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Behavioral/Systems/Cognitive

Cerebral Changes during Performance of Overlearned Arbitrary Visuomotor Associations

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The posterior parietal cortex (PPC) is known to be involved in the control of automatic movements that are spatially guided, such as grasping an apple. We considered whether the PPC might also contribute to the performance of visuomotor associations in which stimuli and responses are linked arbitrarily, such as producing a certain sound for a typographical character when reading aloud or pressing pedals according to the color of a traffic light when driving a motor vehicle. The PPC does not appear to be necessary for learning new arbitrary visuomotor associations, but with extensive training, the PPC can encode nonspatial sensory features of task-relevant cues. Accordingly, we have tested whether the contributions of the PPC might become apparent once arbitrary sensorimotor mappings are overlearned.

We have used functional magnetic resonance imaging to measure cerebral activity while subjects were learning novel arbitrary visuomotor associations, overlearning known mappings, or attempting to learn frequently changing novel mappings. To capture the dynamic features of cerebral activity related to the learning process, we have compared time-varying modulations of activity between conditions rather than average (steady-state) responses.

Frontal, striatal, and intraparietal regions showed decreasing or stable activity when subjects learned or attempted to learn novel associations, respectively. Importantly, the same frontal, striatal, and intraparietal regions showed time-dependent increases in activity over time as the mappings become overlearned, i.e., despite time-invariant behavioral responses. The automaticity of these mappings predicted the degree of intraparietal changes, indicating that the contribution of the PPC might be related to a particular stage of the overlearning process. We suggest that, as the visuomotor mappings become robust to interference, the PPC may convey relevant sensory information toward the motor cortex. More generally, our findings illustrate how rich cerebral dynamics can underlie stable behavior.

Key words: **posterior parietal cortex; striatum; premotor cortex; inferior frontal cortex; conditional motor learning; fMRI**

Introduction

Distinctions have been drawn between spatially guided responses and arbitrarily instructed movements. Spatially guided movements rely on information available online for immediate performance (Goodale et al., 1994), possibly through the automatic implementation of the motor plan afforded by an object or location (Grezes et al., 2003); they are controlled by a dedicated parietofrontal circuit (Milner and Goodale, 1995). In contrast, movements instructed by visual cues according to arbitrary rules are learned voluntary actions, selected among alternatives according to an expected outcome (Passingham, 1993), and they are indifferent to the temporal relationship between stimuli and responses (Brasted and Wise, 2005); they are controlled by a distributed frontostriatal circuit (Wise and Murray, 2000).

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Humans, however, have a lifetime of experience with spatially guided movements but limited practice with the arbitrary visuomotor associations that have been used in previous imaging studies (Deiber et al., 1997; Grafton et al., 1998; Toni and Passingham, 1999; Toni et al., 2001b; Weeks et al., 2001; Boettiger and D'Esposito, 2005). This raises the issue of whether the distinctions detailed above reflect intrinsic neurocomputational differences or training effects. Do spatially guided and arbitrarily instructed movements remain neurally distinct categories of sensorimotor transformations even when the latter class of movements has become automatic?

Here we address this issue by testing whether and where changes in cerebral activity are generated during overlearning of arbitrary visuomotor mappings as compared with initial learning of novel mappings. It has been shown that premotor–striatal circuits are necessary for the retention and retrieval of learned visuomotor mappings (Passingham, 1985; Nixon et al., 2004b), whereas other portions of the striatum, the hippocampal system, and the ventral prefrontal cortex appear to be concerned mainly with the rapid acquisition of novel mappings (Bussey et al., 2001; Brasted et al., 2005; Pasupathy and Miller, 2005). In contrast, evidence of the contributions of the posterior parietal cortex

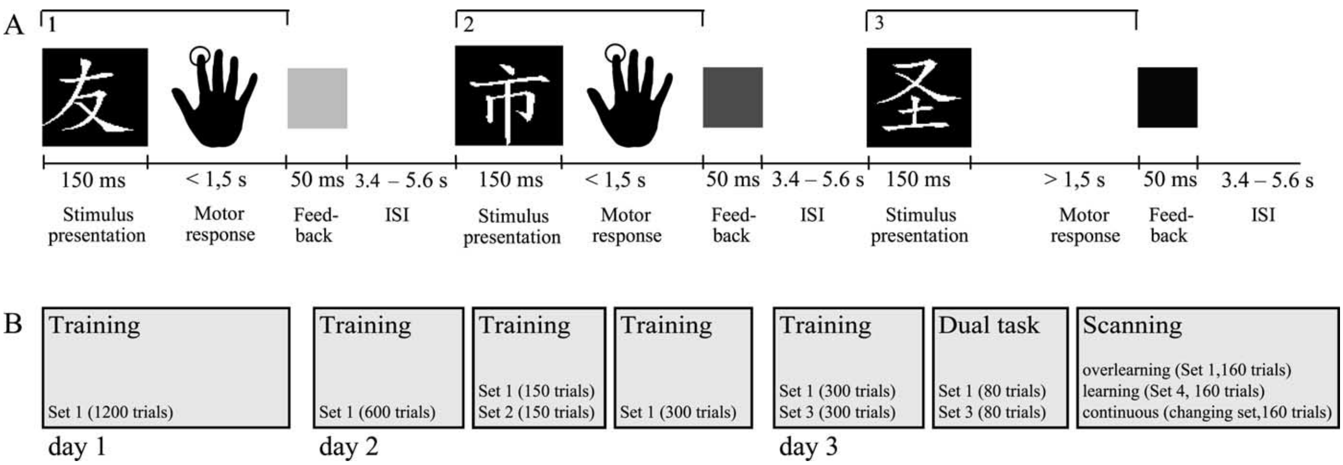

Figure 1. Experimental setup. ***A***, Task setup. Subjects were asked to associate visual stimuli (white line patterns on black background) with motor responses (flexion of one of four fingers of the right hand to press a button on a four-button keypad). After presentation of a visual stimulus, the subjects had to flex one of four fingers of the right hand. After the motor response, visual feedback stimuli indicated whether the movement was incorrect (red square; example 1), correct (green square; example 2), or too late (blue square; example 3). ***B***, Experimental setup. During fMRI scanning, trials from three different conditions were intermixed pseudorandomly. In the visuomotor overlearned condition (overlearning), subjects retrieved a set of visuomotor associations learned before scanning (set 1; 2630 trials over 3 d). In the visuomotor learning condition (learning; set 4), subjects learned novel visuomotor associations between four new visual patterns and the four finger movements. In the continuous learning task (continuous), subjects attempted to learn novel visuomotor associations. In this latter condition, novel visual patterns (unseen during the training) were introduced constantly and removed from the stimulus set. To assess the degree of automaticity achieved during overlearning, we compared performance during a dual-task procedure involving overlearning trials (set 1) and a set of learned trials (set 3) (Fig. 3). ISI, Interstimulus interval.

