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Dynamic cortical involvement in implicit and explicit motor sequence learning

A PET study

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Summary

We examined the dynamic involvement of different brain regions in implicit and explicit motor sequence learning using PET. In a serial reaction time task, subjects pressed each of four buttons with a different finger of the right hand in response to a visually presented number. Test sessions consisted of 10 cycles of the same 10-item sequence. The effects of explicit and implicit learning were assessed separately using a different behavioural parameter for each type of learning: correct recall of the test sequence for explicit learning and improvement of reaction time before the successful recall of any component of the test sequence for implicit learning. Regional cerebral blood flow was measured repeatedly during the task, and a parametric analysis was performed to identify brain regions in which activity was significantly correlated with subjects' performances: i.e. with correct recall of the test sequence or with reaction time. Explicit learning, shown as a positive correlation with the correct recall of the sequence, was associated with increased activity in the posterior parietal cortex, precuneus and premotor cortex bilaterally, also in the supplementary motor area (SMA) predominantly in the left anterior part, left thalamus, and right dorsolateral prefrontal cortex. In contrast, the reaction time showed a different pattern of correlation during different learning phases. During the implicit learning phase, when the subjects were not aware of the sequence, improvement of the reaction time was associated with increased activity in the contralateral primary sensorimotor cortex (SM1). During the explicit learning phase, the reaction time was significantly correlated with activity in a part of the frontoparietal network. During the post-learning phase, when the subjects achieved all components of the sequence explicitly, the reaction time was correlated with the activity in the ipsilateral SM1 and posterior part of the SMA. These results show that different sets of cortical regions are dynamically involved in implicit and explicit motor sequence learning.

Keywords: PET; serial reaction time task; implicit learning; explicit learning; motor sequence

Abbreviations: PRE = training block; rCBF = regional CBF; RND = random condition block; SEQ = sequence condition block; SMA = supplementary motor area; SM1 = primary sensorimotor cortex; SRTT = serial reaction time task; VIS = visual control condition block

Introduction

The acquisition of knowledge can be described as implicit learning and explicit learning (Graf and Schacter, 1985; Schacter, 1992; Schacter *et al.*, 1993). Implicit learning is characterized as an unintentional, non-conscious form of learning recognized by behavioural improvement. Explicit learning involves conscious recollection of previous experiences. Studies have shown that amnesic patients can acquire new motor (Milner *et al.*, 1968) and cognitive (Cohen and Squire, 1980; Saint-Cyr *et al*., 1988) skills, despite their inability to recollect the experience explicitly. Similar dichotomous distinctions of memory have also been proposed (Squire, 1987; Curran and Keele, 1993). Acquisition of a complex motor sequence can also involve implicit and explicit learning. The serial reaction time task (SRTT), introduced by Nissen and Bullemer (1987), in which subjects are required to press a key corresponding to each visual cue presented according to a sequence, has been widely used to study implicit and explicit aspects of motor sequence learning. Primarily, implicit learning can be assessed by improvement of reaction time, and explicit learning can be assessed by awareness or conscious generation of the sequence (Willingham *et al*., 1989), although reaction time can also be affected by explicit learning to some extent (Perruchet and Amorim, 1992; Curran and Keele, 1993). Studies on amnesic patients (Knopman and Nissen, 1987; Nissen and Bullemer, 1987) and normal subjects (Willingham *et al*., 1989) have shown that the development of knowledge of one type seemed not to depend on knowledge of the other type, and they suggest that the two types of learning may have different neuronal correlates in the brain.

Using transcranial magnetic stimulation and a variation of the SRTT, Pascual-Leone *et al*. (1994) observed modulation of activity in the primary sensorimotor cortex (SM1) with motor sequence learning. Zhuang *et al*. (1997), using EEG techniques, made a similar observation. However, the limited scope of these techniques makes it difficult to assess all the cortical and subcortical regions differentially involved in implicit and explicit motor learning. There is little correspondence between previous neuroimaging studies using modified versions of the SRTT (Grafton *et al*., 1995; Rauch *et al*., 1995; Doyon *et al*., 1996; Hazeltine *et al*., 1997). Grafton *et al*. (1995) and Hazeltine *et al*. (1997) reported that the contralateral SM1, supplementary motor area (SMA) and putamen were involved in implicit learning, whereas the frontoparietal network was involved in explicit learning. In contrast, Rauch *et al*. (1995) showed that the implicit condition involved the right ventral premotor cortex, right ventral caudate, right thalamus and bilateral visual association cortex, and that the explicit condition involved the primary visual cortex, perisylvian cortex and cerebellar vermis. Moreover, Doyon *et al*. (1996) argued that the striatum and cerebellum are involved in implicit learning, and that the mid-ventrolateral frontal cortex is involved in explicit learning. None of these studies explored the correlation between dynamic changes in activity and actual performance improvement during learning.

The objective of the present study was to identify the brain regions specifically correlated with implicit and explicit phases of motor sequence learning, with PET. Because the learning process can be considered a dynamic phenomenon occurring over time, it is of crucial importance to account for the inter-individual variability in the learning curves. To address this issue, we used a parametric approach to identify brain regions where activity was significantly correlated with different behavioural parameters associated with individual behavioural blocks, where reaction time and conscious generation of the sequence reflect implicit and explicit aspects of motor sequence learning. We also categorized the time course of individual learning into different phases according to the subject's performance, and employed separate parametric analyses. This method enabled us to clarify the dynamic involvement of different neuronal circuits in different phases of a single learning process.

Methods

We studied 21 healthy normal volunteers (15 men and 6 women), aged 20–52 years (mean, 30.4 years). The subjects were all right-handed according to the Oldfield handedness questionnaire (Oldfield, 1971). The protocol was approved by the Institutional Review Board, and subjects gave their written informed consent for the study.

Behavioural task

A variation of the SRTT (Pascual-Leone *et al*., 1994) was employed. Subjects lay supine on a PET scanner bed with their right hand on a response keypad with four buttons. A number (1, 2, 3 or 4) was presented in the centre of a computer screen situated ~1 m in front of the subject's eyes. Each number subtended a visual angle of 2.4°. Subjects were instructed to press each button with a different finger of the right hand in response to each number (index finger for button 1, middle finger for 2, ring finger for 3 and little finger for 4) as quickly and accurately as possible. Because the subjects kept their fingers on the buttons, which were sensitive to changes in pressure, the motor responses were primarily isometric. Feedback information on the response was given as follows. When the correct response button was pressed, the number (stimulus) disappeared from the screen immediately. When an incorrect button was pressed, the number remained visible until the next number appeared on the screen, and subjects were not required to press any other buttons. A total of 13 behavioural blocks was administered. Each behavioural block consisted of the presentation of 100 numbers at a regular pace of 0.5 Hz, taking 3 min 40 s, so that the number of movements per block was controlled. Three different stimulus conditions were imposed: a random condition, a sequence condition and a visual control condition (see Table 1). The random condition consisted of 100 numbers presented in a random order. The sequence condition consisted of 10 repetitions of a 10-number test sequence (4–3–2–1–3–4–2–3–1–2), with each block starting at a different point in the test sequence. This test sequence can be considered an 'ambiguous sequence' (Cohen *et al*., 1990) because no component can be uniquely predicted by its predecessor. The same sequence was used for all subjects. The visual control condition consisted of 100 numbers presented in a random order, but no response was required. The duration of each number's presentation for this condition was controlled using

Table 1 *Behavioural blocks and PET scans*

PET scan	Block name	Stimulus condition
Transmission scan	PRE1	Random
Transmission scan	PRE2	Random
Transmission scan	PRE3	Random
Scan 1	RND1	Random
Scan 2	SEQ1	Sequence
Scan 3	SEQ2	Sequence
Scan 4	SEQ3	Sequence
Scan 5	SEQ4	Sequence
Scan 6	SEQ5	Sequence
Scan 7	SEQ6	Sequence
Scan 8	SEQ7	Sequence
When subjects correctly reported all components of the sequence		
Scan 9	RND2	Random
Scan 10	VIS	Visual control
When subjects could not report all components of the sequence		
Scan 9	SEQ8	Sequence
Scan 10	SEQ9	Sequence

PRE = training block; SEQ = sequence block; RND = random block; VIS = visual control block.

the stored reaction times from the preceding block of the random condition to minimize the difference in visual stimuli. No attempt was made to control attention during the visual control condition, because this condition was used only to confirm the regions of the brain related to motor execution in the population studied (see Data analysis section). During the transmission scan of PET, three blocks of the random condition, with 100 randomly presented numbers in each block, were used as training (PRE1, PRE2 and PRE3) to familiarize the subjects with the task. After the training, 10 behavioural blocks were performed with PET scanning. After one block of the random condition (RND1) was performed, seven blocks of the sequence condition (SEQ1–SEQ7) were performed.

