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NETWORK ACTIVATION DURING BIMANUAL MOVEMENTS IN HUMANS

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Abstract

The coordination of movement between the upper limbs is a function highly distributed across the animal kingdom. How the central nervous system generates such bilateral, synchronous movements, and how this differs from the generation of unilateral movements, remains uncertain.

Electrophysiologic and functional imaging studies support that the activity of many brain regions during bimanual and unimanual movement are quite similar. Thus, the same brain regions (and indeed the same neurons) respond similarly during unimanual and bimanual movements as measured by electrophysiological responses. How then are different motor behaviors generated?

To address this question, we studied unimanual and bimanual movements using fMRI and constructed networks of activation using Structural Equation Modeling (SEM). Our results suggest that (1) the dominant hemisphere appears to initiate activity responsible for bimanual movement; (2) activation during bimanual movement does not reflect the sum of right and left unimanual activation; (3) production of unimanual movement involves a network that is distinct from, and not a mirror of, the network for contralateral unimanual movement; and (4) using SEM, it is possible to obtain robust group networks representative of a population and to identify individual networks which can be used to detect subtle differences both between subjects as well as within a single subject over time. In summary, these results highlight a differential role for the dominant and non-dominant hemispheres during bimanual movements, further elaborating the concept of handedness and dominance. This knowledge increases our understanding of cortical motor physiology in health and after neurological damage.

INTRODUCTION

The coordination of movement between the upper limbs is a function omnipresent throughout the animal kingdom (Iwaniuk and Whishaw 1999). The complex mechanisms by which the central nervous system (CNS) generates such movements are only partly elucidated. Although it is now commonly considered that bimanual movements are the product of integrated motion of the two hands, rather than a summation of independent movements (Bogaerts and Swinnen 2001; Cardoso de Oliveira et al., 2001; Carson et al., 2000; Franz et al., 2001; Gribova et al., 2002; Swinnen et al., 1991), such actions likely consist of both independent and integrated features. Thus, bimanual movements involve coordinated motion in time and space, but also rely on the ability of movements performed with each hand to be different (Massion et al.,

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1989; Perrig et al., 1999). The neurobiological mechanisms underlying the production of such orchestrated behaviors are as yet unclear.

Lesion studies have shown that whereas damage to the basal ganglia, cerebellum, corpus callosum, superior parietal lobule (PAR), supplementary motor area (SMA), and cingulate motor area (CMA) affect different aspects of bimanual control, they do not abolish them (Brown et al., 1993; Cardoso de Oliveira et al., 2001; Doody and Jankovic 1992; Eliassen et al., 2000; Franz et al., 1996; Geffen et al., 1994; Jackson et al., 2000; Leonard et al., 1988; Obhi et al., 2002; Serrien et al., 2001a; Serrien et al., 2001b; Stancak et al., 2003; Stephan et al., 1999a; Tanaka et al., 1996). Brain imaging and electroencephalographic (EEG) studies in humans have provided confirmatory information about brain areas active during bilateral hand movements, and have added additional areas, including the inferior parietal lobule, secondary somatosensory area, dorsal lateral premotor cortex, medial prefrontal area, precuneus, primary motor (M1) and somatosensory areas, and superior temporal area, with some particular attention to the left (dominant) hemisphere (Andres et al., 1999; de Jong et al., 1999; Disbrow et al., 2001; Goerres et al., 1998; Immisch et al., 2001; Jancke et al., 1998; Nair et al., 2003; Sadato et al., 1997; Toyokura et al., 2002; Ullen et al., 2003; Urbano et al., 1998). Among these regions, SMA has been a prime candidate for the coordination of movements (Debaere et al., 2001; Gerloff and Andres 2002; Swinnen 2002; Swinnen et al., 2002). For some authors, however, the role of SMA relates more to the coordination of complex movements than to bimanual synchronization *per se* (Lang et al., 1988; Stephan et al., 1999b). Crucially, all of these studies reinforce the notion that large distributed circuits are involved in coordination and synchronization of bimanual movements, though they do not explain how these movements are encoded in such a system.

Basic mechanisms of bimanual control have been described in electrophysiological studies in macaques. Single cell recordings in M1 and SMA have shown that individual neurons in these areas respond differentially to unimanual and bimanual movements, with responses during bimanual movements that are not the product of a linear combination of the unimanual movements (Donchin et al., 1998; Donchin et al., 2002; Steinberg et al., 2002) (but see (Aizawa et al., 1990) for an alternative view). Surprisingly, the proportion of neurons with these differential responses appears to be similar in M1 and SMA. These results, along with results from functional imaging experiments (Habas and Cabanis 2007; Toyokura et al., 1999; Toyokura et al., 2002; Ullen et al., 2003), suggest that bimanual activation is produced not by specific brain regions, but rather involves the differential activation of populations of neurons located in M1 and SMA. Additional studies of the possible physiological underpinnings of bimanual movements are particularly interesting because they use ecologically appropriate and skilled hand movements and they focus on characterizing networks rather than specific loci of activity (Kazennikov et al., 1999; Kazennikov et al., 1998; Kermadi et al., 2000; Kermadi et al., 1998; Kermadi et al., 1997). These studies show that lesions of SMA affect the initiation, but not the actual performance, of bilateral movements. Furthermore, they show that about 50% of neurons in SMA and M1 respond during both unimanual and bimanual movements, whereas neurons encoding only bimanual movements are rare in M1 (5%) and only slightly more common in SMA (19%). Moreover, other areas such as dorsal premotor cortex (PMd), PAR, CMA, and basal ganglia also have similar responses in unimanual and bimanual movements.

Thus, numerous electrophysiologic and functional imaging studies reinforce the notion that multiple brain regions are involved in the production of bimanual movements, and that general activation of these regions during bimanual movements does not differ greatly from responses during unimanual movements. Consequently, it appears that the same brain regions (and, indeed, the same neurons) respond during unimanual and bimanual movements. This presents

the major challenge of explaining how different motor behaviors are generated using similar neural substrates.

