction, with its length equal to the number of voxels in the ROI. The entries in each row of the matrices were the five centered activation values of a single voxel for the five directions (i.e., the target direction). We calculated the correlation coefficient (CC) between the columns of the baseline and the rotation run (each corresponding to the pattern of activation across all voxels for a given condition). If the estimated β weights contained information about the direction of movement, we expected to find a higher CC for vectors that represent movements to the same direction (in the two datasets) compared with the CC calculated for two different directions. Because the CCs were between baseline movements and rotated cursor movements, we could distinguish between conditions that shared the same hand movement and those with the same visual aspects (i.e., target location and cursor trajectory).

The CCs between compared movements typically drop with increased angular difference (Eisenberg et al., 2010). Because the rotation angle was rather small (45°), the positive CCs between trials of “same” target locations could be caused by the similar (although not identical) hand movements. To control for this possibility, we calculated the correlations between neighboring movement directions (−45°; CW instead of CCW) in which the visual aspects of the task (target location and cursor trajectories) differed by 90°. These CCs served as a “target control” group. Similarly (although highly unlikely), a positive CC between same hand movements could result from the fact that the two movements have similar target locations (separated by only 45°). The correlations between neighboring targets (−45°) with different hand movements (separated by 90°) served as “movement control.” To assess the statistical significance of the correlations, we applied the Fisher’s z transformation to the CCs (thereby converting the CC values into a normally distributed variable amenable for parametric statistical testing) and then used paired t tests across participants to compare the visual and the motor CCs with their control CCs. Finally, in the separate “observation” scan, performed in a smaller control group (n = 6), the CCs between “observation” runs for same movements versus different movements were compared using the nonparametric Wilcoxon rank-sum test.

Analysis of accurate trajectories. Despite some practice that participants had before the rotation run, trajectories in some rotation trials tended to be slightly curved. This could possibly lead to presumed visual correlations between a given rotation run and its corresponding baseline run, which are actually due to hand movement. To minimize these effects, we repeated the correlation analysis using only the more accurate trials. To that end, we divided the trials of each direction in the rotation run into two groups of 25 trials each according to their accuracy. Accuracy was determined by the angular error of movement trajectory at peak velocity. Trials were classified as “inaccurate” when the angular error was larger than the participant’s median. Trials in which the target was not reached within the time limit were considered to have large angular errors regardless of actual trajectory curvature. The mean cutoff angular error was 11.4°. The baseline run was not divided into large and small errors because movements in this run were relatively straight. The β weights of the rotation run were estimated using the 25 most accurate movements of each participant in each direction.

Informativeness of voxels about motor and visual aspects of the reaching task. Do the visual and motor correlations for similar movements largely result from the activation patterns of the same set of voxels, or are there two separate subgroups of voxels, one selective for visual components and the other for motor components? To study this, we calculated two measures for each voxel based on its sensitivity to the motor and visual aspects of the task. The motor informativeness (In,m) measure was defined as

$$I_{m} = \sum_{i=1}^{N_{v}} \frac{(b_{ij} - \bar{b}_{m})^2}{\sum_{i=1}^{N_{v}} (b_{ij} - \bar{b}_{m})^2}$$

where $b_{ij}$ denotes peak activation during the baseline run, $\bar{b}_{m}$ denotes peak activation during the rotation run, and $\bar{b}_{m}$ denotes the direction of hand movement. Thus, $b_{ij} - \bar{b}_{m}$ is the difference between activation values during the baseline run and the rotation run while making the same hand movement; $j$ denotes direction of the “movement control” (45° CW from the target direction) such that $b_{ij} - \bar{b}_{m}$ is the difference in activation values for the control condition. Thus, if the direction of hand movement is the only factor determining the voxel’s fMRI activation, the motor...
informativeness is maximal. Visual informativeness ($I_v$) was calculated in the same way:

$$I_v = \frac{\sum_{i=1}^{N} (b_i - \bar{b})^2}{\sum_{i=1}^{N} (b_i - \bar{b})^2},$$

where $k$ denotes target direction and $d$ denotes the direction of “target control” (45° CCW from movement direction). Both measures were used to split the data into the more informative and less informative halves of the voxel population, in two different ways, according to the motor and visual criteria, respectively.

**Results**

Twelve participants were scanned while carrying out a center–out reaching task in an fMRI experiment. Using an MRI-compatible joystick, they moved a cursor from the center toward five different targets located in the periphery (between 0° and 180°). The baseline center–out reaching task comprised 250 trials (50 in each direction). Next, the participants practiced the visuo-motor rotation task, in which the cursor was rotated 45° CCW with respect to the hand movement. After a short practice period, in which the participants learned to reach the targets successfully, they were scanned again while performing 250 “rotation” trials (Fig. 1). The target was reached successfully in 93.6% of the trials in the baseline run and in 92.9% in the rotation run. The mean absolute error at peak velocity was 8.4° for baseline runs and 11.7° for rotation runs.

Within each run, the time course of activation for each voxel in M1 was analyzed using the deconvolution method, allowing assessment of the activation profile ($\beta$ weights) generated by each of the five directions of movements. For each voxel, the average of the $\beta$ weights measured 6 s and 8 s after the beginning of the trial, which usually corresponded to the peak activation, served as the parameter of activation level for each direction. This activation level (per voxel, per direction) was centered by subtracting the voxel’s mean response across directions.

**Multivoxel pattern analysis**

We have previously reported that M1 voxels typically display sensitivity to movement direction (Eisenberg et al., 2010). This selectivity could arise from the direction of hand movement, but it could also be due to the covarying visual elements of the task (i.e., the direction of the cursor trajectory and/or target location). To distinguish between these possibilities, we calculated the CC between the multivoxel activation patterns elicited by two movements, one from the “baseline” run and the other from the “rotation” run (Fig. 2a). The resulting correlation matrix is shown in Figure 2c. Note that in the “rotation” run, the visual attributes were rotated by 45° CCW compared with the hand movements. This allowed assessment of the effect of hand movement and visual attributes separately from one another. Specifically, entries along the main diagonal of the matrix (Fig. 2c, depicted in blue) represent the CCs between same target directions that differ in the directions of hand movement. The entries along the next diagonal (in green) specify the CCs between movements in the same direction that differ in their target position and cursor trajectories. In both cases, all entries are positive and the average CC (across participants and matching conditions) is significantly greater than zero (motor: $t_{(11)} = 3.34, p < 0.01$; visual: $t_{(11)} = 4.3, p < 0.005$) (Fig. 2d). This suggests that both motor and visual directional cues (in the context of the task) are encoded in the patterns of activation across M1 voxels. However, because the rotation angle was small (45°), the positive CCs between trials of “same” target locations may be caused by the similar (although not identical) hand movements. Indeed, we previously reported that the patterns of activation for hand movements separated by 45° are still positively correlated (Eisenberg et al., 2010). To control for this possibility, we calculated the correlations between neighboring movement directions (45° difference) that do not share the same target location and cursor trajectories (“target control”, compare with “target alignment” condition; Fig. 2a). A direct comparison between the CCs evoked by the visual match alignments (“target”) and the corresponding control alignment (“target control”) showed that the CC difference between the two alignments was indeed significant (paired t test; $t_{(11)} = 4.28, p < 0.005$). Thus, M1 voxels contain genuine information about the visual components of the task.

Similarly (although highly unlikely), a positive CC between same hand movements may result from the fact that the two movements have similar target locations (separated only by 45°). Not surprisingly, the CC for “movement” alignments was significantly higher than during “movement control” alignments ($t_{(11)} = 3.16, p < 0.01$).

**The effects of trial accuracy**

Another issue of concern is that despite the practice in the “rotation” trials before the scan, participants may not be fully adapted and, therefore, might show a consistent bias toward the “baseline” movement direction. Indeed, the distribution of errors in the rotation trials (Fig. 3b) was slightly skewed toward positive errors (mean angular error $\pm$ mean SD across participants $= 7.37 \pm 13.57$°). Although this effect is clearly minor compared with the 45° angle difference, it could still possibly lead to presumed visual correlations between a given rotation run and its corresponding baseline run, which are actually due to hand movement. To minimize these effects, we recalculated the CCs between baseline and rotation runs, taking into account only the 25 most accurate trials for each direction in the “rotation” run (now the mean angular error at peak velocity $\pm$ mean SD across participants was 2.78 $\pm$ 9.9°). The resulting multivoxel patterns in M1 still show significantly positive correlations when the rotation run matched the baseline run in both the motor ($t_{(11)} = 5.1, p < 0.005$) and visual ($t_{(11)} = 3.48, p < 0.01$) alignments (“movement” and “target” comparisons in Fig. 3c, respectively). These correlations were also significantly greater than their corresponding control alignments (paired t test; motor: $t_{(11)} = 4.22, p < 0.005$; visual: $t_{(11)} = 3.5, p < 0.005$).