After completing each block, subjects performed a generation task in which they were systematically questioned about the sequence. Question 1: this was 'Did you notice anything about the task?'. Question 2: if the answer was yes, they were asked 'What did you notice?'. Question 3: if the answer was 'a sequence,' they were asked to 'report the sequence, as far as you noticed, verbally'. This questionnaire is a slightly modified version of the one used by Willingham *et al*. (1989). Subjects were not forced to report if they were not aware of the sequence. Accuracy was measured, on the verbal report, as the longest continuous series of numbers that matched the actual sequence (Willingham *et al*., 1989) (report accuracy). If the subjects reported the existence of a repeating sequence in response to question 2, it was judged that the subject had become aware of the sequence. If fewer than three successive components matched the actual sequence, the response was not to be recognized as accurate, although none of the subjects had such a response. If, after a training block, the subjects incorrectly answered that they noticed a repeating sequence they were told that the sequence was random. Otherwise, subjects were not told whether their answers were correct or incorrect. When subjects correctly reported all components of the test sequence after SEQ7, one block of the random condition (RND2) and one block of the visual control condition (VIS) were performed. If subjects could not report the whole test sequence after SEQ7, then two more blocks of the sequence condition (SEQ8 and SEQ9) were performed instead. The mean reaction time of the correct responses and the number of erroneous responses in each block were calculated. The accuracy of the verbally reported sequence was also recorded (as a percentage); when question 3 was not asked, this score was given the value 0%.

According to the performance of each subject, the blocks were categorized into three phases: (i) the implicit learning phase, defined as blocks performed before the subject became aware of the existence of the test sequence, namely, before the subject reported the existence of a sequence in reply to question 2 of the questionnaire; (ii) the explicit learning phase, defined as blocks performed from the beginning of the explicit knowledge state until the first block when subjects could correctly generate the whole test sequence; and (iii) post-learning phase, defined as blocks performed when subjects correctly reported the whole test sequence in the generation task. Because of the variable learning ability of each subject, these phases were not necessarily identifiable in all subjects.

After completing the generation task of SEQ3, 12 out of the 21 subjects were instructed to find a repeating sequence, regardless of whether or not they were already aware of the repeating sequence. To obtain a longer implicit learning phase, no such instruction was given to the other 9 subjects. It is reasonable to combine the data from these two subgroups for the implicit learning and post-learning phases, because the behavioural states were essentially identical. In contrast, it is possible, and likely, that the instruction affected the explicit learning phase. However, since we focused on the contrast between explicit learning and implicit learning, rather than on the effect of the instruction on the explicit learning phase, we also analysed the combined data from both subgroups for the explicit learning phase.

PET procedure

The subject lay supine on a scanner bed in a dimly lit, sound-attenuated room. The head was immobilized with an individually fitted thermoplastic face mask. A small plastic catheter was placed in the left cubital vein for injection of the radioisotope. PET was performed with a Scanditronix PC 2048–15B scanner (Uppsala, Sweden), which collected 15 contiguous planes with an in-plane resolution of 6.5 mm full-width half-maximum after reconstruction, and with a centre-to-centre distance of 6.5 mm, covering 97.5 mm in the axial direction. Field of view and pixel size of the reconstructed images were 256 mm and 2 mm, respectively. A transmission scan was obtained with a rotating ^{68}Ge /^{68}Ga source. Based on the reconstructed transmission images, the subject's head was carefully positioned so that the scan covered the entire frontal lobe, including primary and supplementary motor areas, and the superior half of the cerebellum, where activation associated with motor execution most frequently occurs (e.g. Grafton *et al*., 1993). However, with a limited field of view in the axial direction of the scanner, the inferior half of the cerebellum was not covered. During the transmission scan, three training blocks were performed, as described earlier, at 2–3-min intervals. Then, 10 consecutive scans were made at 10-min intervals during the performance of each block. A bolus of 30 mCi of ^{15}O-labelled water was injected into the subject's left cubital vein 1 min after the task was started. Reconstructed images were obtained by summing the activity during the 60-s period following the first detection of an increase in cerebral radioactivity after the injection. No arterial blood sampling was performed, and thus the images collected were those of tissue activity. Tissue activity recorded by this method is linearly related to regional CBF (rCBF) (Fox *et al*., 1984; Fox and Mintun, 1989).

Data analysis

The data were analysed with statistical parametric maps (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks, Sherborn, Mass., USA). The statistical parametric maps are spatially extended statistical processes that are used to characterize regionally specific effects in imaging data (Friston *et al*., 1991, 1994; Worsley *et al*., 1992). The scans from each subject were realigned to the first image as a reference with rigid transformation and a least-squares approach (Friston *et al*., 1995*a*). After realignment, the images were transformed into a standard anatomical space (Talairach and Tournoux, 1988; Friston *et al*., 1995*a*). Each image was smoothed with an isotropic Gaussian kernel (full-width half-maximum = 15 mm) to account for the variation in gyral anatomy. The effect of global differences in rCBF between scans was removed by scaling activity in each pixel proportional to the global activity so as to adjust the mean global activity of each scan to 50 ml/100 g/min.

Eigenimage analysis

The data were first subjected to eigenimage analysis (Friston *et al*., 1993) to observe the general characteristic of variance–covariance structure in the data introduced by the experimental design in both the spatial and temporal domains without any a priori assumption. Only data from the subjects who completed all conditions were used for this analysis. Images recorded from each block were averaged separately across subjects with respect to the time course regardless of the learning phases, after a systematic difference among subjects was removed. To extract the predominant spatial correlation (C_{USV}) patterns that account for most of the variance–covariance structure of the time-series data, the data were divided into two sets of (orthogonal) vectors by the use of singular value decomposition (SVD), where C_{USV} = SVD$\{\mathbf{M}\}$, such that $\mathbf{M} = \mathbf{U}*\mathbf{S}*\mathbf{V}^{T}$ (T denotes transposition, and * denotes a product of matrices), and where **M** is the original time-series data matrix with 10 rows (one for each block) and one column for each voxel, and **U** and **V** are unitary orthogonal matrices denoting pattern in time and space, respectively, and **S** is a diagonal matrix of decreasing singular value. Therefore, in short, these procedures correspond to principal component analysis. Each eigenvector (each column of matrix **V**) can account for the predominant inter-regional correlation introduced by the experimental design, and can be shown as an image by the use of a standard grid (eigenimage). An eigenimage can be interpreted as a spatially distributed neuronal network representing functional connectivity. Each column of **U** corresponds to the temporal profile associated with each eigenimage. These scores can be interpreted as showing how the neuronal network (extracted as an eigenimage) is involved over time. The correlation between temporal profiles and behavioural scores, averaged across subjects, was also calculated. Note that the inter-subject variability in the time-course is not taken into account in this analysis and, therefore, the results represent only a tendency as a whole.

Statistical inference

To assess the statistical inference of a regionally specific effect of the experimental design, both subtraction and parametric analyses were employed. In the following analyses, the condition effects (in a subtraction analysis) or covariate effects (in a parametric analysis) were estimated according to the general linear model at each and every voxel (Friston *et al*., 1995*b*). A systematic difference across subjects was removed as a confounding effect. To test hypotheses about regionally specific conditions or covariate effects, the estimates were compared by the use of appropriate linear contrasts. The resulting set of voxel values for each contrast constituted a statistical parametric map of the *t*-statistic. The *t*-values were transformed to the unit normal distribution (*Z*-scores), which was independent of the degrees of freedom of the error, and a threshold was set at 3.09. To correct for multiple, non-independent comparisons, the significance of the activation in each brain region detected was estimated by the use of distributional approximations from the theory of Gaussian fields, in terms of spatial extent and/or peak height (Friston *et al*., 1994). A corrected *P*-value of 0.05 was used as a final threshold for significance. The resulting set of *Z*-scores for the significant brain regions was mapped on a standard spatial grid (Talairach and Tournoux, 1988).

Subtraction analysis. To confirm the regions of the brain related to motor execution in the population studied, the data were subjected to a conventional subtraction analysis. As in the eigenimage analysis, only data from the subjects who completed all conditions were used. The planned comparison was all blocks with movement versus the visual control condition.

Parametric analysis. To address the systematic effect of behavioural change on regional brain activity, images were analysed separately using different behavioural parameters as covariates. The results showed the regions where activity was significantly correlated with changes of each covariate. Since a systematic difference across subjects was removed as a confounding factor in the general linear model, the results can mainly reflect an intra-individual correlation with each covariate over time, without confounding correlations across subjects of no interest.

Images obtained from all blocks of the sequence condition of all subjects were analysed using the report accuracy associated with each PET scan as a covariate. It is reasonable to include not only the explicit learning phase but also the implicit learning and post-learning phases in this analysis, because a high correlation of rCBF with the covariate can denote activity that is stable during the latter two phases and increases only during the explicit learning phase.

