Long-Term Consequences of Switching Handedness: A Positron Emission Tomography Study on Handwriting in “Converted” Left-Handers

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Until some decades ago, left-handed children who attended German schools were forced to learn to write with their right hand. To explore the long-term consequences of switching handedness, we studied the functional neuroanatomy of handwriting in 11 adult “converted” left-handers and 11 age-matched right-handers. All participants had used exclusively their right hand for writing since early childhood. Using [15O]H2O positron emission tomography, changes in normalized regional cerebral blood flow (rCBF) were assessed while participants repetitively wrote a stereotyped word with their right hand. The kinematics of handwriting did not differ between converted left-handers and right-handers. In innate right-handers, handwriting caused a preponderant left-hemispheric activation of parietal and premotor association areas. In contrast, converted left-handers demonstrated a more bilateral activation pattern with distinct activation foci in the right lateral premotor, parietal, and temporal cortex. Moreover, foci in the right rostral supplementary motor area and the right inferior parietal lobule demonstrated a positive linear relationship between the degree of “left-handedness” and normalized rCBF during right-hand writing. Functional activity in the primary sensorimotor cortex was not affected by handedness. Our findings provide evidence for persisting differences in the functional neuroanatomy of handwriting between right-handers and converted left-handers, despite decades of right-hand writing. Right-hemispheric activation in converted left-handers may reflect suppression of unwanted left-hand movements. Alternatively, this activity may represent persistent left-handedness and, as such, demonstrate a hemispheric asymmetry of hand movement representations in cortical motor association areas in relation to the direction and degree of handedness.

Key words: converted left-hander; functional brain imaging; handwriting; handedness; human; plasticity; positron emission tomography; regional cerebral blood flow

Most humans exhibit some degree of handedness, that is, a preference to use one hand for tasks requiring precise coordination, exact calibration of forces, and accurate timing. Approximately 90% of humans are right-handed and show a left-hemispheric dominance for manual skills (Gilbert and Wysocki, 1992; Porac and Friesen, 2000). It is commonly agreed that handedness is caused by a functional hemispheric asymmetry within the motor network responsible for controlling hand movements. The neurobiological basis for hand preference, however, is still a topic of debate (Peters, 1991; Haaland and Harrington, 1996; Amunts et al., 2000). Several studies on hemispheric dominance related to hand preference have provided evidence for interhemispheric structural and functional differences in the primary sensorimotor cortex (SM1) related to handedness (Kim et al., 1993; Amunts et al., 1996; Dassonville et al., 1997; Volkmann et al., 1998). It is unclear, however, whether an asymmetry in SM1 merely reflects long-term consequences of hand preference (i.e., use-dependent plasticity) or constitutes a causal factor that drives human handedness. Alternatively, some investigators have attributed handedness to a hemispheric asymmetry of cortical motor association areas, especially in the frontal premotor cortex (Peters, 1991; Haaland and Harrington, 1996).

Studies on “converted” left-handers offer a unique opportunity to gain deeper insights into the functional neuroanatomy of human hand preference. Until some decades ago, innately left-handed children who attended German schools were often forced to use their right hand for writing. Because of life-long practice, these converted left-handers became as proficient at right-hand writing as innate right-handers. Yet most of these converted left-handers continued to use their left hand for other manual skills, which were less subject to social control. Indeed, attempts to switch handedness usually failed to establish a consistent preference for the right hand in innately left-handed subjects (Porac and Buller, 1990). Such considerations raise the question of whether converted left-handers use the same brain areas as innate right-handers for the selection and execution of handwriting and how much (covert) left-handedness might persist during right-hand writing in converted left-handers.

To address this issue, we investigated the functional neuroanatomy of right-hand writing in converted left-handers and innate right-handers. Because most converted left-handers still demonstrate overt left-handedness during manual skills other than handwriting (Porac and Buller, 1990), we postulated that the functional neuroanatomy of right-hand writing in converted left-handers would differ from innately right-handers, showing persisting features of covert left-handedness. We further predicted that both...
executive motor areas (especially SM1) and motor association areas, which are involved in “higher-order” aspects of manual motor control, would demonstrate a functional interhemispheric asymmetry during right-hand writing depending on the direction and degree of handedness.

MATERIALS AND METHODS

Subjects. Participants were recruited through announcements at our medical school specifically calling for participation in a study relating to functional correlates of handedness. Each subject’s medical history was assessed using a questionnaire. Inclusion criteria were defined as follows: (1) normal achievement of motor developmental milestones during childhood; (2) estimated time spent for handwriting > 5 min/d; (3) no history of a neuropsychiatric disease; (4) no history of early brain damage, especially perinatal complications; and (5) no report of a temporary shift in hand use caused by injury of the preferred hand.