To address this question, we combined task-dependent fMRI with Structural Equation Modeling (SEM) (Solodkin et al., 2004) to explore not only which brain regions are active in production of unimanual and bimanual movements, but also how the same brain regions interact to produce these varied behaviors. Few studies have directly assessed the characteristics of neural networks responsible for these movements (Swinnen 2002; Swinnen and Wenderoth 2004), i.e., the nature of the effects exerted by different brain areas over those with which they are anatomically connected. This approach changes the emphasis of investigation from the individual brain regions active during specific conditions to their interrelationships during production of behavior. Therefore, the primary objective of the present study was to assess the patterns of network activation during simple, in-phase, unimanual and bimanual movements in order to begin to understand how changes in the relationships between brain regions result in different motor behaviors. We chose to concentrate on simple in-phase movements to limit the confounding variables involved in using anti-phase and non-synergistic movements, and to facilitate SEM analysis. Thus, this approach will provide a framework to pursue future network investigations of more complex movement tasks.

METHODS

EMG study

Electromyography (EMG) during unpaced unimanual and bimanual thumb-forefinger opposition was performed prior to the scanning session, and was used to screen for the presence of mirror movements (particularly in stroke subjects who can sometimes exhibit such behavior). Though the EMG-recorded movements were unpaced, unlike the paced movements in the scanner, the subjects were asked to keep their movements as rhythmic and consistent as possible approximating one finger-thumb opposition per second, similar to previous studies (Viviani et al., 1998; Ullen et al., 2003). Surface electrodes were placed on the *extensor digitorum communis* (EDC) of both arms. EMG was recorded using a Biopac 100B amplifier (Santa Barbara, CA), and band-pass filtered at 20–500 Hz. The EMG data were analyzed by rectifying and integrating the signal and then smoothed by resampling it (mean value of 100 samples). To assess differences in the initiation of movements by the right and left hands (while performing a mirror bimanual task) we superimposed the two EMG recordings and then calculated the difference in time to peak between the traces from the two hands. This was done by placing markers at the initial peaks of the function and then computing the difference between them on the abscissa. Comparisons of movement initiation times during the bimanual task from the two hands were made using Student's *t* test.

Imaging study

Subjects—The subjects participating in the study included twelve right-handed and two left-handed healthy adults (scores -0.5 and -0.1 as assessed by the Edinburgh Handedness Inventory (Oldfield 1971)), and a right-handed adult in the chronic phase of left MCA distribution ischemic stroke (25 months post-stroke) affecting primarily left superior parietal lobule (BA 7), left primary and association somatosensory cortices (BA 1,2,3,5), and left primary motor cortex (BA 4). Please see MRI images in the supplementary material for visualization of the lesion. The patient had moderate right hemiparesis (4/5 per MRC scale) and profound right hemisensory loss along with increased tone and hyperreflexia in the right upper extremity. In addition, his scores on the Wolf Motor Function Test (Wolf et al., 2001) were 6.71 (sec) and 2.5 FA, the Fugl-Meyer Score (Fugl-Meyer et al., 1975) was 0.48, and the nine hole peg test (Mathiowetz et al., 1985) score was > 2 min, FIM 100. The study was

approved by the Institutional Review Board of the Biological Science Division of The University of Chicago. All subjects understood 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. Electrostatic headphones (Resonance Technologies, Northridge, CA) were wrapped around the ears and connected to a stereo system controlled by a Macintosh™ computer. The computer used the PsyScope psychological software system (Cohen et al., 1993) to present the experimental conditions. The movement task was thumb-forefinger opposition (e.g. left forefinger to left thumb, right forefinger to right thumb) externally paced by auditory stimulus at a rate of 2Hz. We employed a boxcar design for alternating unimanual and bimanual movement with a period of rest following each movement period. The onset of each task was signaled with an auditory command for rest, right-hand, left-hand, or bimanual movement. Blocks of activity lasted 24 seconds each, alternating with rest blocks lasting 12 seconds. One experimental run consisted of twelve active blocks with intercalated rest blocks with a total duration of 7:12 ((24 sec + 12 sec) × 12 blocks = 432 sec). The first experimental run (a dominant hand run) contained sequences of dominant hand movement, rest, bimanual movement, and rest. The second run (a non-dominant hand run) contained sequences of non-dominant hand movement, rest, bimanual movement, and rest. These two runs were followed by another dominant hand run and another non-dominant hand run, for a total of four runs per participant.

Imaging—Data acquisition used the spiral k-space method (Noll et al., 1995) on a 3T Signa™ scanner (GE Medical Systems, Milwaukee, WI) with a standard quadrature GE head coil. Thirty contiguous 5mm 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 $1.875 \times 1.875 \times 5$ mm resolution over a 24 cm field-of-view (FOV). T_2^* -weighted imaging was accomplished with a gradient echo time (TE) of 25 ms, and a repetition time (TR) of 2000 ms with a flip angle of 80° . High-resolution anatomical images were acquired with a 3D Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence that used the following parameters: TE=3.2ms, TR=8ms, preparation time=725ms, flip angle 6° , field of view 24cm for a resolution of $0.9375 \times 0.9375 \times 1.5$ mm.

Image analysis

Intra-subject analysis: Data analysis began with rigid-body three-dimensional registration of images to align the functional and anatomical datasets. The alignment parameters were computed by an iterative weighted least squares fit to a reference volume (Cox and Jesmanowicz 1999). Statistical analysis of individual subject data was performed using multiple linear regression in which the signal time course for each voxel was compared to a reference waveform of expected activity for each task for each hand. The reference waveform was based on the convolution of a square wave with an empirical model of the hemodynamic response (Cox 1996). Voxels were considered active if the single voxel p -value was less than 1×10^{-5} , and a three-dimensional contiguity requirement was enforced, requiring clusters (sets of contiguous voxels) to contain at least three voxels (53 mm^3). These values were determined following a Monte-Carlo simulation that established a corrected whole brain significance level ($\alpha < 0.05$) (Forman et al., 1995). The resulting clusters that survived both the initial F-test and the clustering threshold defined the presence of activation in the brain for each subject.

