Impairment of Online Control of Hand and Eye Movements in a Monkey Model of Optic Ataxia

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The parietal mechanisms for online control of hand trajectory were studied by combining single-cell recording and reversible inactivation of superior parietal area 5 (PE/PEc: SPL) of monkeys while these made reaches and saccades to visual targets, when the target position changed unexpectedly. Neural activity was modulated by hand position, speed, and movement direction, and by preand/or postsaccadic signals. After bilateral muscimol injection, an increase in the hand reaction- and movement-time toward both the first and second targets was observed. This caused an increase in the time necessary for the trajectory correction, and therefore an elongation of the hand-path toward the first target location. Furthermore, hand trajectories were different in shape than control ones. An elongation of the eye reaction time to both first and second targets was also observed, which could partially explain the deficit of planning and correction of hand movement. These results identify the superior parietal lobe as a crucial node in the online control of hand and eye movement and highlight the role of the eye impairment in the emergence of the reaching disorder so far regarded as the hallmark of optic ataxia.

Keywords: double-step paradigm, eye–hand coordination, eye movements, online control of movement, parietal cortex

Introduction

Online control of movement allows changing motor plan, as required for fast corrections of the hand trajectory, when the target moves in space. When enough time is allowed for correction, human subjects and monkeys will not complete hand movement to the first target’s location, but will produce a curved trajectory toward the final one (Carlton, 1981; Georgopoulos et al. 1981, 1983; Soechting and Lacquaniti 1983; Archambault et al. 2009). Movement can be adjusted without awareness of the target’s shift, that is, during saccades (Blouin et al. 1995), in the absence of visual feedback about arm movement (Pelisson et al. 1986), as well as by deafferented patients devoid of limb proprioception (Bard et al. 1999; Sarlegna et al. 2006). Online corrections might reside on motor outflow (Desmurget and Grafton 2000) and/or on sensory information, such as retinal error (Blouin et al. 1995; Desmurget et al. 1999).

Although resistant to peripheral lesions or to lack of peripheral information, online hand correction is severely affected by central lesions, such as those involving the posterior parietal cortex (PPC). A case report of optic ataxia (OA) from bilateral PPC lesion has shown a marked difficulty in producing smooth corrections of hand trajectory, while reaching to stationary targets remained unaffected (Pisella et al. 2000; Grea et al. 2002). This result conforms to previous studies performed in humans by perturbing the PPC activity through transcranial magnetic stimulation (Desmurget et al. 1999; Johnson and Haggard 2005). Recent studies in behaving monkeys have revealed a differential role of premotor, motor and PPC (Archambault et al. 2009, 2011; see also Georgopoulos et al. 1983) in signaling the change in the target location and implementing the hand trajectory correction. These studies were of correlative nature and, therefore, did not allow determining a causal relationship between parietal neural activity and online control of hand trajectory.

In the present study, we explored whether the inactivation of the superior parietal lobule (SPL) in monkeys leads to difficulties in producing smooth online corrections of hand movement in response to a shift in the target location. We also studied the potential contribution of concurrent eye deficits to the difficulty of adjustment of hand trajectory. We first characterized the functional properties of parietal cells, by recording neural activity in monkeys performing direct as well as corrected reaches. Then, the region of recording was reversibly silenced by injecting the γ-aminobutyric acid (GABA)-A agonist muscimol, and the animal behavior was reassessed under such condition. A constellation of deficits affected both the spatial and temporal aspects of online control of hand movement trajectory, of eye movement, and of eye–hand coupling.

These results are relevant for the identification of the parietal region responsible for the deficits observed in humans, since so far these deficits have only been described in a case report of a patient with a large, bilateral occipito-parietal lesion, which does not provide a precise localization of the relevant critical region. They also relate to the elucidation of the eye contribution to the hand reach disorder typical of OA.

Methods

Animals

Two male Macaca mulatta monkeys (with a body weight of 5.2 and 6.0 kg) were used in the study, in accordance with the European (Directive 86/609 EEC) and the Italian (D.L. 116/92) laws on the use of animals in scientific procedures.

Behavioral Tasks

Reaching Tasks

The monkeys performed arm reaches to visual targets in 3D space under 2 conditions (Fig. 1A,B):

1. Direct reach. Under this condition, the animal was required to make direct reaches from a central push-button to 1 of 8 peripheral visual targets, consisting of push buttons that were presented by 2 robotic arms at the vertices of a virtual cube and in total darkness.
When the central button was turned green, the monkey was required to press and fixate that button for a variable control time (CT; 800–1500 ms; Fig. 1B), at the end of which a red peripheral target was lit and the animal was required to reach and press it for a variable target holding time (THT; 500–1000 ms; Fig. 1B).