(PPC) to the automatic performance of arbitrary visuomotor mappings remains inconclusive. Partial lesions of the PPC in macaques do not influence visuomotor conditional learning (Rushworth et al., 1997). On the other hand, large PPC lesions in humans can impair movement selection on the basis of arbitrary cues, such as the verbal commands or the "token" objects used to instruct pantomimes during neuropsychological tests of ideomotor apraxia (Haaland et al., 2000; Buxbaum et al., 2003). Token here refers to the fact that, in these tests, objects are used to instruct movements rather than being the target of the action. Furthermore, although the PPC is known for controlling visually guided hand movements (Sakata et al., 1995), intraparietal cells can be trained to encode both the identity of task-relevant cues (Sereno and Maunsell, 1998; Toth and Assad, 2002) and the motor relevance of visual stimuli specifying arbitrary movements (Thoenissen et al., 2002).

To test the hypothesis detailed above, we used functional magnetic resonance imaging (fMRI) to measure cerebral activity while subjects were performing arbitrary visuomotor mappings at three different levels of task proficiency: namely, learning novel mappings, overlearning known mappings, or attempting to learn frequently changing mappings between visual patterns and finger movements. Given the intrinsically dynamic nature of learning, these three conditions were compared in terms of differential time-varying modulation of cerebral activity rather than in terms of average (time-invariant) responses. Our rationale was that overlearned performance, although behaviorally invariant, might still display a rich neural dynamic (Hasselmo and McClelland, 1999).

Materials and Methods

Subjects. We studied 24 right-handed [Edinburgh Handedness Inventory (Oldfield, 1971); 85 ± 13%; mean ± SD] male volunteers (22 ± 3 years) with normal or corrected-to-normal vision. Participants gave informed consent according to institutional guidelines of the local ethics committee (Commissie Mensgebonden Onderzoek Region Arnhem-Nijmegen, The Netherlands), and they were paid €35 for their participation. Data from six subjects were discarded for the following reasons: failure to overlearn visuomotor associations (one subject), anatomical distortions (two subjects), head-movement artifacts (one subject), and scanner artifacts (two subjects).

Task. Subjects were asked to learn (by trial and error) arbitrary associations between visual stimuli (line patterns derived from Asian characters, which were unfamiliar to the subjects) (Fig. 1*A*) and motor responses (finger presses). After presentation of the visual stimulus (0.15 s; stimulus onset asynchrony, 4.6 s; range, 3.4 –5.8 s; uniform distribution), the subjects had to flex one of four fingers of the right hand to press a button on a four-button keypad. After the motor response, visual feedback stimuli (green–red– blue squares) indicated whether the movement was correct, incorrect, or exceeded a reaction time (RT) cutoff (Fig. 1*A*). Subjects were instructed to try to avoid exceeding the RT cutoff. The RT cutoff was 1.5 s during both the training and scanning sessions.

Procedure. The experiment consisted of a series of training sessions that took place on 3 consecutive days, followed by a scanning session. On day 1, the subjects had to learn, by trial and error, the correct associations between a set of four visual patterns and four different movements; they performed a total of 1200 trials (Fig. 1*B*, set 1). On days 2 and 3, the subjects practiced the same set of associations learned on day 1 and performed a total of 1350 additional training trials. During the training sessions on days 2 and 3, overlearned trials were pseudorandomly intermixed with trials requiring novel visuomotor associations (Fig. 1*B*, set 2); i.e., on these trials, novel visual patterns were presented that needed to be associated with one of the four fingers of the right hand. This procedure allowed the subject to become accustomed to learning more than one set of mappings at a time. During the training sessions, the visual stimuli (visual angle, ~6°) were presented on a computer screen in front of the subject. Motor responses were recorded via a four-button keypad that was positioned on the right armrest of the subjects' chair. Subjects positioned their index, middle, ring, and little fingers on a corresponding button of the keypad.

Before starting the scanning session (on day 3), we assessed the degree of automaticity in the performance of the overlearned associations. Automaticity was tested by means of a dual-task procedure, a standard method to assess whether a given task could be performed with minimal interference at the same time as another task (Passingham, 1996; Oliveira et al., 1998). Our goal was to show that performance of the overlearned associations suffered less interference from a concurrent task as compared with performance of newly learned associations. Accordingly, we asked subjects to simultaneously execute the visuomotor associative task and an overt verbal fluency task on every trial and to give priority to the verbal fluency task. During the visuomotor associative task, subjects were asked to retrieve either the previously learned visuomotor associations (overlearning: already practiced over 2550 trials) (Fig. 1*B*, set 1) or newly learned visuomotor associations (learned: practiced for 300 trials before the start of the dual-task procedure) (Fig. 1*B*, set 3). Note that during overlearning and learned conditions, accuracy was indistinguishable when tested under single-task conditions; that is, subjects produced virtually error-free performances in both conditions. During the verbal fluency task, subjects were asked to either repeat an auditorily presented noun (repeat) or generate a verb semantically congruent with the noun (generate). The auditory presentation of the noun was synchronous with the visual presentation of the pattern instructing the finger movement. The auditory stimuli were presented by speakers placed in front of the subjects at both the left and right sides. The auditory stimuli and the subjects' vocal responses were recorded via a microphone on a digital audio tape. This dual-task procedure involved the presence of two concurrent sensory inputs (auditory nouns and visual patterns) and two concurrent motor responses (vocal utterances and finger presses), and the subjects were given explicit instructions to give priority to the verbal fluency task. Accordingly, here we have operationalized "overlearned performance" in terms of differential interference effects evoked by the verbal fluency task on visuomotor associations that were practiced extensively or just learned. This can be contrasted with other uses of dual-task techniques, as when one wants to show that the performance of a given primary task is not affected by a secondary task (Poldrack et al., 2005).

