Brain-Behavior Relationships: Evidence From Practice Effects in Spatial Stimulus-Response Compatibility

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SUMMARY AND CONCLUSIONS

1. We measured relative cerebral blood flow (rCBF) changes with positron emission tomography and $H_2^{15}O$ in six normal subjects repeatedly performing a spatial stimulus-response compatibility task. Subjects had two motor response conditions. They were instructed to respond with the left hand to a left visual field light stimulus and with the right hand to a right visual field light stimulus (compatible condition), and with the right hand to a left visual field light stimulus and with the left hand to a right visual field light stimulus (incompatible condition). Six rCBF measurements per condition were performed in each subject.

2. Reaction times were faster (P < 0.0005) in the compatible (287 ms) than the incompatible (339 ms) condition (spatial stimulus-response compatibility effect). A bilateral increase (P < 0.05) in rCBF in the superior parietal lobule of the two hemispheres was observed during the incompatible condition when compared with the compatible one. No rCBF decreases were observed. Reaction times correlated (P < 0.0001) with the rCBF in the two activated superior parietal lobule areas.

3. Reaction times decreased with practice according to a linear trend (P < 0.05). Practice-related linear rCBF increases (P < 0.05) were observed in the dorsolateral prefrontal, premotor, and primary motor cortex of the left hemisphere. No significant rCBF decreases were observed.

4. Practice did not affect the spatial stimulus-response compatibility effect. A parallel shortening of reaction times was observed in both compatible and incompatible conditions, in both left and right hand responses, and in both left and right visual fields. Accordingly, when rCBF was analyzed, the spatial stimulus-response compatibility by practice interaction did not show any significant activated area.

5. These findings suggest that the two activated areas in the left and right superior parietal lobules subserve the mapping of the visual stimulus spatial attributes onto the motor response spatial attributes and that the rCBF increases in the incompatible response condition represent the more complex computational remapping required when stimuli and response do not match spatially.

6. The dorsolateral prefrontal, premotor, and motor rCBF linear increases in the left hemisphere seem to reflect the effect of practice on cortical processes common to both compatible and incompatible response conditions. These cortical processes presumably strengthen the links between stimuli and responses under different stimulus-response compatibility conditions. The lateralization of the rCBF increases suggests a left hemisphere superiority in these processes.

INTRODUCTION

A central tenet in cognitive neuroscience is that the neural counterparts of complex human behavior are composed of

large-scale cortical networks that integrate separate local neural assemblies that subserve specific cognitive processes (Mesulam 1990). A relevant question in brain-behavior relationships is whether the relations between the specific cognitive processes converging in a given complex human behavior, as evidenced by human performance, are reflected by the relations of their neuronal underpinnings. We address here the behavioral profiles and the underlying cerebral activity of two aspects of human performance in sensorimotor integration tasks that are known to be orthogonal and noninteracting: I) the sensorimotor integration phenomenon known as spatial stimulus-response compatibility and 2) the procedural learning acquired with practice.

Sensorimotor integration and procedural learning are two basic aspects of human behavior. Sensorimotor integration is essential for our ability to attend to the outside world, to move our body accurately in space, and to interact with objects around us, whereas the procedural learning acquired with practice is essential to become faster and more accurate in sensorimotor skills. Practice effects follow a common pattern in a variety of different sensorimotor integration tasks. When the logarithm of the performance is plotted against the logarithm of the amount of practice, a linear function, called the "power law of practice," is typically obtained (Newell and Rosenbloom 1981). Despite the pervasive effect of procedural learning in sensorimotor tasks, there exists a robust sensorimotor integration phenomenon, the stimulus-response compatibility effect, that is known to be substantially unaffected by practice (Dutta and Proctor 1992; Proctor and Dutta 1993).

In its simplest spatial version, stimulus-response compatibility occurs when ipsilateral (compatible condition) and contralateral (incompatible condition) motor responses to lateralized sensory stimuli are compared. Even though the two conditions have identical sensory inputs and motor outputs, incompatible responses are on average 40-80 ms slower ("spatial stimulus-response compatibility effect") than compatible responses (Proctor and Reeve 1990). This delay is not due to the callosal relay of information from one hemisphere to the other. Indeed, interhemispheric transmission time is known to be from 10 to 20 times shorter than the compatibility effect in normal subjects (Iacoboni and Zaidel 1995; Iacoboni et al. 1994; Marzi et al. 1991). Further, the compatibility effect is observed even when subjects respond with crossed arms, in which case a motor response in the same hemispace as the stimulus is still the

faster, even though it is controlled by the hemisphere contralateral to the one receiving the sensory input (Anzola et al. 1977; Umiltá and Nicoletti 1990). The spatial stimulusresponse compatibility effect is thought to be produced by the more complex computational remapping of the stimulus spatial attributes onto the response spatial attributes in the incompatible condition.