Images were also analysed using the mean reaction time associated with each PET scan as a covariate. Correlation was calculated separately in each learning phase. Since only the blocks belonging to the individual learning phases were used for the analysis, the number of subjects and scans varied among analyses (see Results). To ensure the removal of a systematic difference in the reaction time across subjects, the mean reaction time in each block for each subject was normalized to that obtained from RND1 of the same subject and used as a covariate. In terms of the explicit learning phase, we added the last block of the implicit learning phase, if it existed, to this analysis, because we were interested in the relative change in activity that is introduced by each learning phase. This enabled us to include the subjects who achieved repetition of the whole test sequence during one block (e.g. a report accuracy of 0% in SEQ3 and of 100% in SEQ4).

We hypothesized that brain regions involved in explicit learning show a positive correlation with the report accuracy (i.e. activity is greater as the accuracy increases), whereas those involved in implicit learning show a negative correlation with reaction time during the implicit learning phase (i.e.

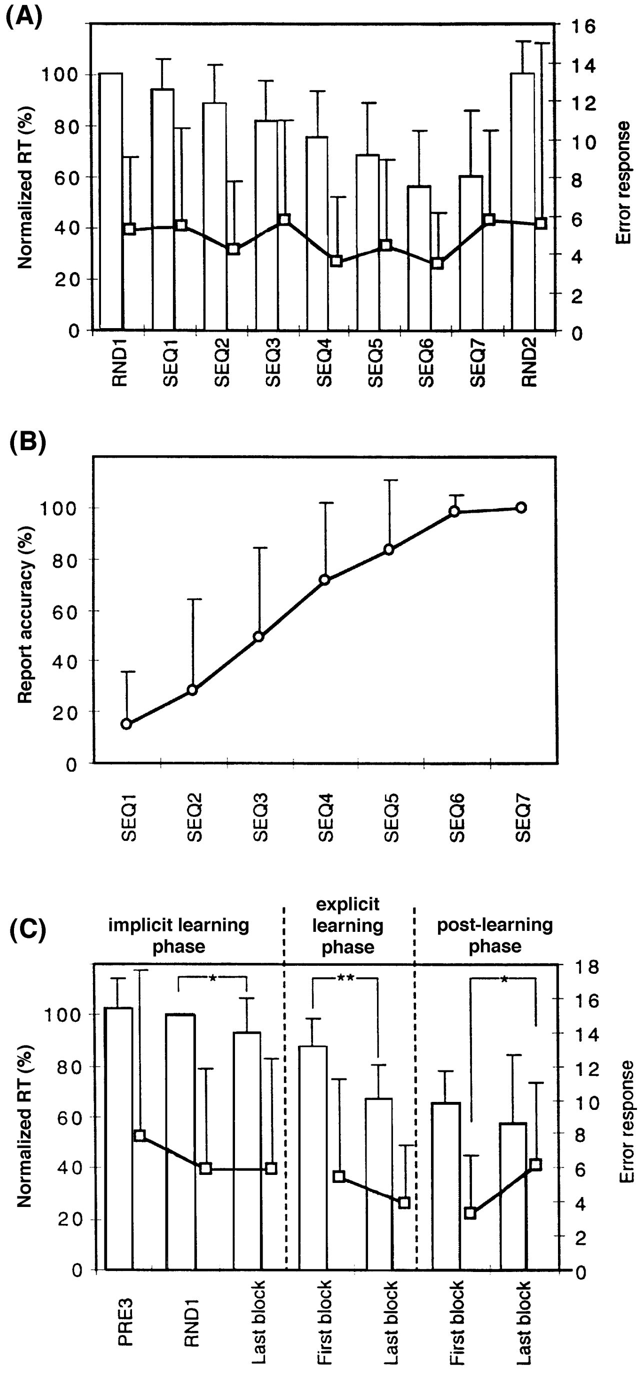

Fig. 1 Behavioural data. (**A**) Mean normalized reaction times (RT) (bars) and error responses (open squares) with standard deviations. Data were averaged across the 18 subjects who completed all of the three conditions with respect to the time series, regardless of different learning phases. (**B**) Mean report accuracy (percentage of correct verbal report of the test sequence) obtained after each block of the sequence condition, with standard deviations. The data were averaged with respect to the time series, as in **A**. (**C**) Mean normalized reaction times (bars) and error responses (open squares) with standard deviations, with respect to the different learning phases, i.e. according to the report accuracy scores of each individual. A different subgroup of subjects was used for each learning phase to take into account the individual variability of the learning course. *Left*: the last block of training (PRE3), the first block of the random condition (RND1) with PET and the last block of the implicit learning phase. Data were obtained from 14 subjects who had an implicit learning phase. The report accuracy scores during this phase were always 0%. *Centre:* the first and last block of the explicit learning phase obtained from 21 subjects. The report accuracy gradually increased during this phase. *Right:* the first and last block of the post-learning phase obtained from 16 subjects. The report accuracy was always 100% during this phase. $^{*}P < 0.05$; $^{**}P < 0.001$.

activity is greater as the reaction time decreases). In addition to a formal conservative threshold ($P = 0.05$, corrected for multiple comparisons), we also applied a more liberal threshold of $Z = 1.96$, corresponding to $P = 0.05$, uncorrected for multiple comparisons, to characterize the spatial extent of regions involved in the two different types of learning without producing too many false-positive results.

Results

Behavioural data

Figure 1 shows the behavioural measurements corresponding to each subgroup used for the separate rCBF analyses. Regarding reaction time, both the raw reaction times and normalized reaction times were used for the following statistical assessments and gave the same results. Only the results of the normalized reaction times, which were used for the rCBF analyses, are presented.

Three of the 21 subjects could not correctly generate all components of the test sequence after SEQ7. Therefore, two more blocks of the sequence condition (SEQ8 and SEQ9) were performed (Table 1). None of these subjects had been instructed to find the repeating sequence after SEQ3. One of them achieved full explicit knowledge in the final block (SEQ9), but the other two subjects failed to achieve it within the whole experimental period. Their report accuracy scores in the final block (SEQ9) were 30% and 40%. Their data were excluded from the eigenimage and the subtraction analyses, because they could not complete all of the three conditions. However, their data were used for the parametric analyses.

As a result, data from 18 subjects (12 with the instruction and 6 without the instruction) were subjected to the eigenimage and subtraction analyses to determine whether there was a general tendency for change. Figure 1 (A and B) shows temporal change in each behavioural measurement obtained from these subjects. The data were averaged across the subjects with respect to block, regardless of the learning phase. As the subjects repeated the blocks in the sequence condition, the reaction time (Fig. 1A, bars) and report accuracy (Fig. 1B) progressively improved. In contrast, the error response (Fig. 1A, open squares) did not show any consistent tendency to change across behavioural blocks. Even with the addition of the three subjects who did not perform blocks RND2 and VIS, the behavioural measurements did not tend to change. The significance of changes in each behavioural parameter was tested using repeated measures ANOVA (analysis of variance) with one within-subject factor, the block. The results revealed significant block effects on the normalized reaction time [$F(17,136) = 26.62$, $P < 0.0001$, ε (Greenhouse–Geisser correction) = 0.412] and on the report accuracy [$F(17,102) = 35.41$, $P < 0.0001$, $\varepsilon = 0.478$], but not on the error response [$F(17,136) = 0.84$, $P = 0.48$, $\varepsilon = 0.383$]. Even in these subjects, there was considerable inter-individual variability in the time course of learning, which was partially reflected as the large standard deviations in the reaction times and report accuracy. For example, the first block when these subjects achieved full explicit knowledge varied between SEQ2 and SEQ7. Therefore, the data were significantly influenced by a 'jitter' in the individual learning curves.

Eleven subjects showed an implicit learning phase, and their data, consisting of 44 blocks, were used for the parametric analysis of reaction times during the implicit learning phase. In the group of subjects who were given instruction on the existence of the repeating sequence after SEQ3, none of the blocks performed after they learned about the repeating sequence was categorized as implicit learning. There was only one block from one subject in which the subject was aware of the sequence but could not generate any components of it. By definition, this block was not included in this (implicit learning) phase. Behavioural data from these 11 subjects are presented in Fig. 1C (left). The report accuracy during this phase was always 0%. The reaction time in the last block of the implicit learning phase was shortened, with a marginally significant difference from that during RND1 ($P = 0.037$, one-tail paired t test). Regardless of whether or not the instruction was given, improvement of the reaction time was not significantly different between the two groups (51.8 ms with the instruction, 18.7 ms without the instruction; $P = 0.21$, one-tail unpaired t test). The reaction time in the last training block (PRE3) was not significantly different from that in RND1 ($P = 0.18$), indicating that any non-specific practice effect had already occurred by the time the test sequence started. There were no significant differences in error responses among these conditions.

Data from all 21 subjects were subjected to parametric analysis of reaction times during the explicit learning phase. As shown in Fig. 1C (centre), the reaction time decreased significantly between the first and last blocks of this phase ($P < 0.0001$), whereas the error response showed a non-significant decrease ($P = 0.073$). The normalized reaction times and report accuracy were highly correlated during this phase ($r = -0.559$, $P < 0.0001$).