On day 3, after the dual-task procedure, subjects participated in the scanning session in which trials from three different conditions were pseudorandomly intermixed. In the visuomotor overlearned condition (overlearning) (Fig. 1*B*, set 1), subjects retrieved the visuomotor associations learned before scanning. In the visuomotor learning condition (learning) (Fig. 1*B*, set 4), subjects learned novel visuomotor associations between four new characters (not present during the training) and the four finger movements. In the continuous learning task (continuous), subjects attempted to learn novel visuomotor associations. In this latter condition, novel visual patterns (unseen during the training) were introduced and removed from the stimulus set after a pseudorandom and stepwise algorithm devised to keep subjects' performance in a state of initial learning over the whole scanning session. During the scanning session, subjects performed a total of 160 trials for each of the three conditions. Before the start of image acquisition, subjects practiced the task in the scanner for 50 trials using a different set of stimuli for the learning and continuous conditions and the same overlearned set for the overlearning condition. During the scanning session, subjects lay supine in the scanner. Head movements were minimized by a padded, adjustable head holder. Subjects viewed the visual stimuli (visual angle, $\sim$6°), which were projected onto a screen behind the subjects' heads, via a mirror attached to the head coil. Motor responses were recorded via an MR-compatible keypad (MRI Devices, Waukesha, WI) that was positioned on the right side of the subject's abdomen with the four fingers of the right hand on the four buttons. During the entire experiment, stimulus presentation and response collection were controlled by a PC running Presentation 0.51 (Neurobehavioral Systems, San Francisco, CA).

Behavioral analysis. Mean RTs and error rates (ERs) measured during the scanning session were analyzed separately and considered as independent variables of a 3 $\times$ 8 repeated measures ANOVA with main effects of task (three levels: overlearning, learning, and continuous) and time (eight levels: blocks 1–8, arising from the subdivision of the RT time series and the ER of each participant into eight equal-length blocks, after removal of missed trials).

Subjects were considered as a random factor. Simple main effects were tested with a least square difference *post hoc* test. The α level was set at $p =$ 0.05, using a multivariate approach (Pillai's trace corrected).

For the dual task, RTs and ERs measured during performance of the visuomotor associative task were analyzed in a 2 $\times$ 2 repeated measures ANOVA with main effects of training (two levels: overlearning and learned) and verbal fluency task (two levels: repeat and generate).

Image acquisition. Images were acquired with a 3T Trio scanner (17 subjects) and a 1.5T Sonata scanner (1 subject) (Siemens, Erlangen, Germany). Blood oxygen level-dependent (BOLD) sensitive functional images were acquired with a single shot gradient echo planar imaging sequence (repetition time, 2.56 s; echo time, 40 ms; 32 transverse slices; interleaved acquisition; voxel size 3.5 $\times$ 3.5 $\times$ 3.5 mm). At the end of the scanning session, structural images were acquired with a magnetization-prepared rapid gradient-echo sequence (repetition time, 1960 ms; echo time 5.59 ms; longitudinal relaxation time, 1100 ms; voxel size, 1 $\times$ 1 $\times$ 1 mm).

Image analysis. Functional data were preprocessed and analyzed with Statistical Parametric Mapping (SPM2) (www.fil.ion.ucl.ac.uk/spm). The first five volumes of each participant's data set were discarded to allow for longitudinal relaxation time equilibration. The image time series were spatially realigned with a sinc interpolation algorithm that estimates rigid body transformations (translations and rotations) by minimizing head movements between each image and the reference image (Friston et al., 1994). The time series for each voxel were realigned temporally to acquisition of the middle slice. Subsequently, images were normalized onto a custom Montreal Neurological Institute (MNI)-aligned echo planar imaging template (based on 28 male brains acquired on the Siemens Trio at the F. C. Donders Centre) with both linear and 16 nonlinear transformations and resampled at an isotropic voxel size of 2 mm. Finally, the normalized images were spatially smoothed with an isotropic 10 mm full-width–half-maximum Gaussian kernel. Each participant's structural image was spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997) and spatially normalized by using the same transformation matrix applied to the functional images.

The fMRI time series were analyzed with an event-related approach in the context of the general linear model. Analysis of the imaging data considered main effects of task and outcome [seven levels: overlearning correct, overlearning incorrect (where applicable), learning correct, learning incorrect, continuous correct, continuous incorrect, and trials with responses exceeding the RT cutoff] and task $\times$ time interactions, i.e., differential changes in activity over time between conditions. Each effect was modeled on a trial-by-trial basis as a concatenation of square-wave functions, with onsets time-locked to the presentation of the relevant visual patterns and offsets time-locked to the corresponding motor response. Each of these seven square-wave functions was then convolved with a canonical hemodynamic response function and its temporal derivative and down sampled at each scan to generate 14 regressors modeling the main effects described above (Friston et al., 1994). This approach intrinsically accounted for trial-by-trial differences in trial duration and allowed us to assess differences in intensity of the BOLD signal between conditions over and above differences in BOLD signal caused by differences in trial duration.

Time-dependent modulations of task-related activity (task $\times$ time interactions) were modeled as first- and second-order parametric effects of (scanning) time on the regressors describing the main effects of task and outcome. Separate covariates including the first derivatives of the head-related movements (as estimated by the spatial realignment procedure) and a constant term over scans were also considered in the model. Data were high-pass filtered (cutoff, 128 s) to remove low-frequency confounds such as scanner drifts. Temporal autocorrelation was modeled as an autoregressive process.