A variety of cortical neural assemblies are known to be involved in the spatial stimulus-response compatibility effect. Nonhuman primates performing this paradigm have shown neuronal activity coding specific stimulus-response association rules in the posterior parietal cortex (Seal et al. 1991, 1992), in the dorsal premotor cortex (Crammond and Kalaska 1994), and in the primary motor cortex (Riehle et al. 1994). Neurophysiological evidence in humans performing stimulus-response compatibility tasks is consistent with nonhuman primate findings (see review in Eimer 1995). In none of the above cited studies, however, has the effect of practice on the neurophysiological responses been reported.

The spatial stimulus-response compatibility effect is basically unchanged by practice, despite the overall shortening of reaction times produced by the effect of practice (Dutta and Proctor 1992; Proctor and Dutta 1993). In other words, reaction times shorten in parallel in both the compatible and incompatible response condition. The most likely explanation of this phenomenon is that spatial stimulus-response compatibility and practice effects entail cognitive processes that are substantially orthogonal to each other and subserved by separate local neural assemblies. More precisely, the parallel improved efficiency in compatible and incompatible responses due to practice is likely to reflect the effect of procedural learning on a cognitive process (and on the activity of the local neural assembly subserving it) common to both compatible and incompatible responses. To test this hypothesis, we measured reaction times and relative cerebral blood flow (rCBF) changes with positron emission tomography (PET) in normal volunteers repeatedly performing a spatial stimulus-response compatibility task with lateralized light flashes. Preliminary analyses of the present data have been previously reported in abstract form (Iacoboni et al. 1995a,b).

METHODS

Subjects

Six normal subjects, four males and two females between 24 and 28 yr old who gave their informed consent in accordance with the UCLA Human Subjects Protection Committee, participated in this study. All subjects were recruited by advertisement. They underwent medical interview and physical and neurological examination, and were right handers as assessed by a handedness questionnaire.

Spatial stimulus-response compatibility paradigm

A monitor of a Macintosh computer was positioned 57 cm from subjects' eyes. A microswitch in each hand was used to monitor motor responses. A software program for Macintosh, MacProbe, was used to present the lateralized stimuli and to record reaction times and accuracy. A fixation cross subtending 1° of visual angle was presented in the middle of the screen throughout the entire experimental session. Stimuli consisted of lateralized squareshaped light flashes on a black background, subtending 1° of visual angle. Stimuli were presented for 50 ms at 8° of eccentricity from the vertical meridian either in the right or in the left visual field in a random, counterbalanced fashion.

Subjects, with arms in the uncrossed position, were instructed to respond with the right hand to a right-sided light stimulus and with the left hand to a left-sided light stimulus in the compatible condition, and to respond with the right hand to a left-sided light stimulus and with the left hand to a right-sided light stimulus in the incompatible condition. Subjects were trained with four blocks of 120 trials each before the imaging session. To obtain a counterbalanced number of lateralized stimuli and responses in each scan, each trial lasted exactly 1.25 s, regardless of the response time of the previous trial. As has frequently been observed in this paradigm, reaction times were consistently between 250 and 500 ms, allowing sufficient time from the execution of the motor response to the presentation of the next stimulus. Subjects began the task 30 s before the 60-s scan, performing 24 trials (12 right and 12 left stimuli) before the scan and 48 trials (24 right and 24 left stimuli) during the scan.

Imaging

A customized foam head holder was used to reduce head movements (Smithers, Akron, OH). A transmission scan, collected by the use of a ⁶⁸Ge ring source, was used to locate the two main regions of interest, the posterior parietal cortex and premotor-motor areas, in the center of the field of view, where three-dimensional (3D) PET imaging sensitivity is optimized (Cherry et al. 1993). These two main regions of interest were selected on the basis of published neurophysiological evidence in humans and nonhuman primates (see INTRODUCTION).

For each subject, the imaging session involved 12 rCBF measurements, 6 per condition. Compatible and incompatible conditions were alternated during the imaging session. Three subjects started with the compatible condition and the other three with the incompatible one. For each rCBF measurement, subjects were injected with a 10-mCi (370 MBq) bolus of $H_2^{15}O$ in 7 ml of normal saline via an intravenous line in the left hand and counts were collected in a single 60-s time frame that started at the time of injection. Arterial blood sampling was not performed and absolute cerebral blood flow values were not computed.

