Lateralization of motor circuits and handedness during finger movements

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Although functional lateralization in the human brain has been studied intensively, there remains significant controversy over the brain mechanisms that instantiate it. The main objective of the present study is to characterize the regions associated with the generation of different movements by the fingers of both hands by right- and left-handed people. Thirteen right- and left-handers were studied using blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) during performance of single and sequential finger movement tasks. We used single-shot whole-brain spiral fMRI to map the functional components of the motor system during these tasks. Regions of interest included the primary motor and sensory cortices, the pre-motor cortices and the cerebellum.

Sequential movements were associated with intense brain activation in several bilateral regions, whereas single movements were associated with less activation in fewer regions, but with greater laterality. Right- and left-handers differed in their pattern of activation, sharing a pattern of activation on simple movements but responding differently to sequential movements. On simple movements, the brain activation patterns of left- and right-handers were similar in volume, number of areas and laterality. By contrast, on sequential movement, left-handers activated larger volumes and a larger number of brain areas than right-handers, and showed significantly less brain lateralization.

These results highlight differences in the functional organization of motor areas in right- and left-handed people. The discrepancies that might reflect differences in the network features of motor systems in these two groups, could also determine differences in motor activity that occur during recovery from injury (e.g. after stroke).

Introduction

The study of the organization and function of the motor system in humans has relied on a variety of techniques at different levels of description, from lesion analysis and brain imaging to single neurone physiology and anatomy. The relatively recent development of in vivo functional neuroimaging has provided a novel point of view, by relating the neuroanatomy of the human motor system directly to its functional manifestations. The most significant advantage of these techniques is to permit the characterization of the brain areas that participate in specific motor behaviours, and to do so in a physiologically valid manner. Functional magnetic resonance imaging (fMRI) has the added advantage of being non-invasive.

Thus far, many investigations have mapped brain activation patterns during motor control (for a review, see Roland and Zilles, 1996). The general consensus of these studies is that complex movements produce activation of the primary motor and sensory areas, as well as the motor association areas and cerebellum. Although several of these studies have addressed the issue of handedness (Kim \textit{et al.}, 1993a; Dassonville \textit{et al.}, 1997; Kawashima \textit{et al.}, 1997; Singh \textit{et al.}, 1998; Jancke \textit{et al.}, 1999), there remains a lack of consensus regarding the relationship between handedness and brain activation. In some cases, brain activation in left- and right-handers has not been shown to be different (Dassonville \textit{et al.}, 1997), whereas in others, right-handers have larger ipsilateral activation in the primary motor cortex (M1) (Kim \textit{et al.}, 1993b; Singh \textit{et al.}, 1998), or left-handers (but not right-handers) have bilateral activation in the lateral premotor cortex (LPMC) (Kawashima \textit{et al.}, 1997).

Other studies have investigated the differences in brain activation patterns between movements of the dominant and non-dominant hands, regardless of handedness, and found a significant difference. Hand use is influenced by both intrinsic and extrinsic factors and interacts strongly with hand preference. First,
genetic and perinatal factors influence hand preference, leading to differential patterns of use (Kim et al., 1993b; Amunts et al., 1996; Dassonville et al., 1997; Singh et al., 1998). Second, the right hand and the left hand are different in their own right, independent of handedness (and of cerebral dominance), with environmental influences leading to differential experience. This is thought to be because of the result of the predominance of right-handed people, with environmental influences on brain development providing the two hands with different experience, and hence different patterns of brain activation (Halsey et al., 1979).

The main objective of the present study is to characterize and to contrast the motor areas associated with the generation of finger movements in both dominant and non-dominant hands by both left- and right-handed people. Previous efforts have shown that different movements show different patterns of brain activation, particularly involving the non-primary cortical regions (Roland et al., 1980, 1982; Colebatch, 1991; Deiber et al., 1991; Graf ton et al., 1991, 1993; Rao et al., 1993; Kim et al., 1993a; van Gelderen et al., 1995; Dassonville et al., 1997; Kleinschmidt et al., 1997), and that right-handed and left-handed people show differences in functional brain architecture for finger movements (Kim et al., 1993b; Amunts et al., 1996; Dassonville et al., 1997; Singh et al., 1998). The difference in the patterns of brain activation between simple and complex movements are not linear, and right- and left-handers seem to differ in these activation patterns. Hence, we hypothesize that the difference between simple and complex movements in left- and right-handed individuals will vary by type of movement.