Sixteen subjects showed a post-learning phase, and their data were used for the parametric analysis of reaction times during the post-learning phase. Behavioural data are shown in Fig. 1C (right). The report accuracy during this phase was always 100%. The normalized reaction times showed a non-significant decrease ($P = 0.12$), whereas the error responses increased ($P = 0.028$).

Eigenimage analysis

Eigenimage analysis was performed on 180 blocks obtained from 18 subjects. The distribution of eigenvalues (squared singular values) revealed that only the first two eigenimages were associated with eigenvalues greater than unity and could account for most of the observed variance–covariance structure. Namely, the first eigenimage accounted for 49.1%

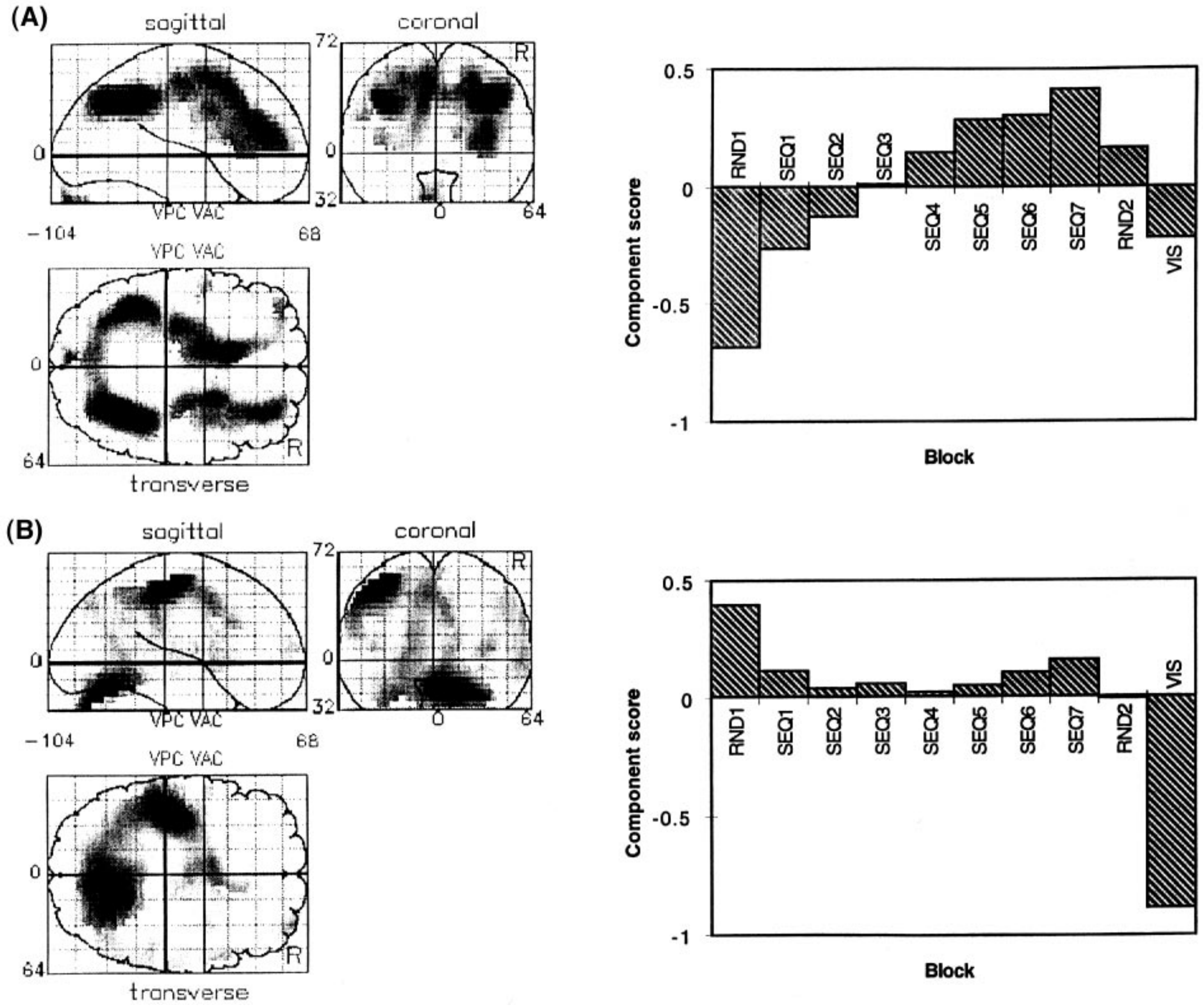

Fig. 2 Eigenimage analysis. (**A**) The first eigenimage and its time-dependent profile. *Left:* the positive component of the first eigenvector (i.e. first column of the matrix **V**). *Right:* the temporal profile shows the expression of the first eigenimage over the 10 blocks (i.e. first column of the matrix **U**). It is characterized by the gradual change over time during the sequence condition. (**B**) Second eigenimage and its time-dependent profile. *Left:* the positive component of the second eigenvector (i.e. second column of the matrix **V**). *Right:* the temporal profile shows the expression of the second eigenimage over the 10 blocks (i.e. second column of **U**). It is characterized by the stepwise change between blocks with movement and visual control. The eigenvectors are displayed in the spatial mode using a standard format as a maximum intensity projection viewed from the back (coronal view), the right side (sagittal view) and the top (transverse view) of the brain. The anatomical space corresponds to the atlas of Talairach and Tournoux (1988). The intensity of display is scaled to the maximum of the eigenimage.

of the total variance–covariance structure, and the second eigenimage accounted for 23.9%. The first eigenimage included the bilateral medial and lateral inferior parietal lobes, bilateral premotor area, bilateral dorsolateral prefrontal cortex and contralateral SMA (Fig. 2A, left). Its temporal profile was characterized by a time-dependent monotonic change over blocks of the sequence condition and then changes in the opposite direction during RND2 and VIS (Fig. 2A, right). We interpret this as a learning-related change, although a non-specific time effect is also evident, because RND2 showed a higher score than RND1. The temporal profile was significantly correlated with the grand average reaction time ($r = -0.729$, $P < 0.05$) and the report accuracy ($r = 0.967$, $P < 0.001$), but not with the error response ($r = -0.185$, $P = 0.63$). The second eigenimage involved the contralateral SM1 and ipsilateral cerebellar hemisphere (Fig. 2B, left) and can be interpreted as a motor execution-related change. This component was characterized by a stepwise change between the visual control block and the blocks involving movement (Fig. 2B, right). The temporal profile was not correlated with any of the behavioural parameters (with mean reaction time, $r = 0.016$, $P = 0.97$; with error responses, $r = 0.245$, $P = 0.52$; with report accuracy, $r = 0.558$, $P = 0.19$).

Subtraction analysis

Subtraction analysis was performed on 180 blocks obtained from 18 subjects. When data from the movement blocks were compared with data from the visual control block,

Table 2 *Brain regions activated by finger movement, as determined by subtraction analysis*

Brain region (Brodmann area)	Coordinates *x*	*y*	*z*	*Z*-score
Left SM1	–34	–20	56	11.13
Right cerebellar hemisphere	22	–60	–20	8.39
SMA (6)	–6	2	44	5.43

Coordinates indicate the location of maximally significant activity.

Table 3 *Brain regions with significant correlations between report accuracy and rCBF, as determined by parametric analysis*

Brain region (Brodmann area)	Coordinates *x*	*y*	*z*	*Z*-score
Regions with positive correlations				
Right posterior parietal cortex (40)	26	–70	32	7.56
Precuneus (7)	–4	–74	36	6.54
Left posterior parietal cortex (40)	–30	–64	40	6.14
Right dorsal premotor cortex (6)	24	4	52	6.05
Right dorsolateral prefrontal cortex (46)	36	42	16	5.47
SMA (6)	–12	2	48	5.20
Left dorsal premotor cortex (6)	–24	–2	48	4.87
Left thalamus	–10	–18	0	4.72
Regions with negative correlations				
Left angular gyrus (39)	–52	–68	12	6.10
Medial prefrontal (9)	–6	48	40	5.95
Right superior temporal gyrus (42, 22)	52	–8	–8	5.49
Right angular gyrus (39)	46	–58	16	4.77
Left transverse temporal gyrus (41)	–40	–24	12	4.24

Coordinates indicate the location of maximally significant correlations between report accuracy and rCBF.

significant activation was observed in the contralateral SM1, SMA, and ipsilateral cerebellum (Table 2). Note that these results correspond well with the second eigenimage.

Parametric analysis

All 153 blocks of the sequence condition obtained from all 21 subjects were used for parametric analysis of the report accuracy. A significant positive correlation of brain activity with the report accuracy was observed in the posterior parietal cortex, precuneus, bilateral premotor cortex, right dorsolateral prefrontal cortex, left thalamus and SMA, predominantly the contralateral anterior portion (Fig. 3A and Table 3). Activity in these areas increased as the report accuracy increased. This analysis corresponds well with the first eigenimage. A negative correlation of brain activity with the report accuracy was found in the bilateral parieto-occipital region, bilateral temporal cortex, and medial prefrontal region (Fig. 3B).

