Reviews/Mini-Reviews

Novel imaging techniques to study the functional organization of the human brain

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Abstract

Despite more than a century of investigation into the cortical organization of motor function, the existence of motor somatotopy is still debated. We review functional magnetic resonance imaging (fMRI) studies examining motor somatotopy in the cerebral cortex. In spite of a substantial overlap of representations corresponding to different body parts, especially in non-primary motor cortices, geographic approaches are capable of revealing somatotopic ordering. From the iconic homunculus in the contralateral primary cortex to the subtleties of ipsilateral somatotopy and its relations with lateralization, we outline potential reasons for the lack of segregation between motor representations. Among these are the difficulties in distinguishing activity that arises from multiple muscular effectors, the need for flexible motor control and coordination of complex movements through functional integration and artefacts in fMRI. Methodological advances with regard to the optimization of experimental design and fMRI acquisition protocols as well as improvements in spatial registration of images and indices aiming at the quantification of the degree of segregation between different functional representations are inspected. Additionally, we give some hints as to how the functional organization of motor function might be related to various anatomical landmarks in brain morphometry.

Techniques for in vivo mapping of human brain function

In the last decades, we witnessed a steadily increasing variety of non-invasive techniques for in vivo mapping of human brain function that includes electroencephalography, magnetoencephalography, positron emission tomography, transcranial magnetic stimulation, near-infrared spectroscopy and functional magnetic resonance imaging (fMRI) to name but a few. fMRI, the topic of this review, takes advantage of the relationship between blood flow and local neuronal activity – that is, neurovascular coupling to measure blood-oxygen-level-dependent (BOLD) contrast and indirectly infer regional metabolism changes in the brain.[1,2] Our current understanding of the physiological basis of the BOLD contrast is that the signal changes are mainly driven by the oxygen consumption rate in addition to activity-dependent modulation of cerebral blood flow and volume. fMRI has the advantage of capturing neural activity with sufficient anatomical precision over the entire brain. The most widely used spatial resolution ranges between 1.5 and 3 mm, which can be further optimized

to submillimetre measurements using ultra-high field MRI scanner.[3–5] The disadvantage of fMRI, however, is its poor temporal resolution limited to the range of seconds, which poses specific challenges to experimental design and task-related manipulations.[6,7]

Preceding the statistical analysis of fMRI data from a single subject or a group of participants, the images are subjected to standardized processing steps aiming at spatial alignment within and across subject(s) over the entire duration of the experiment. Group studies require additionally

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the spatial transformation of data in standardized space, allowing to perform statistical analysis at the voxel level.[8] The sophistication of statistical analysis using mass-univariate or multivariate approaches ranges from implementations of the general linear model while taking into account the spatio-temporal features of the BOLD signal to sophisticated computational modelling or machine learning methods.[9]

Basic principles of functional organization

In the following section, we discuss the basic principles of the functional organization of the brain on the example of its topographical organization. The concept of topographic maps of perceptive or executive functions is based on the principle that information coming from spatially or temporally adjacent points of the perceived stimulus is represented within similar anatomic locations in the brain – for example, neighbouring components of the visual field for retinotopy, cluster of hair cells in the cochlea for tonotopy, set of skin receptors for sensory somatotopy or group of muscles for motor somatotopy.[10] This spatial correspondence forms the basis of our notion of structure-function mapping in the brain.[11,12] The maps have to comply with certain principles of organization such that the spatial dimensions of distribution in the periphery are adequately represented along the corresponding anatomical dimension of the brain.

The homunculus

The pattern of anatomical distribution of sensorimotor somatotopy on the brain surface is often depicted graphically using a homunculus (Figure 1). The evidently disproportional features of the homunculus stem from the fact that the spatial representation of certain body parts, for example, the lips, are overrepresented in the brain in comparison with other body parts. In the context of in vivo imaging of brain functions using fMRI, the obtained somatotopy maps show a continuum of neural representations rather than clear-cut borders, a phenomenon which is further modulated by individual cortical anatomy.[13–18] In general, the deviations in motor somatotopy can be grouped based on two main principles: (i) the first sees the overlap of different motor representations, which is a violation of an idealistic somatotopy corresponding to a one-to-one mapping and (ii) the second considers an abnormal spatial ordering as a desecration that discredits an alleged somatotopy or that the division of the mapping of one body part into multiple representations is an infringement of a strictly ordered somatotopy.