**The sensitivity to visual aspects in M1**

Having found that M1 voxels contain information about the visual aspects of the task, we were intrigued whether similar encoding of visual aspects would also occur in the absence of any hand movement, and whether the participants learn to associate the cursor movements with specific hand movements through prior visuomotor experience. To that end, we conducted a control experiment on six new participants, in which they passively observed the visual display of prerecorded cursor trajectories toward the target without making any hand movements. To ensure that participants paid attention to these cursor trajectories, they were instructed to judge the accuracy of the cursor movements. The session was composed of one “naïve” observation run (125 trials, before the cursor–joystick associations were made), then a baseline run, during which participants used the joystick to move the cursor toward the targets (250 trials), followed by another (“postvisuomotor”) observation run (125 trials).
We found little evidence for significant M1 activation during either observation run (both before and after visuomotor training). Consequently, the signal-to-noise ratio of the individual voxels was very poor. Indeed, during observation runs, the time course of only 6% of the voxels in M1 was significantly correlated with the estimated time course (based on the extracted deconvolution kernels), compared with 89% of the voxels when the same procedure was applied during the baseline movement runs. Not surprisingly, therefore, the correlations between the observation runs and the corresponding baseline runs (when the matched conditions shared the same direction) were not different in the two runs. Note, however, that the target position in the rotation run was displaced by 45° (CW) compared with its position in the baseline run, as in the “movement alignment” condition (45°, CCW). Similarly, in the “target control” alignment, the movements in the baseline and rotation runs differed by 45°, as in the target alignment condition (compare the wedges caused by the green arrows). Examples of the multivoxel activation patterns (see color code) in M1 (axial plane, Talairach coordinates: z = 54) during baseline trials (toward 135°; left) and during rotation trials in which movement was toward 135° (top right; CC between the two patterns was 0.32); the target was toward 135° (middle right; CC = 0.39), and the target was toward 90° (movement control; bottom right, CC = −0.25). Matrix of mean CCs (across participants) between multivoxel patterns of the “baseline” and “rotation” datasets for all possible direction combinations. The main diagonal (blue) shows the “target aligned” CC values, the green diagonal shows CCs between “movement aligned” conditions, the values in the purple diagonal are the “movement control” CCs, and the ones along the red diagonal are the “target control” CCs. Mean CCs across participants and across directions for the different conditions (same color coding as in a–c). “Movement aligned” CCs are significantly larger than the “movement control” CC values (\(p < 0.01\)) and “target aligned” CCs are significantly greater than “target control” values (\(p < 0.005\)). Error bars denote SEM over participants.

Figure 2. Multivoxel spatial patterns of activation contain information about target (and cursor) direction as well as hand movement direction. a, An example showing the procedure of alignment of movements in the baseline run (black arrows denote hand movement and cursor trajectory), with movements during the rotation run (green arrows denote hand movement, blue arrows denote cursor trajectory, and the gray circles denote target location). When the movements are aligned according to the direction of joystick movement (“movement alignment,” left), the baseline and rotation run share the motor component (green arrow) but differ in their visual components (target position and cursor direction). Similarly, during “target alignment” (third column), the two conditions share the same visual components but differ in their motor aspects (by 45°, shaded wedge). In the “movement control” alignment (second column), both visual and motor aspects were different in the two runs. Note, however, that the target position in the rotation run was displaced by 45° (CW) compared with its position in the baseline run, as in the “movement alignment” condition (45°, CCW). Similarly, in the “target control” alignment, the movements in the baseline and rotation runs differed by 45°, as in the target alignment condition (compare the wedges caused by the green arrows). b, Examples of the multivoxel activation patterns (see color code) in M1 (axial plane, Talairach coordinates: z = 54) during baseline trials (toward 135°; left) and during rotation trials in which movement was toward 135° (top right; CC between the two patterns was 0.32); the target was toward 135° (middle right; CC = 0.39), and the target was toward 90° (movement control; bottom right, CC = −0.25). c, Matrix of mean CCs (across participants) between multivoxel patterns of the “baseline” and “rotation” datasets for all possible direction combinations. The main diagonal (blue) shows the “target aligned” CC values, the green diagonal shows CCs between “movement aligned” conditions, the values in the purple diagonal are the “movement control” CCs, and the ones along the red diagonal are the “target control” CCs. d, Mean CCs across participants and across directions for the different conditions (same color coding as in a–c). “Movement aligned” CCs are significantly larger than the “movement control” CC values (\(p < 0.01\)) and “target aligned” CCs are significantly greater than “target control” values (\(p < 0.005\)). Error bars denote SEM over participants.

Voxel sensitivity measures for the visual and movement aspects are independent
Are individual voxels that carry information about the direction of movement more informative about the visual aspects as well? If
so, this would suggest that M1 neurons may be sensitive to both aspects, or at least that the modality-exclusive neuronal populations that are sensitive to visual aspects are in close proximity to populations sensitive to movement (i.e., within a voxel). To that end, we selected half of the voxels that were more informative about movement direction and tested the degree to which their pattern of activation can convey information about the visual properties of the trial. The results are shown in Figure 5 (left panel). As expected, selection of the highly informative “motor” voxels increased the motor CCs (from 0.26 to 0.41; \( t_{11} = 2.69, p < 0.0005 \)), but importantly, it did not improve the visual CCs (0.21 vs 0.15; \( t_{11} = 1.58, p > 0.1 \)). Similarly, we selected the visually informative voxels and tested their sensitivity to the direction of hand movement (Fig. 5, right panel). Again, selection of voxels with a high measure of visual informativeness increased the visual CCs significantly (from 0.21 to 0.37; \( t_{11} = 5.5, p < 0.05 \)), but it did not affect motor CCs (0.26 vs 0.25; \( t_{11} = 0.6, p > 0.5 \)). Thus, whereas visual and motor directional aspects of visually guided reaching movements are represented in the multivoxel patterns of human M1, the visual and motor representations seem to be independent from one another.

**Discussion**

We found that the multivoxel patterns of activation in M1 during visually guided reaching movements carry information about both the direction of hand movement (as implicitly assumed; Eisenberg et al., 2010), as well as the visual elements of reaching. These findings are consistent with previous studies of single neurons in monkeys (Alexander and Crutcher, 1990; Lurito et al., 1991; Shen and Alexander, 1997a). The relevant visual aspects, however, are represented in M1 only when directly coupled with movement and do not play a role when the same viewed actions are passively seen (e.g., in the visual playback “observation” task).

A recent fMRI study (Dinstein et al., 2008) has demonstrated that multivoxel patterns of activation in M1 (during a rock–paper–scissors game) contain information about the executed hand configuration. The same voxels, however, do not contain information about observed hand configurations. This is also
consistent with another study in M1 (Chouinard and Goodale, 2009), which found fMRI adaptation (repetition suppression) to movement but not to the features of the cue that were irrelevant to the required response.

However, our results are seemingly in contradiction with a couple of electrophysiological studies in monkeys: Merchant et al. (2001), who reported that M1 neurons modulated their activity in response to optic flow stimuli in different directions, and Suminski et al. (2009), who found that visual playback of reaching actions is enough to elicit directional tuning in M1 neurons. It is likely that the fMRI signal may be too crude to detect neuronal features that are seen in a minority of the neuronal population.

Ruling out alternative explanations
Humans tend to make eye movements toward the target during visually guided reaching movements (Gielen et al., 1984; Abrams et al., 1990; Ariff et al., 2002). Thus, the “visual” sensitivity of the multivoxel patterns to the target location may actually reflect an oculomotor sensitivity to the target-specific eye movements and not the target location itself. This is highly unlikely because the oculomotor regions are distinctly separate from the hand-related regions in M1: it is generally accepted that the primary areas of representation of eye movements are the frontal eye fields (Chen and Wise, 1995; Passingham, 1995). Indeed, the single neurons in monkey M1 that are sensitive to reaching direction (Mushiake et al., 1997) are not modulated by changes in gaze direction. Similarly, regions in human M1 whose BOLD activation is modulated by pointing are not sensitive to the direction of gaze (DeSouza et al., 2000). Still, to rule out this alternative, we analyzed data from a recent fMRI study by Pertsov et al. (2011), in which participants made saccades in various directions toward remembered targets. We found no significant saccade-induced activation or positive CCs for same-saccade directions in the hand-specific M1 (i.e., the current study ROI) in a participant who took part in both studies. We conclude that target-specific eye movements are unlikely to explain the visual selectivity of the multivoxel patterns to the target location.