Forty-four blocks from 14 subjects were used for parametric analysis of reaction times during the implicit learning phase. A significant negative correlation of brain activity with reaction time was observed only in the contralateral SM1 (Fig. 4). The location was ~15 mm posterior to the maximum activation in the subtraction analysis (Tables 2 and 4). Activity in this area increased as the reaction time shortened. A significant positive correlation was observed in the left anterior insula (Table 4).

Ninety-eight blocks from all 21 subjects were subjected to parametric analysis of reaction times during the explicit learning phase. During this phase, the reaction time showed a significant negative correlation with activity in the left anterior SMA, right premotor cortex and right posterior parietal cortex (Fig. 5A and Table 4). All of these areas corresponded well with the areas where activity was significantly correlated with the report accuracy (shown in Fig. 3A).

Fifty-four blocks from 16 subjects were used for parametric analysis of reaction times during the post-learning phase. A significant negative correlation of brain activity with reaction time was observed in the posterior SMA and ipsilateral SM1 (Fig. 5B and Table 4). These areas also revealed a negative, but non-significant, correlation with reaction time during the implicit learning phase (for ipsilateral SM1, $Z = 3.26$ at $x = 32$, $y = 28$, $z = 56$; for SMA, $Z = 3.21$ at $x = 4$, $y = 28$, $z = 56$). It is also noteworthy that the contralateral SM1 showed the same non-significant tendency during the post-learning phase ($Z = 3.23$ at $x = 34$, $y = 38$, $z = 52$).

Figure 6 shows a superimposition of the same data shown in Figs 4A and 5A, but using a lower threshold of $Z = 1.96$, without correction for multiple comparisons. The illustration shows that activity in the frontoparietal region had a tendency toward a positive correlation with the report accuracy (corresponding to Fig. 4A) and that activity in the central region had a tendency toward a negative correlation with reaction time during the implicit learning phase (corresponding to Fig. 5A). Furthermore, as shown in the transverse view (Fig. 6, lower left), even when a lower threshold is employed, these two sets of regions show scant overlap.

Discussion

The main finding of this study is that activity in anatomically separate brain areas is correlated with different performance measurements. Activity in the frontoparietal region was correlated with the correct recall of the sequence, a measure of explicit learning. Activity in the central region, most significantly the contralateral SM1, showed a correlation with the reaction time during the implicit learning phase. In contrast, during the explicit learning phase, when the subjects developed conscious knowledge about the sequence, the reaction time was significantly correlated with activity in a part of the frontoparietal network. During the post-learning phase, when the subjects already consciously knew all components of the sequence, further improvement of reaction time was correlated with activity in the central region again,

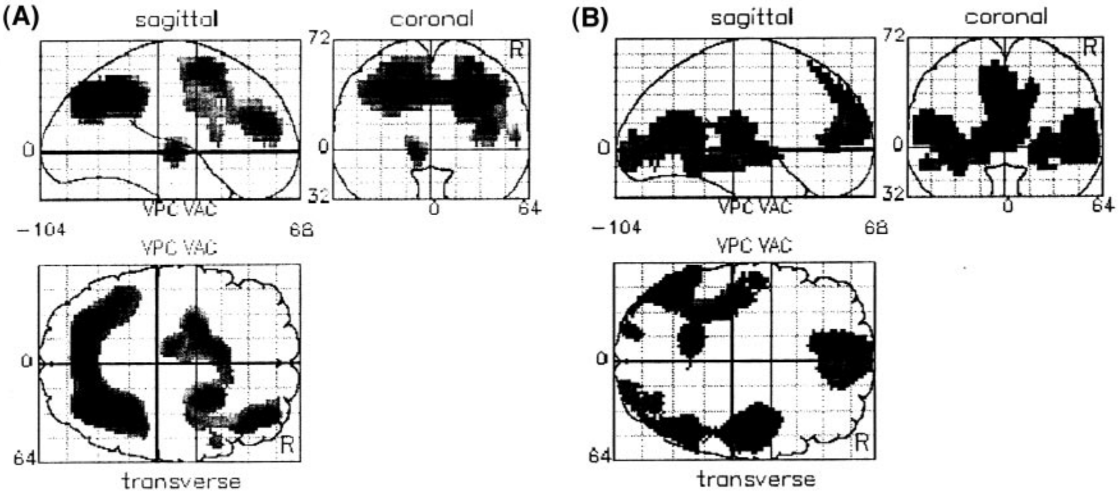

Fig. 3 Statistical parametric maps of the regional effect of report accuracy. Maps of *Z*-scores for the regions where activity was significantly correlated with the report accuracy ($P < 0.05$ with a correction for multiple comparisons) are shown in a standard anatomical space (Talairach and Tournoux, 1988). Positive (**A**) and negative (**B**) correlation maps on which positive (or negative) correlation means increasing (or decreasing) activity as the report accuracy increased on an individual basis.

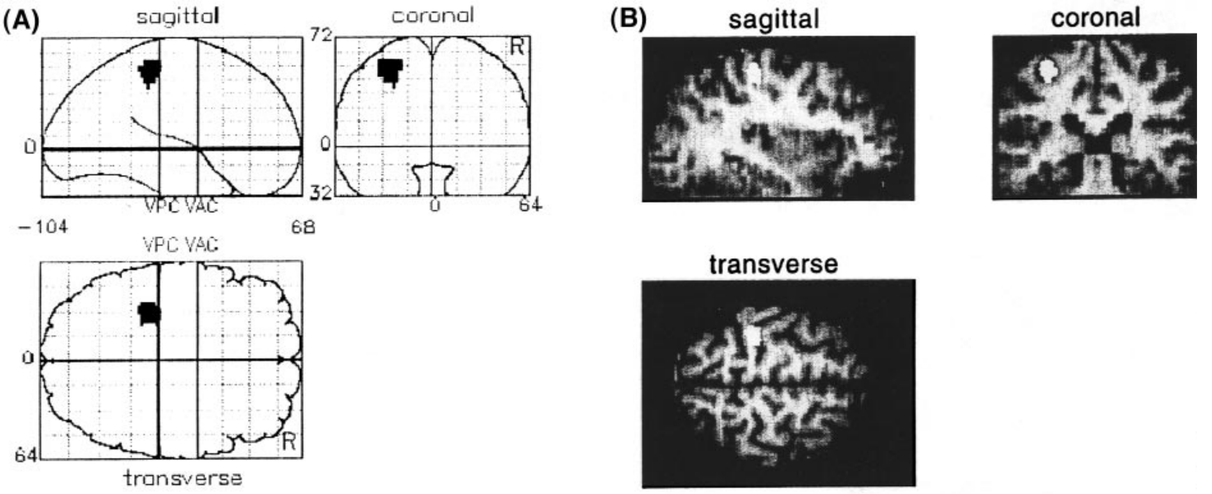

Fig. 4 (**A**) Statistical parametric maps of the regional effect of normalized reaction time during the implicit learning phase, shown in a standard format. The maps show a negative correlation of rCBF with normalized reaction time, meaning that activity increased as the reaction time decreased. (**B**) The same region is superimposed onto three orthogonal slices of spatially normalized MRI images from one subject.

but this time more in the ipsilateral SM1 and posterior SMA. We interpret these results to mean that the frontoparietal network is predominantly responsible for explicit learning, whereas the central area is more responsible for improvement of motor performance, including implicit learning, and that these distinct cortical regions are dynamically involved in learning, although this interpretation requires caution.

Parametric approach and its limitations

Because the learning process is a dynamic phenomenon occurring over time, a parametric approach that identifies a regional change in activity correlated with a parameter of learning (Grafton *et al*., 1995) can be a powerful tool, especially for the SRTT associated with a chronometric measurement of performance. A direct relationship between neuronal activity and rCBF has been shown for the primary visual cortex (Fox and Raichle, 1984), primary auditory cortex (Price *et al*., 1992), primary somatosensory cortex (Ibáñez *et al*., 1995) and primary motor cortex (Sadato *et al*., 1996*b*). However, a change in rCBF (Price *et al*., 1992; Sadato *et al*., 1996*a*, *b*) may not parallel the parameter of behaviour or stimulus in some areas. Chen and Wise (1995) reported what they termed ‘learning-selective activity’ in the cortex, which was high only during some specific period of learning, and did not parallel the learning curve. The parametric approach used in our study may not detect such activity, and the findings should be interpreted with caution, especially the negative results. Regardless of whether a parametric or subtraction approach is used, it is also difficult