Somatotopy maps

With further sophistication of mapping techniques, imaging research has generated somatotopy maps with high
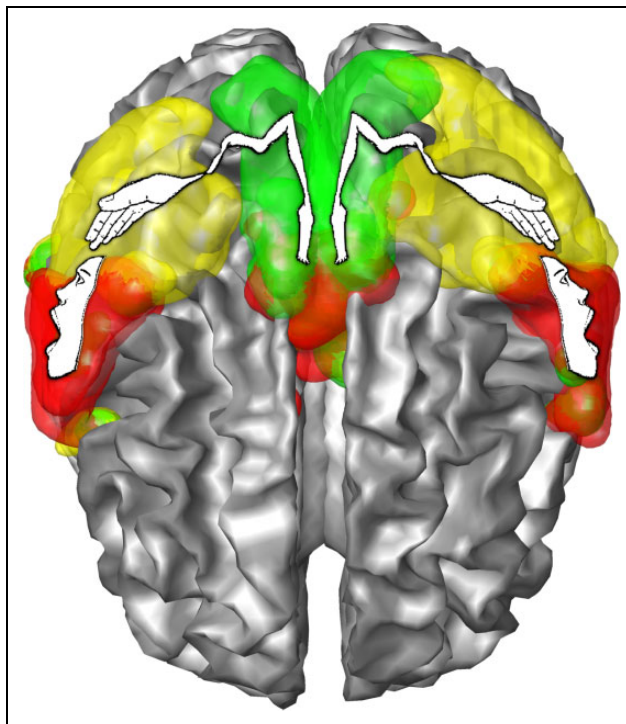

Figure 1. Illustration of motor somatotopy obtained using functional MRI, together with representations of the homunculus in each hemisphere. Brain activity elicited during movements of the toes (green), fingers (yellow) and facial musculature (red) is rendered using a group analysis in the whole brain. Note the brain activity in the supplementary motor area visible in between the two hemispheres. MRI: magnetic resonance imaging.

level of spatial precision referred to as between- and within-limb somatotopy that can include relatively proximal or distal body parts. Indeed, the majority of fMRI studies were able to demonstrate an unambiguous motor somatotopy in the primary motor cortex (M1), whereas non-primary motor areas such as the supplementary motor area (SMA) are associated with more complex patterns of somatotopy. Another aspect along these lines is the existing controversy between the concept of a discrete somatotopy exemplified by the homunculus[19] or simiusculus[20,21] and the more relaxed definition of somatotopy allowing the coexistence of segregated and overlapping representations of body parts. This discrepancy has led to question the existence of motor somatotopy.[20,22] Conclusions regarding the existence of somatotopy of finger or joints of the same limb are particularly conflicting. Some studies propose a more relaxed definition of somatotopy organized in terms of gradients or response predominance. Moreover, somatotopic organization of motor responses seems to be influenced by other factors, such as proximity required for coordination of movements during complex tasks.[23] Below we review studies that aimed at investigating motor somatotopy, mainly in the cerebral cortex using task-based fMRI of voluntary overt movements in healthy human subjects.

The iconic contralateral motor somatotopy and its subtleties

In the contralateral M1, most fMRI studies argue in favour of inter-limb somatotopic organization.[13,15,23–29] Within-limb somatotopy has been much more debated and though some studies argue against it,[17,26] others show evidence attesting its presence.[13,15,18,23,25,27,29,30] However, these studies commonly highlight the fact that motor somatotopy was less clear-cut for within-limb than for between-limb representations. Finger somatotopy is a particular case of within-limb somatotopy, as results of fMRI experiments are even more controversial. Although there are several reports claiming the existence of digit somatotopy,[15,29,31–34] there exists a substantial body of literature sharing a suspicious view of it.[17,35,36] Finally, specific studies focused on speech somatotopy and suggested that substrates supporting specific sets of muscles involved in language production are distributed over specific portions of M1.[37–40] In this case, some representations seem to be relatively well separated, such as the tongue, the lip, the jaw and laryngeal muscles that are essential for phonation,[38,40] whereas others seem to co-localize, such as the muscles necessary for the ab-/adduction and the tension/relaxation of vocal folds.[38] Furthermore, Belyk and Brown[37] show that extrinsic (respectively intrinsic) laryngeal muscles, which allow vertical (resp. horizontal) movements of the main vocalization organ, are located in more ventral (resp. dorsal) portions of the sensorimotor cortex.