Eleven converted left-handers (4 women and 7 men, ages 34–64 years, mean age 47 years) and 11 right-handed adults (2 women and 9 men, ages 26–58 years, mean age 42 years) who met the inclusion criteria participated in the experiment after giving written informed consent before the experiment. Permission to administer radioactive isotopes was obtained from the German radiation protection authorities, and the study had the approval of the Ethics Committee of the Faculty of Medicine of the Technische Universität München.

Handedness was classified according to self-report. Participants were assigned to the group of converted left-handers if they met two criteria: (1) a preferred use of their left hand for skillful manual activities throughout their life and (2) a forced change in hand use for the “target activity” of handwriting based on educational pressure. All converted left-handers clearly recalled that they had started to write with their right hand and were subsequently forced to switch to right-hand writing by their teachers and parents during the first year of education (at the age of ~6 years). The degree of handedness at the time of the study was assessed by the 10-item version of the Edinburgh Handedness Inventory (Oldfield, 1971), which enabled us to calculate a laterality quotient in the range of −100 to +100. Extreme right-handedness corresponds to a laterality quotient of +100, whereas a laterality quotient of −100 indicates extreme left-handedness. The absolute value of the laterality quotient was taken as a quantitative measure of individual hand preference in both right-handers and converted left-handers. Familial left-handedness was determined by the presence of at least one first-degree relative (parent and/or sibling) reporting as being left-handed. The posture of the writing hand was classified as either “inverted” or “noninverted” depending on the relative position of the hand relative to the line of writing (Teasdale and Owen, 2001). Hand posture was classified as noninverted if the writing hand was positioned below or in parallel to the line of writing and the pen was pointed away from the writer. Writing posture was labeled as inverted posture if the writing hand was held above the line of writing and the pen hooked back toward the writer.

Experimental design. We used [15O]H2O positron emission tomography (PET) to study changes in regional cerebral blood flow (rCBF) while subjects wrote with their right hand. Each participant underwent six consecutive [15O]H2O-PET measurements of rCBF (50 sec duration for each measurement). Subjects were scanned in the supine position in a PET scanner in the supine position in a PET scanner while they were writing. Pen-tip position of an inking digitizing pen was stored on a personal computer with a sample frequency of 166 Hz. The spatial resolution was 0.05 mm, and the accuracy was 0.025 mm in the horizontal and vertical direction. Velocity and acceleration signals were calculated and smoothed by nonparametric methods (Marquardt and Mai, 1994).

For each PET scan, only the eight words that were written during the 50 sec period of data acquisition were included in kinematic analysis. Kinematic analysis used a PC-based writing analysis program of single upstrokes and downstrokes (CS-Software; MedCom, Munich, Germany). Movements were segmented in subsequent vertical upstrokes or downstrokes of the pencil, which represent the fundamental modules of regular writing (Hollerbach, 1981; Morasso and Mussa Ivaldi, 1982; Plamondon, 1995). A single stroke is defined as the time segment between two subsequent changes in vertical direction of handwriting. Upstrokes and downstrokes with a duration of <50 msec were excluded from kinematic analysis. The following dimensions of writing performance were calculated for each word: vertical stroke length, vertical stroke duration, and peak vertical writing velocity. Furthermore, the number of inversions in velocity (NIV) per single stroke was estimated to quantify the degree of automation of the handwriting movements (Marquardt and Mai, 1994). An NIV of one per stroke is characteristic of fast open-loop performance, whereas an increase in mean NIV per stroke indicates continuous adjustments of writing velocity to the incoming feedback information during slow closed-loop handwriting (Eichhorn et al., 1996; Marquardt et al., 1999; Siebner et al., 1999).

Each kinematic variable was analyzed separately using ANOVA for repeated measurements (SPSS version 9; SPSS Inc., Chicago, IL). The within-subject factor was “order of PET scans” with three levels (PET scan 1, PET scan 2, and PET scan 3). The between-subject factor was “group” with three levels (converted left-handers, nonconverted left-handers, and right-handers). Significance was accepted at a value of $p = 0.05$.