What are the relevant visual features in the display driving M1?
The visual aspects that affect the pattern of activation across M1 voxels could be related either to target location or to the cursor trajectory. There is some evidence that neurons in monkey M1 are sensitive to the location (or other features) of the visual cue (Zhang et al., 1997; Zach et al., 2008; Saleh et al., 2010). However, previous fMRI studies in humans (Toni et al., 1999; Stark and Zohary, 2008; Chouinard and Goodale, 2009), which contained a visual target or a visual cue, did not show any visually induced M1 activation. Unlike these previous studies, our reaching task required continuous visual feedback in addition to the registration of target location. Perhaps the cursor feedback is more relevant than the target location to the visual representation within M1. Another explanation for this discrepancy could be that we used multivoxel pattern analysis, which can detect differences in representation that other methods (used in the past studies) that measure the mean activation or adaptation over all M1 voxels may miss.

Alternative interpretations
We stress that the online visual feedback and the cue are likely to affect the activation patterns in M1. However, another possibility is that because the baseline mapping is more intuitive than the rotation mapping, learning the rotated mapping does not totally abolish the baseline mapping but, rather, a novel mapping is established in parallel to the baseline mapping and overrides the existing default representation. If this is indeed the case, the activation elicited during rotation trials represents not only the newly acquired mapping but also the baseline (unperturbed) mapping. Thus, the visual correlations we observed may in fact stem from a subthreshold (unexecuted) retained motor program that is activated when the cue is presented. There is some evidence that M1 is in fact involved in the retention of the previous motor program. Activation of M1 using transcranial direct current stimulation (Galea et al., 2010) during rotation learning led to a slower rate of forgetting of the newly learned visuomotor transformation. Conversely, disruption of M1 activity using transcranial magnetic stimulation resulted in a faster rate of forgetting of the newly learned transformation (Hadipour-Niktarash et al., 2007). In any case, even if the visually induced correlations are in fact a result of a remnant motor program, it is important to stress that this program is activated by a visual cue, which is associated with a motor action.

The motor correlations seen in M1 may also stem from the proprioceptive reafferent signals rather than the afferent motor signals. Indeed, Rossett et al. (1995) have shown that displacement of one’s viewed finger location by the use of prisms biases pointing to visual targets by only a third of the true prismatic shift. This suggests that proprioception plays a role in planning movements as well as vision. In addition, Suminski et al. (2010) have shown that adding proprioceptive information (about the hand position), congruent with the visual information, improves the control of a cursor driven by activity of M1 neurons (in a brain–machine interface). Because we do not dissociate motor and proprioceptive components of the task, we cannot rule out the possibility that the proprioceptive signal contributes, at least in part, to the motor correlations in M1.

The sensitivity of other motor cortical areas
Previous studies in monkeys (Shen and Alexander, 1997b; Cisek et al., 2003) have shown that neurons in dorsal premotor cortex (PMd) were more sensitive to the visual aspects of the task than M1. We found no evidence for this in our study. There were no significant visual correlations in PMd (motor correlations were also much lower). One reason for this discrepancy may be that in our study M1 voxels displayed a much stronger BOLD activation than the other motor areas. The poor signal-to-noise ratio in other areas would clearly mask any possibility of observing strong motor or visual correlations in secondary motor areas. Therefore, the level of visual correlations does not necessarily reflect accurately the amount of “visual” neurons in each area. Indeed, Dinstein et al. (2008) found, using a similar multivoxel pattern analysis in a different motor task, that both motor and visual representations of the action can be found in the anterior intraparietal sulcus (IPS). Interestingly, as in our study, there seemed to be little correspondence between the two representations in anterior IPS: decoding level of the executed movements after training the classifier to distinguish between the observed movements was indistinguishable from chance.

Summary and future outlook
We have shown that both movement direction and visual aspects of the task are independently represented in regions encoding hand movements within M1.

It would be interesting to know whether this reflects a change in the single unit preference as the trial unfolds. Lurito et al. (1991) showed that at the population level, M1 neurons tend to
change their tuning throughout the trial such that initially they are sensitive to the target location, and later they become sensitive to the direction of hand movement, as has been shown by Shen and Alexander (1997a). With the current temporal resolution of fMRI, we could not detect this temporal drift. This remains to be shown by separating different epochs of the trials, using paradigms that allow separation of movement planning from movement execution.

References


Eisenberg et al. (2011) Visual and Motor Representations in Motor Cortex

Eisenberg et al. (2011) Visual and Motor Representations in Motor Cortex
Results III:

Repetition Suppression in the Primary Motor Cortex

The findings presented in this chapter have yet to be published in the scientific literature
Abstract

Repetition suppression (RS) is the reduction of the functional MRI response to a repeated stimulus. This phenomenon has been shown for various kinds of visual stimuli (e.g. faces, objects, etc) in many areas along the visual pathway. Recently, RS has been shown in motor areas as well, when repeating a movement to the same direction as in the previous movement. The interest in RS has been enormous because it was suggested to reflect the tuning properties of single neurons, thereby allowing an indirect study of the properties of neuronal populations, using a noninvasive technique. Several models have been suggested to explain the phenomenon at the neuronal level. To that end, electrophysiological studies designed to test which of these alternative models best explains RS have been carried out in monkeys. The findings vary between different visual areas. In the inferior temporal area (IT) for example, RS was found mostly for the preferred stimulus, consistent with the interpretation of synaptic fatigue, whereas the pattern of RS in middle temporal cortex (MT) fit the model of sharpening of the tuning curve.

In motor areas this issue has not yet been studied. In this study, we analyze electrophysiological data from macaque primary motor cortex, during center-out reaching movements in eight different directions. We utilize the task design, in which the same movements were sometimes repeated in successive trials while at other times successive movements were in opposite directions, to look for a difference in the firing rate and/or in the local field potential (LFP) between the same current movements, depending on the movement history (i.e., same or opposite direction of movement in the previous trial).

Our goal here was to look for an adaptation mechanism, possibly similar to one of the previously suggested mechanisms, to shed light on the neuronal basis for RS in the motor pathways. However, unlike the studies in the visual system, we found no sign of RS in the single unit database or in the LFP. Further study is required to fully understand the discrepancy between these neuronal results and the RS found in the fMRI signal, but the lack of any neuronal repetition effect, could suggest that the RS found in the fMRI signal of the motor cortex does not reflect a neuronal process as generally accepted.
Introduction

The functional MRI (fMRI) response to a repeated stimulus is often reduced compared to the response to a non-repeated stimulus. This phenomenon is known as repetition suppression (RS), and has been shown for many different visual characteristics, from intensity and contrast in the early visual cortex (Gardner et al., 2005) to objects in higher areas, such as the lateral occipital complex (Buckner et al., 1998; Grill-Spector et al., 1999; Kourtzi and Kanwisher, 2001).

The importance of fMRI RS derives from suggestions that it can be used as a tool to assess neuronal selectivity (Tootell et al., 1998; Grill-Spector and Malach, 2001; Avidan et al., 2002). Several models have been proposed to explain the fMRI RS at the level of single unit activity: (1) fatigue. According to this model all neurons show a proportionally equivalent decrease in activation in response to a repeated stimulus. The neural mechanism in this case could be either firing rate adaptation or synaptic depression (short term or long term). (2) Sharpening. According to this model we expect a decrease in activation only in neurons that are less responsive to the presented stimulus. Neurons that respond optimally to the stimulus will show no change in activity in response to repetition (3) facilitation. This model predicts that repetition will facilitate faster processing of the stimulus, and therefore a shorter duration of the neuronal firing (Grill-Spector et al., 2006; See figure 1).
Figure 1: Neural network models for RS. (a) The visual stimulus is assumed to cause activity in the input layer (corresponding to early visual cortex) before being processed in a hierarchical sequence of stages. The blue graphs indicate spiking (as a function of time) of the neurons with highest response at each stage (indicated by black circles). (b) Because the BOLD signal integrates neuronal activity over time, all three of these models predict reduced BOLD for repeated stimuli, but for different reasons: Fatigue model (left, lower firing rates); Sharpening model (centre, fewer neurons responding); Facilitation model (right, shorter duration of neural processing). Grill-Spector et al., 2006.