Materials and methods

The study used blood oxygen level dependent (BOLD) fMRI to map the entire brain at high spatial resolution.

Subjects

Thirteen normal subjects (between 24 and 58 years; mean age = 31 years) participated in the study. Six subjects were left-handed and seven were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Handedness indexes for right-handers was 94 ± 9 and for left-handers −42 ± 20. The study was approved by the University of Maryland School of Medicine Institutional Review Board and was performed in accordance with the Declaration of Helsinki. All subjects understood completely the nature of the experimental procedures and provided written informed consent prior to participation.

Stimulus presentation

Subjects were placed in the scanner and head movement was restricted with foam rubber pillows. Air-conduction headphones (Resonance Technologies, Northridge, CA, USA) were wrapped around the ears and connected to a stereo system controlled by a Macintosh computer. The Macintosh computer ran the PsyScope psychological software system (Cohen et al., 1993) to present the experimental conditions. Significant effort was exerted to make the subject as comfortable as possible to reduce head motion.

The motor task paradigm included two different finger movement conditions and a rest condition as shown in Table 1. One task (single movements) involved finger/thumb opposition at an externally paced rate of 2 s⁻¹. The other task (sequential movements) required opposition of the thumb with each of the fingers in succession at the same rate of 2 s⁻¹. The rest condition required that the subject remain still. The onset of the finger/thumb opposition task was forewarned with an auditory tone lasting 1000 ms (long tone). The onset of the sequential finger-tapping task was alerted with a sequence of three short tones (sequence of tones), each lasting 200 ms (total duration 1000 ms). The onset of the rest period was marked by a single short tone (short tone). The external cue to move the fingers was a short high-pitched tone (1000 Hz), which occurred every 500 ms during the complex and simple task periods. The external cue to rest was a short low-pitched tone (200 Hz), which occurred every 500 ms during the rest periods. Thus all three conditions included similar auditory stimuli.

Stimulus presentation was organized sequentially, beginning with the single task (S), followed by the rest (R), followed by the sequential task (Q), followed by rest. Each active task period lasted 48 s and each rest period lasted 32 s. The entire sequence S–R–Q–R was repeated four times, for a total of 640 s (10 min 40 s)

<table>
<thead>
<tr>
<th>Task</th>
<th>Time per cycle</th>
<th>Time per study</th>
<th>Images per cycle</th>
<th>Images per study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Index-thumb opposition (S)</td>
<td>00:48</td>
<td>03:12</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>2: Rest (R)</td>
<td>00:32</td>
<td>02:08</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>3: Sequential movement (Q)</td>
<td>00:48</td>
<td>03:12</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>4: Rest (R)</td>
<td>00:32</td>
<td>02:08</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>02:40</td>
<td>10:40</td>
<td>40</td>
<td>160</td>
</tr>
</tbody>
</table>

Two active tasks were separated by rest. Time (s) is for each cycle. Number of images (entire brain) must be multiplied by 24 to get the entire number of slices acquired for each cycle. Each cycle was repeated four times, for a total of 10:40 for the entire experimental run.
per experimental trial. This entire experimental trial was performed twice with the left hand and twice with the right hand.

**Imaging**

Data acquisition used the spiral k-space method (Noll and Schneider, 1994; Noll et al., 1995) on a 1.5 T Signa scanner (GE Medical Systems, Milwaukee, WI, USA) with a standard quadrature GE head coil.

Twenty-four contiguous 6 mm axial slices were obtained starting from the vertex through the bottom of the cerebellum. A gradient echo spiral scan pulse sequence used a single spiral to provide 3.2 × 3.2 mm resolution over a 24-cm field-of-view (FOV). \( T_2^* \)-weighted imaging was accomplished with a gradient echo time (TE) of 35 ms, and a repetition time (TR) of 4000 ms with a flip angle of 60°. A complete set of the 24 slice locations was generated every repetition time cycle (4 s). Structural \( T_1 \)-weighted anatomical images (500 ms TR, 16 ms TE, spin echo pulse sequence) were acquired to determine the anatomy of the functional slices.