Statistical inference. The statistical significance of the estimated evoked hemodynamic responses was assessed with T statistics in the context of a multiple regression analysis. Contrasts of the parameter estimates for the main effects and task $\times$ time interactions were calculated and entered into a one-way, repeated measures ANOVA with subjects as a random variable (Friston et al., 1999). Specifically, we were interested in assessing differential modulation of time-related signal changes during performance of overlearning and learning. Linear time-dependent changes in activity during overlearning (correct trials only) were compared with the corresponding effect during learning (correct trials only). For this purpose, SPMs of the T statistic for these two linear time effects were created, with the degrees of freedom corrected for nonsphericity at each voxel.

We report the results of a random effects analysis, with inferences drawn at the cluster level, corrected for multiple comparisons with

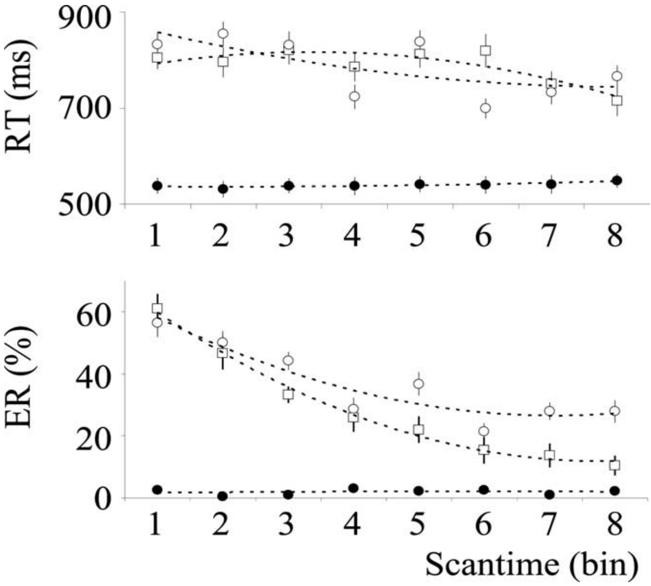

Figure 2. Behavioral performance. Average ERs and RTs over scanning time (binned in blocks of 20 trials; intersubject mean ± SEM) for overlearning (●), learning (□), and continuous (○). During overlearning trials, performance was stable and virtually error free. During learning, ERs dropped from chance level to 10%. During continuous, subjects' learning rate was reduced significantly as compared with learning.

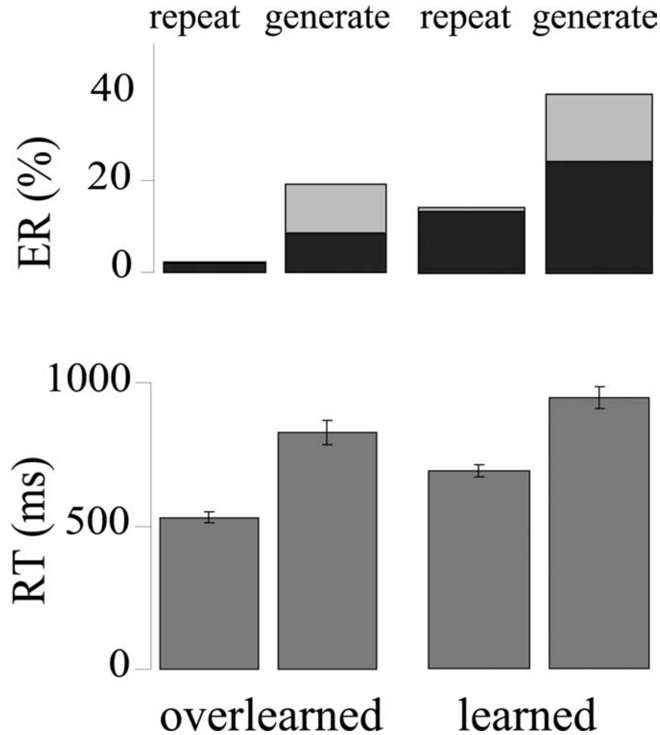

Figure 3. Dual-task performance. Before starting the fMRI measurements, we used a dual-task procedure to assess the degree of automaticity of overlearning performance. This test required concurrent performance of the visuomotor associative task and a verbal fluency task (see Materials and Methods). This figure shows the average ERs (intersubject mean ± SEM) (light gray, incorrect responses; black, missed responses) and RTs (intersubject mean ± SEM) of the visuomotor associative task for both overlearned associations (left) and newly learned associations (right) during concurrent performance of a noun repetition task (repeat) and a verb generation task (generate). During overlearning trials, subjects were faster and made fewer errors compared with the learned condition. Note that on each trial of the dual-task procedure, there were two concurrent sensory inputs (auditory nouns and visual patterns) and two concurrent motor responses (vocal utterances and finger presses). Furthermore, the subjects were given explicit instructions to give priority to the verbal fluency task. Accordingly, our goal here was to show that performance of the overlearned associations suffered less interference from a concurrent task as compared with performance of newly learned associations. This can be contrasted with other uses of dual-task techniques, as when one wants to show that performance of a given primary task is not affected by a secondary task (Poldrack et al., 2005).

family-wise error correction ($p < 0.05$) (Friston et al., 1996). In addition to the procedure described above, in three particular instances we have constrained our inferences on the basis of independent anatomical information by using a volume of interest (VOI) approach. We relied on published stereotactical coordinates of areas that showed learning-related changes during an equivalent task (Toni et al., 2001a) to position VOIs along the PPC (−36, −50, 44), the striatum (−18, 18, 4), and the middle temporal gyrus (60, −6, −18), and we used the full-width–half-maximum of our statistical images to define the radius of the VOIs (12 mm). Finally, on the basis of the results obtained from the main analysis described above (differential modulation of time-related signal changes during performance of overlearning and learning), we performed *post hoc* comparisons on differential time-related effects between overlearning and continuous and between learning and continuous (correct trials only).