2. Corrected reach. In 50% of the trials, the position of the peripheral target changed, either during reaction time (160 ms after the presentation of the first target, Fig. 1A, center) or at the onset of hand movement (Fig. 1B), by turning off the target on 1 robotic arm and lighting the target on the second one. The target “jumped” from its original position either to the opposite vertex of the cube (at 180°; Fig. 1A, right) or to one adjacent (at 90°) and immediately to the left (for right targets), and vice versa for left targets. Therefore, there were 4 corrected conditions characterized by 2 switching times and 2 switching directions. The animal was required to update the original movement plan or the ongoing movement and reach toward the second target.

Saccade Tasks
Two types of saccade tasks (Fig. 1A, right) were used to identify the influence of eye-related signals on neural activity recorded in the reaching tasks, as well as potential deficits of eye movement after muscimol injections:

1. Single-step saccade. The monkey fixated (and pressed) a central button for a variable CT (800–1500 ms). Then, 1 of 8 peripheral targets was presented at 45° angular intervals on a circle of 18° visual field radius. The monkey was required to make a saccade to the target and keep fixation there for 500 ms.

2. Double-step saccade. In 50% of the trials, the peripheral target was turned off during eye reaction time (150 ms after the presentation of the first peripheral target) and replaced by the opposite one at 180° in the circle.

Details on the tasks used for physiological recordings are given in Archambault et al. (2009). The monkeys performed the same tasks after muscimol injection (see below). However, because of the limited duration of the muscimol effect, instead of 8 possible movement targets, we used only the 4 front targets of the workspace, those closer to the animal. Corrected reaches were only made for the 180° target jump, either during reaction time or at the onset of movement time. This led to a total of 4 movement directions for direct reaches and single-step saccade trials, to 8 movement conditions (4 directions × 2 switch times) for the corrected reaches, and to 8 conditions for the double-step saccades. Before and after muscimol injection, each hand or eye movement condition was repeated for at least 10 replications, for a total of 80 trials. To ensure a one-to-one ratio between the occurrence of direct and corrected movements, the former were presented 2 times as frequently (20 replications for each of the 4 directions) for a total of 80 trials.
trials. In both the muscimol and the control trials, all conditions were pseudorandomized and presented in an intermingled design. Successful trials were rewarded with apple juice or water.

**Muscimol Injection**

Each animal was first used for neurophysiological recording for about 3 months. Once this was completed, the inactivation experiment was performed in different sessions. The GABA-A agonist muscimol (Sigma Aldrich) was dissolved in sterile physiological saline (5 μg/μL) and injected through a microsyringe. Each day, the session consisted of testing the effects of parietal inactivation on both the reaching and saccade tasks. In separated sessions, cortical inactivation was performed unilaterally (UL-I) in the left and right hemispheres, or bilaterally (BL-I), as shown in Table 1. At the beginning of each day, the session started by testing the normal animal’s behavior before the muscimol injection, as control. Then, injections (unilateral or bilateral) were made. After 2 h rest, the animals were retested. In each hemisphere, 4 injections (1 μL each), spaced 1 mm apart, were made into the region of physiological recording in the SPL (Fig. 1), or in the homologous region of the other hemisphere. In all cases, the consequences of unilateral and bilateral inactivation were tested on both arms. As a further control, experimental sessions similar to those described above (i.e., behavior → injections → behavior) were repeated, by making 4 injections of sterile physiological saline (SAL-I; 1 μL each) in the same cortical region(s), to exclude that the observed effects of muscimol were due to local edema or to dilution of the extracellular matrix.

**Behavioral Control**

Custom-made software controlled the movement of the robots, the switching of the lights, and recorded the time of button press and release. Arm position was recorded in 3D using an opto-electronic system (Optotak, Northern Digital, Waterloo, Canada) and sampled at 100 Hz. Six markers were attached to a tight-fitting sleeve on the monkey’s forearm to reconstruct hand trajectories. Eye position signals were recorded by using an implanted scleral search coil (1° resolution) and sampled at 200 Hz (Remmel Labs, Ashland, MA). Fixation accuracy was controlled through circular windows (5° diameter) around the targets. During recording, an upper limit was placed on the hand reaction time as the mean reaction time plus 1 standard deviation of all the trials recorded during the last 2 weeks of training. For the eye task, reaction and movement time together had to be less than 400 ms.