Each of the 24 slices was acquired 12 times during each 48-s active task interval. As each active task was repeated four times during each experimental trial, the total number of images obtained for each active condition for each experimental trial was 12 × 4 = 48. Following the end of each trial, a brief (< 1 min) break occurred during which the next trial was prepared. Each trial was repeated twice if possible to improve the statistical power and reliability. Thus, for each subject, there are either 48 images (one trial) or \( 48 × 2 = 96 \) images (two trials) for simple movements and the same for complex movements for each hand. In addition, 64 images during rest were collected for each hand during each trial.

**Image analysis**

**Intra-subject analysis**

Statistical analysis of individual subject data was performed using cross-correlation thresholding (Bandettini et al., 1993; Binder and Rao, 1995). In this analysis, the activation waveform for each voxel was correlated with a reference waveform (a sine wave) corresponding to the temporal pattern of stimulus presentation. In order to account for the haemodynamic lag, several reference waveforms incorporating different temporal delays were all used and the one with the best correlation was used in the final analysis.

The data were thresholded at a correlation coefficient of \( r = 0.4 \). Under the null hypothesis that the activation value in each voxel comes from a random Gaussian distribution, and that the values are independently obtained for each voxel in the image, the images shown thus illustrate the pixels for which the null hypothesis is rejected with a probability of greater than 99.9% (i.e. \( P < 0.001 \)). We also enforced a three-dimensional contiguity requirement, requiring particles (sets of contiguous voxels) to contain at least four voxels (≈ 84 mm\(^3\)), which has been shown through formal simulation to minimize false positives (Forman et al., 1995).

**Inter-subject analysis**

Multi-subject analysis was performed using a region-of-interest (ROI) analysis, based on eight specific regions of interest identified \emph{a priori} in each hemisphere on the basis of the known functional neuroanatomy of the human motor system.

In order to automate this analysis, the ROIs were specified as ellipsoid regions of various sizes corresponding to the proposed anatomy of these regions. The shape and size of each ROI schema was based on the axial structural anatomy of the brain using gross anatomical landmarks.

**Primary motor cortex**

For M1, the horizontal centre was positioned on the pre-central gyrus in the centre of the knob that has been identified as a landmark for the hand area of the primary motor cortex (Yousry et al., 1997) where M1 and S1 areas interdigitate (White et al., 1997). The A/P centre of this area is located between the central and pre-central sulci.

**Primary somatosensory and secondary motor areas**

The vertical centres of primary somatosensory area (S1), LPMC, supplementary motor area (SMA) and pre-SMA regions were all defined to be in the same plane as M1. The horizontal centre of the S1 region was placed across the central sulcus from that of M1. The A/P limits of S1 were defined to include the area between the central and the post-central sulci. The anterior limit of LPMC was defined using a coronal plane perpendicular to the AC–PC line through the AC. The posterior limit of LPMC was defined as the pre-central sulcus. The SMA region (SMA proper and pre-SMA) anterior limit was set at the level of the genu of the corpus callosum. Posteriorly, SMA was limited by the paracentral lobule (Picard and Strick, 1996). The inferior limit was the cingulate sulcus. The cingulate motor area (CMA) was defined as the region on both banks of the cingulate sulcus, on the midline, inferior to SMA, the anterior
limit was established at the level of the genu of the corpus callosum (Picard and Strick, 1996).

**Cerebellum**

The vertical centre of the superior cerebellar region was defined as the second axial slice from the top of the cerebellum, and the vertical centre of the inferior cerebellar region was defined as the second axial slice from the bottom of the cerebellum. The centres of these ellipsoids within the horizontal dimensions were defined for each hemisphere as the actual centres of mass of the hemispheres and their (Talairach and Tournoux, 1988) co-ordinates are listed in Table 2.