Inter-subject analysis: Multi-subject analysis was performed using an anatomical region-of-interest (ROI) approach, based on several specific regions of interest identified *a priori* in each hemisphere on the basis of the known functional neuroanatomy of the human motor system. The areas included the following: M1 (primary motor cortex), S1 (primary and association

somatosensory cortices), PMd (lateral premotor cortex, dorsal), PMv (lateral premotor cortex, ventral), SMA (supplementary and pre-supplementary motor areas), PAR (superior parietal lobule and intra-parietal sulcus), and CMA (cingulate motor area). Cerebellum and thalamus were also included as two additional regions. Regions were drawn by hand in each hemisphere of each brain individually by a single investigator (RW) and checked by another (AS) using landmarks reported previously (Bhimani et al., 2006; Solodkin et al., 2004; Solodkin et al., 2001). This individualized approach aims to minimize the effects of anatomic and functional variability between individuals (Brett et al., 2002; Uylings et al., 2005) and the inconsistent correlation between surface anatomy and cytoarchitectonics (White et al., 1997; Zilles et al., 1995). The boundaries for each region were determined based on the following landmarks: the hand area of M1 was defined as the anterior bank of the central sulcus as determined by the location of the knob (Yousry et al., 1997). The posterior corner of the lateral edge of the precentral gyrus was the boundary between M1 and the PMd. The limit with S1 was in the *fundus* of the sulcus. The inferior limit was placed at the lower third of the central sulcus. The PMd was defined as the area between M1 and an imaginary line in the coronal plane through the anterior commissure (Vac), bounded inferiorly by the superior edge of the inferior frontal sulcus. The ventral portion of PM (PMv) was the region of PM located in the lower portion of the precentral gyrus and included in addition, the precentral sulcus and the pars *opercularis* of the inferior frontal gyrus. The reason for combining these two areas into one region are twofold: 1) PMv is more aligned with area 44 than with PMd from a cytoarchitectural viewpoint (Brodmann 1909; Kotter et al., 2001; Rizzolatti et al., 2002), and 2) previous studies suggest contiguity of function across the two areas in imitation (Rizzolatti and Arbib 1998; Rizzolatti et al., 2001; Rizzolatti and Luppino 2001). S1 (sensory complex) was defined as the postcentral gyrus and posterior bank of the central sulcus along the same inferior-superior and lateral extents as M1. SMA was defined as the medial region of the hemispheres superior to the dorsal bank of cingulate sulcus along the same anterior-posterior extent as PMd. Pre-SMA was defined as the medial region bounded posteriorly by the Vac plane and limited anteriorly by a coronal plane at the level of the *genu* of the *corpus callosum* as described previously (Picard and Strick 1996; Picard and Strick 2001). The PAR was defined as the region immediately posterior to sensory complex and bounded posteriorly by a vertical plane at the level of the occipito-parietal sulcus and by the intraparietal sulcus inferiorly (superior bank included in the region). Medially it was limited by the parieto-occipital sulcus posteriorly and the cingulate sulcus inferiorly. The medial pre-frontal region (PF) was limited ventrally by the inferior frontal sulcus, dorsally by the superior frontal sulcus, anteriorly by a vertical plane at the anterior edge of these sulci and posteriorly by the PM area. For images of the ROIs, please refer to Figure 1, and for a list of regions please refer to Table 1.

The image data were subjected to two complementary analytical approaches. Initial analysis involved statistical inferences on the raw data. An analysis of variance (ANOVA) was performed on the thresholded brain activation data with task and region as fixed factors and subject as a random factor. The statistics were performed in StatView 5.0 for Macintosh (SAS Institute, Cary, NC).

Subsequent analysis involved the construction of networks for uni- and bimanual movements using SEM. The modeling was performed using the Amos software (Arbuckle 1989). The procedural steps used to assess networks of activation with SEM have been previously published (Solodkin et al., 2004), but will also be described here:

- a. Determination of an anatomical model: Construction of such a model requires a theoretical anatomical network incorporating “connection strengths” among the nodes (ROIs) of the model. Such theoretical networks are inferred from anatomical connectivity data in macaques. Thus, a theoretical model is developed based on known anatomic connectivity between brain regions in combination with empirically

determined regional volumes of activation to estimate theoretical physiological strengths between each pair of nodes as previously published (Solodkin et al., 2004). Subsequent determination of SEMs for unimanual and bimanual tasks is thus constrained by this initial theoretical model.

- b. Generation of the covariance matrix for each subject: This first requires generation of a representative time series for all active voxels in each ROI for each individual subject, and then calculating the covariance across each pair of regional time series. We created a regional time series from active voxels in each region in four ways: 1) determination of a peak voxel (the voxel with the highest statistical value), 2) a simple average of active voxels (corrected $p < 0.05$), 3) detection of the first eigenvector determined through single value decomposition, and 4) a median time series.
- c. Generation of a group covariance matrix: Based on the above approaches, four group models were generated by averaging the time series of all subjects.
- d. Generation of the structural equations: The interregional correlations of activity were used to assign initial numerical weights to the connections (path coefficients) in the anatomical model, leading to the functional model (Gonzalez-Lima and McIntosh 1994; McIntosh 1999; McIntosh and Gonzalez-Lima 1994).
- e. Solving the equations (AMOS for Windows version 4.0; SmallWaters Corp, Chicago, IL): The equations were solved simultaneously using an iterative Maximum Likelihood Method to obtain an optimal value for each connection that represents the effective connectivity from each pair of ROIs (nodes). The best solution to the set of equations minimizes the differences between the observed and the predicted covariance matrices.
- f. Goodness of fit between the predicted and observed variance matrices: The next step in the use of the model includes the use of goodness-of-fit statistics using χ^2 distribution with $q(q+1)/2 - p$ degrees of freedom (where q is the number of ROIs and p is the number of unknown coefficients which equals the number of path connections plus the residual terms). If the null hypothesis was not rejected ($p \geq 0.05$), a good fit was obtained. This fitting process was continued until residual values on each node (with inputs) were less than 50% (residual values are the amount of variance not explained by the inputs present in the model).
- g. Validation against individual subjects: After obtaining group network models with good fit, we determined if the resulting networks could be applied to the individual subjects.
- h. Only the group models that had good cross-validation were used. Based on these group models, we then individually applied the group right-handed model to the left-handed cases. For this, a mirror right-handed model was used. If the left-handed case did not fit the right-handed group model, then a left-handed model was generated.

Model validation: First, the group model based on the AMOS software was fully identified by calculating the eigenvalues and eigenvectors of the Hessian matrix. Second, before making functional inferences from the network model, we took additional validation steps to ensure that the statistical measures were robust. In particular, we needed to ensure that the Maximum Likelihood Method, used to minimize the difference between the observed and predicted covariance matrices, reached a global, rather than a local, solution. This step is not automatically performed by the AMOS software, and thus additional validation is appropriate.