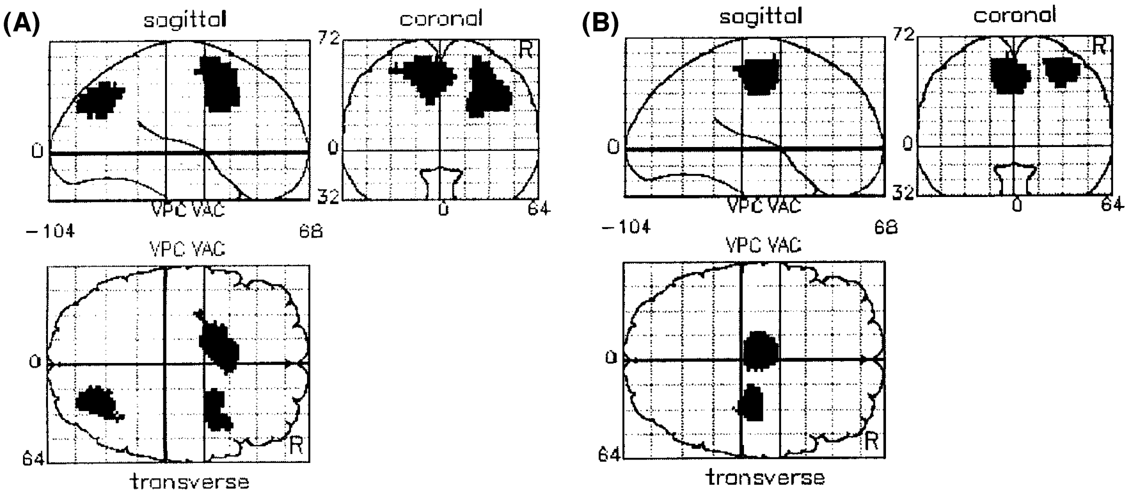

Fig. 5 (**A**) Statistical parametric maps of the regional effect of normalized reaction time during the explicit learning phase. (**B**) Statistical parametric maps of the regional effect of normalized reaction time during the post-learning phase. Both maps show a negative correlation of rCBF with normalized reaction time using a standard format.

Table 4 *Brain regions with significant correlations between reaction times and rCBF, as determined by parametric analysis*

Brain region (Brodmann area)	Coordinates			*Z*-score
	x	*y*	*z*	
Implicit learning phase				
Negative correlation	–32	–34	52	4.48
Left SM1				
Positive correlation	–30	18	4	4.69
Left anterior insula				
Explicit learning phase				
Negative correlations				
SMA (6)	–10	4	52	4.37
Right dorsal premotor cortex (6)	28	4	48	4.15
Right posterior parietal cortex (40)	26	–70	32	4.11
Positive correlations				
Right superior temporal gyrus (42, 22)	50	–8	–8	4.67
Left fungiform gyrus (36)	–30	–40	–4	4.50
Left angular gyrus (39)	–52	–62	12	4.23
Left inferior occipital gyrus (18, 19)	–12	–86	–12	4.17
Post-learning phase				
Negative correlations				
SMA (6)	0	–14	44	4.81
Right SM1	30	–20	48	4.39
Positive correlations				
Left ventral premotor cortex (6)	–44	4	44	5.59
Left posterior parietal cortex (40)	–42	–62	44	4.50
Right inferior frontal gyrus (44)	50	16	16	4.30

Coordinates indicate the location of maximally significant correlations between reaction times and rCBF.

to distinguish whether observed changes are ‘essential for’ learning *per se*, or simply ‘associated with’ learning, because learning essentially affects performance in a SRTT.

Task design and interpretation

The generation task that we used is a slightly modified version of the one used by Willingham *et al.* (1989); it also compares closely with the ‘free generation task’ used by Perruchet and Amorim (1992), in which a minimal contribution of the implicit form of learning is expected. The SRTT used in our study employed a number instead of the spatial position in the conventional SRTT, and a verbal report was used for the generation task, rather than the usual sequence production method. These procedures are expected to require more explicit mechanisms to generate the sequence compared with those requiring the motor response used in the SRTT itself. On the other hand, in this study, the reaction time task and the questionnaire measure of explicit knowledge alternated. This procedure contrasts with the standard version of the task, in which explicit knowledge is not assessed until several blocks of reaction time training have been completed, and is likely to encourage subjects to look for regularities, and to develop explicit knowledge more quickly than is usual in the standard task. We should also consider the possibility that the score may underestimate the explicit knowledge actually used during the task. Explicit learning may start when subjects become aware of the repeating feature of the presentation, even if the report accuracy is 0%. In the study of Willingham *et al.* (1989), subjects who performed a generation task only at chance levels were above chance on a cued recall measure of explicit knowledge. However, in the present study, there was only one block from one subject when the subject was aware of the existence of the sequence but unable to generate it, and such an effect may be minimal. It is noteworthy that the areas explored by this analysis corresponded well with the first eigenimage, whose temporal profile was highly correlated with the report accuracy. Since an eigenimage can be interpreted as a distributed neural network (Friston *et al.*, 1993), the finding may suggest that

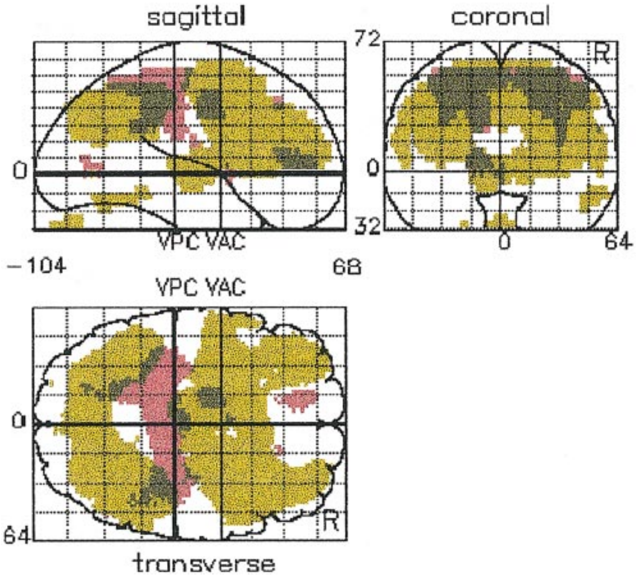

Fig. 6 Statistical parametric maps of the regional effect of report accuracy (khaki yellow) and the normalized reaction time during the implicit learning phase (wine red). The data are the same as those shown in Figs 3A and 4A except that a lower threshold of $Z = 1.96$ without correction for multiple comparisons was used. Note that two sets of areas slightly overlap (dark green), as shown best in the transverse projection (lower left).

these regions were involved in the explicit learning process as a whole network rather than as separate regions.

The different spatial pattern of the correlation with reaction time in the different learning phases suggests that the observed changes are not likely to be due to a general effect of a shortened reaction time (e.g. more acceleration resulting in more outflow from the motor executive area as the reaction time decreases), but are specific to each different phase. During implicit learning, when the subjects were not aware of the sequence, shortening of the reaction time was significantly correlated with increasing activity in the contralateral SM1. It is conceivable that the change in reaction time can reflect aspects of learning other than implicit sequence learning. For example, because the relationship between the stimulus and the actual motor response was arbitrary in our version of the SRTT (i.e. there is less spatially compatible correspondence between the number '1' and the 'index finger' compared with the situation where the spatial position of a stimulus represents the index finger), this arbitrary sensorimotor association might also be the subject of learning. This kind of learning has been termed conditional motor learning (Passingham, 1993). However, the sensorimotor association was so simple that subjects learned it very quickly, and errors did not show significant change over experimental blocks. On this basis, we argue that any conditional motor learning effect had already occurred by the time the test sequence started. The finding that the reaction time in PRE3 was not significantly different from that in RND1 supports this conclusion. On the other hand, both the ambiguous sequence (Cohen *et al*., 1990) and the relatively long inter-stimulus interval (Frensch and Miner, 1994) that we used have been shown to have a detrimental effect on implicit learning, and might be responsible for a somewhat smaller than usual decrease of reaction times during the implicit learning phase. This might partly explain an absence of significant findings in some areas.

During the explicit learning phase, the improvement in reaction time paralleled an increase in the report accuracy, and a significant correlation was shown in a part of the frontoparietal network. This supports neuropsychological evidence that explicit learning contributes to the improvement of reaction time (Perruchet and Amorim, 1992; Curran and Keele, 1993; Schmidtke and Heuer, 1998). Although the explored frontoparietal network was distinguishable from what we interpret as implicit learning-related areas, we do not think that the two sets of cortical regions 'exclusively' contribute to implicit and explicit learning. Pascual-Leone *et al*. (1994) showed that the increase of cortical excitability in the contralateral SM1 started during the implicit learning phase, and that it lasted until the subjects fully achieved explicit learning. This suggests that the implicit learning-related change may continue during the explicit learning phase. The absence of a significant correlation between activity in the contralateral SM1 and reaction times during the explicit learning phase in the present study may be explained by normalization of global activity in PET. The longitudinal change in activity in a smaller area, such as the SM1, may be obscured by the net activity in the larger frontoparietal network, once it becomes active. On this basis, we conclude that the different regions may each be 'more responsible' for different types of learning.

The change in reaction time during the post-learning phase can be interpreted in different ways. This phase can represent a consolidation phase of the sequence learning. Alternatively, since we used a fixed inter-stimulus interval, the timing of the response may be learned when subjects completely predict the forthcoming movement. Moreover, since the change in reaction time was not definitive over time, the correlation with reaction time may simply represent more efficient motor expression, including preparing and withholding movement.