**Data analysis**

Three different measures were derived for each region on each of the two tasks. The first is a simple binary indicator of the presence or absence of activation, where activation is considered present if the region contains one or more clusters (> 4 coalescent voxels, each with \( r = 0.4 \)) of activation. The second measure is the total volume of activation in the region, using the same activation criterion as for the binary indicator. The third measure is a derived index of regional laterality, and is computed once for each homologous pair of regions for each task. This laterality index consists of the fractional activation in each hemisphere with the task performance. The laterization index is defined as follows:

\[
L = |(V_{\text{left},j} - V_{\text{right},j})/(V_{\text{left},j} + V_{\text{right},j})|,
\]

where \( V_{\text{left},j} \) and \( V_{\text{right},j} \) with \( j \) as the region of interest, the volume of activation in left hemisphere region \( j \) and the volume of activation in right hemisphere region \( j \), respectively. Separate laterization measures are computed for single (\( L_s \)) and sequential (\( L_c \)) movements.

The image data were subjected to three complementary analytical approaches. Initially, the raw data and images were examined visually and presented descriptively, both through tables and activation images. Additional information can be gleaned from statistical inferences on these raw data. The main statistical results presented come from an analysis of variance (ANOVA) on the thresholded brain activation volumes to assess differences and statistical interactions among region of interest, task type, hand of use, and handedness of subject. A second ANOVA was used to assess these same factors with respect to the laterality indices. Finally, the data on presence or absence of regional activation were analysed with respect to task complexity only, and this was carried out with a pairwise Student’s \( t \)-test.

In order to make specific inferences about the effects of handedness on brain activation patterns, including amount, distribution, and laterality, the results of the ANOVAs were subjected to post-hoc testing using the Student–Newman–Keuls statistic. All of these analyses were performed in StatView 5.0 for Macintosh.

**Results**

**Descriptive results**

The results demonstrate a distributed pattern of activation on sequential movements that differs in intensity, extent, and laterality from that on single movements. Furthermore, this pattern is modified by hand dominance. The overall summary of the ROI data is shown in two tables: Table 3 shows the mean activation in each brain region with single and sequential movements. Table 4 shows the percentage of subjects with significant activation in each area of interest. Figures 1 and 2 are graphic representations of the activated sites in each condition.

**Hand dominance: influences on the pattern of brain activation**

Analyses were undertaken to see if there were effects of handedness on movement type. The ANOVA showed a significant three-way interaction between ROI, movement type, and handedness (\( F(3.219, 10); P = 0.0011 \)). In addition, there were significant two-way interactions between handedness and movement type (\( F(14.81, 1); P = 0.0027 \)).

Post-hoc analysis using the Student–Newman–Keuls statistic (z-level = 5%), comparing volumes of activation during single versus sequential movements, showed

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**Table 2** Co-ordinates according to the Talairach and Tournoux Atlas, for the centres of mass of the regions of interest described in the text.

<table>
<thead>
<tr>
<th>Regions of interest</th>
<th>Talairach and Tournoux co-ordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-M1</td>
<td>-33, 24, 65</td>
</tr>
<tr>
<td>L-M1</td>
<td>28, 25, 66</td>
</tr>
<tr>
<td>R-S1</td>
<td>-38, 38, 66</td>
</tr>
<tr>
<td>L-S1</td>
<td>38, 38, 67</td>
</tr>
<tr>
<td>R-LPMC</td>
<td>-30, 5, 65</td>
</tr>
<tr>
<td>L-LPMC</td>
<td>30, 5, 65</td>
</tr>
<tr>
<td>R-SMA</td>
<td>-7, 4, 67</td>
</tr>
<tr>
<td>L-SMA</td>
<td>6, 3, 66</td>
</tr>
<tr>
<td>R-CMA</td>
<td>-9, -34, 6</td>
</tr>
<tr>
<td>L-CMA</td>
<td>6, -24, 8</td>
</tr>
<tr>
<td>R-CRB</td>
<td>-21, 50, -18</td>
</tr>
<tr>
<td>L-CRB</td>
<td>18, 50, -18</td>
</tr>
</tbody>
</table>
that in both left- and right-handed individuals, sequential movements produced significantly larger volumes of activation than finger opposition movements. Not all areas reacted to complexity in the same way. Whereas regions such as M1 and S1 contralateral and CRB ipsilateral to finger movements were always active, regardless of complexity, this was not uniformly the case for other regions. Areas such as the CMA, and cCRB, iM1, and bilateral LPMC and SMA play a larger role in sequential finger movements than in finger opposition (Table 5). In addition, volumes of activation during sequential movements by the left-handed group were significantly larger than that of the right-handed group, whereas volumes of activation during simple finger opposition movements did not differ between groups (Figures 1 and 2).