A decrease in the firing rate of single units has been shown for non-human primates in response to repeated stimuli in the primary visual cortex (V1) (Movshon and Lennie, 1979; Müller et al., 1999; Sharpee et al., 2006), in the inferior temporal cortex (IT) (Sawamura et al., 2006; De Baene and Vogels, 2010) and in the middle temporal cortex (MT) (Kohn and Movshon, 2004). In IT (De Baene and Vogels, 2010), as well as in V1 (Movshon and Lennie, 1979; Müller et al., 1999), firing rate decreases most when the adapting and test stimuli are the same, concurring with the fatigue model, while in MT, Kohn and Movshon (2004) have shown a decrease in firing rate in stimuli near the adapter but not in the exact same stimulus, which concurs with the sharpening model.
Recently, fMRI RS has been shown in the primary motor cortex (M1) for movements as well, by us (Eisenberg et al., 2010) and by others (Dinstein et al., 2007; Fabbri et al., 2010). However, it has never been studied in single unit activity, and it is unknown whether RS can be found at the neuronal level in motor areas or if it occurs in a pattern similar to those found in visual areas.

In this study, I analyzed electrophysiological data recorded from macaque M1, and tried to find a difference in responses to repeated movements compared to non-repeated movements. I utilized the task design, in which movements in the same direction were sometimes repeated in successive trials, while at other times successive movements were in opposite directions. My goal was to determine if RS can be found in the single unit activity of M1, and test whether the change in response fits any of the suggested models explaining RS of the fMRI signal. In addition, I compared the local field potential (LFP) in M1 that was generated by repeated and non-repeated movements. The LFP is generally considered a population signal of many thousands of neurons, reflecting mainly the synaptic inputs (Mitzdorf, 1987). It has been found to correlate with the BOLD signal better than single- and multi-unit firing rates (Logothetis et al., 2001). Therefore, it seemed feasible that the RS patterns seen at this level may be more correlated with the BOLD signal. The results of the experiments discussed in this section show no difference between repeated and opposite movements, either in the single unit data or in the LFP signal. This could suggest that the RS found in the fMRI signal of the motor cortex does not reflect a neuronal process, as generally accepted.

Materials and Methods

Animals, recordings and behavioral task

One male monkey (Macaca fascicularis, 4 kg) was chronically implanted with a microelectrode array (Cyberkinetics Neurotechnology Systems) under anesthesia and aseptic conditions, in the arm region of M1, contralateral to the performing arm. Animal care and surgical procedures complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and with guidelines defined by the Institutional Committee for Animal Care and Use at the Hebrew University.
Monkeys used a robotic arm (Phantom Premium 1.5 High Force; SensAble Devices) to control the movements of a cursor on a video screen in a two-dimensional plane. Before surgery, monkeys were well trained to perform a standard eight-target center-out reaching task using this device. The robotic arm moved the cursor from the starting point at the center of the screen to a visual target in a delayed go-signal paradigm. Each trial began when the monkey positioned the cursor at the central circle. After a variable hold period of 0.75–1.25 s, a target appeared at one of the eight possible positions, which were uniformly distributed in a circle 4cm from the center. After an additional 0.75–1.25 s hold period, the central circle disappeared (go signal), prompting the monkey to move to the target in less than 1 s. This generous time constraint allowed relatively natural reaching movements. After another 0.4s, a liquid reward was delivered. A scheme of the trial flow is shown in figure 2.

Session flow: Each session began with standard trials (with no perturbation) introduced in sets of three trials with targets in the same direction in a row, and after completion of the set, another set was presented with the neighboring clockwise target, etc. After completing trials in all eight directions, the next round was the same, except the directions changed in a counter-clockwise order. Finally, the third round had random assignments of the eight movement directions. In the second part of the experiment (block 2), the monkey was introduced with a visuomotor rotation, where in order to move the cursor in one direction the monkey needed to move its arm in another direction. There were several days in which block 2 had no rotation, and the monkey simply had to make repeated movements to the same specified direction. (In each session the repeated movement was to a different direction). Block 3 was standard again (with no rotation). In this block the sequence of target appearances was in a pseudo-random order.

Monkeys were trained for several months with the default eight-target task.

For further analysis we did not use the first standard block, where trial directions did not appear randomly, or the rotation block. Therefore, we focus here on the third block, which was the second standard phase. Since the rotated movement in the previous block probably caused an aftereffect (i.e., movements were curved to the direction opposite from the learned direction), at least in the first several trials in the learned direction (Paz et al., 2003), we excluded the rotated direction from the analyses, thereby nullifying the learning affect.
Figure 2: Trial flow. (a) Each trial began with the appearance of the central target ("origin"). The monkey had to hold the red X (the cursor) inside the origin for a variable hold period of 0.75-1.25 s. Next, a target appeared in one of 8 possible positions. The monkey had to keep the cursor in the origin for another 0.75-1.25 s. After this second hold period, the origin disappeared and the monkey had to move towards the target within 1 s. In this example, there are two consecutive trials in the same direction (45°). (b) An example of two consecutive opposite trials, where a trial in the direction of 45° came after a trial with a target in 225°.

Neuronal data analysis

Neurons were selected on the basis of their directional tuning. The sample includes neurons with tuning curves that show a good fit ($R^2 > 0.65$) to the cosine function $[r(d) = a + b \times \cos(d - d_0)]$ (Georgopoulos et al., 1982). The reasoning for choosing directionally selective neurons was that the RS can be explored separately for different distances from the preferred direction (PD), helping to distinguish between the different models explaining the fMRI RS.

Firing rate was computed for the epochs 100 to 600 ms after target onset and 200 ms before movement onset to 300 ms after movement onset.
Repeated and opposite trials: For the main analysis I used repeated trials, which were sequential trials with the same movement direction, and opposite trials, which were 180° from the movement in the previous trial. The opposite trials were used instead of taking all non-repeated trials, because some degree of adaptation is expected for movement directions that differ slightly (e.g. 45°) from the previous trials. We wanted to examine the maximal effect by comparing the most expected amount of adaptation (repeated movements, which were identical to the previous movement) with the least expected amount of adaptation (opposite directions, which differed the most from the previous movement, at least in the population of neurons activated). Note that during performance the monkeys could not anticipate the direction of the next trial, since the trials were introduced in a pseudo-random fashion. Thus, there was no fixed number of repeated trials. We discarded sessions with less than two repeated trials or opposite trials in each direction.

Adaptation Index (AI) was calculated for each neuron, and was defined as \[
\frac{\sum O_i - \sum R_i}{\sum O_i} \times 100,
\]
where \(O_i\) is the mean response of the opposite trials in the \(i\)th direction, with \(i\) ranging between 1 to 8, and \(R_i\) is the mean response of the repeated trials in the \(i\)th direction. The AI was computed for the mean response both after target appearance, and around movement onset.

Tuning Curve: For each neuron the tuning curve was computed by averaging over trials in each of the 8 directions, and was fitted to a cosine function. We computed the \(R^2\) and the PD (the angle corresponding to the peak of the cosine wave). For the comparison between repeated and opposite trials at the PD and at the direction opposite from the PD we used the direction of movement closest to the PD, and the direction farthest from the PD, respectively.

LFP data analysis

For the LFP analysis we averaged the recorded signal in the low frequency band (0.3-250 Hz) from each electrode over trials in each direction separately, and found the second positive peak (P2) of the movement evoked potential (mEP). P2 was the first positive peak after the first negative peak (N1), and was defined as the maximum value in the range of 350 to 1150 ms after movement onset. This peak was shown to have the highest signal-to-noise (at the time domain) by Rickert and colleagues (2005).
Next, we fitted the tuning curve of the peak-to-peak amplitudes for the various directions to a cosine function, as was done for the single unit data, and calculated the $R^2$ and the PD.

Paired T-tests were used for the single units and for the LFP data to assess significance in all comparisons between the repeated trials and the opposite trials.

**Results**

The monkey made center-out reaching movements towards 8 targets in the periphery, presented in a pseudo-random fashion. We used this task design to separately analyze trials in which the same movement direction was repeated in consecutive trials ("repeated") and trials in which the current movement followed movement in the opposite direction in the previous trial ("opposite").

**Performance in repeated and non-repeated movements**

First of all I wanted to see if a learning process was still going on, and if there was any difference between the repeated and non-repeated movements in how straight the movement trajectories were to the target. To that end I assessed the angular deviation for each trial by calculating the angle between the actual trajectory at the peak velocity and the direct trajectory to the center of the target. For non-repeated movements the angular deviation was 7.36°, and for repeated movements it was 6.65°. The difference was not significant ($t_{(509)}=1.4$, $p=0.16$). The angular deviations were not significantly different in the fMRI experiment either ($t_{(10)}=0.8$, $p=0.44$).