Therefore, we performed two different randomization tests to ensure that path connections were estimated at the global minimum not the local minimum. The first approach was iterative,

in which we assigned initial values to all path connections and fit the model, chose a path connection and assigned an initial value, and refitted the model keeping all other path connections fixed. Several different initial values were used for the randomly chosen path connections and several different path connections were tested. The second randomization test was more parallel, in which we chose a set of path connections, assigned random initial values, and then fitted the model. This step was performed for several randomly chosen sets of path connections. Crucially, these two different procedures yielded the same chi-square value and path coefficient estimations as those included in the paper. This suggests that the final model was independent of initial values of path coefficients.

RESULTS

EMG

Muscle activation of the right hand preceded activation of the left hand during ‘simultaneous’ bimanual movement in right-handed subjects by an average 53 ± 39 ms (from 180 ms vs. 350 ms; $p = 0.029$) (Figure 2A). This trend was not observed in the weakly left-handed individual or in the stroke patient.

BRAIN IMAGING

Volumes of activation (Figure 2B, C, D)

Unimanual Movement: Volumes of functional activation were increased in the hemisphere contralateral to the movement compared to the ipsilateral hemisphere in most brain regions (M1, S1, PMd, SMA) for both right- and left-handed unimanual movements. Volumes of activation were similar, however, in both hemispheres during right- and left-handed movement in PMv, CMA, and PAR. Despite these general ROI-activation similarities for both right- and left-handed unimanual movements, the patterns of hemispheric activation were not mirror images. In particular, larger volumes of activation were noted in contralateral (left) M1 and PMd for right-handed movements compared to left-handed movements, and in contralateral (right) S1 for left-handed compared to right-handed movements.

Bimanual movement: For all brain regions, unilateral volumes of activation during bimanual movement were larger than those for unimanual movements. Despite the overall similarities between right and left hemisphere brain activation in bimanual movements (as for unimanual movements), the hemispheric activation patterns were not mirror images. For example, the regional volumes of activation increased similarly in the two hemispheres from unimanual to bimanual movement, except in SMA (L increase $>$ R) and PMd (R $>$ L). Furthermore, increases in activation in bimanual movement were less in ‘primary’ than in ‘secondary’ or ‘association’ regions: primary brain regions subtract out almost completely when compared with unimanual movement, though with different patterns in the two hemispheres (Figure 2C and D).

Network analysis

Statistical group analysis in right-handed subjects: Our results showed that two of the four approaches to creating regional time series -- the peak-voxel or the simple average methods -- led to group models with good fits to the experimental data (using the first eigenvector and the median did not provide models with good fit). Thus, only these two models were considered for the second stage, in which we validated the group model against the individual models for each experimental subject. The cross validation assessment for the “simple average” group model only fit 5 of 12 subjects, whereas the “peak-voxel” group model fit all individual subjects. The probability values obtained for each subject with these two methods are listed in Table 2. Based on these results, subsequent analysis was performed exclusively on group networks constructed with the peak-voxel method. It should be noted here that the thalamus

and cerebellum were excluded from the final network analysis. This was due to an inability to build reliable SEMs that included these structures, a problem that derived from insufficient *a priori* anatomic sub-parcellation of these regions probably necessary to describe interactions among thalamus, cortex, and cerebellum. This technical limitation is being addressed in ongoing studies. Thus, the SEM presented here emphasizes the cortical networks involved in bimanual movement.

Unimanual movement: The final networks associated with unimanual and bimanual movements are shown in Figure 4. For all the network models described, primarily forward connections were considered since the behavioral paradigm involved overt movements.

The network model obtained during movements with the dominant right hand in right-handed subjects ($\chi^2=29.6$, DOF=22, $p=0.128$) showed two features (Figure 4A):

- a. The effective connectivity values within the dominant hemisphere tended to be larger (i.e., stronger) than those in the non-dominant hemisphere.
- b. The strength of inter-hemispheric connections was greater from the dominant to the non-dominant hemisphere than in the opposite direction. Furthermore, the connectivity values in the dominant to non-dominant direction tended to be strongest among homologous sensory areas.

The final network model during movements with the non-dominant left hand (Figure 4B) was not the mirror image of the network obtained during movements with the right hand ($\chi^2=25.4$, DOF=17, $p=0.086$). Interestingly, whereas the pattern in the cortico-cortical connections in the dominant, left hemisphere was similar to the cortico-cortical network in the same hemisphere during right hand movements, the inter-hemispheric connections did not display the strong bias from the dominant to the non-dominant hemisphere observed among some sensory regions for the right hand.

Bimanual movement: The final group network model for bimanual movements in right-handed subjects ($\chi^2=9.6$, DOF=5, $p=0.087$) shows several interesting features (Figure 4C):

- a. Even when movements executed with both hands appear similar (mirror movements), the cortico-cortical connections within the dominant and the non-dominant hemispheres are different. In fact, the effective connectivity values in the dominant hemisphere were similar to those seen in the dominant hemispheres during unimanual movements. In contrast, the cortico-cortical network for bimanual movements in the right hemisphere was shifted towards sensory areas (S1 and PAR).
- b. The effective connectivity of the inter-hemispheric connections tended to be stronger from the dominant SMA to the non-dominant SMA, paralleling the right-handed unimanual network. In contrast to unimanual movement, the effects of sensory regions and M1 on the homologous contralateral side were now weak, leaving callosal SMA connectivity as a primary component of bimanual movements.

Left-handed models during bimanual movement: The comparison of individual bimanual models for each of the two left-handed participants with the right-handed group model produced interesting results. To make this comparison, we switched the group right-handed model to its mirror image (hence the dominant hemisphere would now be represented by the right hemisphere). The individual model for one of the left-handed participants fit the mirror group right-handed model ($p = 0.119$). This participant was strongly left-handed by the Edinburgh Handedness Index. In contrast, the individual model for the second left-handed participant with weaker handedness did not fit the mirror right-handed group model ($p = 0.034$).

Figure 4D shows the final model for the weakly left-handed case ($\chi^2=4.79$, DOF=4, $p=0.31$) and Figure 3 shows the fMRI activation and EMG.

Two aspects of the model for the weakly left-handed participant are remarkable: first, the networks of activation between the dominant and the non-dominant hemispheres are less biased than in the right-handed group model. Second, the strength of inter-hemispheric connections between sensory regions (S1) remained high, whereas the SMA connection did not. Instead, connectivity between PMd regions was high from the left to the right hemisphere.