Positron emission tomography. The rCBF was measured by recording the regional distribution of radioactivity after the intravenous injection of [15O]H2O-labeled water (Fox and Mintun, 1989). PET scans were obtained in three-dimensional mode using a Siemens ECAT 951 R/31 PET scanner (CTI Inc., Knoxville, TN). For each measurement of rCBF, 250 mBq of [15O]H2O was administered in the left cubital vein as a semibolus injection using an infusion pump. A 50 sec PET scan was initiated when a rising radioactivity count in the brain was first detected (~30 sec after radioisotope injection). After corrections for randoms, dead time, and scatter, all emission data were reconstructed by filtered backprojection (Hanning filter; 0.5 cycles/pixel cutoff frequency) to 31 consecutive axial planes with an interplane separation of 3.375 mm. Reconstructed slices
were displayed in a matrix consisting of $128 \times 128$ voxels. The interscan interval was $10$ min. A $20$ min headholder transmission scan with a rotating $^{68}$Ge/$^{68}$Ga source was obtained before each session and used to correct for effects of radiation attenuation. Note that the PET scanner had a total axial view of $10.5 \ cm$ and no interplane dead space, ensuring coverage of the upper two-thirds of the brain from the vertex to the upper cerebellum. All calculations and image transformations were performed on Sun SPARC 2 workstations (Sun Computers Europe, Inc., Surrey, UK). PET data were analyzed using statistical parametric mapping software (www.fil.ion.ucl.ac.uk/spm/) implemented in the PRO MatLab environment (Mathworks Inc., Natick, MA). The scans from each subject were realigned using the first scan as a reference. The six parameters of this rigid body transformation were estimated using a least-squares approach on a voxel-by-voxel basis (Friston et al., 1995a). After realignment, PET images were transformed into stereotactic space using a template from the Montreal Neurological Institute (Montreal, Canada). Spatial normalization was performed using linear and nonlinear three-dimensional transformations to match each scan to a reference image that already conformed to the standard stereotactic space (Friston et al., 1995a). As a final preprocessing step, the normalized images were smoothed using an isotropic Gaussian kernel of $12 \ mm$ full width at half maximum for all directions to increase the signal-to-noise ratio and reduce variance attributable to interindividual differences in gyral anatomy (Friston et al., 1995a). Each voxel of the resulting normalized and smoothed images was $2 \times 2 \times 4 \ mm$ in size.

The effect of changes in global cerebral blood flow across subjects and scans was removed by linear scaling across the entire data set. The mean rCBF value was then arbitrarily normalized to a global mean of $50 \ ml \cdot 100 \ ml^{-1} \cdot min^{-1}$. The adjusted voxel values were then used for additional statistical analysis (Friston et al., 1990). The statistical analysis was performed according to the general linear model and the theory of Gaussian fields at each and every voxel (Friston et al., 1991, 1995b; Worsley et al., 1992). The resulting statistical parametric maps based on the $t$ statistic were subsequently transformed into normally distributed statistical parametric $Z$ maps (Friston et al., 1995b). The locations of peak activations were reported as stereotaxic coordinates according to the system introduced by Talairach and Tournoux (1988).

PET data were analyzed in three different ways: First, using linear weighted contrasts, a within-group subtraction analysis between the writing condition and the baseline condition was performed to define those brain areas that were functionally active during right-hand writing in right-handers and converted left-handers. The significance level was set at a value of $p = 0.05$ after correction for multiple nonindependent comparisons, which corresponds to a $Z$ score of $4.26$. Brain areas showing increases in rCBF at an uncorrected value of $p < 0.001$ (corresponding to a $Z$ score of $3.09$) but that did not survive correction for multiple nonindependent comparisons were considered as trend activations.

In a second set of analyses, we explored specific regional differences in the handwriting-induced activation pattern between right-handers and converted left-handers. Using appropriately weighted linear contrasts, a between-group subtraction analysis was computed to pinpoint those brain areas that showed stepwise differences in writing-related functional activation depending on the direction of handedness. Both resting scans and activation scans were included in the design matrix of the between-group subtraction analysis. Although suitable to map stepwise differences in activation changes across groups, between-group subtraction analysis may fail to detect those brain areas that gradually scale their activity according to a given variable, such as the degree of handedness. Therefore, we computed a third independent ANCOVA with the individual laterality quotient of each participant being treated as a "covariate of interest" to delineate those brain areas that show a linear relationship between functional activation during handwriting and the degree of handedness. In contrast to between-group subtraction analysis, only PET scans acquired during handwriting were included in the design matrix.

As for between-group analyses, an uncorrected value of $p = 0.001$ was accepted as a statistical threshold for those brain regions that had already shown at least trend activation during right-hand writing, as indicated by within-group analyses. Otherwise, significance level was set at a corrected value of $p = 0.05$. Foci revealing a differential activation that exceeded an uncorrected value of $p = 0.001$ but did not reach a corrected value of $p = 0.05$ are only descriptively reported. This approach provided a reasonable trade-off between a maximized sensitivity of data analysis and an increased risk for false positives (Boecker et al., 1998).