**Neuronal data analysis**

I analyzed the activity of neurons that were directionally tuned during two time epochs: (a) target related activity, 100 ms to 600 ms after target appearance; and (b) movement related activity,
200 ms before to 300 ms after movement onset. Sixty two neurons (37% of all neurons) were classified as “target-related” based on their directional selective activity in the interval following target appearance. One hundred and seventeen neurons (70% of all neurons) had movement-related activity (i.e., directional selectivity during the movement execution interval).

For each neuron, we plotted the peri-event time histogram (PETH) of each of these two conditions. We found no difference in the overall firing rate between trials in which the direction was repeated ("repeat trial") and trials in which the previous movement was in the opposite direction ("opposite trial"). We quantify this by the adaptation index (AI). We show that this was true when the PETH was aligned to both the movement onset (figure 3a, $t_{(116)}=-1.34$, $p=0.18$) and to target appearance (figure 4a, $t_{(61)}=-0.96$, $p=0.34$). Next, for each neuron we calculated the AI (see materials and methods). The AI of a neuron should be positive if its firing rate is lower for repeated trials or negative if its firing rate is higher for repeated trials. If there is no adaptation, the AI should be 0. In figure 3b we show a histogram of the adaptation indices across all directionally tuned neurons during movement. We found that the AIs were distributed around 0 (mean AI=-1.2%; $t_{(116)}=-0.69$, $p=49$). Therefore, no adaptation was found. We calculated the AI after target appearance as well (figure 4b), and here we find no significant difference from 0 either (mean AI=1.4%; $t_{(61)}=0.8$, $p=0.43$).
Figure 3: Directionally selective M1 neurons show no RS around movement onset. (a) PETH of the mean over the entire sample of selected M1 neurons for repeated trials (blue) and for opposite trials (red) in all directions of movement. Time point 0 indicates movement onset. Gray lines denote the PETHs for opposite trials +/-standard error of opposite trials. (b) Histogram of AIs for movement related activity. The arrow denotes the mean AI value. Note that the mean AI is not significantly different from 0, indicating that there is no significant adaptation.

Figure 4: Directionally selective M1 neurons show no RS after target appearance. (a) PETH of the mean over the entire sample of selected M1 neurons for repeated trials (blue) and for opposite trials (red) in all directions of movement. Time point 0 indicates target appearance. Gray lines denote the PETHs for opposite trials +/-standard error of opposite trials. (b) Histogram of AI for target related activity. The arrow denotes the mean AI value. Note that the mean AI is not significantly different from 0, indicating that there is no significant adaptation.

Another possibility is that the adaptation might manifest itself by a change in the tuning curve width. For example, repeated movement would lead to a decrease in activation only in directions close to the PD of the neuron, leading to a wider tuning curve; or a decrease in firing only in directions far from the PD, causing a narrowing of the tuning curve. To that end, I computed the
direction tuning curve of each neuron, for the repeat and opposite conditions, separately, and then aligned the resulting tuning curves according to the direction of movement closest to their PD. Again, we found no significant difference between repeated and opposite directions for any of the distances from the PD either for the movement-related activity (figure 5, at PD for example, \( t_{(116)} = 1.36, p = 0.18 \)) or for the target-related activity (figure 6, at PD \( t_{(61)} = 0.99, p = 0.33 \)).

**Figure 5:** Directional tuning of repeated vs. opposite trials around movement onset. (a) PETHs of the mean over the entire sample of selected M1 neurons for repeated and opposite trials in the PD of each neuron. (b) PETHs for repeated and opposite trials in the direction 180 degrees from the PD of each neuron. (c) Tuning curves for repeated (blue) and for opposite (red) trials. Error bars denote standard error of the mean over neurons.
The same analysis was carried out over all neurons, with no selection criteria, figuring that this would be most similar to the fMRI data, which is affected by the entire population of neurons, not only the well isolated and directionally tuned ones. For these analyses we used 169 neurons. No difference was found between the repeated and opposite trials around movement onset (mean $AI= -0.19; t_{(168)} = -0.12, p = 0.91$), or after target appearance (mean $AI= 0.26; t_{(168)} = 0.14, p = 0.89$).

**LFP data analysis**

It’s possible that adaptation will be found in the LFP signal, which has been shown to be much more correlated to the fMRI signal than single unit activity (Logothetis et al., 2001). Finding RS
of the LFP signal would suggest that the discrepancy between single unit activity and the fMRI signal is not due to the difference in species (human vs. nonhuman primates) or in the different experiment parameters, but rather in the nature of the signal. LFP reflects the input to the area more than its output (Mitzdorf, 1987), as may be the case with the BOLD signal. Therefore, if the RS is a synaptic process, it might be reflected in the fMRI and in the LFP signals, but not necessarily in the single unit activity.

For the LFP data, I did a similar analysis as for the neuronal data. I computed the tuning curve of each electrode by taking the measure of the second positive peak (P2) of the mEP. There is no significant difference in the mEP between repeated and opposite trials (t(734) = -0.88, p = 0.38; figure 7a). When I looked only at the activation at the PD or only at the direction 180 degrees from the PD, I found no difference between repeated and opposite trials either (at PD: t(96) = 0.88, p = 0.38 and 180 degrees from PD: t(88) = 0.48, p = 0.64; figure 7b & c, respectively).

**Figure 7**: M1 mEPs show no RS around movement onset. (a) MEP for repeated and opposite trials. The dashed lines marked N1 and P2 indicate the points in time of the negative and positive peaks of the mEP. (b) MEP for the PD of each electrode (c) MEP for the direction 180 degrees from the PD of each electrode.
I show LFP results only for movement related activity, because when aligned to target appearance, the data was too noisy to extract a reasonable signal, and it is not clear which parameter or what time interval is best for comparison of the repeated and the opposite trials.

**Discussion**

We found no RS in the firing rate of monkey single neurons in M1 at the population level, nor have we found RS in the LFP. This is in contrast with the RS found in human M1 in functional imaging studies (Dinstein et al., 2007; Eisenberg et al., 2010; Fabbri et al., 2010). Furthermore, electrophysiological recordings in visual cortical areas, such as IT and MT, indicate that both single neurons and the LFP signal do show RS in response to a repeated visual stimulus (Kohn and Movshon, 2004; De Baene and Vogels, 2010). There are several possible explanations to our results:

**Learning vs. repeating**

Recently, there has been growing debate about whether the RS phenomenon is due to an automatic process, or to a top-down process, reflecting our expectation (Summerfield et al., 2008; Pedreira et al., 2010; Larsson and Smith, 2012). It is possible that the RS observed during movement repetition is in fact due to our expectation, and would be better accounted for by motor learning.

Paz and colleagues (2003) have shown narrowing of the neurons’ tuning curve in M1 when monkeys were learning a novel visuomotor rotation. This narrowing was found when the monkeys made repeated movements to the same target with the novel transformation, but not when they simply repeated the same movement with standard mapping (i.e., no rotation). The sharpening of the tuning curve, therefore, reflects the learning process taking place in M1.

Similar narrowing of the tuning curve was found by Kohn and Movshon (2004) in MT in response to repetition of observed moving gratings. However, while in Kohn and Movshon’s study the narrowing was caused by a decrease in the activity for neighboring directions while
maintaining the level of activation in the PD, the narrowing of the tuning in the study by Paz and colleagues is obtained by an increase in firing rate at the PD.

**Figure 8**: Sharpening of Tuning curves of example single neurons. (a) Tuning curves of MT neurons before (white circles) and after (black circles) adaptation to the PD of these neurons (adapted from Kohn and Movshon, 2004). (b) Tuning curves of M1 neurons before (gray line) and after (black line) learning a rotation in a direction near the PD of these neurons (adapted from Paz et al., 2003).