Neuroimaging studies of sequence learning

There is little correspondence between neuroimaging studies that have used modified versions of the SRTT (Grafton *et al*., 1995; Rauch *et al*., 1995; Doyon *et al*., 1996; Hazeltine *et al*., 1997). The present results provide strong support for the results of Grafton *et al*. (1995) and Hazeltine *et al*. (1997). From the point of view of dichotomous distinction of learning in the previous studies, as the authors acknowledged, the implicit phase in the study of Rauch *et al*. (1995) had a 'non-significant' contamination of explicit learning, and in the study of Doyon *et al*. (1996), all of the subjects were aware of the sequence during both newly and highly learned sequences. It is also conceivable that implicit components persisted during explicit learning (Perruchet and

Amorim, 1992; Curran and Keele, 1993). The contamination and complicated interaction between two learning processes make the interpretion of the results from the subtraction analysis that they used somewhat problematic. In addition, the cortical areas showing the most marked findings in the present study, as well as in the studies of Grafton *et al.* (1995) and Hazeltine *et al.* (1997), i.e the SM1, SMA, dorsal premotor cortex and, presumably, a part of the posterior parietal cortex, were not covered by the PET scan in the study of Rauch *et al.* (1995).

Grafton *et al.* (1995) showed a longitudinal increase of rCBF in different regions during a SRTT with, and without, a secondary task to interfere with attention. The findings were recently supported by a study from the same group (Hazeltine *et al.*, 1997) using a different stimulus modality (colour instead of spatial position) to present a sequence. In both studies, since the secondary task may confound the SRTT itself, two SRTTs (with and without the secondary task) may not reflect dynamic aspects of the single learning course. In addition, five of the 12 subjects in Grafton *et al.* (1995) and four of the 11 subjects in Hazeltine *et al.* (1997) did not develop any explicit knowledge during either task, meaning that a non-negligible number of subjects remained at the same stage of learning from the point of view of the dichotomous distinction of implicit and explicit learning. This view raises the question of whether their findings might reflect the distinction between attentional versus non-attentional learning (Curran and Keele, 1993), which may be only indirectly related to implicit versus explicit learning. Nevertheless, the good agreement of our results with those of Grafton *et al.* (1995) and Hazeltine *et al.* (1997) suggests that these different dichotomous representations of motor sequence learning may share common neuroanatomical correlates.

The absence of significant findings in the basal ganglia and cerebellum in the present study could be partly due to a limited amount of implicit learning, or a non-linear change in activity with the learning curve, as discussed earlier. It is noteworthy that, despite clear evidence of a role of the basal ganglia in motor control (Saint-Cyr *et al.*, 1995), the findings of PET studies are largely controversial (Brooks, 1995). Activity in a complex ensemble of excitatory and inhibitory neurons might result in a complicated net change in rCBF in this region. Furthermore, the site in the cerebellum responsible for sequence learning might be different from that where we observed extensive activation when all movement conditions were compared with the visual control condition, and it might not be covered by the PET scan in this experiment. Further studies are needed in this regard.

Neuroanatomical correlates

There is evidence that the premotor cortex (Luria, 1966; Joseph and Barone, 1987; Halsband and Freund, 1990; Mushiake *et al.*, 1991; Kettner *et al.*, 1996*a*, *b*; Sadato *et al.*, 1996*a*), the dorsolateral prefrontal cortex (Barone and Joseph, 1989; Petrides, 1991; Jenkins *et al.*, 1994; Jueptner *et al.*, 1997*a*, *b*) and the anterior SMA (for review, see Picard and Strick, 1996) play an important role in controlling and/or learning sequential movement. Neuroimaging studies also provide evidence of the involvement of the posterior parietal cortex (Jenkins *et al.*, 1994; Grafton *et al.*, 1995; Petit *et al.*, 1996; Sadato *et al.*, 1996*a*; Jueptner *et al.*, 1997*a*) and thalamus (Sadato *et al.*, 1996*a*). Jenkins *et al.* (1994) showed that the dorsolateral prefrontal cortex, lateral premotor cortex, posterior parietal cortex and cerebellum were more activated during new sequence learning than during prelearned sequences. Using a paradigm similar to that of Jenkins *et al.* (1994), Jueptner *et al.* (1997*a*) showed that, compared with the simple execution of a prelearned sequence, the dorsolateral prefrontal cortex was activated during both new sequence learning and the execution of a prelearned sequence with conscious attention to the performed sequence. However, the degree of activation in the dorsolateral prefrontal cortex was more extensive during new sequence learning than during execution of a prelearned sequence with attention. Hikosaka *et al.* (1996) reported that the pre-supplementary motor area was more activated during new sequence learning than during a sensorimotor control task. Since the subjects attempted to find the sequence by ‘trial and error’ in these studies, it is conceivable that the explicit strategy, as well as a factor of ‘problem solving,’ contributed. The present study explores a learning-dependent change in parallel with performance improvement in these regions. This suggests that the large frontoparietal network may store and utilize the knowledge about a stimulus-motor sequence in a form accessible by a conscious, explicit strategy.

The primary motor cortex has been shown to play a role in procedural motor learning (Grafton *et al.*, 1992, 1994; Pascual-Leone and Torres, 1993; Pascual-Leone *et al.*, 1993, 1995; Schlaug *et al.*, 1994; Karni *et al.*, 1995). It is noteworthy that the maximum significant change was situated posterior to the motor representation in a subtraction analysis, because the importance of the somatosensory cortex has been proposed to account for plastic changes in the motor cortex (Sakamoto *et al.*, 1987; Iriki *et al.*, 1989) and learning of new motor skills (Sakamoto *et al.*, 1989; Pavlides *et al.*, 1993). However, this interpretation requires caution because active and passive movement of the elbow showed similar foci of activation in the contralateral SM1 (Weiller *et al.*, 1996). The relative contribution to improvement in reaction times shifted from the contralateral SM1 during the implicit learning phase to the ipsilateral SM1 and posterior SMA during the post-learning phase. During both phases, the contribution of explicit learning was minimal. Although these two stages have significant elemental differences, it is postulated that the contralateral SM1 might play a critical role in the earlier stage, and the ipsilateral SM1 and posterior SMA might become more important in the more advanced stage to achieve a more efficient motor response. The importance of the ipsilateral SM1 for controlling sequential movement

(Kitamura *et al*., 1993; Shibasaki *et al*., 1993; Chen *et al*., 1997) supports this view.

An open question is whether subjects learn the sequence of presentations (sensory domain), the sequence of responses (response domain) or the sequence of stimulus–response relationships (Keele *et al*., 1995). The good agreement between our study and the studies of Grafton *et al*. (1995) and Hazeltine *et al*. (1997), despite the use of different sensory information to present a sequence (number, spatial position or colour), suggests indirectly that sequence learning, especially its implicit aspect, does not occur solely in the sensory domain. However, the findings in the motor execution area do not necessarily mean that the implicit form of sequence encoding occurs solely in the response domain, because neurons in the contralateral SM1 have selective responsiveness to specific sensory information as well as sensorimotor transformation (Zhuang *et al*., 1997). The role of each region for the different domains of learning should be further examined.

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References

Barone P, Joseph JP. Prefrontal cortex and spatial sequencing in macaque monkey. Exp Brain Res 1989; 78: 447–64.

Brooks DJ. The role of the basal ganglia in motor control: contributions from PET. J Neurol Sci 1995; 128: 1–13.

Chen LL, Wise SP. Neuronal activity in the supplementary eye field during acquisition of conditional oculomotor associations. J Neurophysiol 1995; 73: 1101–21.

Chen R, Gerloff C, Hallett M, Cohen LG. Involvement of the ipsilateral motor cortex in finger movements of different complexities. Ann Neurol 1997; 41: 247–54.

Cohen NJ, Squire LR. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of ‘knowing how’ and ‘knowing that’. Science 1980; 210: 207–10.

Cohen A, Ivry RI, Keele SW. Attention and structure in sequence learning. J Exp Psychol Learn Mem Cogn 1990; 16: 17–30.

Curran T, Keele SW. Attentional and nonattentional forms of sequence learning. J Exp Psychol Learn Mem Cogn 1993; 19: 189–202.

Doyon J, Owen AM, Petrides M, Sziklas V, Evans AC. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur J Neurosci 1996; 8: 637–48.

Fox PT, Mintun MA. Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of $H_2{}^{15}O$ tissue activity. J Nucl Med 1989; 30: 141–9.

Fox PT, Raichle ME. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. J Neurophysiol 1984; 51: 1109–20.

Fox PT, Mintun MA, Raichle ME, Herscovitch P. A noninvasive approach to quantitative functional brain mapping with $H_2{}^{15}O$ and positron emission tomography. J Cereb Blood Flow Metab 1984; 4: 329–33.

