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Mapping dexterity and handedness: recent insights and future challenges

Andersen, Kasper Winther; Siebner, Hartwig Roman

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Kasper Winther Andersen[1] and Hartwig Roman Siebner[1,2]

Manual ability (dexterity) and hand preference (handedness) are key features of human motor control. Recent magnetic resonance imaging (MRI) studies casted new light on the neural underpinnings of dexterity. In right-handers, MRI identified structural brain features related to the right–left difference in dexterity or skill acquisition. Functional MRI disclosed a hierarchical and modular representation of discrete finger sequences in sensorimotor cortical areas and uncovered representational plasticity of the deprived sensorimotor cortex in congenital one-handers. Functional MRI studies also identified differences in sensorimotor activity and connectivity between right-handers and left-handers. However, these results are inherently ambiguous, because they may reflect a consequence of handedness rather than its underlying cause. We discuss future scientific strategies that might help to resolve this ambiguity.

Addresses
[1] Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
[2] Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark

Corresponding author: Siebner, Hartwig Roman (h.siebner@drcmr.dk)

Introduction

Dexterity refers to the ability to perform skilled hand actions such as using tools with our hands. Dexterous actions rely on finely tuned sequences of synergistic muscle activity which enables us to 'manipulate' our environment with a high degree of flexibility [1]. Dexterous movements are highly automated and over-learned and therefore require only whole-field sensorimotor control rather than close on-line monitoring of every movement detail [2,3]. The high degree of automation renders dexterous movements resistant to the interference of concurrent motor or cognitive tasks [2,3]. Another key feature is that dexterous movements rely on the ability to make independent (non-enslaved) finger movements [4,5]. The fast-conducting monosynaptic connections from M1-HAND to cervical motoneurons are an important anatomical substrate of independent finger movements [6,7]. Both, the right and left M1-HAND, make monosynaptic connections with the cervical motoneurons. Hence, both hands are able to perform dexterous movements, showing similar usage statistics [5].

The strong preference to use one of our hands for manipulative actions is another striking feature of human motor control. In most individuals, a strong preference for one hand over the other can be observed for skilled manual actions such as writing or tooth brushing. This strong preferential bias to act with the right or left hand is called handedness. The vast majority of humans show a strong preference for using the right hand for fine motor skills with the relative frequency of left-handedness varying between 3% and 27% depending on the cultural background [8,9]. This preponderance of right-handed individuals in the general population explains why the word 'dexterity' stems from the Latin word 'dexter' (English: 'right'). Yet, dexterity describes the general ability to act with our hands quickly and skillfully, irrespective of hand preference. Handedness can be quantified using laterality scales, like the Edinburgh Handedness Inventory [9,10]. These scales yield a hand preference score (i.e., laterality index) scaling from strongly left-handed to strongly-right handed (see Figures 1 and 2).

Handedness reflects the habitual preference of acting with one hand; but a strong habitual preference for one hand cannot be equated with a strong asymmetry in dexterity (see Figure 2). Many individuals with a strong right-hand preference may perform a unimanual motor skill equally well with both hands (or even slightly better with the left non-dominant hand) [11]. For instance, a recent study on circle drawing confirmed that the asymmetry in dexterity and handedness for a given skill may substantially vary at the individual level [12•]. In this review, we highlight recent lines of research in which magnetic resonance imaging (MRI) was used to unravel the structural and functional underpinnings of handedness and dexterity in the human brain.