Perhaps motor RS differs from visual RS, in that it occurs only during learning, when the task is not automatic. Since the monkey had months of training on the standard center-out movements, and no difference was found in task performance between repeated and non-repeated movements, maybe we shouldn’t expect to find adaptation to repeated movements in the same direction? The explanation for fMRI RS in human participants could be that they weren’t as proficient at the task as the monkey (they had only several minutes of practice before the task). However, no difference in performance was found in the fMRI experiment, and there was no difference in RS between participants who did better at the task (smaller angular deviations), and participants who did worse (data not shown).
Motor vs. visual adaptation

It is possible that the motor adaptation mechanism is fundamentally different from the visual one. For the perception of sensory stimuli, adaptation makes sense: we need to be alert to change, as is seen for luminance and contrast in areas as early as the lateral geniculate nucleus (Solomon et al., 2004) and the retina (Enroth-Cugell and Shapley, 1973; Smirnakis et al., 1997; Chander and Chichilnisky, 2001). This requirement is irrelevant for voluntary motor actions. Perhaps the mechanism is different. One speculative possibility is that the BOLD RS we have found in M1 is merely a residual of visual adaptation to the different targets. However, RS was recently found in M1, even when there was no visible target or compatible visual feedback (Dinstein et al., 2007). In addition, to see if RS might be found in M1 during repeated observation of the same target, we aligned the neuronal responses to target appearance. No difference was found in the average neuronal response during repeated and opposite trials. It still remains to be seen whether there is RS in the LFP signal in the frequency domain [perhaps in the gamma range, as shown by De Baene and Vogels (2010) for visual stimuli], especially when aligned to target appearance. This would indicate that the fMRI RS could be caused by visual inputs from other areas, since both LFP and BOLD activation are thought to reflect inputs rather than action potentials. This is consistent with our finding of RS in anterior and medial intraparietal areas, as well as in M1 (data not shown).

Is BOLD RS a reflection of adaptation at the neuronal level?

It’s possible that the BOLD RS is an artifact that does not always reflect the neuronal activity, both in motor and in visual cortex. According to this hypothesis, the adaptation found in visual areas for firing rate and for BOLD response are two independent phenomena. This is in line with the results of Sawamura et al. (2006), who found that macaque IT neurons adapt when presented with two successive different images to which the neurons are equally responsive, but less than when the repeated stimuli are identical. Therefore, the neuronal adaptation is more selective to visual stimuli than the neuronal response, complicating the interpretation of RS of the fMRI signal. Perhaps the BOLD RS reflects something other than neuronal or synaptic adaptation. It has been suggested by Krekelberg and colleagues (2006) that the RS attributed to neuronal adaptation could in fact be due to nonlinearities in the neurovascular coupling process. For
example, maybe the blood flows towards a certain population of neurons in excess. When we reactivate the same population at approximately the same level as in the previous trial, the level of oxygen in the area is already saturated, which brings to less blood flow in response to repeating the same trial, and therefore to a smaller BOLD response.

A word of caution is in place here: Before we can accept any of these interpretations, we should keep in mind that the experiment that was used for my analysis was different from the one generally used for visual stimuli; The trials here are individual movements with long inter-trial intervals, while in the visual studies trials are generally comprised of an adapter and a repeated or non-repeated test stimulus with a short (300 ms) time interval between them (for example see Sawamura et al., 2006). In future studies the experiment should be run on monkeys before they reach a performance ceiling affect, so a possible relation between behavioral performance and a repetition affect can be examined. Additionally, in order to be sure that the difference isn’t due to the difference in species or in task parameters, the unit recordings should be done in parallel with the fMRI response in monkeys, or at least in the same monkeys, as was done by Sawamura and colleagues (2005) for visual stimuli.
Discussion

Summary of results

Functional organization of human motor cortex: directional selectivity for movement

In the first chapter of the results I show, using several methods of analysis, that voxels in human M1 are tuned to the direction of movement. This leads us to the conclusion that neurons in human M1 are likely to be organized according to their directional preference; i.e., neighboring neurons tend to have close preferred directions (PDs). Additionally, I use a model based on the depth of modulation of the fMRI response to the various directions in order to estimate the average size of a cluster of neurons with the same PDs. We find that the diameter of such a cluster is of the order of 85-470 micrometers, which is in the same order of magnitude as estimated in studies with primates (Amirikian and Georgopoulos, 2003; Stark et al., 2009).

The representation of visual and motor aspects of reaching movement in the human motor cortex

In the second chapter of the results I show that in addition to the robust movement representation in human M1, there is also a significant visual representation of the direction of motion. This representation, however, exists only when the visual stimulus is relevant to the motor task, either by indicating the target, or by providing cursor feedback during the task. When the task required observation only, with no hand movement, no activation was found in M1, nor was there any information in the multi-voxel patterns of activation. This supports the notion that M1 plays a role in a higher level of movement planning than originally accepted.

Repetition Suppression (RS)

In the last chapter I looked for evidence of suppression of neuronal activity in macaque area M1 when repeating a trial in the same direction. However, no such evidence was found. This is in marked contrast with the RS found in the homologues areas in humans using fMRI, by us (chapter 1 of results) and in previous studies (Dinstein et al., 2007). This mismatch raises doubts about the interpretation of the source of RS in the fMRI signal, which is considered to reflect the
properties of single neurons (Grill-Spector and Malach, 2001). Therefore, either the mechanism of RS in the motor cortex is entirely different from sensory areas, or perhaps the mechanism is not as directly related to neuronal properties as previously thought. I will elaborate on this further in the next section.

**Human fMRI vs. monkey electrophysiology**

Overall, the prime goal of this thesis was to study the representation of movement directions in M1; from how neurons with different PDs are organized in M1 to the representation of the visual and motor components of reaching. Another goal was bridging over the gap, both between different methods of data acquisition, i.e., electrophysiology and fMRI, and between different species, i.e., human and non-human primates, to try to establish commonalities between these levels.

In the first two studies, I used multi-voxel pattern analysis. Although there is some evidence from electrophysiological studies done on macaques towards functional organization and towards a visual representation in M1, these questions have not been previously addressed in humans. There are many reasons for the scarcity in human imaging studies of movement; including lack of room for movement inside the scanner, joysticks and devices recording movement are usually metal and not MRI-compatible, the difficulty of scanning a person making hand movements without too much head movement (thus lowering the signal to noise ratio), etc. Despite these constrains, there have been several fMRI studies of reaching (Schaal et al., 2004; Diedrichsen et al., 2005; Filimon et al., 2007). Dinstein and colleagues (2008) successfully decoded different hand configurations in M1. They used the rock-paper-scissors game and found different patterns of activations for each of the three hand configurations. The strength of my work is the use of reaching movements in different directions (using a joystick) such that the dissimilarity between their neural correlates could be quantified. I show that the spatial patterns of activation elicited by different movements change gradually as the angular difference between the movements increases. This allows us to draw conclusions about the likely functional organization of neurons in human M1, given certain assumptions about the response of single
neurons to reaching movements in different directions from previous monkey studies (Georgopoulos et al., 1982).

In the third study I focus on finding evidence for repetition suppression (RS) in macaque M1. This effect that has previously been shown in fMRI studies in humans, and has become one of the most widely used techniques to indirectly infer the neuronal properties of the studied area (Tootell et al., 1998; Grill-Spector and Malach, 2001; Avidan et al., 2002). My motivation was to establish this phenomenon in the motor cortex, and to examine its neuronal mechanism, which is unclear at this point in time. However, I did not succeed in finding neuronal evidence for the RS phenomenon in monkey M1. RS has been shown in electrophysiological recordings from monkeys in visual areas in response to repeated visual stimuli (e.g., De Baene and Vogels, 2010). It is possible that designing the task differently, placing trials in pairs (an adapter trial followed by a repeated or non-repeated test trial) rather than in a semi-random order would change our results by allowing averaging over a larger number of repeated trials and by better controlling the time interval before the test trials while allowing a longer rest before adapter trials. However, it is also possible that the relation between the BOLD signal and single-unit activity is not as generally assumed.

**Is RS a bottom-up or a top-down phenomenon?**

The origin of RS has recently been under debate. Does RS reflect an automatic process in the brain, or does it reflect expectation of the coming trial? Several years ago Summerfield and colleagues (2008) showed that the RS in the fusiform face area is affected by the likelihood of the specific face stimulus to appear. They found much weaker RS when the specific stimulus was improbable (i.e., unexpected). This contradicts models of automatic processes previously suggested to explain RS, such as synaptic fatigue or sharpening of the tuning curves, and implies that the RS phenomenon reflects a top-down perceptual “prediction error”. Their results were later confirmed by Larsson and Smith (2012), who also found that the expectation effect is attention dependent. By diverting subjects’ attention, they showed that RS still exists in the absence of the expectation effect. These results suggest that fMRI RS reflects a combination of attention-dependent expectation effects and neuronal adaptation.
When the effect of expectation was tested on macaque inferior temporal (IT) neurons, no expectation effect was found (Kaliukhovich and Vogels, 2011). This could be explained by the effect being exclusive to the FFA. Alternatively, this could strengthen our hypothesis, that the fMRI RS is essentially different from the adaptation found in single neurons in the visual stream. If we try to interpret these results in ‘motor’ terms, it is possible that there needs to be a learning process in order to exhibit RS, in an analogy to the effect reported by Paz and colleagues (2003). They had monkeys repeat a movement to the same direction under a novel visuomotor rotation for an entire learning block. In response, they found sharpening of tuning curves in neurons with PDs close to the learned direction. This sharpening was not found when the monkey merely repeated the same movement with standard mapping, and no learning was required.