Ipsilateral somatotopy in M1 and brain laterality

Motor somatotopy in the ipsilateral M1 is an even more contentious topic and has been reported as being less clear-cut as compared to its contralateral correspondent.[24,35,36] Likewise, it has been shown that finger somatotopic representations were easier to predict in the contralateral than in the ipsilateral sensorimotor cortex.[33] Furthermore, the centres of gravity were more anterior in the ipsilateral M1 as compared to the contralateral counterpart although the representations were highly similar.[33] Interestingly, during bimanual finger presses, these ipsilateral representations vanished.[33] The relationship between motor somatotopy and brain laterality has been examined.[33,41,42] Kapreli et al.[41] and Luft et al.[42] showed that the SMA and M1 were differentially involved in upper and lower limb movements and that some movements were more lateralized than others.

Motor and somatosensory somatotopy

The exclusion of motor performance and sensory stimulation is particularly difficult as movements often evoke activity in the primary somatosensory cortex (S1). Whether this phenomenon is linked to horizontal connections between regions in the cortex responsible for, for example, grasping behaviour, to simultaneous tactile stimulations or to information processing linked with proprioception remains open for discussion. For example, Kleinschmidt et al.[15] performed somatosensory control experiments to exclude the possibility of fMRI being incapable of determining different activation foci. Indeed S1 is known to unveil a more segregated somatotopy than M1, as shown in subsequent fMRI experiments, which explicitly compared M1 and S1 somatotopy.[23,31,34] In contrast to M1, finger representations were shown to be associated with more posterior locations in the ipsilateral as compared to the contralateral S1.[33]

Somatotopy in other cortical structures

Somatotopy in the SMA is thought to be constituted of more overlapping representations in comparison to those in M1.[18,35] Ipsilateral somatotopy is still more integrated than the contralateral equivalent.[35] In contrast to within-limb and finger somatotopy, between-limb somatotopy appears to be present in the SMA and other non-primary motor areas such as the cingulate motor area.[28,43,44] Somatotopy representations are more mixed in the SMA as compared to S1.[23] Conversely, it has been reported that other non-primary motor areas, such as the premotor cortex, present more segregated representations than M1, at least when the motor task performed by the volunteers requires cognitive operations, such as reaching complex targets with flexion of the ankle, elbow and index finger.[23] In the aforementioned study, superior and inferior parietal lobules were also shown to exhibit a motor somatotopy. Multisensory maps can likewise be elicited in parietal areas of the cortex, which seem to be the site of high-level integration between retinotopic and somatosensory maps.[45,46] Somatotopy during movements has also been shown in the insula.[47] Again, one has to bear in mind that induction of concomitant sensory stimulation is usually inevitable during motor tasks.

The possible reasons for the overlap

The substantial overlap between representations has led some researchers to argue against the existence of motor somatotopy. Others propose a more relaxed definition for motor somatotopy, which rather than being discrete is constituted by a combination of overlap and discrete centres or gradients of neuronal response predominance, allowing for flexible motor control and coordination of joints during complex movements.[17,20,22,30,32,35,48,49]

Co-activation of muscle effectors. The lack of motor somatotopy has also been considered as a methodological issue arising from the co-activation of multiple muscle effectors, even during the simplest motor tasks.[13,23,25,41,50] It has been argued that the effort required to restrain movements to a specific body part would require the involvement of

even more muscle effectors.[17,20] For example, moving only the middle finger requires simultaneous efforts not to move the other fingers. Technical developments such as electromyography (EMG) during fMRI acquisition[23,41,50] or the design of adaptable splints to restrain unwanted movements[13,25] have been used to partially solve this issue. Finger somatotopy constitutes a special case, as finger presses can be easily recorded with commercial response boxes or customized keyboards.[33] Nonetheless, Ejaz et al.[14] showed that the correlational structure of finger representations in M1 was only partially predicted by muscle activity as recorded using EMG and that quotidian finger muscle usage was a better predictor of the functional organization of fingers in M1. The quest for control of movements is particularly a challenge in speech somatotopy studies. Indeed Belyk and Brown[37] attempted to dissociate vertical and horizontal movements of the larynx, which are, in principle, controlled by extrinsic and intrinsic laryngeal muscles, respectively. Participants needed to be trained before scanning to execute the movements appropriately, and researchers checked for the absence of subvocalization or concomitant movements of the tongue or jaws.