Images were acquired with the use of a Siemens/CTI 831– 08 tomograph (Siemens, Hoffman Estates, IL), which has been modified to allow removal of the interplane septa for 3D PET acquisition (Cherry et al. 1993). The scanner has eight data collection rings with an axial field of view of 101.25 mm. Data were acquired in the 3D mode and reconstructed with the use of a fully 3D reconstruction algorithm. 3D image reconstruction leads to a three- to fivefold increase in sensitivity when compared with twodimensional reconstruction. A detailed description of the scanning procedure and 3D image reconstruction have been provided elsewhere (Cherry et al. 1993). Attenuation correction was calculated as in Siegel and Dahlbom (1992) and no scatter correction was implemented.

Reconstructed PET images consisted of 15 planes of 128×128 pixels with an interplane distance of 6.75 mm. Head movements were corrected with the use of the algorithm described by Woods et al. (1992). The original axial planes were interpolated to 55 planes, and the resulting images had cubic voxels of $1.75 \times 1.75 \times 1.75$ mm. Differences in global activity across scans were removed by the use of global normalization, according to Mazziotta et al. (1985). Additional in-plane smoothing of the images was applied with the use of a two-dimensional 8-mm isotropic Gaussian filter. The final resolution of the resulting images was $10.12 \times 10.12 \times 10$ mm full width at half-maximum.

In separate imaging sessions, each subject returned for magnetic resonance imaging (MRI) of the brain performed on a GE Signa scanner with the use of a 3D spoiled GRASS sequence. MRI-PET registration was performed with the use of the algorithm described by Woods et al. (1993a). Intersubject stereotaxis was performed with the use of a 12-parameter affine registration model, as described elsewhere (Woods et al. 1993b).

Data analysis

ACCURACY AND REACTION TIMES. As previously described, subjects began the task 30 s before the 60-s scan, performing 24 trials (12 left visual field and 12 visual field right stimuli) before the scan and 48 trials (24 left visual field and 24 right visual field stimuli) during the scan. Only trials performed during each scan were analyzed.

Repeated-measures analyses of variance (ANOVAs) were performed with the use of accuracy of responses and median reaction times for correct responses as the dependent variables, and with replication scan (from 1 to 6), spatial stimulus-response compatibility condition (compatible, incompatible), and visual field (left, right) or response hand (left, right) as within-subject variables. Reaction times <150 ms were considered anticipatory errors, whereas reaction times >600 ms were considered attentional errors. Anticipatory and attentional errors were both removed from the analysis.

The effect of practice was also tested with a linear trend approach (Rosenthal and Rosnow 1985) and plotting the logarithm of the performance against the logarithm of the amount of practice (power law of practice, Newell and Rosenbloom 1981).

BLOOD FLOW. A three-way ANOVA was performed with the use of normalized counts in each voxel as the dependent variable and with replication scan, spatial stimulus-response compatibility condition, and subjects as between-voxel effects (the effect of left and right visual field and response hand cannot be separated in this analysis, given that subjects responded with both hands to flashes presented in both visual fields during each scan). This statistical approach, when compared with the more common statistical approach in neuroimaging of treating each replication scan in the same subject as an independent observation, does not result in a loss of statistical power, because the loss in degrees of freedom is offset by a decrease in the estimate of the intrinsic variance of the data set under investigation (Woods et al. 1995, 1996). Furthermore, with this approach, the likely incorrect assumption of no subject by task interaction (Cronbach 1970; Lord and Novick 1968) need not to be made.

The effect of practice was also tested with a linear trend approach (Rosenthal and Rosnow 1985). In addition, the logarithm of the coefficients of the linear trend was used as weighting for a trend analysis with the use of the logarithm of the normalized counts in each pixel as dependent variable (power law of practice).

Given that pixel-by-pixel ANOVAs require multiple spatial comparisons, the significance t and F thresholds were corrected in all analyses according to the brain volume in the scanner field of view (excluding deep gray and white matter, which were a priori deemed not to be areas of interest) and the final image resolution (Worsley et al. 1995). This correction was used because it is more cautious than the use of arbitrary (even though conservative) thresholds in significance level, frequently used in functional neuroimaging.

REACTION TIME-rCBF CORRELATION ANALYSES. The behavioral meaning of the significant rCBF changes due to spatial stimulus-response compatibility was investigated with correlation analyses. Because the linear trend analyses performed on practice-related changes in reaction times and rCBF are similar to correlation analyses, practice-related changes were not tested further.