**RESULTS**

**Degree and history of handedness**

Innate right-handers showed little interindividual variability of handedness, with laterality quotients ranging from $+80$ to $+100$ (mean laterality quotient $96$), whereas the magnitude of left-handedness was more variable among converted left-handers with laterality quotients ranging from $-80$ to $+40$ (mean laterality quotient $-29$). Figure 1 illustrates the relative frequency for right-hand use and left-hand use for each individual item of the Oldfield questionnaire in the group of converted left-handers. Apart from writing, which was consistently performed with the right hand, a preferential use of the right hand was relatively often reported for everyday manual activities, such as drawing or handling a spoon (Fig. 1). Use of the right hand during these activities was often enforced throughout the education period.

Five converted left-handers had a familial history of left-handedness, as opposed to only one innate right-hander. In the group of consistent left-handers, two of six subjects reported having at least one left-handed first-degree relative.

All innate right-handers and converted left-handers used a noninverted posture for handwriting. In contrast, writing posture was not standardized in the group of consistent left-handers.
Three consistent left-handers used an inverted posture of handwriting, whereas the remaining three used a noninverted position.

**Kinematic data**

Innate right-handers needed a mean total movement time of 2.29 \pm 0.61 sec, and converted left-handers required 2.21 \pm 0.59 sec to write a single target word. Table 1 gives the average group values of each kinematic variable for innate right-handers and converted and nonconverted left-handers. Repeated-measures ANOVA showed no significant group effect on any of the kinematic variables of interest, indicating that motor performance was well matched between right-handers and left-handers. In both groups, kinematics of handwriting movements were highly automated, as evidenced by a mean number of inversions in velocity per stroke below 2. Furthermore, there was no significant effect of order of PET scans and group, confirming stable motor performance throughout the PET experiment after 10 min of training. In each participant, >98% of the recorded strokes met predefined criteria and were included in the kinematic analysis.

**PET data**

**Within-group subtraction analyses**

In innate right-handers, handwriting caused a significant relative increase in normalized rCBF in a large bihemispheric cortical cluster, with a preponderant activation of left-hemispheric regions (Fig. 2, Table 2). In the left hemisphere, right-hand writing activated most of the components of the frontoparietal cortex that have been shown to be involved in the generation of skilled hand movements, with the foci of strongest activation being located in the left SM1, the left caudal supplementary motor area (SMA), and the left dorsal lateral premotor cortex (LPC). In addition to a widespread increase in the left parietal cortex, including most of the superior and inferior parietal lobule, there were two foci of activation in the right parietal cortex, namely in the right precuneus and the right anterior intraparietal sulcus. Converted left-handers demonstrated a similar activation pattern during right-hand writing, when contrasting the writing condition to the resting condition (Fig. 2, Table 2). Functional activation was considerably less lateralized to the left hemisphere, however, showing a relative shift in handwriting-evoked activation from left to right frontoparietal motor areas. For instance, converted left-handers showed a distinct peak of activation in the right dorsal LPC and a strong activation of the right superior and inferior parietal lobule (Fig. 2, Table 2). Subcortically, innate right-handers showed a bilateral activation in the thalamus during handwriting, whereas converted left-handers demonstrated an activation in the right thalamus and the left globus pallidus (Fig. 2, Table 2). In the control experiment on six consistent left-handers, within-group analysis revealed a strong right-hemispheric lateralization of cortical activity during left-handed writing (Fig. 2, Table 2).

<table>
<thead>
<tr>
<th>Kinematic measures</th>
<th>Innate right-handers</th>
<th>Converted left-handers</th>
<th>Innate left-handers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical stroke length (mm)</td>
<td>6.9 (3.2)</td>
<td>6.5 (3.0)</td>
<td>7.1 (4.9)</td>
</tr>
<tr>
<td>Vertical stroke duration (msec)</td>
<td>144 (30)</td>
<td>138 (25)</td>
<td>131 (24)</td>
</tr>
<tr>
<td>Vertical writing velocity (mm/sec)</td>
<td>62 (29)</td>
<td>63 (25)</td>
<td>66 (40)</td>
</tr>
<tr>
<td>Numbers of inversions in velocity per vertical stroke</td>
<td>1.39 (0.37)</td>
<td>1.30 (0.24)</td>
<td>1.46 (0.24)</td>
</tr>
</tbody>
</table>
Innate left-handers (n = 2820) demonstrated a more prominent functional activation during handwriting compared with right-handers, four cortical clusters in the right hemisphere were observed in innate right-handers (Fig. 3). In contrast, the focus in the left dorsal LPC was activated during right-hand writing in converted left-handers as opposed to left-hand writing (Fig. 3, Table 3). These areas included foci in the posteromedial part of the right superior temporal gyrus, the right precuneus, the right parietal operculum, and the right LPC. The premotor cluster included two separate peaks of activation, located in the dorsal and ventral part of the LPC. The activity profiles, which describe the relative activation of a given voxel across experimental conditions, revealed that the right superior temporal gyrus, right precuneus, and right parietal operculum including the secondary somatosensory cortex were activated during right-hand writing in converted left-handers as opposed to a relative deactivation of these areas in innate right-handers (Fig. 3, Table 3). In contrast, the cluster in the right LPC showed some handwriting-induced activation in both groups, with a considerably stronger activation in converted left-handers.