Structural and functional correlates of handedness

The preferred use of the right or left hand for skilled manual actions and its neural correlates continue to be a key area of motor control research. Some studies reported
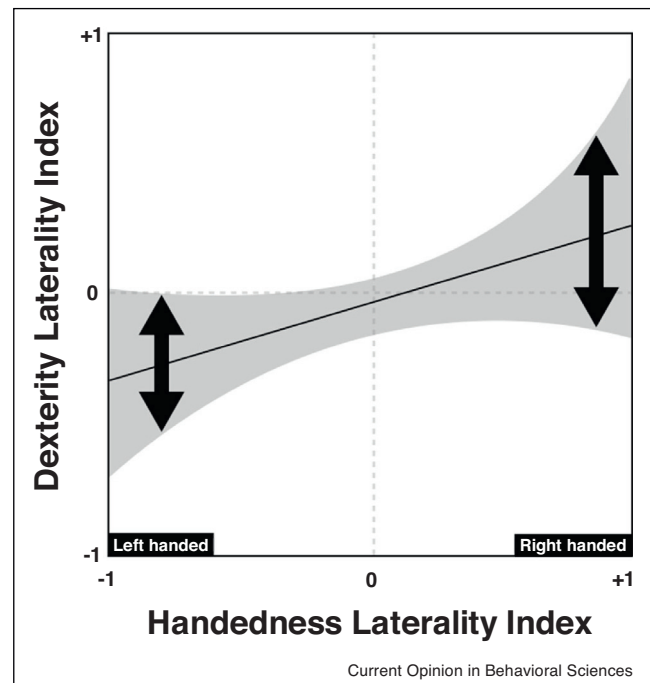
Figure 1
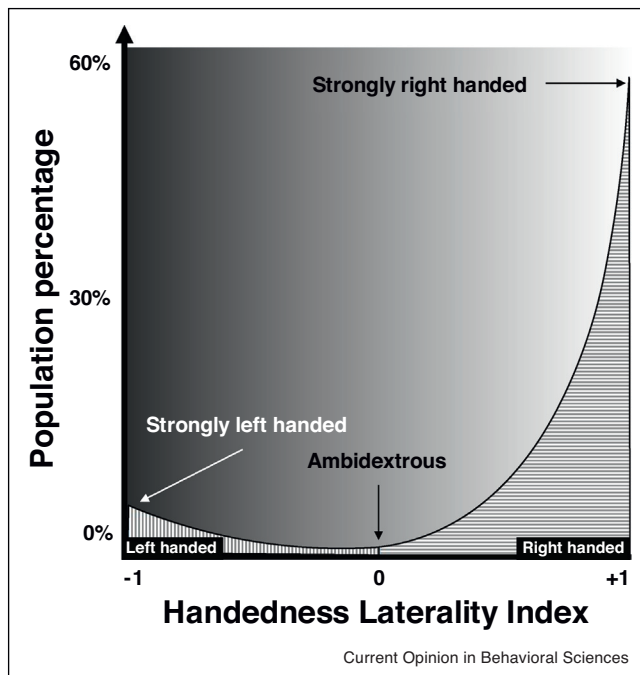
This figure schematically shows the population distribution in handedness laterality index. Overall, about 90% of the world population is believed to be consistent right-handers (positive handedness laterality index scores), with about 60% being strongly right-handed (handedness laterality index close to 1) and about 10% being strongly left-handed (handedness laterality index close to −1). This figure is a schematic representation inspired by Figure 2 in [9].

Figure 2

Relationship between lateralization in handedness and dexterity. It is important to acknowledge that the individually expressed asymmetry in manual motor abilities (dexterity) is related but not identical to asymmetry in preferred hand use (handedness) [11]. Rather than displaying a simple one-to-one mapping, lateralization in dexterity varies substantially in groups with identical levels of hand preference. This figure is a schematic representation inspired by Figure 1 in [11].

associations between gray matter macrostructure and handedness [13–16], while others have not found such associations [17]. The lack of an association between regional gray matter and handedness was recently confirmed in a large structural MRI study [18]. Cortical surface area of regions related to manual motor control, language, or visual processing showed no statistically consistent difference between 1960 right-handers and 106 left-handers [18]. Accordingly, voxel based morphometry showed no asymmetry differences between 30 left-handers and 30 right-handers [19]. Together, these results speak against major differences in gray matter macrostructure related to handedness.