In spatial stimulus-response compatibility tasks, performance (as measured by overall reaction times, error rate being usually negligible in this task, see Proctor and Reeve 1990) depends on the interaction between stimuli and responses. According to this, we considered the overall median reaction times in compatible and incompatible scans as a general index of spatial stimulus-response compatibility. Evidence in normal subjects and brain-damaged patients (Nicoletti and Umiltá 1989; Nicoletti et al. 1982, 1984; Perenin and Vighetto 1988), however, has suggested a differential role of the two hemispheres in the encoding of spatial attributes of visual stimuli and motor responses (see RESULTS). For this reason, we used indexes of visual field and response hand asymmetries in compatible and incompatible scans as behavioral indexes of hemispheric asymmetries in visual processing and motor control. Left (L) and right (R) visual field and response hand asymmetries were computed through the use of a laterality index (L - R)L + R), as suggested and extensively discussed by Zaidel (1979).

First, we correlated the three behavioral indexes and the rCBF in the significantly activated areas. To further test the relationships between the three behavioral indexes and the rCBF in the significantly activated areas, we used the variance partitioning approach in multiple regression analysis (Pedhazur 1982; Snedecor and Cochran 1976; Stevens 1986), which is more appropriate for explanation purposes than correlation analyses, as discussed by Pedhazur (1982).

RESULTS

Accuracy

As previously observed (for a review see Umiltá and Nicoletti 1990), incorrect responses and anticipatory and attentional errors were rare ($\sim 2\%$) and not significantly different between compatible and incompatible conditions, across scans, or between visual fields and response hands.

Reaction times

ANOVA revealed a main effect of condition [F(1,5) = 66.200, P < 0.0005], with faster reaction times for the compatible (287 ms) than the incompatible condition (339 ms). A main effect of response hand was also observed [F(1,5) = 78.514, P < 0.0005], with faster reaction times for the right hand (299 ms) than the left hand (328 ms). Reaction times to left visual field flashes (312 ms) were not different [F(1,5) = 0.023, P > 0.8] from reaction times to right visual field flashes (313 ms).

Overall reaction times decreased according to a linear trend [F(1,5) = 4.279, P < 0.05] (Fig. 1A). When the logarithm of the reaction times was plotted against the logarithm of the amount of practice, a linear function was obtained (power law of practice) (r = -0.816, P < 0.05) (Fig. 1B). This implies that the power law is approximately linear over the range of practice investigated here. The expected parallel decrease for both compatible and incompatible condition was also observed (Fig. 1C). Similar parallel decreases were observed in both left and right visual field and in both left and right response hand.

A compatibility condition by visual field interaction was observed [F(1,5) = 78.514, P < 0.0005], with reaction times to right visual field flashes (273 ms) faster than reaction times to left visual field flashes (301 ms) in the compatible condition [F(1,5) = 38.519, P < 0.002], and with reaction times to left visual field flashes (325 ms) faster than



FIG. 1. A: overall reaction times decreased according to a linear trend (P < 0.05). B: when the logarithm of reaction time is plotted against the logarithm of the number of trials performed, a linear function emerges, P < 0.05 (the "power law of practice"). C: reaction times decreased in parallel in both compatible and incompatible conditions and no spatial stimulus-response compatibility by practice interaction was observed.

reaction times to right visual field flashes (354 ms) in the incompatible condition [F(1,5) = 40.002, P < 0.002].

No other higher-order interactions were significant. In particular, the replication scan (as index of amount of practice) by spatial stimulus-response compatibility interaction [F(1,5) = 0.842, P > 0.5] was not significant.

Blood flow

A contrast analysis revealed significant increases in rCBF in the incompatible condition compared with the compatible one (df = 25, t = 5.585524, P < 0.05) in the two superior parietal lobules. The rCBF increases were located in the anterior bank of the right transverse parietal sulcus and in the posterior bank of the marginal ramus of the left cingulate sulcus, where it emerges onto the lateral surface of the posterior parietal cortex (Fig. 2). No significant cerebral blood flow decreases were observed.

Because practice effects produced a shortening of reaction times according to a linear trend and also fit the power law of practice, we first tested rCBF changes showing the same trend in both linear and "log-log" space. We first performed a 6 (subjects) \times 2 (condition: compatible, incompatible) \times 6 (replication scans) ANOVA contrast analysis with a linear trend approach, using as dependent variable the normalized counts in each voxel and the appropriate weights for each replication scan (Rosenthal and Rosnow 1985). Subsequently we performed a second 6 \times 2×6 ANOVA contrast analysis in log-log space, using as dependent variable the logarithm of the normalized counts in each voxel and as weights the logarithm of the weights assigned to each replication scan in the previous ANOVA. The two ANOVAs showed the same results: significant linear rCBF increases (df = 25, t = 5.585524, P < 0.05) were observed in a left dorsolateral prefrontal area, in the middle frontal gyrus (Fig. 3), and in premotor (superior



FIG. 2. Surface (top left), transverse (top right), and sagittal views (bottom left: left hemisphere; bottom right: right hemisphere) of the only relative cerebral blood flow (rCBF) increases (black) reaching statistical significance during the incompatible condition compared with the compatible condition. Only brain regions included in the scanner field of view are rendered. Subjects' heads were positioned to place the posterior parietal cortex in the center of the field of view, where 3-dimensional (3D) positron emission tomography (PET) imaging sensitivity is optimized. The magnetic resonance imaging (MRI) of the brain of a single subject, located in the stereotaxic space, is used for anatomic reference in these renderings. Volume renderings were made with the use of the software package Sunvision (Sun Microsystems, Mountain View, CA).