**Neural Recording**

The activity of single neurons was recorded with extracellular electrodes, using a 7-channel array (Thomas Recording GmbH, Giessen, Germany). Electrodes were glass-coated tungsten–platinum fibers (1–2 MΩ impedance at 1 kHz).

**Data Analysis**

**Behavioral Epochs**

The time of change in the direction of hand movement during corrected reaches was determined by first calculating the mean and confidence interval of the hand trajectory in the x-, y-, and z-coordinates, over all direct reaches to each of the targets. The 95% confidence interval was obtained using the bootstrap statistics. The instant of change of movement trajectory (switch time) was then calculated by comparing each corrected reach trajectory with the mean direct reach movement to the same target. This time was defined as the first of a series of 3 points exiting its confidence interval in any of the x-, y-, or z-coordinates.

For the eye, the angular velocity was first derived from the position signal. The onset and offset of the saccade were taken as the first of a sequence of 3 points exceeding or falling below a threshold of 50°/s, respectively. There was no need to calculate a switch time for the double-step conditions, as the eye always completed the saccade to the first target before moving to the second one.

With these values, we could define various epochs describing the animal’s behavior (Fig. 1B). In the *Direct reach* task, the CT ended with the presentation of the first target and the RT was defined as the time elapsing from the presentation of the target to the onset of hand movement. Only one period of hand movement (MT) was detectable in this task condition. In the *Corrected reach* task (Fig. 1D), 2 RTs were defined: RT1 as the interval from the presentation of the first target to the onset of hand movement and RT2 elapsing from the second stimulus onset to the change of hand movement direction, as determined by the instant of hand trajectory switch (Fig. 1B). In this task, the MT could be divided into 2 distinct epochs, based on the time the hand traveled toward the first target (MT1) and second (MT2) targets. For the *single-step saccade* task, the division into behavioral epochs was similar to that of the *Reaching* task. In the *double-step saccade* task, we defined 2 periods for eye RT and MT (RT1 and MT1 followed by RT2 and MT2).

Appropriate statistical tools, such as analysis of variance (ANOVA; *P < 0.01*) or Kolmogorov–Smirnov (K-S) test (*P < 0.01*), were used to assess differences in the task performance after muscimol and saline injection, relative to control.

**Neural Data**

A 2-way ANOVA (factor 1: epoch; factor 2: target position) was used to study the modulation of neural activity in different epochs of the tasks. In the reaching tasks, we compared the mean spike frequency of *Direct reach* trials, collected during RT, MT, and THT to the one recorded during CT. In the *Saccade task*, the comparison was performed between mean spike frequency of single-step trials in RMT (RT+MT) and THT with the corresponding CT. A cell was defined as being modulated in a given epoch if factor 1 or the interaction term was significant (*P < 0.05*). A cell classification was also attempted to identify the main influence on cell activation between hand movement (reaching) and saccade behavior. Cells were classified as hand-dominant, eye-dominant, or eye–hand related on the basis of ad hoc modulation indices (see Archambault et al. 2009). The available kinematic data were used to calculate the length in time of the different behavioral epochs and the time of switch of hand trajectory in the corrected reaches trials. To examine hand-dominant cells in more detail, the relationships between their neural activity and the hand’s kinematics during both direct and corrected reaches were modeled through a multiple linear regression (Archambault et al. 2009).

**Reconstruction of Hand Trajectory**

The relationship between hand position and the 6 markers placed on the monkey’s forearm was calculated using a known reference point, that is, the hand’s resting position on a fixed peripheral target at the end of movement. We adopted an algorithm based on singular value decomposition, which makes use of the redundant information, in the least-squares sense (Soderkvist and Wedin 1993). This method allows for the optimal calculation of the position and orientation of the forearm (6 degrees of freedom) from 6 sets of coordinates (18 degrees of freedom).