**Between-group subtraction analysis**

Between-group subtraction analysis revealed distinct hemispheric asymmetries in the handwriting-related activation pattern between innate right-handers and converted left-handers. In innate right-handers, left-hemispheric foci in the dorsal and ventral LPC and in the inferior and superior parietal lobule were consistently more activated during writing (Table 3). The activity profiles revealed that the left parietal clusters as well as the cluster in the left ventral LPC were selectively activated during the writing condition in the innate right-handed participants only (Fig. 3). In contrast, the focus in the left dorsal LPC was activated during handwriting in both right-handers and converted left-handers, but task-related activation of the left dorsal premotor cortex was more pronounced in innate right-handers (Fig. 3).

With regard to hemispheric asymmetry, a reverse pattern of differential activation emerged in converted left-handers. In converted left-handers, four cortical clusters in the right hemisphere demonstrated a more prominent functional activation during right-hand writing (Fig. 3, Table 3). These areas included foci in the posteromedial part of the right superior temporal gyrus, the right precuneus, the right parietal operculum, and the right LPC. The premotor cluster included two separate peaks of activation, located in the dorsal and ventral part of the LPC. The activity profiles, which describe the relative activation of a given voxel across experimental conditions, revealed that the right superior temporal gyrus, right precuneus, and right parietal operculum including the secondary somatosensory cortex were activated during right-hand writing in converted left-handers as opposed to a relative deactivation of these areas in innate right-handers (Fig. 3, Table 3). In contrast, the cluster in the right LPC showed some handwriting-induced activation in both groups, with a considerably stronger activation in converted left-handers.

**Converted left-handers (n = 11): right-hand writing**

<table>
<thead>
<tr>
<th>Activated brain regions during handwriting (Brodman area)</th>
<th>Z score of peak activation</th>
<th>Coordinates of peak activation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left primary sensorimotor cortex (3/4)</td>
<td>7.09</td>
<td>-38  -24  58</td>
</tr>
<tr>
<td>Caudal supplementary motor area (6)</td>
<td>6.70</td>
<td>-16  -8   56</td>
</tr>
<tr>
<td>Left dorsal premotor cortex (6)</td>
<td>6.59</td>
<td>-26  -8   60</td>
</tr>
<tr>
<td>Right precuneus (7)</td>
<td>4.3</td>
<td>18  -64  62</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>3.70*</td>
<td>-12  -22  8</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>3.64*</td>
<td>14  -18  12</td>
</tr>
<tr>
<td>Right anterior intraparietal sulcus</td>
<td>3.42*</td>
<td>38  -44  52</td>
</tr>
</tbody>
</table>

**Converted left-handers (n = 11): left-hand writing**

<table>
<thead>
<tr>
<th>Activated brain regions during handwriting (Brodman area)</th>
<th>Z score of peak activation</th>
<th>Coordinates of peak activation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left primary sensorimotor cortex (3/4)</td>
<td>6.53</td>
<td>-38  -20  58</td>
</tr>
<tr>
<td>Caudal supplementary motor area (6)</td>
<td>5.27</td>
<td>2   -4   60</td>
</tr>
<tr>
<td>Right dorsal premotor cortex (6)</td>
<td>4.42</td>
<td>38  -2   50</td>
</tr>
<tr>
<td>Right anterior intraparietal sulcus</td>
<td>5.80</td>
<td>34  -38  52</td>
</tr>
<tr>
<td>Right superior parietal lobule (7)</td>
<td>5.21</td>
<td>26  -60  58</td>
</tr>
<tr>
<td>Right inferior parietal lobule (40)</td>
<td>4.77</td>
<td>54  -32  48</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>3.79*</td>
<td>18  -10  8</td>
</tr>
<tr>
<td>Left precuneus (7)</td>
<td>3.71*</td>
<td>-24  -62  62</td>
</tr>
<tr>
<td>Left globus pallidum</td>
<td>3.57*</td>
<td>-24  -12  2</td>
</tr>
<tr>
<td>Right parietal operculum</td>
<td>3.56*</td>
<td>58  -24  24</td>
</tr>
</tbody>
</table>