FIG. 3. A: transverse view of practice-related rCBF increases (black) in the middle frontal gyrus of the left hemisphere. B: sagittal view of practice-related rCBF increases (black) in the middle frontal gyrus of the left hemisphere showing also the practice-related rCBF increases in left premotor and motor areas. Graph: linear increase in normalized counts in the dorsolateral prefrontal area during the 1st 5 scans and the decrease in the last scan.

frontal gyrus) and motor (precentral gyrus) areas of the left hemisphere (Fig. 4). No practice-related rCBF decreases were observed.

In addition, given that a nonlinear relationship between performance and rCBF changes is a priori possible, we also performed another ANOVA without prespecified contrasts to test the main effect of replication scans (as index of amount of practice) on rCBF values, in order to detect other trends in other locations (this may also include time effects independent of learning effects). Not surprisingly, this ANOVA [F(5,25) = 14.29983, P < 0.05] showed the same two areas identified by the contrast analyses. No additional rCBF changes were identified. This clearly indicates that the only significant time-dependent (and practice-dependent) rCBF changes showed a linear increase. Time-activity profile analyses of the two areas revealed by the



FIG. 4. Transverse (A-C) and sagittal (D) views of practice-related rCBF increases (black) in the left superior frontal and left precentral gyrus. Graph: linear increase in normalized counts in these regions during the 1st 5 scans and no further increase in the last scan.

Activated Areas	Talaraich Coordinates			
	X	Y	Z	Brodman Nomenclature
Right superior parietal				
lobule (Fig. 2)	22	-64	48	Area 7
Left superior parietal				
lobule (Fig. 2)	-18	-52	48	Area 7
Left dorsolateral prefrontal				
cortex (Fig. 3)	-45	38	22	Area 46
Left premotor cortex				
(Fig. 4)	-16	-12	55	Area 6

TABLE 1. Talairach coordinates of the activated areas andrelative Brodmann areas

Values for Talaraich coordinates are in mm.

three ANOVAs¹ overlapped completely and showed that the rCBF increased linearly during the first five scans and then showed a decrease in the dorsolateral prefrontal area (Fig. 3) and a plateau in premotor and motor areas (Fig. 4). The only other cerebral regions in the scanner field of view showing a very marginal significance in linear rCBF increases (df = 25, t = 2.059539, P < 0.05, without correction for multiple spatial comparisons) were the contralateral right hemisphere dorsolateral prefrontal, premotor, and motor regions. This argues for a large asymmetry between left and right linear rCBF increases. The Talairach coordinates (Talairach and Tournoux 1988) of all activated areas and the relative putative Brodmann areas are summarized in Table 1.

Finally, we tested with ANOVA the replication scan (as index of amount of practice) by spatial stimulus-response compatibility interaction and did not find any significant rCBF increase or decrease.

Correlation analyses

The rCBF increases in the superior parietal lobule observed in the incompatible condition when compared with the compatible one are asymmetric in both size and location. This asymmetry could simply reflect the morphological asymmetry between left and right superior parietal lobules in right handers (Geschwind and Galaburda 1984), so that the two asymmetric rCBF increases might represent functionally homologous cortical areas subserving the overall spatial stimulus-response compatibility transformation. However, unilateral posterior parietal lesions have suggested hemispheric specialization in the human posterior parietal cortex, with right posterior parietal superiority in visuospatial skills and left posterior parietal superiority in motor functions (Perenin and Vighetto 1988). As a result, the right posterior parietal cortex might subserve an early stage of coordinate transformations in the spatial stimulus-response compatibility task, (i.e., encoding stimulus spatial attributes in egocentric coordinates), whereas the left posterior parietal cortex might subserve a late stage of coordinate transformations, (i.e., encoding body part spatial attributes for correct responses). These two stages of coordinate transformations are likely to be used by normal subjects performing spatial stimulus-response compatibility tasks (Nicoletti and Umiltá 1989; Nicoletti et al. 1982, 1984).