**Comparison of Hand Trajectories**

The first evaluation of the consequences of parietal inactivation was focused on the analysis of hand trajectories. To this aim, we used

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**Table 1**

Schematic representation of experimental protocol

<table>
<thead>
<tr>
<th>Session</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
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<tr>
<td><strong>Control No-I</strong></td>
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<td>Muscimol injection</td>
<td>Muscimol injection</td>
<td>Muscimol injection</td>
<td>Muscimol injection</td>
<td>Saline injection</td>
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<tr>
<td>Unilateral right (UL-I)</td>
<td>Bilateral (BL-I)</td>
<td>Unilateral left (UL-I)</td>
<td>Bilateral (SAL-I)</td>
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<td>Rest (2 h)</td>
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<td>Behavioral testing (hand and saccade tasks) before injection</td>
<td>Behavioral testing (hand and saccade tasks) after injection</td>
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2 approaches: one aimed at assessing significant modifications of the trajectory configuration (shape and dispersion) and the other designed to specifically evaluate the change in the spatial dispersion within groups of repeated trajectories under identical movement conditions. The similarity of 2 hand trajectories were, in both instances, evaluated by measuring the spatial correlation (ρ) between the time-series of the velocity vectors of one particular trajectory with those related to a reference trajectory (Shadmer and Mussa-Ivaldi 1994). For the first analysis, we considered as a reference the means of the control trajectories (MCTs) computed for each arm and for each movement direction and condition (direct and corrected trials), for a total of 24 MCTs. Then a correlation analysis was made between the individual trajectories observed under different experimental conditions, that is, before inactivation (Control No-I), under UL-I (left and right), BL-I, and SAL-I and the corresponding MCT. In this way, 160 comparisons for corrected trials (10 reps × 8 conditions × 2 arms) and 160 comparisons for direct ones (20 reps × 4 movement direction for direct trials × 2 arms) have been performed. This led to 160 r-values for each type of movement (direct or corrected) and for each type of experimental condition (Control No-I, BL-I, UL-I left, UL-I right, and SAL-I condition). These r-values were plotted as cumulative distributions (Control No-I - green; UL-I - blue; BL-I - red; SAL-I - yellow) separately for direct and corrected trials. Data obtained from the UL-I of the 2 hemispheres were pooled together within the same distribution, thanks to the similarities of results when data were considered separately. Finally, for each inactivation condition, the relative distribution of r-values was compared, through a K-S test (P < 0.01), with that obtained from the comparisons of the individual control trajectories (Control No-I) with their own means. The second analysis, aimed at evaluating the differences in the dispersion of the hand trajectories within each group of repeated trials, consisted on a procedure, in part, identical to the one described above, with the only difference that each hand trajectory was compared with its own mean (computed across different replications), instead of the MCT.

Analysis of Eye-Hand Coupling
A correlation analysis was performed between the hand and the eye reaction times during both direct and corrected reaches. This analysis was performed on data obtained before and after muscimol injection. To evaluate the influence of parietal inactivation on the correlation between the 2 above-mentioned variables, a comparison between pairs of linear regressions was performed to test hypotheses about regression coefficients equality (Zar, 1996) before and after inactivation. For those pairs of linear regressions with slopes not significantly different (analysis of covariance; P > 0.01), their "common slope" has been computed (Zar, 1996) and then the test for equality of intercepts has been performed.

Results

Functional Properties of SPL Neurons
We will first provide a brief summary of the physiological properties of neurons in the parietal region that was later silenced by muscimol injection. A full account of these properties can be found in Archambault et al. (2009, 2011). The activity of 240 neurons was recorded in the SPL of 2 left hemispheres of 2 monkeys while these performed the tasks described above. Microelectrode penetrations (Fig. 1C) were made in a region of the SPL identified as Brodmann’s area 5 (area PE/PEc). The ANOVA performed (Fig. 2A) revealed that the activity of most parietal cells was significantly related (P < 0.05) to reaching movements, as it can be inferred by the proportion of them modulated in the different epochs of Reaching and Saccade tasks (Fig. 2). Furthermore, the majority of cells (n = 167/240; 70%) were classified as hand-dominant, 20% (n = 47/240) as eye-dominant, and the remaining (n = 26/240; 11%) as eye–hand related.

Hand-dominant Cells
During direct reaches, the activity of SPL cells was modulated as a function of the position, velocity, and direction of hand movement, as revealed by the regression analysis. During corrected reaches (Fig. 2B), the pattern of cell activity associated with the hand movement to the first target changed after presentation of the second one. Cell activity was visibly modulated by hand speed across all the corrected conditions tested. For this cell, the multiple regression yielded an r² = 0.6, and a temporal lag of ~70 ms, indicating that the changes in activity led those in motor behavior.