**Innate left-handers (n = 6): left-hand writing**

<table>
<thead>
<tr>
<th>Activated brain regions during handwriting (Brodman area)</th>
<th>Z score of peak activation</th>
<th>Coordinates of peak activation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left primary sensorimotor cortex (3/4)</td>
<td>5.13</td>
<td>52   -22  58</td>
</tr>
<tr>
<td>Right anterior intraparietal sulcus</td>
<td>4.65</td>
<td>48   -14  56</td>
</tr>
<tr>
<td>Right dorsal premotor cortex (6)</td>
<td>4.32</td>
<td>42   -46  62</td>
</tr>
<tr>
<td>Right superior parietal lobule (7)</td>
<td>4.30</td>
<td>44   -6   56</td>
</tr>
<tr>
<td>Right inferior parietal lobule (40)</td>
<td>4.86</td>
<td>10   -20  50</td>
</tr>
<tr>
<td>Anterior cingulate cortex/caudal SMA</td>
<td>4.92</td>
<td>6    2   48</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>4.86</td>
<td>-8   2   48</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>4.98</td>
<td>70   4   20</td>
</tr>
<tr>
<td>Right ventral premotor cortex (6)</td>
<td>3.56*</td>
<td>16   56   24</td>
</tr>
</tbody>
</table>

The asterisks indicate trend activations (i.e. activations with maximum Z scores ranging between 3.09 and 4.26).
considerable spatial overlap of the respective clusters of activation is illustrated in Figure 3, which provides an overlay of the statistical parametric maps for both within-subject analysis and between-subjects analysis.

In both groups, an additional prefrontal cluster was observed that showed a differential effect of handedness on task-related activation (Table 3). In contrast to premotor, temporal, and parietal clusters, however, within-group analyses revealed no trend activation of the prefrontal cortex during handwriting per se. Indeed, the prefrontal cortex was deactivated during automatic right-hand writing. As a consequence, the differential effect on writing-related activation in the prefrontal cortex was attributable to differences in writing-related deactivation rather than writing-related activation (Fig. 3). Because the prefrontal clusters were located outside the predefined brain regions of interest (i.e., those brain regions showing at least trend activation during right-hand writing per se as indicated by within-group analyses) and failed to reach an uncorrected value of \( p = 0.05 \), the prefrontal clusters are only descriptively reported.

**Table 3. Between-group differences in handwriting-related regional brain activation**

<table>
<thead>
<tr>
<th>Activated brain regions (Brodmann area)</th>
<th>Z score of peak activation</th>
<th>Coordinates of peak activation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate right-handers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left superior parietal lobule (7)</td>
<td>3.96</td>
<td>(-26) (-52) 60</td>
</tr>
<tr>
<td>Left precuneus (7)</td>
<td>3.24</td>
<td>(-12) (-66) 56</td>
</tr>
<tr>
<td>Left inferior parietal lobule (40)</td>
<td>3.74</td>
<td>(-54) (-32) 44</td>
</tr>
<tr>
<td>Left dorsal premotor cortex (6)</td>
<td>3.63</td>
<td>(-20) (-8) 64</td>
</tr>
<tr>
<td>Right superior frontal gyrus</td>
<td>3.61*</td>
<td>10 38 58</td>
</tr>
<tr>
<td>Left ventral premotor cortex (6)</td>
<td>3.60</td>
<td>(-66) (-10) 32</td>
</tr>
<tr>
<td>Converted left-handers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right precuneus (7)</td>
<td>3.83</td>
<td>18 (-44) 54</td>
</tr>
<tr>
<td>Right parietal operculum (1/2)</td>
<td>3.74</td>
<td>66 (-16) 22</td>
</tr>
<tr>
<td>Right superior temporal gyrus (22)</td>
<td>3.67</td>
<td>56 (-28) 22</td>
</tr>
<tr>
<td>Right dorsal premotor cortex (6)</td>
<td>3.33</td>
<td>40 (-40) 10</td>
</tr>
<tr>
<td>Right ventral premotor cortex (6)</td>
<td>3.25</td>
<td>44 (-8) 54</td>
</tr>
<tr>
<td>Left superior frontal sulcus</td>
<td>3.25*</td>
<td>46 0 34</td>
</tr>
</tbody>
</table>

The asterisks indicate brain regions that are located outside the predefined search volume.

Innate right-handers demonstrated more asymmetrical functional activation during right-hand writing, with a relative increase in right-hemispheric activity of frontoparietal motor association areas ipsilateral to the writing hand. Consistent left-handers demonstrated a mirrored activation pattern with preponderant right-hemispheric activation when writing with their dominant left hand. In contrast, converted left-handers demonstrated more symmetrical functional activation during right-hand writing, with a relative increase in right-hemispheric activity of frontoparietal motor association areas ipsilateral to the writing hand.