Given the importance of monosynaptic corticospinal connections for independent finger movements [6], a number of MRI studies have related asymmetries in white matter (WM) microstructure with handedness. Of note, the human corticospinal tract (CST) displays a structural asymmetry independent of handedness with higher mean fractional anisotropy (FA) in left versus right CST [20–22]. A recent diffusion tensor imaging (DTI) study examined the topology of left-hemispheric and right-hemispheric WM structural networks in 32 right-handed and 24 left-handed healthy individuals [23]. Graph-theoretical

analyses of the DTI-based tractography data yielded stronger small-world attributes in the right as compared to the left hemisphere [23]. Right-handers but not left-handers showed a significant asymmetry of topological network properties. This discrepancy might be a consequence of life-long preferential use of the right hand rather than a structural trait of handedness. Indeed, a previous MRI-based shape analysis of the central sulcus showed that cortical morphology in adults reflects both, the innate preference of hand use (i.e., nature) as well as early developmental experience (i.e., nurture) [24].

At the functional level, motor areas in the dominant hemisphere might play a more prominent role in the control of hand movements performed with the dominant and non-dominant hand. Several recent studies employed functional magnetic resonance imaging (fMRI), to address the question of how hand preference influences functional interactions among sensorimotor areas. Using dynamic causal modeling, effective connectivity within the motor network was examined during fist closures of the dominant or non-dominant hand in 18 right-handed and 18 left-handed individuals [25]. When performing fist closures with the dominant hand, the contralateral

supplementary motor area (SMA) in the left dominant hemisphere exerted a stronger influence on other cortical and subcortical motor areas in right-handers as compared to left-handers [25]. This effect was not present when moving the non-dominant hand. In the same cohort, resting-state functional connectivity between left M1-HAND and right dorsal premotor cortex was found to be stronger in right-handed relative to left-handed individuals [26].

Handedness-related differences in inter-hemispheric interactions may also be a neural substrate of hand preference. In particular, a functional deactivation of ipsilateral M1-HAND during unilateral finger tapping might differ depending on whether tapping is performed with the dominant or non-dominant hand. In a sample of 142 right-handed and 142 left-handed individuals, the ipsilateral M1-HAND was more strongly deactivated when right-handed subjects tapped with their dominant hand relative to tapping with their non-dominant hand [27]. In contrast, left-handed individuals displayed a similar amount of ipsilateral M1-HAND deactivation for unilateral finger tapping with either hand [27]. Importantly, the amount of deactivation in right M1-HAND scaled proportionally with the right-hand advantage in dexterity. Hence, the reduced functional asymmetry between the dominant and non-dominant hemisphere as well as the reduced inter-hemispheric functional connectivity seen in left-handers compared with right-handers, as discussed in the previous section, may simply reflect a less prominent lateralization of manual abilities.

Even if one assumes that the differences in functional activity and connectivity between consistent right-handers and left-handers are related to handedness rather than dexterity, it still remains unclear whether these differences reflect the primary cause of hand preference or a secondary brain change caused by experience-dependent plasticity due to the life-long preferential use of the right hand in right-handers or left hand in left-handers, respectively.

Some neuroimaging studies included 'forced' right-handers as additional group to disentangle brain correlates related to innate left handedness from use-dependent brain alterations [24,28–30]. These studies show that forcing innate left-handers to become right-handers (at least regarding writing) partly changes brain structure [24,28] and function [29,30]. Forced right-handedness is associated with a smaller volume of the left middle putamen, presumably reflecting increased pruning during motor development [28]. Forced right-handedness resulted in a right–left asymmetry of central sulcus size which is typical of innate right-handers [28]. Measurements of functional activation with fMRI revealed greater movement-related activity in the primary sensorimotor hand area and caudal dorsal premotor cortex of the non-dominant left hemisphere, the more successfully innate left-handers had been switched to right-handedness [29].