**RS in human and in monkey**

In a study by Sawamura and colleagues (2005), fMRI RS has been shown to be very similar in humans and in awake monkeys, in homologous areas lateral occipital complex and IT, respectively, using the same experimental paradigms. Later, Sawamura et al (2006) recorded from IT neurons in one of the monkeys from the fMRI experiment (thus ensuring that the single-cell recording was done from the same region that exhibited fMRI RS), and found RS in the firing rate of single neurons as well. However, the stimulus selectivity of the RS effect was different from the selectivity of the neurons’ response, contradicting the claim that fMRI RS directly reflects neuronal properties. In light of these studies, the difference I found between the human fMRI results and the monkey electrophysiological results was more likely due to the different methods of data acquisition rather than the different species.

**FMRI techniques and their relation to neuronal activity**

Many fMRI studies done on humans in the past couple of decades are in agreement with parallel electrophysiological studies, but in the large majority of fMRI studies, the goal was to show that regions of at least dozens of voxels are activated in response to certain stimuli (or movements), using a block design (i.e., coarse-scale mapping). Trying to research the human brain at a finer spatial resolution (using MVPA and RS, for example) and at a finer temporal resolution (fast event related designs) is a much less explored territory (although these methods have become
Directional selectivity and functional organization in other areas of the brain

In the first study, I showed that M1 voxels are directionally selective. However, I have found additional directionally selective areas, such as PMd and SMA (although to a lesser extent; data not shown). Fabbri and colleagues (2010) have also found directional selectivity in other areas besides M1; including PMd, intraparietal sulcus (IPS) and the parietal reach region (PRR). This raises questions regarding the interpretation of functional organization. Are other frontal and parietal areas organized in the same way as M1? Directional tuning has been shown in electrophysiological studies for neurons in PMd (Caminiti et al., 1991), PMv (Kakei et al., 2001), cerebellum (Fortier et al., 1989) and area 5 (Kalaska et al., 1983). There is also some evidence towards functional organization according to direction in PM (Stark et al., 2007). Perhaps this directional selectivity is found in different areas for different reasons. Neurons could be organized according to visual elements in parietal cortex, changing gradually into a motor representation in the frontal cortex. I attempted to answer this question in my second study by dissociating the visual and motor elements of the reaching task, utilizing the advantage of scanning the whole brain, rather than just M1. However, I found no significant motor or visual correlations for any area besides M1, despite a general trend we found in PMd, the cerebellum and SMA. The statistical tests we used were extremely stringent and activation was not as strong as in M1. It's possible that if instead of using fine joystick movement, we had used a manipulandum typically used by the monkeys, or a motion-capture system, it would result in a much more robust signal in areas beyond M1. A larger pool of subjects could have also given us a clearer picture about other areas, perhaps a gradient of visual vs. motor representation. Additionally, allowing extensive practice before the scan, thereby reducing the directional errors, would help us achieve a better separation between visual and motor representations. Note that we are not claiming that there is a stronger visual representation in M1 than in PM. The observation of cursor motion resulted in no response. Our correlation analysis can produce significant results
only if the BOLD response is strong enough, which occurred only during movement. Therefore, we cannot compare the visual and motor components of the different areas.

Functional Organization of Neurons in M1

In the first chapter I show that there is a functional organization according to movement direction by showing that voxels respond differentially to movement direction. In the second chapter, this differential response is shown to be related both to movement and to visual aspects.

Shen and Alexander (Shen and Alexander, 1997) showed that the same neurons can be sensitive to the target at first, while preparing for movement, and then, during movement, become more sensitive to movement direction. Based on these results, since we did not separate the different trial epochs, we would expect a large overlap between the visual and the motor preferences within a voxels. However, the overlap was no larger than expected by chance. The lack of a subset of voxels that is informative about both visual and motor aspects also indicates that the visually-selective and motor-selective neurons with the same directional preference are not in the same cluster. Alternatively, if we imagine two separate populations of neurons; a visual population (perhaps the more anterior neurons) and a motor population (the posterior neurons?), we would expect two mutually exclusive groups of voxels. This option is also ruled out by our results.

Since visual and motor groups of voxels were found to be independent (i.e., movement selectivity of a voxel does not affect its probability to be visually-selective), the question of how the clusters of the two modalities are spatially organized remains open. One possible explanation is that the visually-selective neurons are at different cortical layers than the motor-selective neurons, with each layer organized separately and independently. An alternative explanation is that clusters of visually-selective neurons and of motor-selective neurons are interleaved within a voxel. In this case, each voxel contains both visual and motor clusters. A voxel that is sensitive to movement more than to visual aspects, for example, simply has more movement-selective clusters. More research at the neuronal level is required to further address this question.
Another issue regarding functional organization is that at a very macroscopic level (cm) M1 is organized according to body parts (Penfield and Boldrey, 1937; Woolsey et al., 1952). Within the arm area, despite extensive overlap (Fetz and Cheney, 1980; Cheney and Fetz, 1985; Cheney et al., 1985; Buys et al., 1986; Lemon et al., 1986; Fetz et al., 1989; Schieber and Hibbard, 1993 etc.), there is an organization according to fingers (Penfield and Rasmussen, 1950) and joints (Murphy et al., 1978). How does this organization coincide with that according to movement direction? Is M1 organized according to movement direction outside the arm area as well? Furthermore, directionally tuned neurons were shown to change their PD while arm movements in the same direction were made in different parts of extrapersonal space (Caminiti et al., 1990), with different arm postures (Scott and Kalaska, 1995, 1997) and in different locations in the workspace (Sergio and Kalaska, 1997, 2003). If neurons can change their PD under different conditions, this might not be a basic property of the neurons. Does the entire cluster shift its PD? How does this affect the organization? These questions remain to be answered.

**Visual Representation in M1**

In chapter 2 of the results we found a significant visual representation of the direction of motion, which is in agreement with previous electrophysiological studies (Alexander and Crutcher, 1990; Crutcher and Alexander, 1990; Hocherman and Wise, 1991; Lurito et al., 1991; Riehle et al., 1994; Shen and Alexander, 1997). No activation was found in M1, however, when the task required observation only even though the visual parameters were exactly the same as in the movement task. Our results are in contradiction with many electrophysiological studies in monkeys (Merchant et al., 2001; Musallam et al., 2004; Wahnoun et al., 2004; Santhanam et al., 2006; Wahnoun et al., 2006; Velliste et al., 2008; Suminski et al., 2009; Dushanova and Donoghue, 2010) and in humans with tetraplegia (Hochberg et al., 2006; Truccolo et al., 2008), who did find observation-related activity in M1. Observation-related activity in M1 was also found using TMS when it was associated with action (Petroni et al., 2010). It's likely that the fMRI signal in an event-related design is too noisy to detect neuronal features that are seen in a minority of the neuronal population, or perhaps the task given to the participants during the observation task in order to keep them alert interrupted the association of the observed cursor motion with hand movements.
Nevertheless, despite the lack of representation of observing cursor motion in M1, we are still able to detect a correlate of target direction and/or cursor feedback. Thus, it is possible that what we term "visual representation" is in fact a correlate of a higher order representation, beyond simple observation. It could be related to gouging the error signal based on the visual feedback, used to make online corrections and to make a more accurate movement in the next trials. This possibility is in agreement with an fMRI study by Diedrichsen et al. (2005), that showed strong M1 activation in response to both target errors (unpredictable changes in target location) and execution errors (when prisms alter visual feedback or a force field alters limb dynamics). Alternatively, the visual representation could stem from the representation of the goal of the task in more general terms, namely to bring the cursor to the target by a hand movement in a different direction. This possibility is consistent with several studies in monkeys that found M1 neurons sensitive to visual features of the cue (Zhang et al., 1997b; Salinas and Romo, 1998; Zach et al., 2008; Saleh et al., 2010) and with an fMRI study that found stronger M1 BOLD activation when target distractors were present in a reach-to-grasp task (Chapman et al., 2007). Thus, M1 seems to be involved in initial stages of movement planning.