Because this PET study used only writing as the task of interest, the present study cannot be generalized to other manual skills. Although a control task in which the subjects would have performed manual tasks other than handwriting (e.g., drawing, sequence of key-presses) would have been desirable, there are several problems in defining an appropriate control task that allows a meaningful comparison. First, it would have been difficult to match any control task for executive aspects of the task (i.e., number of submovements and complexity of the movement patterns). Second, the degree of automaticity is likely to differ among tasks because of differences in the amount of daily practice throughout life. Third, handwriting was the only manual skill that was consistently switched in converted left-handers. Thus, other tasks would probably be less sensitive at picking up functional changes associated with switching hand preference.

**Premotor cortex**

Using functional magnetic resonance imaging (MRI), Rintjes et al. (1999) mapped the cerebral activation pattern while right-handed subjects wrote their signature with the right index finger or right big toe. The anterior parts of “hand areas” in the dorsal and ventral LPC, as well as the SMA, were activated during both conditions, suggesting an “effector-independent blueprint” of writing in frontal premotor association areas. Our findings suggest that this blueprint is preferentially stored in the left LPC of right-handers and in the right LPC of left-handers. Thus, right-handers demonstrated more prominent activation in the left dorsal and ventral LPC during right-hand writing, whereas a stronger activation of the right LPC was observed in converted left-handers.

Functional imaging studies on innately left- and right-handers substantiate this handedness-dependent functional lateralization...
in the LPC. In left-handers, the right dorsal LPC is activated by both contralateral and ipsilateral finger movements, whereas the left dorsal LPC is active only during contralateral finger movements (Kawashima et al., 1997). Furthermore, left-handers preferentially activate the right ventral LPC during cycling movements of both hands, but right-handers demonstrate the opposite pattern (Vivani et al., 1998).

In the present study, the right rostral SMA showed a positive linear relationship with the degree of left-handedness. This suggests that the right rostral SMA contributes to adaptive plasticity.
of manual motor control in converted left-handers. Two alternative mechanisms related to task execution or initiation, however, may also contribute. First, converted left-handers perhaps paid more attention to right-hand writing because task execution was more difficult. If present, relative differences in task difficulty could partially account for activation of the rostral SMA, which is involved in higher-order aspects of manual motor control, including a range of supervisory functions (Deiber et al., 1991; Hikosaka et al., 1996; Tanji, 1996; Boecker et al., 1998; Nagahama et al., 1999; Sakai et al., 1999). It is unlikely, however, that discrepancies in task execution explain all activation differences between converted left-handers and right-handers. Right-hand writing was highly overlearned after several decades of everyday practice in both groups, suggesting that right-hand writing was not more complex for converted left-handers. Indeed, kinematic analysis of writing movements confirmed a high and comparable degree of automaticity for both groups. Furthermore, within-group analyses revealed no writing-related activation in the lateral prefrontal cortex and anterior cingulate cortex of either group, suggesting that both right-handers and converted left-handers wrote without paying particular attention (Jenkins et al., 1994; Juceptner et al., 1997; Toni et al., 1998). Significantly, between-group differences in writing-related activity in the medial prefrontal cortex were caused by task-related deactivation, which argues against differences in the amount of active task monitoring during writing.

A second possibility for the differences in rostral SMA activity is that converted left-handers with residual left-handedness have more difficulties in initiating right-hand writing and may also have to inhibit movements with the preferred left hand. Thus, response selection and suppression could cause increased activation of the right rostral SMA, which has been shown to participate in response initiation, selection, and suppression (Deiber et al., 1991, 1996, 1999; Humberstone et al., 1997; Schluter et al., 1998, 2001; Sakai et al., 2000; Waldvogel et al., 2000). Response selection may be activated subconsciously when converted left-handers with strong residual left-handedness engage in manual activities that have been successfully switched to the right hand.

Only the right rostral SMA demonstrated a positive relationship between the degree of left-handedness and the rCBF during right-hand writing. This finding extends previous imaging studies that have observed a functional asymmetry of the rostral SMA (Hikosaka et al., 1996; Deiber et al., 1999), suggesting a complex interhemispheric distribution of activity in the rostral SMA. When learning a new movement sequence, six of eight right-handed subjects showed a predominant focus of learning-related activation in either the right or left pre-SMA, according to the subject (Hikosaka et al., 1996). Furthermore, Deiber et al. (1999) reported a preponderant activation of the right rostral SMA for self-initiated finger movements with the right hand in innate right-handers.