In the ANOVA using laterality values as a dependent variable ($V$), we observed a significant interaction between sequentiality and handedness ($F(19.702, 1); P = 0.001$). In a post-hoc analysis using the Student–Newman–Keuls was seen that in right-handed subjects, the laterality indices during single and sequential movements were not statistically different. In contrast, the laterality indices of left-handed subjects were significantly lower during sequential movements than single movements.

In summary, right- and left-handed individuals share a pattern of activation on single movements. In particular, the brain activation pattern during single movements is comparable in volume of activation, number of areas activated and degree of lateralization. By contrast, brain activation during sequential movements differs as left-handers tend to activate larger volumes in a larger number of areas (i.e., association cortices) with less lateralization than right-handers.

**Discussion**

**Effects of task complexity**

There was a significant difference in brain laterality between single and sequential movements. Virtually all

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**Table 3** Region of interest analysis: volumes of activation ± SD

<table>
<thead>
<tr>
<th>Region</th>
<th>Finger opposition</th>
<th>Sequential movement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right-handed</td>
<td>Left-handed</td>
</tr>
<tr>
<td>Ipsi M1</td>
<td>0</td>
<td>273 ± 265</td>
</tr>
<tr>
<td>Ipsi S1</td>
<td>0</td>
<td>105 ± 110</td>
</tr>
<tr>
<td>Ipsi SMA</td>
<td>21 ± 19</td>
<td>252 ± 175</td>
</tr>
<tr>
<td>Ipsi LPMC</td>
<td>0</td>
<td>400 ± 613</td>
</tr>
<tr>
<td>Ipsi CRB</td>
<td>546 ± 675</td>
<td>2226 ± 2003</td>
</tr>
<tr>
<td>Contra M1</td>
<td>2184 ± 1032</td>
<td>3213 ± 1597</td>
</tr>
<tr>
<td>Contra S1</td>
<td>945 ± 836</td>
<td>1743 ± 1456</td>
</tr>
<tr>
<td>Contra SMA</td>
<td>63 ± 151</td>
<td>189 ± 289</td>
</tr>
<tr>
<td>Contra LPMC</td>
<td>84 ± 154</td>
<td>567 ± 935</td>
</tr>
<tr>
<td>Contra CRB</td>
<td>0</td>
<td>315 ± 308</td>
</tr>
<tr>
<td>CMA</td>
<td>21 ± 17</td>
<td>126 ± 251</td>
</tr>
</tbody>
</table>

For each ROI, this table shows the mean volume of activation (mm$^3$). To convert to number of voxels, divide by the voxel size ($1.875 \text{mm} \times 1.875 \text{mm} \times 6 \text{mm} = 21 \text{mm}^3$).

**Table 4** Region of interest analysis: percentage values

<table>
<thead>
<tr>
<th>Region</th>
<th>Finger opposition</th>
<th>Sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right-handed</td>
<td>Left-handed</td>
</tr>
<tr>
<td>Ipsi M1</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Ipsi S1</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Ipsi SMA</td>
<td>14</td>
<td>33</td>
</tr>
<tr>
<td>Ipsi LPMC</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Ipsi CRB</td>
<td>57</td>
<td>83</td>
</tr>
<tr>
<td>Contra M1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Contra S1</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>Contra SMA</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Contra LPMC</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>Contra CRB</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>CMA</td>
<td>0</td>
<td>33</td>
</tr>
</tbody>
</table>

For each ROI, this table shows the percentage of subjects with at least one cluster of activation (number of voxels of 4) in that region. The denominator for these values is the number of subjects (seven right-handed and six left-handed) in each particular group.