The multiple regression revealed that all cells displayed a significant relationship between hand kinematics and neural activity (P < 10⁻³). Because of the large number of data points available for the regression analysis (n ~ 3500), an r² = 0.01 was statistically significant at the 1% level. The distribution of the temporal lags yielding the highest regression coefficient for the population of hand-related cells showed that the activity of most of them had a negative delay, indicating that their modulation led hand movement onset.

Eye-dominant Cells
During direct saccades to visual targets (Fig. 2C), the modulation of cell activity mostly led the onset of the saccade. When a second target was presented during eye-RT (Fig. 2D), the eye completed the saccade to the first target and then moved to the second one. In such instances, cell activity could be predicted by the activity pattern associated with the 2 direct eye movements performed in sequence, as shown for hand-related cells (Archambault et al. 2009).

Behavioral Data

Hand Reaching Movement
During direct reaches (Fig. 3A), the hand moved directly to the target with a slightly curved trajectory that was similar for all movement directions. During corrected reaches (Fig. 3A), the hand initially moved toward the first target and then suddenly curved toward the second one. In the absence of corrections, the hand described a typical bell-shaped velocity profile (Fig. 3B), whereas when a correction of trajectory was required, the hand velocity profile displayed 2 peaks (Fig. 3B). The first one was characterized by an initial acceleration, followed by a deceleration at the end of which the change in direction of the hand movement toward the second target occurred; then, a second acceleration occurred, at the end of which the hand attained the highest peak in speed, to decelerate again and land on the target. The overall shape of the hand velocity profile also depended on the time of occurrence of target change. When the second target was presented at the onset of hand movement, the deceleration following the first velocity peak was longer than the corresponding one observed when the target jumped during the reaction time.

Consequences of Muscimol Injection on Hand Reaching
We first analysed the effects of parietal inactivation on hand trajectories, by comparing their shapes and dispersion to the controls recorded in the absence of any injection (Fig. 4A) and after saline injection. After BL-I, hand movement trajectories in many instances were more variable and dispersed in space than control ones (Fig. 4A). In fact, the comparison of individual trajectories collected during control condition and
after UL-I and SAL-I with their respective MCT (see Methods for details) yielded in the majority of cases a correlation close to 1. On the contrary, the distributions of the \( r \)-coefficients (Fig. 4B) showed that bilateral inactivation (red distribution) led to significant decrease of \( r' \)-values (K-S test; \( P < 0.001 \)) relative to those obtained from the control condition, as well as from UL-I and SAL-I. This decrease was observed for both direct and corrected reaches (Fig. 4B). Since smaller \( r' \)-values can either indicate that the hand trajectories had different shapes or that they were more dispersed in space when compared with control ones, the contribution of the spatial dispersion was assessed through a second analysis. This was performed by comparing for each experimental condition every single hand trajectory to the mean one computed across the 10 replications of each movement condition. The results showed that in this case there was no significant difference between the distribution of \( r' \)-values obtained before and after BL-I. Overall, these results suggest that the shape rather than the spatial dispersion of hand trajectory was affected by the bilateral SPL inactivation.

From now on in the manuscript, we will only illustrate the effects of BL-I, the only one that had significant consequences on the behavior of both animals. Figure 5A illustrates the effect on the RTs (toward the first target) of the right and left arms for both monkeys. Since, for this variable, no difference has been observed across reaching conditions, the data from direct and corrected trials were pooled together. In all cases, but left arm in Monkey 2, a significant increase (K-S

![Figure 2](http://cercor.oxfordjournals.org/content/dam/cercor/figures/2648/C2648fig2.jpg)
seen in a movie (Supplementary Movie 1) created from the time sequence of the instantaneous positions of the hand during the entire duration of the trial. Hand RT and MT were not affected by saline injection.

When a change in target location occurred (Fig. 6A), the hand-path toward the first target was longer after BL-I, when compared with control. As a consequence, in-flight trajectory correction was delayed, as also shown by the observation that the double-peaked velocity profile typical of corrected reaches was shifted in time by about 130 ms (Fig. 6B).

To better understand the nature of this delayed correction of hand trajectory, a linear regression between the hand velocity curves of control trials versus those obtained after muscimol injection was performed. First, the corresponding curves were aligned to the onset of hand movement to the first target (Fig. 6C). The time lag of 40 ms was obtained between the correlated (r = 0.989) rising phases of the hand velocity profiles toward the second target, suggesting that a delay occurred in the adjustment of the hand trajectory after muscimol injection. When the velocity profiles were aligned to the onset of hand movement to the second target (Fig. 6D), a second time lag of 90 ms was detected under BL-I relative to controls (r = 0.999), indicating a delayed execution of hand movement toward the second target.