For some areas displaying significant learning-related effects, we plotted the BOLD signal time course during the scanning session for each condition separately. In particular, we calculated the intersubject average and SE of the peak BOLD response for each of eight consecutive blocks of trials equally spaced along the whole scanning session.

Anatomical inference. Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of each subject in MNI coordinates. The atlas of Duvernoy et al. (1991) was used to identify relevant anatomical landmarks. When applicable, Brodmann areas were assigned on the basis of the SPM anatomy toolbox (Eickhoff et al., 2005); i.e., the anatomical position of our significant clusters and local maxima was formally tested against published three-dimensional probabilistic cytoarchitectonic maps.

Brain–behavior correlations. We assessed correlations between changes in BOLD signal and degree of automaticity during overlearning trials. Cerebral effects were indexed by the subjects' rate of change of BOLD signal evoked in the PPC during the overlearning trials. This corresponds to the standardized parameter estimates (SE units) of the linear time-dependent changes in activity during overlearning (correct trials only). Behavioral effects were indexed by subjects' performance during the dual-task test. This corresponds to the difference in error rates evoked during overlearning and learned trials when a word is generated as compared with simply being repeated (training × task interaction) (see Fig. 3). Note that rather than using group-averaged indexes, this analysis exploited the intersubject variability in behavioral and cerebral performance. The purpose of this analysis was to test whether the cerebral increases reported below (see Results) might saturate when performance is highly automatic. A simple linear or quadratic function would not be adequate to capture a possible transient increase in cerebral activity related to a particular stage of automaticity followed by a state during which cerebral activity does not change as automaticity increases. Therefore, we fit the data of the cerebral–behavioral scatterplot (see Fig. 5) to a fourth-order polynomial function.

Results

Behavioral performance

Figure 2 illustrates the mean RT and ER as a function of time during the three experimental conditions. The data indicate that our design was successful in manipulating the degree of learning achieved by the participants during the scanning session. Subjects were faster and made fewer errors in the overlearning than in the learning and continuous conditions [main effect of task (RT: $F_{(2,34)} = 169.8$; $p < 0.01$; ER: $F_{(2,34)} = 121.2$; $p < 0.01$)]. RT and ER decreased over time during both learning and continuous, but not during overlearning [task × time interaction (RT: $F_{(14,238)} = 7.4$; $p < 0.01$; ER: $F_{(14,238)} = 13.6$; $p < 0.01$)]. *Post hoc* comparisons indicated that during learning the error rate decreased faster over time than during continuous ($p < 0.007$).

Figure 3 illustrates the mean RT and ER during the dual-task procedure. The data indicate that the extensive training induced a high degree of automaticity in the performance of extensively trained associations (overlearning condition). Subjects were faster and made fewer errors during the overlearning condition than during the learned condition (RT: $F_{(1,17)} = 69.8$; $p < 0.01$; ER: $F_{(1,17)} = 17.7$; $p < 0.01$). Subjects were faster and made fewer errors during word repetition than during word generation (RT: $F_{(1,17)} = 49.9$; $p < 0.01$; ER: $F_{(1,17)} = 44.6$; $p < 0.01$). The increase in RT and ER during word generation in comparison with word repetition was significantly larger during the learned condition than during the overlearning condition [training × task interaction (RT: $F_{(1,17)} = 6.6$; $p < 0.02$; ER: $F_{(1,17)} = 3.8$; $p = 0.068$)].

Imaging data

We isolated BOLD signals showing differential learning effects during the overlearning and learning conditions by testing, over the whole brain, for time-dependent increases and time-dependent decreases in activity during correct performance of overlearning and learning trials, respectively. By looking specifically at the differences in temporal modulation of the effects evoked in these two tightly matched conditions, we were able to isolate genuine learning-related changes rather than mere time-related effects such as fatigue, habituation, or sensitization.

A small volume correction analysis on the posterior parietal VOI revealed a cluster along the intraparietal sulcus (−36, −48, 46; $p < 0.049$; cluster-level corrected) that increased its activity during the overlearning condition and modestly decreased its activity during learning, as illustrated in Figure 4*A*. The intraparietal activity is caudal to the 10% probabilistic boundary of cytoarchitectonically defined Brodmann area (BA) 2 (Eickhoff et al., 2005). There was no change in activity over time during the continuous condition, a further indication that the changes observed during learning and overlearning are related to learning rather than nonspecific effects of time.

We found significant task × time interactions (overlearning vs learning; correct responses only) in two clusters along the left superior frontal gyrus and in the left inferior frontal gyrus (Table 1). The superior frontal cluster consisted of maxima in the dorsal precentral sulcus, in the mesial aspects of the superior frontal gyrus, and in the paracingulate sulcus. The dorsal precentral activity (Fig. 4*B*) is located within the 60% probabilistic boundary of cytoarchitectonically defined BA 6 (Eickhoff et al., 2005) and rostral to the anterior border of BA 4. The inferior frontal cluster consisted of maxima in the left inferior frontal gyrus, stretching toward the inferior frontal sulcus, the frontal operculum, and the insula. The inferior frontal activity (Fig. 4*C*) is located within the 20 and 40% probabilistic border of cytoarchitectonically defined BA 45 and BA 44, respectively, and rostral to BA 6 (Eickhoff et al., 2005).

Figure 4*B* illustrates the portion of the dorsal precentral sulcus (−20, 2, 62) that increased its activity over time during the overlearning condition and decreased during the learning condition (correct trials only; Z-score = 3.54). Figure 4*C* shows a similar pattern of activity along the inferior frontal sulcus (−40, 28, 28), although the learning increase levels out in the second half of the scanning session (Z-score = 3.66).

A small-volume correction analysis on the striatal VOI (Fig. 4*D*) showed activity (bilaterally) around the head of the caudate nucleus ($p < 0.016$; family-wise error-corrected). This region increased its activity during overlearning and quickly decreased its activity during the first half of the learning condition converging onto the time course of overlearning.