Stroke model for bimanual movement: Similar to the case of the weakly left-handed participant, the individual model for the stroke participant did not fit the right-handed group model, but in this case the difference between them was much more pronounced ($p = 0.009$). Figure 5 shows the final model for the stroke data ($\chi^2=22.67$, DOF=16, $p=0.123$) along with fMRI activation maps and EMG. Note that most of the effective connectivity values in both the affected and the non-affected hemispheres were lower than in controls. The higher values, however, were still seen in the dominant (affected) hemisphere. Probably the most remarkable difference between the stroke model and the model for each of the controls was the recruitment of additional brain regions during bimanual movements. These were located in the prefrontal regions including the middle frontal gyrus and the inferior frontal gyrus and sulcus. Interestingly, effective connectivity in the commissural pathways tended to be low except between the recruited prefrontal regions that showed lateralization from the dominant (affected) to the non-dominant hemispheres.

DISCUSSION

The key findings of this paper are as follows: (1) in right-handed individuals, the dominant hemisphere appears to initiate bimanual movement; (2) bimanual movement activates regions similar to those observed during unimanual movement; (3) the production of dominant-hand unimanual movement involves a network that is distinct from, and not a mirror of, the network for the non-dominant hand; (4) intra-hemispheric connectivity during bimanual movements is not identical in both hemispheres; (5) inter-hemispheric connectivity changes from unimanual to bimanual movements; (6) using SEM, it is possible to obtain robust group network models (from individual models) that are representative of a population; and (7) SEM models are sensitive enough to allow comparisons between such group models and individual cases, thus quantifying the degree of similarity between an individual and a normative group.

EMG and volumes of activation

The EMG data presented here indicate that during a bimanual task, movement of the dominant hand precedes movement of the non-dominant hand. Thus, dominant-hemisphere activation appears to drive bimanual movement with subsequent recruitment of the non-dominant hemisphere to perform a 'simultaneous' task with both hands as previously suggested by some (Serrien and Brown 2002; Serrien et al., 2003; Swinnen et al., 1996; Viviani et al., 1998), but not by others (Franz et al., 2002). This finding leads to the question of how the dominant and non-dominant hemispheres produce such coordinated movements. To address this question, we analyzed the volumes of fMRI activation in brain regions during unimanual and bimanual movement.

Similar brain regions were activated in this experiment as have been previously reported for simple in-phase movements, including M1, S1, CMA, SMA, and premotor and parietal cortices (Debaere et al., 2001; Rocca et al., 2007; Ullen et al., 2003). Furthermore, the analysis of volumes of activation contralateral to hand movement in unimanual and bimanual tasks revealed that very similar regions are active, and that volumes of activation within these regions are similar. This is strikingly apparent when volumes of activation during unimanual movement

are subtracted from those observed during bimanual movement (Fig. 2D). Thus, similar groups of neurons are involved in both unimanual and bimanual movement, as suggested by studies done in macaques (Cardoso de Oliveira 2002; Donchin et al., 2002; Kazennikov et al., 1999; Steinberg et al., 2002). The question then becomes how similar groups of neurons produce both unimanual and bimanual behaviors. To investigate this, we utilized SEM to determine how similar brain regions active during unimanual and bimanual tasks interact both within and between hemispheres to produce these different movements.

SEM-derived networks of brain activity

Unimanual movement—Dominant and non-dominant unimanual hand movements were produced by dissimilar networks, even though in principle participants performed the same task with each hand (see Fig. 4 A&B). In right-handed subjects, effective connectivity within the left hemisphere during right hand movement differed from connectivity within the right hemisphere during left hand movement. In addition, there was a striking difference in inter-hemispheric connectivity in dominant versus non-dominant hand movement. The strong connectivity exhibited between reciprocal regions during unimanual right-handed movement was replaced by overall weaker inter-hemispheric connectivity during unimanual left-handed movement. Thus, right hand movements in right-handed subjects are generated by strong cortico-cortical networks within the left hemisphere along with strong inter-hemispheric influence from the left PAR, SMA, and S1 regions to their right-hemisphere homologues. The connectivity between the left and right M1 areas was also strong. This is consistent with several TMS studies suggesting that dominant-to-non-dominant M1 hemispheric connections are inhibitory in nature in order to avoid mirror movements during unimanual tasks (Chen 2003; Chen et al., 2003; Daskalakis et al., 2002; Di Lazzaro et al., 1999; Duque et al., 2005; Liepert et al., 2001; Meyer et al., 1995; Meyer et al., 1998; Rokni et al., 2003; Salerno and Georgesco 1996). The relevance of interhemispheric connections has also been highlighted in brain imaging using DTI (Johansen-Berg et al., 2007) and fMRI (Aramaki et al., 2006). The latter work suggested a larger and predominantly inhibitory effect from the dominant to the non-dominant M1 during bimanual movements versus the effect in the opposite direction. This type of inhibitory interaction has also been proposed between sensory regions (Hlushchuk and Hari 2006). In contrast, left hand movements in right-handed subjects had weaker inter-hemispheric connectivity between homologous regions. Thus, the distributed networks involved in dominant and non-dominant unimanual movement are not mirror images of one another, and instead rely on a shift both of intra- and inter-hemispheric connectivity to produce unimanual movement.

Bimanual movement—The unique nature of the networks involved in the production of dominant versus non-dominant unimanual movements was recapitulated in bimanual movement, in which intra-hemispheric networks were not mirror images of one another. Rather, the network within the left hemisphere was very similar to the intra-hemispheric network observed with contralateral hand movement during the unimanual task. At the same time, the cortico-cortical network in the right hemisphere changed dramatically, reinforcing the strength of connections biased towards sensory areas (S1 and PAR) and their connectivity with PMd. The prominent role of PMd activation during bimanual tasks has been highlighted previously by others (Debaere et al., 2004; Pollok et al., 2005). The question remains as to how these non-mirror intra-hemispheric networks result in individual hand movements that mirror one another during the bimanual task. The answer appears to lie in inter-hemispheric connectivity (Andres et al., 1999; Geffenet et al., 1994; Gerloff and Andres 2002; Serrien and Brown 2002; Serrien et al., 2003). Examination of inter-hemispheric connectivity during bimanual movement revealed a predominant unilateral role for dominant-hemisphere SMA (see Fig 4C). This leads naturally to the idea that SMA connectivity, driven by the dominant hemisphere, may be important in the production of bimanual movement. Such high SMA inter-

hemispheric connectivity is consistent with that already demonstrated for unimanual movements with the dominant hand (Stephan et al., 1999a; Stephan et al., 1999b). While SMA inter-hemispheric connectivity remained high, PMd inter-hemispheric connectivity increased while primary sensory and motor connectivity decreased with the consequent decrease or disappearance of the inter-hemispheric inhibition seen during unimanual movements (Stinear and Byblow 2002).