Importantly, these studies also identified structural and functional correlates of handedness that were resistant to this early environmental challenge, forcing the use of the right non-dominant hand. The 'hand knob' is a prominent landmark of the hand motor representation in the central sulcus and located more dorsally in the left hemisphere in innate right-handers than in innate left-handers [24]. Forced right-handedness did not shift the hand knob location: left-handed individuals forced to write with the right non-dominant hand show a hand knob location typical for innate left-handers [24]. Evidence for a persistence of left-handedness was also found at the functional level: compared to innate right-handers, functional activation studies showed that 'forced' right-handers continue to recruit higher-order premotor and parietal motor areas in their dominant right hemisphere, when they perform handwriting or simple motor tasks [29,30]. Together, the functional and structural neuroimaging studies on forced right-handedness show that the adult brain holds an accumulated record of both innate biases of preferred hand use (nature) and early developmental experience (nurture).

Bimanual coordination

Dexterity often requires skillful coordination of both hands. For instance, when opening a jar lid, one hand is holding the jar, while the other hand is unscrewing the lid [31]. A recent behavioral study found little or no transfer of acquired skill across unimanual and bimanual sequential finger movements [32], suggesting that motor integration of both hands is represented at a different level of the motor hierarchy than unimanual hand movements.

Inter-hemispheric interactions between sensorimotor areas of both hemispheres are thought to be critical to bimanual coordination. A DTI study showed that the inter-individual variation in bimanual coordination skill correlates with the microstructural properties of the inter-hemispheric pathways connecting the left and right SMA and caudal cingulate motor area [33]. A resection or agenesis of the corpus callosum results in a decoupling of forces and kinematics [34]. Extending these findings, a recent electroencephalography (EEG) study showed a decrease in cortico-cortical coherence between right and left sensorimotor hand areas, when healthy individuals performed a strong bimanual isometric contraction [35]. The decrease in inter-hemispheric coherence was found in the alpha frequency band and was associated with an increase in transcranial inhibition as probed with transcranial magnetic stimulation (TMS).

Another study combined DTI with dual-site TMS to assess how normal aging alters inter-hemispheric

interactions related to bimanual control [36]. The ability to disinhibit projections from the right dorsolateral prefrontal cortex to the contralateral primary motor cortex was reduced in older adults during the preparation of a complex bimanual coordination task. DTI revealed altered microstructural properties in the corresponding transcallosal cortico-cortical tracts as indicated by a regional change in FA. Age-related microstructural changes scaled with the changes in inter-hemispheric prefrontal-premotor interaction as revealed by dual-site TMS as well as with the age-related decline in bimanual performance.

Complementary insights into inter-hemispheric bimanual motor control stem from recent studies on patients. In patients with relapsing-remitting multiple sclerosis and healthy controls, a combined DTI-TMS study showed that the accuracy of out-of-phase bimanual tapping movements correlates with structural and functional measures of inter-hemispheric connectivity between the primary motor hand areas [37]. Reductions in regional FA, as measured with DTI, and inter-hemispheric inhibition, as revealed by dual-site TMS, scaled with reduced temporal accuracy of out-of-phase tapping movements. In another study, resting-state functional connectivity was found to be altered in individuals with congenital mirror movements due to Kallmann Syndrome (KS), a syndrome presenting with hypogonadotropic hypogonadism, hyposmia or anosmia with or without congenital mirror movements [38]. Only KS individuals with congenital mirror movements showed altered spectral patterns of cortico-cortical and subcortico-cortical connectivity within the sensorimotor network.

Sensorimotor representations of dexterity

In recent years, methodological advances have expanded the possibilities of human brain mapping to trace sensorimotor activation patterns during skilled manual motor tasks [39••,40••,41]. The advent of ultra-high field (7 Tesla) MRI has enabled neuroscientists to push the spatial resolution of sensorimotor mapping, zooming in on relevant sensorimotor areas [40••,41]. Concurrently, multivariate pattern analysis (MVPA) has been applied to fMRI data to delineate sensorimotor representations that are distributed over multiple voxels and thus, cannot be captured by standard univariate data analysis at single-voxel level [42,43••,44]. Previously, it was difficult to map synergistic digit representations in humans, but this has recently become feasible by combining fMRI with novel analysis methods [39••,40••].