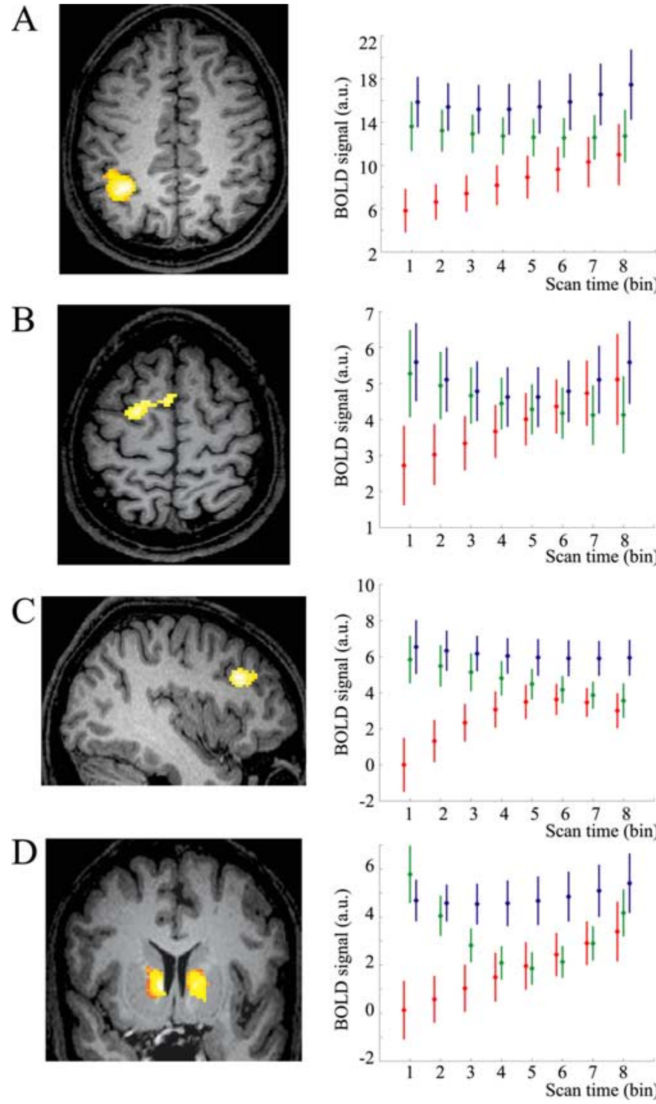

Figure 4. Imaging results. Differential time-related changes of cerebral activity across conditions, relative to the contrast between time-dependent increases and time-dependent decreases in activity during correct performance of overlearning and learning trials. Right column, Peak BOLD signal change over scanning time (binned in blocks of 20 trials; intersubject mean ± SEM) for overlearning (red), learning (green), and continuous (blue). Left column, SPM{t} of the relevant contrast superimposed on anatomical sections of a representative subject. ***A***, Left intraparietal sulcus (−36, −48, 46); ***B***, left superior precentral sulcus (−20, 2, 62); ***C***, left inferior frontal sulcus (−40, 28, 28); ***D***, left caudate nucleus (−10, 12, −2). a.u., Arbitrary units.

We also assessed time-dependent increases and time-dependent decreases in activity during correct performance of learning and overlearning trials, respectively (Table 2). A cluster spanning the right fusiform gyrus and the parahippocampal gyrus increased its activity over time during learning but not during continuous, whereas overlearning activity decreased over time. Activity in the lingual gyrus and in the middle temporal gyrus was somewhat increasing during learning and continuous, with a strong decrease during the overlearning condition.

Relation between behavioral and cerebral effects

We have used a *post hoc* correlational analysis to test whether the increase in parietal activity observed during overlearning might

Table 1. Differential signal changes over time between overlearning and learning (correct trials only)

Anatomical region	Cluster size (voxels)	Z-score	Stereotactic coordinates
Left superior precentral sulcus	556	3.54	−20, 2, 62
Left superior frontal gyrus		3.78	−4, 8, 60
Left paracingulate sulcus		3.51	−2, 20, 44
Left inferior frontal sulcus	816	3.66	−40, 28, 28
		3.36	−44, 6, 26
Left intraparietal sulcus[a]	601	3.07	−36, −48, 46
Left caudate nucleus (head)[a]	(76)	3.80	−10, 12, −2

List of significant local maxima ($p < 0.05$; corrected for multiple comparisons) showing time-related increases during overlearning and decreases during learning.

[a]Corrected for multiple comparisons within a predefined search volume (see Materials and Methods).

Table 2. Differential signal changes over time between learning and overlearning (correct trials only)

Anatomical region	Cluster size (voxels)	Z-score	Stereotactic coordinates
Left inferior occipital gyrus	1071	4.35	−24, −90, −8
Right fusiform gyrus	4075	4.34	28, −70, −14
Right parahippocampal gyrus		4.01	28, −56, −12
Right middle temporal gyrus	280	3.62	56, 4, −22

List of significant local maxima ($p < 0.05$; corrected for multiple comparisons) showing time-related increases during learning and decreases during overlearning.