To test whether the right and left superior parietal lobule activated areas are functionally homologous or functionally different, we correlated the rCBF changes in the two activated areas with the three behavioral indexes described in the Data analysis section. The prediction was straightforward: if the two areas are functionally homologous, rCBFs in the two areas should both correlate with the general index of spatial stimulus-response compatibility and they should not correlate with the visual field and response hand asymmetry index. If they are functionally different, the right one subserving the early stage and the left one subserving the late stage of coordinate transformations, rCBF in the former should correlate with the visual field asymmetry index and rCBF in the latter should correlate with the response hand asymmetry index, and rCBF in both activated areas should not correlate with the general index of spatial stimulus-response compatibility. Results are in support of the first hypothesis, as shown in Fig. 5. Changes in rCBF in both left and right superior parietal lobule areas were significantly correlated (left: r = 0.640, P < 0.0001; right: r = 0.553, P < 0.00010.0001) with the overall index of spatial stimulus-response compatibility, and were marginally inversely correlated (not significant if corrected for multiple correlations) with the visual field asymmetry index (left: r = -0.295, P < 0.05; right: r = -0.273, P < 0.05) and not correlated with the response hand asymmetry index (left: r = 0.064, P > 0.5; right: r = -0.050, P > 0.6).

To estimate the percentage of variance in rCBF in the right and left superior parietal lobule activated areas accounted for by the three behavioral indexes, we used a stepwise multiple regression approach (Pedhazur 1982; Snedecor and Cochran 1976). The general index of spatial stimulus-response compatibility accounted for 40.96% (P <0.0001) of the rCBF variance in the left superior parietal lobule activated area and 30.58% (P < 0.0001) of the rCBF variance in the right superior parietal lobule activated area. The visual field asymmetry index accounted for 8.7% (not significant) of the rCBF variance in the left superior parietal lobule activated area and 7.45% (not significant) of the rCBF variance in the right superior parietal lobule activated area. The response hand asymmetry index accounted for < 2% of the rCBF variance in both left and right superior parietal lobule activated areas.

DISCUSSION

Spatial stimulus-response compatibility maintains that reaction times are faster when there is a spatial correspondence between stimuli and responses than when there is not. This is valid even after extended practice sessions amounting to 2,400 trials (Dutta and Proctor 1992). That is, compatibility effect and practice effect are substantially orthogonal behavioral phenomena. According to this, we reasoned that the local cortical neural assemblies subserving compatibility and

¹ The 3 ANOVAs were not performed to test repeatedly the same hypothesis. The reaction times analysis showed that the power law of practice is approximately linear over the range of practice investigated in our experiment. This suggested the 1st 2 ANOVAs testing linear trends in linear and log-log space. Further, it was necessary to test whether there was a nonlinear brain response to practice or even a time effect independent of any practice effect.

Left Superior Parietal Activated Area



FIG. 5. In both left and right superior parietal lobule activated areas the rCBF changes were highly correlated with the general index of spatial stimulus-response compatibility (P < 0.0001). They showed only a very marginal inverse correlation with the visual field laterality index (P < 0.05, not significant when corrected for multiple regressions), and no correlation with the response hand laterality index (P > 0.5).

practice effects should also be orthogonal and that practice should affect a cognitive computation (and the cortical neural assembly subserving it) necessary to both compatible and incompatible responses. Results are in line with this reasoning: significant rCBF changes from the compatible to the incompatible response condition were observed bilaterally in the superior parietal lobules of the two hemispheres, whereas significant practice-related rCBF changes were observed in the dorsolateral prefrontal cortex and in premotor and motor areas of the left hemisphere. We will address below in three separate sections the issues of 1) spatial stimulus-response compatibility, 2) practice effects, and 3) brain-behavior relationships.

Spatial stimulus-response compatibility

Spatial stimulus-response compatibility depends on the interaction of stimuli and responses, and not on the properties of stimuli alone and responses alone (Kornblum and Lee 1995; Riehle et al. 1994). We manipulated the mapping between the spatial location of a lateralized light flash (left or right) and of a motor response (left or right) such that

compatible and incompatible response conditions differed only with respect to the strategy that subjects were instructed to follow. The amount of sensory inputs and motor outputs was the same in both conditions (see METHODS), as well as, at least in principle, the amount of efference copies of motor commands (Andersen 1987) and shifts in visuospatial attention (Posner et al. 1980; Rizzolatti et al. 1987). This is extremely important given that an unbalancing of these factors in the two conditions would make the interpretation of rCBF changes in the posterior parietal cortex rather difficult. Indeed, previous PET studies have demonstrated a major role of the superior parietal lobule in visuospatial attention (Corbetta et al. 1993; Petersen et al. 1994). Shifts in visuospatial attention, however, are related to the presence of the imperative stimuli in the spatial stimulus-response compatibility task, as demonstrated by Nicoletti and Umiltá (1994). Thus, given that the imperative stimuli (the lateralized flashes) were completely counterbalanced in our experiment, it is unlikely that the rCBF changes observed in the two superior parietal lobules are due to shifts in visuospatial attention.