It has been previously suggested (Serrien et al., 2003) that unimanual movements are mainly generated by the activation of the contralateral hemisphere, whereas bilateral movements require increased interaction between sensorimotor cortices from the two hemispheres (where the dominant hemisphere would drive the non-dominant side). The present report changes and expands this perspective by suggesting that continued inter-hemispheric interaction is prominent during both unimanual and bimanual movements. These data also suggest a different view of the interactions underlying these two motor behaviors: during unimanual movement, inter-hemispheric interaction takes place mainly in primary sensory and motor regions (along with SMA), whereas during bimanual movements, it switches to homologous motor association regions where the dominant hemisphere could be driving activation of the other side (as previously suggested (Serrien et al., 2003)).

Recently, several studies have assessed effective connectivity between brain regions associated with motor behaviors. Although it is difficult to compare directly the results from different approaches employing varying tasks and methods, overall these studies highlight the advantages of investigating effective connectivity to further understand motor function. For example, two recent reports assessed the specific role of SMA in different motor behaviors. Rogers et al. were interested in the role of both supplementary motor areas on the somatomotor regions of each hemisphere during unilateral finger movements. Path analysis showed that the dominant SMA had a dominant role in individual movements with either hand (Rogers et al., 2004). On the other hand, a report by Kasess et al. suggested a suppressive influence of SMA on M1 during motor imagery but not during motor execution (Kasess et al., 2008). Additional studies assessed motor networks with PET after single pulse TMS stimulation (Laird et al., 2008) or with low frequency repetitive trains and subsequent fMRI (Rowe et al., 2006). In the former case, TMS of the hand area of M1 increased effective connectivity with ipsilateral SMA, thalamus, CMA and contralateral CRB and SII. The second study emphasized motor networks in aging, and showed that aging not only exacerbates the inhibitory effects of slow-frequency TMS, but also results in increased effective connectivity related to the PMd. These studies are important and informative, but methodological differences prevent direct comparison with the present study. By contrast, a study by Grefkes et al. (Grefkes et al., 2008a) and one by Rowe et al. (Rowe et al., 2002) can be more directly compared to that presented here: Using fMRI and dynamic causal modeling, Grefkes et al. investigated effective connectivity between brain regions during unilateral and bilateral whole-hand movements in right-handed subjects. Though this study and ours differ in the type of movement performed (gross hand movement v. fine finger movement) and the type of pacing (visual v. auditory), both studies suggest 1) a suppressive effect of M1 contralateral to movement over M1 ipsilateral to movement during single-hand movements, and 2) increased inter-hemispheric connectivity during bimanual movements. Differences in the networks determined by these two studies are also noted, including a less prominent role for dominant-SMA and fewer differences between hemispheric networks ipsi- v. contralateral to movement in the Grefkes study. Furthermore, the importance of analyzing post-stroke brain networks is exemplified in the study of Rowe et al. (Rowe et al., 2002) which found that attention to action during the execution of movements not only increases the activation in PF regions (as in our stroke case), but also increases effective connectivity between this region and PM. In our stroke case, however, strong effective connectivity was seen between the two PF regions and with SMA.

In sum, the results from these as well as other network-based studies in both uninjured (Babiloni et al., 2005; Zhuang et al., 2005) and injured (Chouinard et al., 2006; Grefkes et al., 2008b) brains emphasize the task-specific and dynamic nature of networks of brain activity. Furthermore, the variability in the results from these studies demonstrates the importance of using multiple methods to investigate neural networks to produce a broad and rich understanding of these phenomena. The present study adds to this important field by evaluating within the same experiment, 1) effective connectivity within normative groups during different motor behaviors as well as within individuals (including both right- and left-handed subjects as well as a subject in the chronic phase of stroke), 2) unilateral as well as bilateral movement-based networks, and 3) a broad cortical network of ROIs relevant for the generation of these movements.

Group v. individual SEM networks

Group SEM—An important goal of this study was to determine whether an appropriate model derived from a group could be generalized to individual subjects. At the group level, we found that using the average active voxel and peak voxel time series were effective approaches. This is consistent with previous work in general fMRI image analysis in which the best fits in a motion correction algorithm were obtained when using the most significant voxel time series or the average voxel time series, but not when using the singular value decomposition selected time series (Gavrilescu et al., 2004). In our data, only the peak voxel approach gave good fits for all subjects. The question arises as to why the peak voxel was the best for both the group and individual level networks.

The peak voxel is defined as the voxel with the maximum t-value. This also means that it has the highest signal-to-noise ratio and, thus, is probably the most reliable voxel in the region. Interestingly, our findings seem to contradict a previous study of the auditory cortical region in which the peak voxel fit only 50% of the individual models and 50% of the group models (Goncalves et al., 2001). The authors did state that the poor fit could be due to the lack of anatomical knowledge in the auditory cortical region, and that the peak voxel was chosen to be the most significant one for all tasks. In contrast, anatomy of the motor cortices is much better defined based on previous studies of both macaque and humans. Furthermore, in the present study, the peak voxel used in the bimanual model was chosen from the bimanual task, not from the combination of all tasks. Therefore, we believe that the accuracy of defining the peak voxel along with detailed understanding of motor cortex anatomy explains the good fits in our study.

Given that the long-term goal of our research is to understand network changes after stroke, we are interested in highly robust group models. Thus, the method presented in this paper achieves this purpose and allows a deeper understanding of the relationship between normative groups (e.g., right versus left-handed groups) than can be achieved by comparing task-dependent brain activations in individual regions. In particular, the present study defines a robust group model for a simple task involving in-phase bimanual movement. This has two roles: first, this model can be used directly as a normative network model of baseline regional interaction for use in subsequent studies of reorganization and repair after injury; second, this model can be viewed as a ‘proof of principle’ that will ultimately allow comparison of networks involving increasing motor complexity and varied patient populations. Ultimately, we aim to localize alterations in network connectivity post-stroke and post-recovery.