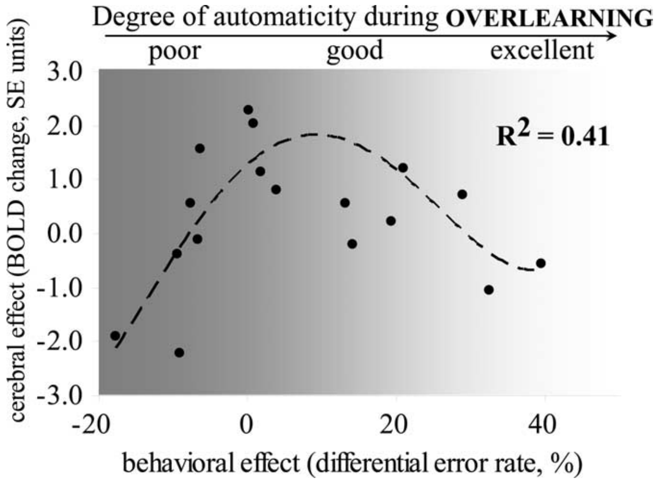

Figure 5. Relation between behavioral and cerebral effects. Relation between the time-related change in cerebral activity observed during overlearning trials and the degree of automaticity of the visuomotor transformation evoked in that condition. The cerebral effect (*y*-axis) denotes the variation in signal over time for each subject, as indexed by the standardized (SE units) parameter estimate of the linear change over time in BOLD signal. The behavioral effect (*x*-axis) denotes the amount of interference generated by the dual-task procedure for each subject, as indexed by the difference in error rates evoked during overlearning and learned trials when a word is generated as compared with being simply repeated. This figure illustrates a significant nonlinear relationship between dual-task performance and parietal increase in BOLD signal (●). Parietal activity decreased over time (negative cerebral effect) for those subjects with a poor degree of automaticity during overlearning (negative behavioral effect; this indicates that the verb generation task hampered performance of the learned trials less than performance of the overlearning trials). Conversely, parietal activity increased over time (positive cerebral effect) for those subjects with a good degree of automaticity during overlearning (moderately positive behavioral effects). Importantly, parietal activity remained constant over time (zero cerebral effect) for those subjects with an excellent degree of automaticity during overlearning (extremely positive behavioral effects). The dashed line indicates the least square fit of a fourth-order polynomial ($R^2 = 0.41$).

eventually saturate. We found that the degree of automaticity achieved in the overlearning condition across subjects explained a considerable portion of the intersubject variance in the rate of change in parietal activity ($R^2 = 0.41$) (Fig. 5). It can be seen that parietal activity decreased over time (negative cerebral effect) for those subjects with a poor degree of automaticity during overlearning (negative behavioral effect; this indicates that the verb generation task hampered performance of the learned trials less than performance of the overlearning trials). Conversely, parietal activity increased over time (positive cerebral effect) for those subjects with a good degree of automaticity during overlearning (moderately positive behavioral effects). Importantly, parietal activity remained constant over time (zero cerebral effect) for those subjects with an excellent degree of automaticity during overlearning (Fig. 5) (extremely positive behavioral effects). Finally, this nonlinear relationship between changes in BOLD signal and automaticity of the visuomotor transformation might be regionally specific, insofar as this characteristic was not observed in the other regions showing time-related increases during the overlearning trials. The inferior frontal sulcus and the dorsal precentral sulcus revealed lower R^2 values (0.20 and 0.18, respectively). The R^2 value observed for the striatum was higher ($R^2 = 0.31$), but it was driven by one outlier, and the brain–behavior relationship was not comparable with the one observed in the PPC. Overall, these results suggest that the increase in parietal activity reported in this study might be transitory and could reflect a particular stage of the overlearning process, which is critically dependent on the degree of automaticity achieved during the training procedure.

Discussion

We have assessed the neural consequences of overlearning arbitrary visuomotor associations, testing whether and where changes in cerebral activity support the automatization of performance as compared with initial learning of new associations (learning). Rather than comparing the average strength of the neurovascular signal evoked during these two conditions, we have isolated differential time-dependent modulations to define cerebral activity associated with the dynamic process of learning and overlearning arbitrary visuomotor associations. Frontal, striatal, and intraparietal regions revealed consistent time-dependent increases in activity while subjects were performing overlearned associations. Learning or attempting to learn novel associations (Fig. 2) resulted in decreased or stable activity in these same areas, together with increases in ventral occipital and temporal regions. These results suggest that different but not completely segregated circuits support visuomotor mappings at different stages of task proficiency. Importantly, the dynamics of parietal activity indicate that, once the mappings are becoming automatic, this region might join frontostriatal circuits and contribute to the performance of arbitrary visuomotor associations.

Behavioral performance

During scanning, subjects performed arbitrary visuomotor mappings at three different levels of proficiency (Fig. 2). During overlearning trials, performance was stable, virtually error free, and more resistant to interference (Fig. 3). During learning trials, performance improved from chance level to occasional errors. During continuous trials, subjects attempted to learn novel mappings, but the rapid stimulus turnover significantly reduced their average learning rate.

PPC

Previous studies have reported learning-related increases in the PPC during tasks in which the visual cue guides the movement through an appropriate spatial transformation (Grafton et al., 2001; Eliassen et al., 2003); however, here the location of the stimuli was not related to the motor response, and PPC activity showed a learning-related decrease during initial learning (Fig. 4*A*), confirming previous reports (Deiber et al., 1997; Toni et al., 2001a). Importantly, this same PPC cluster increased its activity during overlearned performance. These changes in activity cannot be attributed to variations in behavior, because performance did not change during overlearning (Fig. 2). Variations in reward rate cannot explain overlearning changes, because we distinguished correct from incorrect trials. The instruction cues were presented briefly and intermixed pseudorandomly; therefore, overlearning changes cannot be caused by time-dependent alterations of saccadic behavior or preparatory activity. Changes in activity during overlearning cannot be a by-product of novelty effects, because during continuous, the subjects were exposed to a larger number of novel patterns than during learning or overlearning, yet the BOLD signal during continuous did not change. Finally, the overlearning-related increase in parietal activity (as indexed by the rate of change in BOLD signal) is unlikely to be a by-product of changes in task difficulty or stimulus familiarity (as indexed by the decrease in error rate during learning trials), because these two parameters were not correlated across subjects ($R^2 = 0.01$; $p = 0.55$).

It might be argued that the learning-related changes that we observed are an instance of consolidation of procedural memories, known to induce state-dependent increases in neurovascular activity during learning of motor skills (Shadmehr and Holcomb, 1997); however, when considering the average activity measured during overlearning as compared with new learning, the parietal signal decreases. In fact, here we have focused on the changes in trial-by-trial activity between learning stages. By this measure, cerebral activity in the PPC increases during the performance of overlearned visuomotor associations. This result confirms that, in some circumstances, imaging can provide more sensitive measures of cognitive changes than behavior (Wilkinson and Halligan, 2004). Because there were no obvious time-dependent behavioral adjustments during the overlearning trials, however, one might wonder whether the changes in cerebral activity observed during those trials are specifically related to learning. Although learning-related neural adjustments can continue after behavioral signs of learning have disappeared (Chen and Wise, 1996; Wise et al., 1998; Hadj-Bouziane and Boussaoud, 2003), it is implausible that neural activity could steadily increase over a prolonged period of stable behavior. Accordingly, we have tested whether the increase in parietal activity reported in this study is transitory in nature. Figure 5 suggests that the group-related changes in parietal activity during overlearning might depend on the degree of automaticity achieved during the training procedure; i.e., these changes might reflect a particular stage of the overlearning process. Additional experiments are necessary to confirm the learning-related nature of the cerebral changes reported here.