The sensorimotor system coordinates the spatial and temporal aspects of skilled hand movements. A recent line of research used MVPA to chart cortical representations of discrete sequences of finger movements [42,43••,44]. During fMRI, healthy individuals produced discrete sequences of finger movements that differed in

their temporal (i.e., inter-movement interval) and spatial (i.e., spatial order of finger movements). MVPA identified multi-voxel patterns in cortical areas which coded sequence-specific temporal or spatial features [42,43••,44]. The set of cortical clusters representing temporal aspects of the finger sequence were largely distinct from the set of areas representing the spatial properties with some overlap in premotor cortex and posterior parietal cortex [42,43••,44]. Of note, the hand representation of the contralateral primary motor cortex (M1-HAND) was the only cortical region, where the spatial and temporal features of discrete finger sequences were integrated [42]. In another fMRI study, MVPA identified sequence-specific multi-voxel patterns encoding sequential rhythm and sequential order in multiple fronto-parietal cortical areas, but not in subcortical gray matter structures, such as the putamen and ventro-lateral thalamus [44]. These results indicate a modular and hierarchical control of discrete finger sequences at the cortical level with the integration of sequence-specific temporal and spatial features occurring mainly in the M1-HAND [1]. This modular and hierarchical organization is geared to flexibly assemble spatio-temporal patterns of skilled muscle activity.

The MVPA findings may help to interpret the reorganization patterns that were observed in forced right-handers using fMRI [29,30]. Univariate analyses revealed that forced right-handedness shifted motor activation of executive areas such as the primary sensorimotor cortex and caudal dorsal premotor cortex to the non-dominant left hemisphere [29]. This suggests that lower-level hierarchies might be less fixed and may be transferable by learning to the non-dominant hemisphere (i.e., when being forced to learn handwriting with the non-dominant right hand). On the other hand, 'converted' left-handers (i.e., forced right-handers) showed stronger activation of associative motor areas in the lateral premotor and inferior parietal cortex in their dominant right hemisphere when writing with the right hand [29,30]. The findings suggest that higher-order representations in frontal premotor and parietal cortex (reflecting representation at a higher hierarchical level) are more hardwired and thus, cannot be transferred to the non-dominant hemisphere by attempts to convert handedness. Compared to voxel-based univariate analysis, MVPA based approaches take into account activation patterns distributed across multiple voxels. Therefore, MVPA may be more suited to represent the functional representation of different learned movements and MVPA may be more sensitive to detect changes in functional representations during motor skill learning. After learning of novel sequences of discrete finger movements, multi-voxel activity patterns became more distinguishable in fronto-parietal regions for trained finger sequences relative to non-trained sequences [45]. At the same time, task-related activation levels were lower in bilateral PMd and along the intraparietal sulcus for

trained finger sequences indicating that task-related cortical activity had become more discrete and more efficient [45]. However, further studies are needed to fully understand the neural underpinnings of the MVPA changes. For instance, it has been recently shown that a simple modulation of the behavioral context substantially modulates the expression of the multi-voxel patterns that reflect cortical representations [46].