Frensch PA, Miner CS. Effects of presentation rate and individual differences in short-term memory capacity on an indirect measure of serial learning. Mem Cognit 1994; 22: 95–110.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Comparing functional (PET) images: the assessment of significant change. J Cereb Blood Flow Metab 1991; 11: 690–9.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993; 13: 5–14.

Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. Hum Brain Mapp 1994; 1: 210–20.

Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. Hum Brain Mapp 1995a; 3: 165–89.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995b; 2: 189–210.

Graf P, Schacter DL. Implicit and explicit memory for new associations in normal and amnesic subjects. J Exp Psychol Learn Mem Cogn 1985; 11: 501–18.

Grafton ST, Mazziotta JC, Presty S, Friston KJ, Frackowiak RS, Phelps ME. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. J Neurosci 1992; 12: 2542–8.

Grafton ST, Woods RP, Mazziotta JC. Within-arm somatotopy in human motor areas determined by positron emission tomography imaging of cerebral blood flow. Exp Brain Res 1993; 95: 172–6.

Grafton ST, Woods RP, Tyszka M. Functional imaging of procedural motor learning: relating cerebral blood flow with individual subject performance. Hum Brain Mapp 1994; 1: 221–34.

Grafton ST, Hazeltine E, Ivry R. Functional mapping of sequence learning in normal humans. J Cogn Neurosci 1995; 7: 497–510.

Halsband U, Freund HJ. Premotor cortex and conditional motor learning in man. Brain 1990; 113: 207–22.

Hazeltine E, Grafton ST, Ivry R. Attention and stimulus characteristics determine the locus of motor-sequence encoding. Brain 1997; 120: 123–40.

Hikosaka O, Sakai K, Miyauchi S, Takino R, Sasaki Y, Putz B. Activation of human presupplementary motor area in learning of sequential procedures: a functional MRI study. J Neurophysiol 1996; 76: 617–21.

Ibáñez V, Deiber MP, Sadato N, Toro C, Grissom J, Woods RP, et al. Effects of stimulus rate on regional cerebral blood flow after median nerve stimulation. Brain 1995; 118: 1339–51.

Iriki A, Pavlides C, Keller A, Asanuma H. Long-term potentiation in the motor cortex. Science 1989; 245: 1385–7.

Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RS, Passingham RE. Motor sequence learning: a study with positron emission tomography. J Neurosci 1994; 14: 3775–90.

Joseph JP, Barone P. Prefrontal unit activity during a delayed oculomotor task in the monkey. Exp Brain Res 1987; 67: 460–8.

Jueptner M, Stephan KM, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. I. Frontal cortex and attention to action. J Neurophysiol 1997a; 77: 1313–24.

Jueptner M, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. J Neurophysiol 1997b; 77: 1325–37.

Karni A, Meyer G, Jezzard P, Adams MM, Turner R, Ungerleider LG. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 1995; 377: 155–8.

Keele SW, Jennings P, Jones S, Caulton D, Cohen A. On the modularity of sequence representation. J Mot Behav 1995; 27: 17–30.

Kettner RE, Marcario JK, Clark-Phelps MC. Control of remembered reaching sequences in monkey. I. Activity during movement in motor and premotor cortex. Exp Brain Res 1996a; 112: 335–46.

Kettner RE, Marcario JK, Port NL. Control of remembered reaching sequences in monkey. II. Storage and preparation before movement in motor and premotor cortex. Exp Brain Res 1996b; 112: 347–58.

Kitamura J, Shibasaki H, Takagi A, Nabeshima H, Yamaguchi A. Enhanced negative slope of cortical potentials before sequential as compared with simultaneous extensions of two fingers. Electroencephalogr Clin Neurophysiol 1993; 86: 176–82.

Knopman DS, Nissen MJ. Implicit learning in patients with probable Alzheimer's disease. Neurology 1987; 37: 784–8.

Luria AR. Higher cortical functions in man. New York: Basic Books; 1966.

Milner B, Corkin S, Teuber HL. Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. Neuropsychologia 1968; 6: 215–34.

Mushiake H, Inase M, Tanji J. Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. J Neurophysiol 1991; 66: 705–18.

Nissen MJ, Bullemer P. Attentional requirements of learning: evidence from performance measures. Cogn Psychol 1987; 19: 1–32.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 1971; 9: 97–113.

Pascual-Leone A, Torres F. Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. Brain 1993; 116: 39–52.

Pascual-Leone A, Cammarota A, Wassermann EM, Brasil-Neto JP, Cohen LG, Hallett M. Modulation of motor cortical ouputs to the reading hand of Braille readers. Ann Neurol 1993; 34: 33–7.

Pascual-Leone A, Grafman J, Hallett M. Modulation of cortical motor output maps during development of implicit and explicit knowledge [see comments]. Science 1994; 263: 1287–9. Comment in: Science 1994; 265: 1600–1.

Pascual-Leone A, Dang N, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. J Neurophysiol 1995; 74: 1037–45.

Passingham RE. The frontal lobes and voluntary action. Oxford: Oxford University Press; 1993.

Pavlides C, Miyashita E, Asanuma H. Projection from the sensory to the motor cortex is important in learning motor skills in the monkey. J Neurophysiol 1993; 70: 733–41.

Perruchet P, Amorim M. Conscious knowledge and changes in performance in sequence learning: evidence against dissociation. J Exp Psychol Learn Mem Cogn 1992; 18: 785–800.

Petit L, Orssund C, Tzourio N, Crivello F, Berthoz A, Mazoyer B. Functional anatomy of a prelearned sequence of horizontal saccades in humans. J Neurosci 1996; 16: 3714–26.

Petrides M. Functional specialization within the dorsolateral frontal cortex for serial order memory. Proc R Soc Lond B Biol Sci 1991; 246: 299–306.

Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. Cereb Cortex 1996; 6: 342–53.

Price C, Wise R, Ramsay S, Friston K, Howard D, Patterson K, et al. Regional response differences within the human auditory cortex when listening to words. Neurosci Lett 1992; 146: 179–82.

Rauch SL, Savage CR, Brown HD, Curran T, Alpert NM, Kendrick A, et al. A PET investigation of implicit and explicit sequence learning. Hum Brain Mapp 1995; 3: 271–86.

Sadato N, Campbell G, Ibáñez V, Deiber M, Hallett M. Complexity affects regional cerebral blood flow change during sequential finger movements. J Neurosci 1996a; 16: 2691–700.

Sadato N, Ibáñez V, Deiber MP, Campbell G, Leonardo M, Hallett M. Frequency-dependent changes of regional cerebral blood flow during finger movements. J Cereb Blood Flow Metab 1996b; 16: 23–33.

Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. Brain 1988; 111: 941–59.

Saint-Cyr JA, Taylor AE, Nicholson K. Behavior and the basal ganglia. Adv Neurol 1995; 65: 1–28.

Sakamoto T, Porter LL, Asanuma H. Long-lasting potentiation of synaptic potentials in the motor cortex produced by stimulation of the sensory cortex in the cat: a basis of motor learning. Brain Res 1987; 413: 360–4.

Sakamoto T, Arissian K, Asanuma H. Functional role of the sensory cortex in learning motor skills in cats. Brain Res 1989; 503: 258–64.

Schacter DL. Implicit knowledge: new perspectives on unconscious processes. Proc Natl Acad Sci USA 1992; 89: 11113–7.

Schacter DL, Chiu CY, Ochsner KN. Implicit memory: a selective review. Annu Rev Neurosci 1993; 16: 159–82.

Schlaug G, Knorr U, Seitz R. Inter-subject variability of cerebral activations in acquiring a motor skill: a study with positron emission tomography. Exp Brain Res 1994; 98: 523–34.

Schmidtke V, Heuer H. Task integration as a factor in secondary-task effects on sequence learning. Psychol Res 1997; 60: 53–71.

Shibasaki H, Sadato N, Lywhkow H, Yonekura Y, Honda M, Nagamine T, et al. Both primary motor cortex and supplementary motor area play an important role in complex finger movement. Brain 1993; 116: 1387–98.

Squire LR. Memory and brain. New York: Oxford University Press; 1987.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain.Stuttgart: Thieme; 1988.

Weiller C, Jüptner M, Fellows S, Rijntjes M, Leonhardt G, Kiebel, S et al. Brain representation of active and passive movements. Neuroimage 1996; 4: 105–10.

Willingham DB, Nissen MJ, Bullemer P. On the development of procedural knowledge. J Exp Psychol Learn Mem Cogn 1989; 15: 1047–60.

Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain [see comments]. J Cereb Blood Flow Metab 1992; 12: 900–18. Comment in: J Cereb Blood Flow Metab 1993; 13: 1040–2.

Zhang J, Riehle A, Requin J, Kornblum S. Dynamics of single neuron activity in monkey primary motor cortex related to sensorimotor transformation. J Neurosci 1997; 17: 2227–46.

Zhuang P, Toro C, Grafman J, Manganotti P, Leocani L, Hallett M. Event-related desynchronization (ERD) in the alpha frequency during development of implicit and explicit learning. Electroencephalogr Clin Neurophysiol 1997; 102: 374–81.

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