Eye Movements

Eye movements were monitored during direct saccades (single-step) and in double-step trials. Under control conditions, during single-step saccades, the eye moved toward the visual target (Fig. 2C), with a mean peak velocity of $751 \pm 219^\circ/s$ in Monkey 1 and $644 \pm 36^\circ/s$ in Monkey 2. When a second target was presented during RT, the eye completed the saccade to the first target and then moved to the second one (Fig. 2D). During double-step trials, eye movements were characterized by a double-peaked velocity profile (Fig. 2D), with the peak velocity to the first target similar to that seen during single-step saccade. The mean peak velocity to the second target was $1055 \pm 181^\circ/s$ in Monkey 1 and $890 \pm 113^\circ/s$ in Monkey 2, and it was significantly higher (t-test; $P < 0.001$) than that to the first target. The eye RT$_1$ was 148 ± 25 ms in Monkey 1 and 123 ± 16 ms in Monkey 2, whereas RT$_2$ was 178 ± 15 ms in Monkey 1 and 138 ± 14 ms in Monkey 2. Thus, the eye RT to the second target was significantly (t-test; $P < 0.001$) longer than that to the first one. See also the example shown in the movie (Supplementary Movie 1) of the reconstruction of eye movements in the space and time domains.

Consequences of Muscimol Injection on Eye Movement

After BL-I, the endpoints of eye movements in the single-(Fig. 7A) and double-step trials (Fig. 7B) were similar to those of controls, as it can be seen from the analysis of their dispersion around the mean. The similarity of the saccade endpoints across conditions was assessed measuring the deviations of each endpoint from the mean position in a given location, along the x ($Dx$) and y ($Dy$) axes (Fig. 7C), and by comparing their relative distributions (K-S test; $P < 0.01$). It can be noticed that the second saccades of the double-step task, when compared with those of the single-step task, were more dispersed, although in a similar fashion, before and after parietal inactivation. The different amplitude of the second saccade, which was twice longer than the first, can
explain this phenomenon, since the endpoint accuracy of saccades decreases with their amplitude (van Opstal and van Gisbergen 1989; van Beers 2007). In both monkeys, the eye velocity profiles to the first and second targets were not affected by BL-I. The main effect was observed on saccade timing (Fig. 8). The mean eye RT1 was 175 ± 20 ms in Monkey 1 and 135.7 ± 11.8 ms in Monkey 2, whereas mean RT2 was 246 ± 12 ms in Monkey 1 and 158 ± 10 ms in Monkey 2 (Fig. 8A). Thus, the saccades to the first and second targets were both significantly (t-test; P < 0.001) delayed relative to control trials. The elongation of RTs, particularly of RT2, is also evident from the eye speed profiles of 20 collected trials (Fig. 8B), when the eye moved in 4 different directions.

Consequences of Muscimol Injection on Eye–Hand Coupling

We studied whether the delays observed in the reach tasks were a consequence of the above-described eye impairment. For this purpose, the correlation between the hand and the eye RTs to the first (RT1; Fig. 9A) and second (RT2; Fig. 9B) targets was studied before and after BL-I for the data sets in which parietal inactivation led to a significant increase in the hand RT1 and RT2 (Fig. 5A, B). It is worth remembering that the hand RT2 corresponds to the time of hand switch and, therefore, it was studied in relation to the saccade RT to the second target. The correlation between hand and eye RTs was analysed for 4 different data sets (2 monkeys, both tested with left and right arms) and was found to be significant in all of them before, as well as after BL-I (r ranging from 0.3 to 0.5), the only exception being the control data in Monkey 1 (right arm), in which hand RT2 was not significantly correlated with the eye RTs to the second target (r = 0.22; P = 0.06). We then focused on those cases for which an increase in hand RT1 and RT2 was obtained after BL-I, to test whether this impairment depended from the oculomotor deficit and, if so, to which extent. It has been found that the hand and the eye RT1 (Fig. 9A) were similarly correlated before and after BL-I, as evidenced by the lack of a significant difference between the slopes of the 2 linear regressions, which were therefore plotted with their common slope (see Methods). This implies that the increase in the hand RT1 after injection can be, at least in part, explained by the observed increase in the eye RT1. However, parietal inactivation led to a further increase in the hand RT1, which cannot be accounted for by the elongation of eye RT1, as concluded from the significantly