As mentioned in chapter 2 of the results, it's also possible that the "visual representation" is actually a representation of the baseline (unperturbed) mapping. If this is indeed the case, then during the rotation run, the participant is making movements according to the novel mapping, which would lead to "movement representation", while at the same time not fully suppressing the previous mapping. This, in turn, would lead to lower, yet possibly significant, correlations between the same target in the baseline and the rotation runs. Retention of the previous motor programs has been shown in previous studies (Hadipour-Nikitarash et al., 2007; Galea et al., 2011).

**Future Directions**

- It would be interesting to see whether the visual representation in M1 would translate into a cue in a different modality, such as a sensory or an auditory cue. This might also help distinguish between the cue and the visual feedback, and provide a more conclusive answer as to which of them is responsible for the visual representation in M1.
In the discussion of the second chapter of the results, we bring up the possibility that our results of a visual representation could in fact be a representation of novel mapping (rotation) overriding the baseline mapping. In this case, the visual correlations we found could actually stem from the underlying unexecuted motor program that is activated when the cue is presented. This interpretation can be better accounted for in a task that is not fast event-related, with longer trials. We could dissociate the planning from the final stages of the reaching movement, where subjects are mostly fine tuning to accurately reach the target. Such an experiment could also answer questions regarding the visuomotor transformation throughout the trial. Of course, in this case there would be significantly less trials in each direction, which would require decreasing noise, perhaps by using a motion-capture system, which records the hand movement directly and is more accurate than the MRI-compatible joystick.

Decoding movement direction at a single trial by implementing a classifier - This should be done with a slow event-related design (also using a motion-capture system), where deconvolution is not necessary to extract the activation of each condition, and separation between activations of the different trials is much more straightforward. Successful decoding could bring us closer to a brain-machine interface, which would help predict the intended direction of hand movement of a paralyzed person and translate these intentions into movement of a robotic arm. The advantage is that fMRI is not invasive. However, it would be difficult to translate it into everyday life, since a person has to lie inside a scanner without making any head movements.

It would be advantageous to study RS in single neurons, MUA, LFP and fMRI in macaques that did a task with a clear adapter and test trials, with shorter time intervals before the test trials. Such a task would be the optimal way to compare the results with previous visual adaptation studies. In addition, the LFP analysis was done only at the time domain. De Baene and Vogels (2010) found no significant RS in IT in the time domain, while they did find RS at the gamma range in the frequency domain. It remains to be seen whether there is RS at the gamma domain in M1.

Last, we can test whether there is more suppression of the fMRI signal in response to novel movements. For example, we can have subjects practice movements only to horizontal directions, and then see if there is a difference in RS to horizontal and to
vertical movements. Alternatively, we could look at more complex movements, by having subjects practice specific sequences of several reaching movements in a row, and then see whether there is more RS to novel sequences than to the practiced ones.
References


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Supplementary Data for Results I
Supplementary figure 1: Preferred direction maps of 2 independent datasets. Colors denote the preferred direction of the voxels according to the arrows on the left. Black outline denotes significant voxels according to CV analysis. These maps are taken from the axial plane (talairach coordinates: z=50) from participant KN.
Supplementary figure 2: Correlation Coefficients (CC) between patterns are not directionally tuned for data preserving only the global bias towards one direction over others. Left: CCs of different movements for real data (dashed line) and for simulated data with mean and SD of real data for each direction (solid line). Right: zoom of the simulated data.
Supplementary figure 3: Histogram of the P values of Coefficients of Variation across all M1 voxels (of all participants). The distribution of p-values across voxels is skewed to lower values from that expected by chance.

Supplementary table 1: Significant voxels for each subject

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ארגון פונקציונלי בקליפה המוח המוטורית

היבר לשמ כלבה תואר דוקטור לפילוסופיה

מאית

ميיל אייזנברג

הוגש לסמ האוניברסיטה העברית בירושלים

אפריל 2012
עבודה זו נועשת בהדרכתם של

פרופ' אהוד זהרי

פרופ' אילון עדיה
קובץ האחטוגים היהב של תנועה חוסпал במחומ של קופים מקיקים (Macaque מוקדדי פרוטומיר שווי שמות, M1) ובמגמות בר. נמצאו י SWTם בעבירי חומת התנועה החשנתית האורונית (MT) וממקדי פורטיפיילוואר, (M1) נמצאו מתכננים ובמקודם חסמות חום שיאת תורחורים, מבינים צוים חסמות. לאחרים, היהים של תנועות חסמות קופים ובמקודם חסות שיאת תורחורים, (MT) ממקדי פורטיפיילוואר (MT) גלול אלקטרופיזיולוגיים (M1) חסונות הנוכחות הפוטויתית (fMRI) בהחמט המגמות הפוטויתיות MEG) ב-M1, מחזות למל言い, תורחבי בבועדו, וז אטריים חסמות חום השוכנה חום.

כבר חשוב主题ע fMRI, fMRI יושרע על עפרות אלקטרויזיילוגיה בקוף המחומ קיבודיבה בד אודם

היא ברשות h 60 של המחומ הקודמות שהתחית ב-M1, מוקדדי פורטיפיילווארי הפוטויתיות הפוטויתיות: ב-M1 מוקדדי פורטיפיילווארי הפוטויתיות הפוטויתיות: ב-M1, מחזות למל言い, תורחבי בבועדו, וז אטריים חסמות חום השוכנה חום.

לפיир, השаютות הפוטויתית של אימים מעריך ב fMRI דירוג fMRI, fMRI המריבור שהתחית ב-M1, מוקדדי פורטיפיילווארי הפוטויתיות הפוטויתיות: ב-M1, מחזות למל言い, תורחבי בבועדו, וז אטריים חסמות חום השוכנה חום.

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לאור תוצאות אלו, נשאלת השאלה האם ניתן להבחין ברקבי הראיות של המשימה. אם אפשר להזיהות מדדים שונים של התנועה, המק枣庄ין בין רכיבי תנועת היד לבין הרכיבים הראויים של המשימה. האם היצוג הכיווניות הוא אכן ייצוג של תנועת היד, או שמא ישנו ייצוג של רכיבים אחרים, כדוגמת מיקום המטרה או תנועת הסמן על המסך? כדי לענות על שאלה זו הרציתי ניסוי נוסף עם שני חלקים.

החלק הראשון היה בדיוק כמו הניסוי שתואר לעיל. בחלק השני עם זאת, הסמן סובב ב-54 מעלות ביחס ל-design. סיבוב זה אפשר הפרדה בין הרכיבים התנועתיים והראויים של המשימה, מכיוון שהמק componentWillMountי דומה בשני חלקים של הניסוי, תנועה היד שונה ב-54 מעלות, וכשしょう תנועה היא לאותו כיוון בשני החלקים, מיקום המטרה שונה ב-54 מעלות. השתמשתי באות פירוטות בה השתמשתי בניסוי הקודם, אלא ש כאן חישבתי בנפרד את המתאם בין מיקומי מטרה שונים ובין כיווני תנועה שונים. המתאם ב-M1 היה סינרגיニック בשני המקרים.

בעקבות תוצאה זו הרצתי ניסוי נוסף בו נבדקים התבקשו לצפות בסמן נע על המסך לעבר המטרות השונות, כך שהאלמנט הראויי נותר כמוfäll, אך הסמן לא נשלט על ידי הנבדקים, והנבדקים התבקשו לא להזיז את ידיהם במהלך הניסוי. ניסוי זה נבנה על מנת שנוכל לראות אם האלמנטים הראויים מספיקים ב-M1, ואף למתאם גבוה בין תנועות שלge באותו כיוון. אף אחד מהנבדקים בניסוי זה לא הפגין כל פעילות ב-M1 או מתאם חיובי בין תנועות שלge באותו כיוון. לפיכך, האלמנטים הראויים המקודדים או רכיבים נוספים לוחצים לתנועה של מ-54 מעלות, וכלים נוספים לוחצים לתנועה של M1.

שאלה פתוחה נוספת מהניסוי הראשון נוגעת ל-RS. הסברה הרווחת היא שה-SR משקף תכונות של תאי עצב. בניסוחים אחרים, וב-return של המוח שהוא תאי עצביםivid, כדי על מ-54大學, וה-SR משקף תכונות של תאי עצביםivid, ואלא שלבר ה-SR מתראות Gus רם ש-SR ממוקד וה-SR משקף תכונות של תאי עצביםivid, בין חזרתיות של תאי עצבים. המדידה נוספת,_vid מסקפת התמונות של לחץ עצב,