**Table 5** Laterality values for right- and left-handed subjects during finger opposition and sequential movements

<table>
<thead>
<tr>
<th>Region</th>
<th>Finger opposition</th>
<th>Sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left-handed</td>
<td>Right-handed</td>
</tr>
<tr>
<td>M1</td>
<td>0.90</td>
<td>1.00</td>
</tr>
<tr>
<td>S1</td>
<td>0.91</td>
<td>1.00</td>
</tr>
<tr>
<td>CRB</td>
<td>0.85</td>
<td>1.00</td>
</tr>
<tr>
<td>SMA</td>
<td>0.71</td>
<td>0.82</td>
</tr>
<tr>
<td>LPMC</td>
<td>0.79</td>
<td>1.00</td>
</tr>
</tbody>
</table>

In the ANOVA using laterality values as a dependent variable ($V$), we observed a significant interaction between sequentiality and handedness ($F(19.702, 1); P = 0.001$). In a post-hoc analysis using the Student–Newman–Keuls was seen that in right-handed subjects, the laterality indices during single and sequential movements were not statistically different. In contrast, the laterality indices of left-handed subjects were significantly lower during sequential movements than single movements.

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areas studied showed bilateral activation during sequential movements, but not during single movements. This bilaterality has been described previously by others (Salmelin et al., 1995; Wexler et al., 1997; Kawashima et al., 1998; Cramer et al., 1999). As activation volumes increased during sequential movements, brain laterality values decreased because of a recruitment of ipsilateral cortical and contralateral cerebellar areas.

The functional significance of this recruitment is not clear. One postulate by Armatas et al. (1996) has been that the frequency of mirror movements increases during more complex movements. A second alternative is the recruitment of the ipsilateral cortex and contralateral cerebellum, producing more complex interactions among structures. Although previous studies have suggested a prominent role of these areas in the encoding of complex movements (Chen et al., 1997a, b), their precise role remains enigmatic. The interhemispheric interactions could be excitatory or inhibitory as shown previously with TMS studies (Meyer et al., 1995; Salerno and Georgesco, 1996; Schnitzler et al., 1996; Tinazzi and Zanette, 1998).

In the monkey, homo- and hetero-topic callosal connections between the hand areas in M1 and association cortices are relatively sparse, whereas the interhemispheric connections established by association cortices are much more dense (Gould et al., 1986; McGuire et al., 1991; Rouiller et al., 1994). It has been suggested that the sparse connectivity between both M1 areas could facilitate the independent movement of each hand (hence high brain laterality). Conversely, the profuse connectivity of motor association areas would contribute to the production of more complex movements where the co-ordination of both hands is needed (and brain laterality would be expected to be lower). In the present study, the sequential movement task did not require the co-ordinated movement of both hands.

One anatomical explanation of the ipsilateral activation in M1 during complex movements involves input from activity in the contralateral motor association areas rather than from contralateral M1. This could reflect the complexity of the distributed circuit associated with the production of sequential movements.

Differences from previous studies
Several of the results found in this study differ from those in previous studies of motor function using fMRI. The first difference is the large number of regions activated by the motor task, which differs significantly from most studies, because in addition to contralateral M1/S1, they have sometimes found activation in ipsilateral M1/S1 (Kim et al., 1993a; Boecker et al., 1994).
1994; Dassonville et al., 1997), SMA bilaterally (Rao et al., 1993; Boecker et al., 1994; van Gelderen et al., 1995; Wexler et al., 1997) and LMPC bilaterally (Rao et al., 1993; van Gelderen et al., 1995; Wexler et al., 1997), and the ipsilateral superior cerebellum (Rao et al., 1993), but not in other regions, such as CMA, and contralateral cerebellum. This particular difference could be partly because of our system of motor cortex parcellation, but perhaps more importantly, from our use of bilateral hand movements in all subjects, leading to some intertask priming effects in activation.

The second novel feature of the present findings is that SMA is strongly activated despite the fact that the subjects were externally paced (Rao et al., 1997; Deiber et al., 1999) by a metronome. This activation might not be very surprising, however, as SMA has been associated not only with the time-keeping function (during self-paced movements), but also with preparation, sequencing and co-ordination between the hands in bimanual and mono-manual movements (Wiesendanger, 1993; Tanji et al., 1996; Tokuno and Nambu, 2000).