We propose that the two superior parietal lobule areas seen in our study are related to the cortical activity subserving the extracomputational steps required by the incompatible response condition when compared with the compatible one. These additional computations would be required because of the more complex remapping of the visual stimulus spatial attributes onto the motor response spatial attributes. The involvement of the superior parietal lobule in the spatial stimulus-response remapping process is in line with the evidence suggesting that the posterior parietal cortex subserves the processing of spatial attributes of sensory information to be used for motor planning and selection of motor behavior (Andersen 1987; Grafton et al. 1992). The strong relationship between rCBF in the two superior parietal lobule areas and the overall performance of our subjects during compatible and incompatible response conditions, as evidenced by the regression analyses, supports this notion.

An interesting feature of the two activated superior parietal lobule areas is their asymmetry in both size and location. We explored the possibility that this asymmetry may reflect a different functional role of these two cortical areas. The reaction time-blood flow regression analyses, however, did not support this hypothesis and suggest that the observed size and location asymmetries of the two significant rCBF changes probably reflect the underlying morphological asymmetry in the two posterior parietal lobes in right handers (Geschwind and Galaburda 1984). Our data seem to confirm the frequently reported inconsistency between the general symmetry in activation patterns in the posterior parietal cortex observed in PET studies on sensorimotor integration in normal subjects (Corbetta et al. 1993; Grafton et al. 1992; Petersen et al. 1994) and the dramatic differential effect of unilateral posterior parietal lesions in neurological patients (Heilman et al. 1993; Perenin and Vighetto 1988). This inconsistency may be in support of the hypothesis that each parietal lobe inhibits the contralateral one (Kinsbourne 1987). Asymmetries between the two parietal lobes would be detectable only after unilateral lesions, when this reciprocal inhibition would be released.

Practice effects

Practice-related changes in rCBF were observed in the dorsolateral prefrontal cortex and in premotor and motor cortex of the left hemisphere. These cortical areas are known to be involved in learning association rules (dorsolateral prefrontal cortex) and specific association of motor response to sensory stimuli (premotor cortex) (Passingham 1993). With regard to the motor cortex, single-cell recordings in monkeys have shown neuronal activity coding the stimulus-response association rule in the primary motor cortex (Riehle et al. 1994) and the rCBF changes seen in our study in the precentral gyrus are likely to reflect a similar neuronal activity in the human.

The two striking features of the present findings are 1) the linear increase in practice-related rCBF changes in both dorsolateral prefrontal and premotor-motor areas and 2) the lateralization of the rCBF increases even though practice effects were parallel in both response hands. Note that the shortening of reaction times did not produce any change in the actual number of motor responses (see METHODS). Thus the rCBF increases are not due to an increased amount of motor activity. Practice-related linear rCBF increases are

consistent with the evidence that the amount of neuronal discharge in the dorsolateral prefrontal cortex of monkeys performing a delayed-response task is related to learning the task (Fuster 1973), and suggest that practice may have produced the progressive shortening of reaction times by means of three mechanisms: 1) progressively increasing the responsiveness of stimulus-coding and response-coding prefrontal neurons, which are intermixed in the dorsolateral prefrontal cortex (Fuster 1995; Goldman-Rakic 1995); 2) progressively increasing the efficiency of the lateral premotor cortex in triggering externally cued motor outputs; and 3) progressively reinforcing the stimulus-response association rule in primary motor neurons. This is consistent with the evidence that practice effects strengthen links mapping stimuli onto responses in human choice reaction time tasks (Pashler and Baylis 1991), and it is also in line with the notion that rCBF decreases, which are commonly associated with practice and strikingly absent in our study, should be an index of a change of strategy due to procedural learning (Raichle et al. 1994). The change of strategy should be unnecessary in the procedural learning of spatial stimulusresponse compatibility (Pashler and Baylis 1991), and, accordingly, no rCBF decreases occurred in our experiment. We cannot exclude, however, the occurrence of practicerelated rCBF decreases, as well as increases, in cerebral structures outside the field of view of our PET scanner, such as the cerebellum or the basal ganglia.

It is important to note that time effects independent from practice and related to spurious factors (such as discomfort or boredom) may be observed in functional neuroimaging studies. These time effects are a confounding variable that can make the interpretation of practice-related rCBF changes rather difficult. In a separate experiment on spatial stimulusresponse compatibility performed in our lab, however, we have replicated the practice-related rCBF changes reported in this paper (unpublished data). This makes it unlikely that the reported activations are due to random factors. Most importantly, the lack of practice-related modulation of the superior parietal lobule activations is unambiguous. This suggests that the spatial stimulus-response compatibility transformation is an automatic process that cannot be easily modulated (Dutta and Proctor 1992).