Parietal cortex

Depending on the direction of handedness, several foci in the rostral parietal cortex showed a biased activation toward one hemisphere during right-hand writing. A focus in the left anterior superior parietal lobule, extending into the precuneus, and a focus in the left anterior inferior parietal cortex were exclusively activated in innate right-handers. In contrast, distinct foci in the right anterior parietal lobule and the right parietal operculum, covering the secondary somatosensory cortex, were selectively active during right-hand writing in converted left-handers. In addition, innate left-handers showed only a right-sided activation of the parietal cortex during left-hand writing.

Because visual feedback was denied in our study, participants had to rely on previous knowledge, internal feedback from the motor outflow ("effenter copy"), and kinesthetic feedback to estimate their writing movements. The lateralized activation pattern in anterior parietal areas may therefore reflect a kinesthetic representation of writing movements in the parietal cortex contralaterally to the innately preferred hand. Indeed, lesion and functional imaging studies in humans suggest that anterior modules of the human parietal cortex, especially the superior parietal lobule, are related to elaboration of somatosensory input (Roland, 1987; Paus et al., 1989; Binkowski et al., 1999). These somatosensory functions of the parietal cortex include a critical role in generating and maintaining a kinesthetic model of ongoing movements (Sirigu et al., 1996, 1999) and spatiotemporal organization of complex movements (Weiss et al., 2001). Our findings suggest that this also applies to handwriting, regardless of the direction of handedness or conversion at a young age.

The right anterior supramarginal gyrus showed a graded increase in functional activation with the degree of left-handedness. This observation may be explained by motor preparation before actual handwriting. Our participants needed ~2 sec to write the target word. Because the writing task was paced every 6 sec, participants had several seconds left for motor preparation until the next “go” signal. Functional imaging studies on innate right-handers suggested a dominant role in movement preparation and selection for the left inferior parietal lobule (Deiber et al., 1996, 1998; Schluter et al., 2001). Accordingly, lesions of the left supramarginal gyrus impair normal covert motor preparation (Rushworth et al., 1997). Therefore, the positive relationship between functional activity in the right supramarginal gyrus and the degree of left-handedness might indicate a greater effort related to movement preparation in left-handers, who, as mentioned above, may have had more difficulty with task initiation.

Temporal cortex

Although auditory input was matched between the writing and baseline conditions, the behavioral relevance of listening to the tone differed between conditions, because the tone served as the go signal in the handwriting condition only. Converted left-handers showed a relatively stronger writing-related activation of the postero medial part of the right superior temporal gyrus, which forms part of the auditory association cortex (Zatorre and Belin, 2001). This differential activation pattern suggests a functional asymmetry of auditory processing related to the direction of handedness. This concept corroborates morphometric MRI studies that demonstrated a weaker leftward asymmetry of the planum temporale in left-handers as opposed to right-handers (Steinmetz, 1996). Alternatively, the activation pattern in the superior temporal gyrus may be related to the language aspect of writing and thus indicate a less pronounced left-hemispheric dominance for language in converted left-handers compared with right-handers (Knoch et al., 2000).

SM1

The hand area of the SM1 unexpectedly demonstrated no interhemispheric differences in writing-related activation between right-handers and converted left-handers. At first glance, this finding is in contrast to studies that reported structural and functional differences in SM1H depending on the direction or degree of handedness (Yoshii et al., 1989; Kim et al., 1993;
Triggs et al., 1994, 1997; Amunts et al., 1996; Dassonville et al., 1997; Volkman et al., 1998). However, these studies did not control for proficiency in handwriting skills. This is particularly relevant when investigating task-related changes in neural activity, because the SM1 is subject to profound long-term reorganization as a result of motor practice and learning (Jenkins et al., 1990; Sanes et al., 1992; Pascual-Leone et al., 1994; Karni et al., 1995; Xerri et al., 1999). Therefore, long-term differences in motor practice could have caused functional and structural differences between the dominant and non-dominant SM1 in previous studies. Furthermore, previously reported ipsilateral activations of SM1 during movements of the non-dominant hand were perhaps caused by a lower automaticity of movement performance (Mattay et al., 1998; Schluter et al., 2001). These two mechanisms (use-dependent cortical plasticity and reduced automaticity) played a much smaller role in our study. The absent relationship between neural activity in the SM1 and handedness in the present study suggests that asymmetries in the SM1 primarily reflect a long-term consequence of handedness, rather than its primary driving source.

Conclusion
Adult converted left-handers show persistent features of left-handedness during right-hand writing. Extending previous studies, which emphasized functional asymmetries at the executive level of the motor system (e.g., the SM1), our results provide evidence for a neural substrate of human handedness in premotor and parietal motor association areas.

REFERENCES