Motor somatotopy and artefacts in fMRI. Increased distortions of the magnetic field due to the movements of face and neck muscles and head motion during scanning are major concerns that drove some research on the optimal fMRI acquisition protocols[51] or the use of sparse temporal sampling techniques.[40] It has to be mentioned that even movements of the limbs, especially proximal body parts, can substantially corrupt the interpretation of fMRI results. Realignment parameters computed during spatial registration of fMRI data are therefore usually reported in fMRI studies, especially in fMRI studies of motor function. Alternatives, such as passive movements, have been proposed in order to reduce the participant's head motion.[52]

Spatial ordering of motor function

The issue of somatotopic order, sometimes referred to as orderly somatotopy, is also a source of controversy. Depending on the region of interest, several axes potentially enable the separation of body part representations. One can identify the dorsoventral axis, which segregates the representation of fingers in S1[34] as well as the knees and toes in the sensorimotor cortex.[25] It also separates the lip, tongue and jaws in M1[40] together with the mediolateral axis. The latter dissociates the representations of the knee, toes and ankle. Together with the rostro-caudal axis, it also separates the fingers and lower limb representations in the primary sensory and motor cortices.[25,34] Nevertheless, Meier et al.[27] revealed that the hand and arm representations in contralateral M1 violate the orthodox somatotopic ordering along the superior–inferior direction by presenting a core and surround organization, with the activity clusters corresponding to the arm and wrist

bracketing the finger. This double representation was confirmed by Strother et al.,[18] although their results indicate that the representations of fingers, wrist and elbow differ at least on one dimension in the SMA. The orthonormal bases represented by x-, y- and z-dimensions in the Montreal Neurological Institute (MNI) space can therefore shed light on the topographical organization of motor function and give clues about the relevance of each axis for different brain regions.

Spatial registration for the improvement of motor somatotopy mapping

Considering the conformation of the cortical sheet, the three dimensions mentioned above might not be appropriate when studying spatial organization of functions, especially when the functional representations are close to major cortical gyri and sulci. Methods performing unfolding and flattening of the cortical sheet allow for the projection of functional representations into a 2D space where the significance of topographical organization can be revealed more accurately.[14,18,25–27,32,33] This procedure can improve not only the visualization of topography but also the calculation of distances between activation sites.

Quantification of segregation

The disagreements regarding the existence of within-limb motor somatotopy relate to the as yet unresolved issue of segregated or overlapping representations. Some studies explicitly tested for the degree of segregation using metrics such as Euclidean distances between activation maxima or centres of gravity.[13,18,23,24,26,30–32,34,35,40] Centres of gravity were sometimes weighted by the strength of the BOLD contrast at each coordinate,[34] and other methods, such as selectivity indices, were also developed.[36] Generally speaking, the overlap between representations was frequently found to be significant, while geographic approaches, which used distance metrics, were able to reveal somatotopic order and segregation.[13,15,18,23–27,30,31,34,35] This was especially true for within-limb and finger somatotopy, where subtractive approaches, which contrast each movement against all other movements rather than against motor rest conditions, helped to reveal somatotopic patterns when combined with geographic procedures.[15,32,36] Excluding voxels corresponding to representation overlap also improved the separation of motor somatotopy activity patterns.[30,31] Recent studies employed more advanced methods to investigate the predictability and dissimilarity of representations of motor somatotopy such as classification and similarity analyses.[14,29,33,47,53]

Design of experiments for the improvement of motor somatotopy mapping

Instead of focusing on post-processing methods enabling the measure of topography, other studies concentrated on

the improvement of the experimental design of the fMRI paradigm.[29,36] Somatotopic gradients were revealed across an impressive set of body parts in Zeharia et al.[29] but geographic coordinates of peaks or centres of gravity were not explicitly tested, although BOLD activation varied along different portions of the SMA and M1 in a continuous fashion. Additionally, the authors reported the presence of a negative BOLD homunculus in M1, suggesting that where the BOLD response increases for a specific body part, the activity decreases for other body parts. Nevertheless, the explanation that their design induced temporal contamination from one trial to the next cannot be fully rejected, even if the slow event-related design, comprising 9-s epochs, revealed negative correlations. Indeed, it has been shown that the hemodynamic response function can last more than 9 s.[54] Moreover, Olman et al.[36] demonstrated that, in contrast to retinotopic experiments, sequential designs are less well suited to motor somatotopy mapping, which is possibly linked to the predictability of the upcoming movement. Random-order designs provide more even distributions of activations for finger movements.