Individual SEM—The individual comparisons of two left-handed healthy subjects and one right-handed stroke subject (whose lesion affected his dominant hemisphere) illustrate the high sensitivity of our analysis. The fitting of the models ranged from not significant (good fit) for the strongly left-handed individual to highly significant (poor fit) for the right-handed stroke

subject, while the weakly left-handed case was close to being non-significant. Previous studies comparing left vs. right-handed individuals during bimanual movements have not assessed the differences in brain activation as a function of the penetrance or degree of left-handedness (Kloppel et al., 2007; Viviani et al., 1998). The difference with the left-handed subjects in this study was reflected mostly in the inter-hemispheric connectivity. Note that the EMG responses during bimanual movements reflected this fact in that the activity delay from the left to the right hand was only present in the strongly left-handed subject. Hence, the network models (and the effective connections shown in the inter-hemispheric connections) reflect the degree of dominance at the behavioral level as identified by both EMG and the handedness inventory. In contrast, in the stroke subject (strongly right-handed pre-stroke) not only did the EMG not follow a regular pattern, but the network of activation also displayed new nodes not included in any of the healthy controls. Thus, the probability values obtained by fitting the group model using different individuals can provide an estimate of the magnitude of the difference of individual cases from the normative group network.

Caveats

Theoretical

In-phase hand movements: In this study, we focused on in-phase hand movements. The question naturally arises as to how the results presented here generalize to more complex movements. This issue becomes important given the known differences in brain activation between simpler, in-phase, isodirectional, synergistic movements and more difficult anti-phase, nonisodirectional, nonsynergistic movements (Cardoso de Oliveira 2002; Debaere et al., 2001; Ehrsson et al., 2002; Rocca et al., 2007; Sadato et al., 1997; Stephan et al., 1999a; Stephan et al., 1999b; Sternad et al., 2007; Ullen et al., 2003). Although the more stable in-phase movements do result in less robust activation, they nevertheless activate a similar core ‘motor network’ of brain regions as anti-phase and nonsynergistic movements, including M1, S1, premotor cortex, CMA, SMA, and parietal regions. Furthermore, kinematic and behavioral studies demonstrate that anti-phase and nonsynergistic movements are less accurate and consistent than in-phase synergistic movements (Cattaert et al., 1999), and thus present a challenge to the interpretation of imaging data derived from such movements. Therefore, to limit confounding variables in this ‘proof of principle’ study, we elected to concentrate on in-phase movements. Future studies, however, will be directed at broadening this technique to analyze more complex bimanual tasks.

Coarse anatomical parcellation: The anatomical areas considered in this study were parcellated based on known anatomical landmarks. Although this approach takes into consideration inter-subject variability, it may have some limitations with respect to the construction of network models. The reason for this is that such anatomical regions are quite heterogeneous, in terms of both cyto- chemoarchitectonics and connectivity (Zilles et al., 2002). In future studies, further sub-parcellation of the anatomical regions might be necessary to determine finer features of the networks.

Methodological—Even though using the peak voxel approach provided a good fit in our study, there are still questions that could limit its use. First is whether individual models with a poor fit are the result of the voxel selection procedure or instead from inter-subject variability. Second is the extent to which a good model fit and related estimated path coefficients depend on a representative voxel selection procedure. These issues have been explored before by several groups (Gavrilescu et al., 2004; Goncalves and Hall 2003) but the answer remains unclear. Another important issue is that all of these procedures are aimed at ruling out bad or inappropriate models, but they do not guarantee that a particular model with a good fit is the best one. In other words, there might be other models that are statistically and physiologically equivalent or even superior. In our case, we want to contrast changes over time in stroke

subjects compared to healthy controls, and thus we have selected a few nodes that comprise the common network. Our method detects a core network for healthy controls, which is then compared to the core network for each of the individual subjects. In this way, SEM can be a valuable approach for performing comparisons between different behaviors (e.g., see (McIntosh et al., 2001)).

Conclusion

In summary, the present study leads to an intriguing model of bimanual movement common to all subjects with strong handedness: (1) the dominant hemisphere initiates bimanual movement; (2) the dominant intra-hemispheric network is activated, ultimately resulting in dominant hand movement which precedes non-dominant hand movement; (3) dominant to non-dominant SMA inter-hemispheric connectivity drives activation of the non-dominant intra-hemispheric network resulting in non-dominant hand movement; and (4) the non-dominant hemisphere relays with sensory and motor association regions (mainly PMd) to allow the dominant hemisphere to organize movements in space and time. Thus, bimanual movement results from a redistribution of inter-hemispheric connectivity to coordinate intra-hemispheric networks that produce the corresponding unimanual movement. Whereas small variations in this model are seen in weakly left-handed individuals, deep differences are seen in subjects after stroke affecting hand movements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1. Graphic display of the regions of interest (ROIs) included in the study
 These regions were drawn by hand on every subject and verified by an independent investigator. The borders for each region were based on specific common landmarks as detailed in the methods section.

FIGURE 2. Physiological measures during finger opposition movements in a right-handed individual

A) EMG recording during bimanual mirror movements in the right (blue trace) and left (green trace) EDC. The signal has been rectified and integrated. Note that the muscle activation in the right EDC precedes activation of left EDC during these bimanual movements. In addition, the rise time on muscle activation is faster in the dominant hand. **B)** Example of brain activation assessed with fMRI during finger opposition movements with the right hand (left panel), left hand (middle panel), and both hands (right panel). **C)** Graphic representation of volumes of activation per brain region in the left hemisphere during movements with the right hand and both hands. Note the close similarity of volumes in each region. **D)** Representation of residual

activation after subtracting activation in the corresponding contralateral hemisphere during right or left hand movements from activation in both hemispheres during bimanual movements. This subtraction suggests that not only are the volumes similar, but also the location of the active voxels are similar during unimanual and bimanual movements. Since these are radiological images, the left hemisphere is represented on the right side.

FIGURE 3. Physiological measures during finger opposition movements in a weakly left-handed subject

A) EMG recording during bimanual mirror movements in the right (blue trace) and left (green trace) *extensor digitorum communis* (EDC). The signal has been rectified and integrated. Note that the muscle activation in the left EDC does not precede activation of right EDC during these bimanual movements. **B)** Example of brain activation assessed with fMRI during finger opposition movements with the right hand (left panel), left hand (middle panel), and both hands (right panel). Note that all movements produce bilateral activation.