The contrasting patterns of change observed during overlearning and learning might reflect a transition in the sensorimotor mapping encoded in this region. During learning, the PPC might have attempted to find an appropriate spatial transformation for mapping stimuli to responses. Because the location of the visual patterns was not related to the motor response, this procedure was not reinforced, leading to decreased PPC activity over time. During overlearned performance, the stimulus–response statistics would have become stable, allowing slow Hebbian plasticity to emerge (Houk and Wise, 1995). In this scenario, BOLD signal could increase by virtue of the increases in synchronous firing associated with Hebbian learning (Paulsen and Sejnowski, 2000; Singh et al., 2002; Niessing et al., 2005), generating the dynamic changes in PPC activity observed during overlearning. Although speculative, this account suggests that once visuomotor associations become robust to interference, a portion of the PPC might start to convey relevant sensory information toward the motor cortex. It remains to be seen whether this information relates to the identity of the visual cue or to the selection of the motor response, and whether this activity is necessary for overlearned performance of arbitrary visuomotor mappings.

Premotor cortex

There has been a surprising consistency in the failure of previous imaging studies to find significant learning-related changes of neurovascular activity in the dorsal precentral region (Deiber et al., 1997; Toni and Passingham, 1999; Toni et al., 2001a; Boettiger and D'Esposito, 2005), yet we know that the firing rate of precentral neurons changes during the learning of novel arbitrary visuomotor associations (Mitz et al., 1991; Chen and Wise, 1995; Wallis and Miller, 2003) and that precentral tissue is necessary for relearning previously acquired associations (Passingham, 1985). Our findings suggest that previous negative reports might have resulted from merging different learning epochs into a single experimental unit. Figure 4*B* illustrates the opposite dynamics generated in dorsal premotor cortex during different learning stages, confirming that this region contributes to both initial learning and retention of arbitrary visuomotor associations (Halsband and Freund, 1990; Kurata and Hoffman, 1994; Petrides, 1997).

Striatum

Electrophysiological studies of striatal and precentral activity during learning of arbitrary visuomotor associations have shown persistent changes in neural activity even during stable behavioral performance (Hadj-Bouziane and Boussaoud, 2003; Brasted and Wise, 2004) but also rapid changes during initial learning of the same associations (Hadj-Bouziane and Boussaoud, 2003; Pasupathy and Miller, 2005). Our results provide independent evidence supporting both early and late changes in striatal responses (Fig. 4*D*), confirming the role of the striatum during overlearned performance of arbitrary visuomotor associations (Nixon et al., 2004b). Furthermore, our study reveals that, in contrast with the linear pattern of changes observed in other cortical structures, during initial learning the striatum displays a rapid decrease followed by an increase in BOLD signal. It has been suggested that reward-prediction signals processed in the striatum (Seymour et al., 2004; Tobler et al., 2005) might support the generation of rapid stimulus–response associations during the early stages of learning (Pasupathy and Miller, 2005). In this potential scenario, it is conceivable that as learning of novel associations progresses, the temporal difference signal carried by dopamine afferents to the striatum is extinguished (Suri, 2002), and the local synaptic activity indexed by BOLD could decrease (Lauritzen, 2005). This might explain the rapid signal decrease that we observed in the striatum; however, we also know that this region increases its coupling with frontal areas during learning of novel arbitrary mappings (Toni et al., 2002), and this increased (or more effective) afferent activity might possibly lead, in turn, to the increasing BOLD signal observed once performance becomes less dependent on error feedback (Fig. 4*D*).

Inferior frontal gyrus

In macaques, disconnection of ventrolateral and orbital prefrontal cortex [i.e., areas 46/9v, 47/12, and 45/44 of Petrides and Pandya (2002)] from inferior temporal regions severely impairs both the acquisition and retention of novel visuomotor associations (Bussey et al., 2002). Figure 4*C* illustrates a clear and specific time-dependent decrease in BOLD signal during learning, localized within the probabilistic borders of BA 44/45 (Eickhoff et al., 2005), followed by an increase during the first blocks of automatic performance. Our findings confirm and localize the contribution of this region to both the initial learning and the long-term retention of arbitrary visuomotor associations. Given that this region has been linked with a particular class of arbitrary visuomotor transformations, i.e., orthographic-to-phonologic transformations (Indefrey and Levelt, 2004; Nixon et al., 2004a), the pattern of activity that we observed could reflect the labeling of the visual cues with verbal tags; however, this account does not explain why the increase in signal seen during overlearning trials disappeared during the second half of the scanning session (Fig. 4*C*). An alternative interpretation is suggested by the contributions of this region to rule-based and prospective behavior (Rainer et al., 1999; White and Wise, 1999; Bunge et al., 2003; Wallis and Miller, 2003); i.e., it is conceivable that this region might abstract cue-finger pairs, not only in terms of stimulus–response mappings but also in terms of response–stimulus mappings. Accordingly, establishing novel stimulus–response mappings would imply the updating of the existing response–stimulus mappings, because novel stimuli map into a constant number of fingers. By this account, improvements in learning performance are meant to induce the updating of response–stimuli pairs during overlearning while they reduce the amount of possible mappings during learning. The concurrent flattening of both learning error rate and overlearning BOLD changes (Fig. 4*C*) is consistent with this interpretation.

Conclusions

Our results indicate that overlearned performance of arbitrary visuomotor associations involves not only striatofrontal circuits but also parietal regions. We suggest that once visuomotor associations become robust to interference, PPC might start to convey relevant sensory information toward the motor cortex.

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