Interestingly, in the last scan, the practice-related rCBF increases show a plateau in premotor and motor areas and even a drop in the dorsolateral prefrontal cortex. This pattern resembles the pattern observed in primary sensory areas in response to increasing stimulation (Fox and Raichle 1985), which suggests similar "exhaustion" mechanisms in primary and associative areas, even though the magnitude of the rCBF changes is much larger in primary cortices than in associative areas (Roland 1993). The rCBF plateau in the premotor and motor areas and the rCBF decrease in the dorsolateral prefrontal cortex observed in the final scans may be a "physiological" prelude to the progressively smaller practice effects usually observed in behavioral experiments. We did not observe such reduction in practice effects only because the imaging session was probably too short. This hypothesis, however, needs to be more systematically addressed in future experiments in order to be substantiated by further experimental data.

The second striking feature of the present findings is the

robust left hemisphere lateralization of practice-related rCBF changes. To the best of our knowledge, in previously published functional neuroimaging studies no functional asymmetries in procedural learning have been reported. It is well known, however, that the right hand is much faster than the left hand in choice reaction time tasks than in simple reaction time tasks in normal human subjects, suggesting a left hemisphere specialization for response selection (Anzola et al. 1977). Left hemisphere prefrontal and premotor neurons may have produced the learning pattern observed in the left hand, which parallels the practice effect in the right hand, via corpus callosum, using largely symmetrical connections (McGuire et al. 1991a,b). This would be consistent with the general principle that the neural circuitry of motor learning is, to a large extent, the same as that of motor action (Fuster 1995).

Brain-behavior relationships

In our study, significant rCBF changes related to the stimulus-response spatial remapping process were observed in the posterior parietal cortex (left and right superior parietal lobules), whereas practice-related rCBF changes were observed in left dorsolateral prefrontal, premotor, and motor areas. Posterior parietal and dorsolateral prefrontal cortices are densely interconnected (Cavada and Goldman-Rakic 1989a.b). These corticocortical connections are thought to subserve complex sensorimotor integration behavior, and their richness and intricacy suggest that several simultaneous, parallel computations are required for an efficient human behavior in space (Friedman and Goldman-Rakic 1994; Goldman-Rakic 1988; Passingham 1993; Selemon and Goldman-Rakic 1988). This notion is also supported by the variety of sensorimotor integration disorders reported in braindamaged patients with lesions in associative areas (among others, see Chieffi et al. 1993; Goodale and Milner 1992; Heilman et al. 1993; Humphreys 1995; Humphreys and Riddoch 1994, 1995; Humphreys et al. 1994; Jeannerod et al. 1994).

Functional neuroimaging activation studies with normal subjects have to face the underlying complexity of neuronal systems subserving parallel computations converging in perceptuomotor behavior in the intact brain. For a better understanding of brain-behavior relationships with functional neuroimaging techniques, it is important to disentangle the subcomponents of a given complex behavior under investigation and, if possible, to counterbalance all the other subcomponents such that they cancel each other when different experimental conditions are contrasted. In-depth behavioral analyses and performance monitoring, as in the case of spatial stimulus-response compatibility and practice effects, are helpful in designing experiments and making predictions regarding brain activity in a given behavior. In our study, robust and largely replicated behavioral observations (Dutta and Proctor 1992; Newell and Rosenbloom 1981; Proctor and Dutta 1993; Umiltá and Nicoletti 1990) suggested that the two orthogonal behavioral phenomena of spatial stimulus-response compatibility and practice effect have separate neural substrates. Further, the parallel shortening of reaction times due to practice, in both compatible and incompatible response conditions, suggested that practice should be effective on a cognitive process common to both conditions. This predicts no spatial stimulus-response compatibility by practice interaction, just as we observed in our experiment. This also predicts that when incompatible and compatible conditions are contrasted, the cortical areas showing practice-related rCBF changes should cancel, because they are common to both response conditions. Again, this is confirmed by our data.

In conclusion, our findings suggest that the rCBF changes observed in the superior parietal lobule represent the extracomputational steps required by the remapping of the stimulus spatial attributes onto the response spatial attributes in the incompatible response condition compared with the compatible one. The behavioral counterpart of these additional computations is the spatial stimulus-response compatibility effect (i.e., the cost in reaction times from compatible to incompatible response condition). In contrast, the dorsolateral prefrontal, premotor, and motor rCBF changes represent the increasing efficiency of the cortical processes, common to both compatible and incompatible response conditions, linking visual stimuli to the selection and execution of the appropriate motor responses under different stimulus-response conditions.

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