Dexterity and microstructure in the corticospinal tract

We have already mentioned that the microstructure of transcallosal motor tracts reflect inter-individual variation in bimanual coordination abilities. A structure–function relationship also exists between the microstructure of the CST and dexterity. A recent DTI study on typically developing, right-handed adolescents revealed that the right–left asymmetry in dexterity is reflected in the microstructure of the CST [12•]. Although all subjects were consistently right-handed, they showed a large between-subject variability regarding the right-hand advantage for circle drawing [12•]. The right–left asymmetry in dexterity scaled proportionally with the right–left asymmetry of mean FA between the left and right CST. The stronger the dexterity advantage for the right hand the higher was mean FA of the left compared to the right CST. This might indicate increased myelination or larger axon diameters in the left relative to the right CST, contributing to a better drawing skill of the right hand in consistent right-handers. Future studies need to address whether an analog relationship between the right–left asymmetry in CST microstructure and dexterity levels is also present in individuals who are consistently left handed.

A stronger right–left asymmetry of FA was found in the CST of musical string players (violinists and cellists) relative to keyboard players and non-musicians [47]. In the combined group, dexterity, measured using maximum index finger-tapping rate, correlated with contralateral FA in the pathway descending from primary motor cortex [47]. In another study, congenital one-handers showed increased laterality of FA in the CST as compared with controls, with decreased FA in the contralateral hemisphere to the missing hand [48]. In congenital one-handers and arm-amputees, the degree of intact hand representation in the deprived cortex was associated with increased FA in the underlying CST [49]. Immobilization of the right upper limb after injury led to a FA decrease in left CST, while behavioral improvement of the left (non-injured arm) was correlated with increased FA-values in the right CST [50]. Taken together, these studies provide consistent evidence for a close link between the structural CST properties and dexterous movements. The results also show that one has to take into account right–left asymmetries in dexterity, when testing for structural correlates of preferred hand use.

Sensorimotor reorganization in congenital one-handers

Another interesting line of recent research on dexterity and preferred hand use focused on individuals who were born without one hand, shedding light on the capability of the deprived sensorimotor cortex to undergo functional reorganization [48,49,51••]. Reorganization in these individuals is determined by two mechanisms. First, the missing hand causes life-long sensorimotor deprivation of the hand representation contralateral to the missing hand. Second, the missing hand enhances the skilled use of the residual hand, but also of distant body parts, such as lips and feet, to substitute the function of the missing hand in daily life. In congenital one-handers, the residual arm representation as well as representations of distant body parts were found to be functionally represented in the 'deprived' cortical territory of the missing hand [48,49,51••]. The fMRI results show that the congenital absence of a hand does not only lead to local remapping within the upper limb representation of the missing hand, but triggers large-scale somatotopical reorganization with the deprived sensorimotor hand area hosting functional representations of distant body parts. Magnetic resonance spectroscopy also revealed reduced regional GABA levels in the cortical territory of the missing hand [51••]. This finding was interpreted as metabolic evidence for reduced connectional selectivity which 'could unmask normally silenced inputs, allowing for increased representation of cortically displaced inputs from other body parts in the missing-hand territory' [51••]. While these findings are interesting, the impact of the reorganization on dexterity has not yet been convincingly shown. One might predict that the strength of representations of the residual arm or of a remote body part in the deprived cortex should correlate with the level of dexterity in the residual arm or the remote body part. Since there were no significant correlations between the functional reorganization patterns and behavioral performance on motor tasks [51••], the functional relevance of the experience-dependent reorganization of the cortex contralateral to the missing limb remains to be clarified.

Conclusion

In recent years, state-of-the-art MRI-based methodology has provided important new insights into the functional and structural underpinnings of dexterity, including skilled use of a single hand or both hands in combination. Yet it remains a challenge to identify the neural substrate of handedness with MRI. Most MRI studies have compared brain structure or function of adult right-handers and left-handers. This approach cannot separate between primary mechanisms that cause handedness and secondary mechanisms that are the consequence of preferred hand use. This chicken-egg problem needs to be tackled in future MRI studies designed to establish causal links between the individual expression of handedness and brain structure and function. One way to disentangle

these factors is to prospectively capture the developmental trajectories of handedness and dexterity at the behavioral and brain level, integrating information about hand use and hand function during early motor development with prospective multimodal MRI of brain maturation.

Conflict of interest

Acknowledgements

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