Thirdly certain motor areas are much more sensitive to task sequentiality than others. Whereas regions such as M1 and S1 contralateral and CRB ipsilateral to finger movements are always active, areas such as the CMA and cCRB, iM1 and bilateral LMPC and SMA

Figure 2 Single subjects fMRI with sequential movements. Figure 2(A and B) show brain activation in a left-hander; 2C–D in a right-hander. Panels A–C depict brain activation during movement of the right hand; panels B–D show brain activation during movements with the left hand. Note the bilaterality of brain activation in the motor areas of the left-hander only. The colour codes are the same as in the previous figure.
are more involved in more complex finger movements than simple ones. In addition, some regions show highly lateralized response to unilateral finger movements, whereas others show a more equal bilateral response. Prominently lateralized areas such as M1/S1 (contralateral) and cerebellum (ipsilateral) may play a fundamentally different role in motor control (and ultimately recover after brain injury) than less lateralized areas such as SMA and LPMC.

**Effects of handedness**

The differences between left-handers and right-handers were present during sequential but not single movements, suggesting that the neural structures controlling single movements are similar in these two groups.

During sequential movements, all subjects showed a larger volume of activation in both ipsilateral and contralateral areas than during single movements. However, right-handers but not left-handers also showed a decrease in brain lateralization concomitant with this bilateral increase in activation. This is consistent with anatomical data (Foundas et al., 1998) showing a clear anatomical asymmetry of M1 between the hemispheres in right-handers but not in left-handers. One previous study showing the opposite effect (Kim et al., 1993b) is difficult to interpret, but it did involve different tasks (the subjects were not paced and there was a relatively large emphasis in cutaneous input) and a different definition of M1 (including the entire pre-central gyrus as opposed to the anatomically identified hand area of the pre-central gyrus, Yousry et al., 1997).

Different motor areas are associated with the generation of sequential movements in right- and left-handed individuals, particularly in the motor association areas (i.e. motor cortical areas other than M1). Note that the fractional activation of association areas compared with total brain activation was much larger in left-handed than in right-handed subjects (34 vs. 11%), with all left-handed subjects (but not all right-handed subjects), having pre-motor activation. Furthermore, in the cingulate motor area, 14% of right-handers vs. 51% of left-handers showed activation (Table 4). Finally, the volumes of activation in left-handers were larger and tended to be bilateral.

These factors suggest that motor physiology differs in right- and left-handed individuals. The behavioural testing (handedness inventory) suggests that right-handers depend more on the use of their right hand than do the left-handers on their left hand, and the anatomical data show that the left-handers have lower brain lateralization during complex movements than right-handers. Several related brain/behaviour correlations have been previously described, including between brain activation and behavioural lateralization (but not handedness) (Dassonville et al., 1997), degree of handedness and expansion of dominant motor cortex (Volkmann et al., 1998), and handedness and dominant muscle threshold (Triggs et al., 1994).

One theory proposed to explain the ‘ambidexterity’ in the left-handed population is that they have more practice using their non-dominant hand (right hand) in order to better adapt to a preferential right-handed world. Thus, the genetic/perinatal factor of handedness is modified by the environmental factor of hand use, with the right hand required in many situations. There are even data on muscle fibre composition resulting from preferred use (Adam et al., 1998). It may be that these competing influences are responsible for the relative bilaterality of the functional circuits, particularly involving the association areas, in left-handed people.

**Conclusions**

The present study demonstrates that two complementary systems participate in externally paced finger opposition movements, with certain motor areas much more sensitive to task complexity than others. Whereas regions such as M1 contralateral and CRB ipsilateral to finger movements are always active, regardless of complexity, this is not the case for many other motor regions. Areas such as SMA, CMA, and contralateral CRB are far more involved in sequential finger movements than finger opposition.

Furthermore, some regions show a lateralized response to unimanual finger movements, whereas others show a far less lateralized response. Prominently lateralized areas such as M1/S1 (contralateral) and cerebellum (ipsilateral) may play a fundamentally different role in motor control than less lateralized areas such as SMA, CMA and LPMC.

Finally, the physiology of simple unitary digit movements is similar in right- and left-handed subjects, whereas that of the more complex system is markedly different. Left-handers have larger volumes of activation than right-handers and less brain laterality. As hand preference in left-handers is weaker than that of right-handers, brain activation in the extended system may correlate with the overall degree of hand dominance.

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