Motor somatotopy and its prediction by anatomical landmarks

Anatomical landmarks have been proposed to predict the topography of motor functions. For example, the 'hand knob' is renowned to encompass activity related to fist movement in M1[55] and was used as a boundary for data acquisition and analyses in the study conducted by Dechent and Frahm.[32] Other studies have explicitly considered the links between brain structure and function; for instance, Chainay et al.[43] found that the paracentral sulcus may be considered as an anatomical landmark of limb representation in the SMA. The location of fingers, elbow and wrist representations seems to be well predicted by the hand knob.[18] Ejaz et al.[14] recently demonstrated that everyday hand usage reliably predicts the correlational structure of finger representations in M1 and S1. This correlational structure was stable in time although substantial variability between individuals was observed. The study also showed that this similarity between representations is not necessarily linked to the position of activation clusters along the cortical sheet.

Conclusion and perspectives

We showed that the overlap between body representations was substantial, especially in non-primary motor cortices. However, geographic approaches were able to reveal somatotopic ordering. From contralateral motor cortex somatotopy, which matches the iconic homunculus relatively well, to the subtleties of ipsilateral somatotopy and its relation to brain laterality, we overviewed potential reasons explaining the lack of separation between representations, including the lack of separability of muscular effectors,

integration for flexible motor control and coordination for complex movements and artefacts in fMRI. Methodological developments in terms of the design of experimental paradigms, MR acquisition, spatial registration and the quantification of the degree of segregation between different functional representations were emphasized. Finally, we provided some clues as to how functional organization of motor function might be predicted by anatomical landmarks. This approach requires highly accurate spatial registration algorithms which make use of nonlinear transformations to a 3D standardized space or the projection to a flattened 2D representation to escape inter-individual variability in cortical folding. However, inter-individual variability in the organization of functional representations persists,[14] and we highlighted the advantages of more recent methods provided by similarity analyses, classification schemes and other multivariate analyses in combination with mass-univariate analyses. For example, repeated-measures multivariate analysis of variance could be used to assess segregation of functions along a linear combination of stereotaxic dimensions. The latter suggestion could be particularly interesting when multiple dimensions yield contradictory results among different subjects. Here, surface-based methods represent a major development in the study of spatial distribution of activation sites as they make the use of Euclidean distances more valid. However, the latter method is limited to the investigation of cortical structures.

Biomechanical and postural constraints were proposed as a mechanism preventing the existence – or the assessment – of a discrete somatotopy. Self-organizing maps were shown to be effective in reconstructing the observed motor somatotopy maps and explaining their discrepancy with the predicted discrete homunculus by the multiple constraints in play, such as the relevance of movements in an ethological context and coordination of movements for complex actions.[56–58] The aforementioned hypotheses might also explain why motor somatotopy represents a more integrated case of topography as compared to retinotopy and somatosensory somatotopy. Geographic approaches, which consider the location of representations in the 3D space, remain the most commonly used technique to assess the segregation of functional representations, and several limitations need to be mentioned regarding these techniques. Estimating centres of gravity requires the thresholding of continuous multivariate spatial processes. The threshold value can vary from one study to another and from one individual subject to another. This procedure has been shown to pose serious issues, for example, in test–retest fMRI studies.[59] The crucial point is that estimating centres at the subject level is the only option for the statistical assessment of spatial organization of functional representations at the group level, but it is exactly at the subject level that the reliability of thresholding is questionable. Activation maxima would in principle eschew this problem but have been found to be more sensitive to noise and less

reliable than centres of gravity.[13,26] Furthermore, activation maxima do not take into account the spatial extent of the activation clusters. The above points explain why recent developments such as multivariate analyses are particularly promising for the evaluation of organization of functions using fMRI.

We mentioned above that methods applying a projection of functional representations onto a surface couldn't be used beyond cortical areas. This point is particularly important as deeper brain nuclei are thought to contain motor somatotopy, although the conclusions from fMRI studies are highly controversial. There is indeed some evidence that the striatum, the pallidum and the thalamus contain a topographic organization of motor function.[47,60–64] While high-resolution fMRI has been suggested as a promising tool in most of fMRI studies of motor somatotopy, deep brain nuclei probably necessitate fMRI especially for small voxel size. However, this has a non-negligible cost in terms of signal to noise ratio. The observation of Meier et al.[27] concerning the variability of the hemodynamic response function across subjects could be extended to deep brain nuclei, which could elicit further variability in the shape of the BOLD response. The investigation of pathological conditions such as movement disorders would probably benefit from methodological advances to map and quantify the organization of motor function in deep brain nuclei. Moreover, the assessment of changes in cortical organization induced by pathological conditions and the follow-up of cortical reorganization are of vital importance for the understanding of the underlying mechanisms of brain disease and recovery. Furthermore, the use of non-invasive methods such as fMRI holds promise as tools for measuring these mappings and building a predictive model of brain function.

Declaration of conflicting interests

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