FIGURE 4. Graphic representation of motor networks assessed with SEM

A) Group motor network representing unilateral movements with the dominant hand in right-handed and strongly left-handed individuals. **B)** Corresponding group network associated with unilateral movements of the non-dominant hand and **C)** during bimanual mirror movements. **D)** Individual motor network representing bimanual movements in a weakly left-handed individual. Note the great difference in the inter-hemispheric connectivity between this case and the right-handed/strongly left-handed group network. The thickness of the lines represents

the absolute value of strength of connection as follows: $\uparrow >0.6$ $\uparrow <0.6$ $\uparrow >0.3$ $\uparrow <0.3$

FIGURE 5. Physiological measures during finger opposition movements in a right-handed subject in the chronic phase of stroke

A) EMG recording during bimanual mirror movements in the right (blue trace) and left (green trace) *extensor digitorum communis* (EDC). The signal has been rectified and integrated. Note that the muscle activation in the right EDC does not precede activation of left EDC during these mirror bimanual movements. **B)** Example of brain activation assessed with fMRI during finger opposition movements with the right hand (left panel), left hand (middle panel), and both hands (right panel). **C)** Individual motor network representing bimanual mirror movements. Note the large difference in the connectivity between this case and the right-handed/strongly left-handed group network. Interestingly, new regions not active in the healthy

controls are present in this network. The thickness of the lines represents the absolute value of strength of connection.

TABLE 1

List of brain regions studied.

Name	Label	Areas included	Brodmann's Number	Tailarach MNI Coordinates
Primary Motor cortex	M1	Primary motor cortex	4	−31.78 −31.80 64.88
Somatosensory Areas	S1	Primary and association somatosensory Cortices	1, 2, 3, 5	−33.33 −37.24 68.02
Lateral Premotor Cortex, dorsal	PMd	Lateral premotor cortex dorsal	6l	−37.37 −15.61 53.90
Lateral Premotor Cortex, ventral	PMv	Lateral premotor cortex ventral and Inferior frontal gyrus	6l, 44	−52.71 −1.20 27.41
Supplementary Motor Area	SMA	Supplementary motor area and Pre-supplementary area	6m, 24c	−5.71 −3.13 59.83
Superior Parietal Lobule	PAR	Superior parietal lobule, Intraparietal sulcus	7	−33.33 −45.46 59.44
Pre-Frontal Region	PF	Medial frontal gyrus and medial frontal sulcus	46, 44	−49.53 14.81 39.89
Cerebellum	CRB	Cerebellum		24.24 −63.69 −35.05
Basal Ganglia	BG	Caudate and putamen		−25.25 −9.89 9.47
Thalamus	THAL	Thalamus		−9.09 −17.68 11.56

TABLE 2

Cortical connectivity values and some references in the macaque

Connection	Regression Weights			References
	Right hand	Left hand	Bimanual	
L PMd ← L SMA	0.782	-0.194	0.698	(Kurata 1991)
L PMd ← L PAR	0.084	-0.132	0.2	(Kurata 1991)
L PMd ← R PMd		-0.175	-0.487	(Marconi et al., 2003)
L PMd ← R M1		1.0	0.482	(Marconiet al., 2003)
L M1 ← L PMd	0.390	0.683	0.252	(Tokuno and Tanji 1993)
L M1 ← L S1	0.736	-0.237	0.793	(Tokuno and Tanji 1993)
L M1 ← L SMA	-0.246	0.463	-0.038	(Tokuno and Tanji 1993)
L M1 ← L PAR	0.020	0.099	0.011	(Rizzolatti et al., 1998)
L M1 ← R M1	0.069	-0.053	-0.088	(Rouiller et al., 1994)
L S1 ← L PMd	0.985	0.403	0.757	(Stepniewska et al., 2006)
L S1 ← L SMA	-0.113	0.141	0.317	(Pons and Kaas 1986)
L S1 ← L PAR	0.103	0.042	0.106	(Pons and Kaas 1986)
L S1 ← R S1		0.389	-0.236	(Killackey et al., 1983)
L SMA ← L PAR	0.648	0.286	0.546	(Cavada and Goldman-Rakic 1989)
L SMA ← R SMA		0.450	0.055	(Rouiller et al., 1994)
L PAR ← R PAR		0.156	0.137	(Caminiti and Sbriccoli 1985)
R PMd ← L PMd	0.128		-0.167	(Marconiet al., 2003)
R PMd ← L M1	0.346		0.106	(Marconiet al., 2003)
R PMd ← R SMA	0.066	0.589	0.261	(Kurata 1991)
R PMd ← R PAR	0.400	0.354	0.645	(Kurata 1991)
R M1 ← L M1	0.378	-0.001	-0.011	(Marconiet al., 2003)
R M1 ← R PMd	0.257	0.194	0.129	(Tokuno and Tanji 1993)
R M1 ← R S1	0.334	0.842	0.784	(Tokuno and Tanji 1993)
R M1 ← R SMA	0.025	0.087	-0.002	(Tokuno and Tanji 1993)
R M1 ← R PAR	0	-0.102	0.073	(Rizzolatti et al., 1998)
R S1 ← L S1	0.661		0.258	(Killackey et al., 1983)
R S1 ← R PMd	0.042	0.417	0.624	(Stepniewska et al., 2006)
R S1 ← R SMA			-0.047	(Pons and Kaas 1986)
R S1 ← R PAR	0.218	0.529	0.283	(Pons and Kaas 1986)
R SMA ← L SMA	0.583		0.649	(Rouiller et al., 1994)
R SMA ← R PAR	0.105	0.784	0.437	(Cavada and Goldman-Rakic 1989)
R PAR ← L PAR	0.873		0.093	(Caminiti and Sbriccoli 1985)

TABLE 3
Probability values obtained by applying the group model to the individual right-handed cases.

Subject	1	2	3	4	5	6	7	8	9	10	11	12
Average	0.055	0.197	0.04	0.001	0.894	0	0.156	0.027	0.381	0.16	0.376	0
Peak Voxel	0.073	0.403	0.375	0.2	0.607	0.585	0.57	0.459	0.6	0.258	0.99	0.053

Note that for the average model, five of the subjects did not show a good fit (bold fonts). In contrast, using the peak voxel method all individual models fit the group model.