Figure 4. Effects of parietal inactivation on hand trajectories. (A) Repeated hand trajectories in 4 different types of movements, before (green) and after BL-I (red). (B) Quantitative assessment of the change in the trajectory features under different conditions (Direct reaches and Corrected reaches). Plot of the cumulative distributions of the correlation coefficients obtained from the comparison of the individual hand trajectories observed under BL-I (red), UL-I (blue), SAL-I (yellow) and before injection (green) to the relative mean control trajectory (MCT), taken as a reference. The distribution referring to BL-I (red) is significantly different from the one before (K–S test; P < 0.001) and Corrected (K–S test; P < 0.001) reaches from that relative to control trajectories (green), and from those obtained after UL-I or SAL-I, that showed little or no effects relative to controls. Data are from Monkey 1. Similar results were obtained in Monkey 2.
higher value \((P<0.001)\) of the intercept of the linear regression for the data obtained under this condition. In the corrected reaches, the preexisting significant correlation \((P<0.001)\) between the hand RT2 and the eye RT2 (Fig. 9B), observed during control testing, remained similar following BL-I (as in the case of RT1, the common slope of the 2 regressions has been plotted). However, contrary to what has been observed to RT1, a negligible or no increase in intercept has been observed. For the data set relative to Monkey 1 (right arm) where in normal condition the regression was not significant, BL-I led to the emergence of a significant correlation between hand and eye RTs.

Overall, the results shown in Figure 9B suggest that the elongation of the time necessary to update hand movement direction can be largely explained by the delayed eye movement to the second target. It is worthwhile noticing that for both RT1 and RT2, BL-I led to an increase of the dependence of the hand from the eye behavior, as it can be inferred by the higher \(r\)-values measured after inactivation, particularly when looking at the times needed to update hand movement toward a new direction (RT2).

**Discussion**

**Online Control in Fast Reaching**

The inactivation of the SPL affected both the timing and the kinematics of hand reaches. In both the direct and corrected trials, we observed a significant elongation of the hand reaction time to the first target; similarly, an increase in the hand reaction time to the second target was also detected in the corrected trials. When the target jumped at the onset of hand movement, corrective reaches were slower than controls. In control conditions, after target jump, the hand smoothly changed trajectory to land on the new target location. After muscimol injection, the hand-path toward the first target was significantly longer, due to a delayed trajectory correction.

An in-depth analysis of the hand velocity profile revealed that a first delay occurred at the moment of the trajectory update, consisting in the lengthening of the reaction time to the second target. A second delay was observed during movement time toward the second target. Thus, both the preparation and execution of the corrective reach were delayed in time by SPL silencing.
An additional deficit consisted in a change in shape, rather than on spatial dispersion, of the hand movement trajectories relative to controls. This reveals an impaired selection of the shorter and most appropriate hand-path (Morasso, 1981) to the target, or it can be a consequence of the disturbance of the mechanism which seems to be common to the formation of both unperturbed and corrected reaching movements (d’Avella et al. 2011), for which the SPL can be regarded as a central neural node. However, the constant pattern of trajectory curvature observed after SPL inactivation raises the possibility that the impaired performance can be a consequence of the breakdown in the transformation of the desired hand-path into a sequence of appropriate joint rotations and/or in the control of the posture and geometry of the arm during hand reach (Lacquaniti et al. 1995).

These results provide the first available model of OA in monkeys, at least as far as one of its main feature is concerned, that is, the impaired online control of hand movement. In humans, bilateral parieto-occipital lesion results in delayed online correction of hand trajectory and elongation of hand-path toward the second target (Pisella et al. 2000; Grea et al. 2002), a clinical picture fully reproduced by our result, which also conform to those of an fMRI study of the brain areas activated by different types of reach errors (Diedrichsen et al. 2005), which attributes to the posterior SPL a specific role in online corrections after target displacement.

We did not detect constant and significant effects after unilateral inactivation of SPL. The need of a bilateral inactivation of parietal cortex to impair online visual control of hand movement, which normally occurs in central vision, might be dependent on the concurrent processing of both hemispheres under this condition. However, it cannot be excluded that muscimol injections involving a larger SPL region could result in deficits of online control. Ongoing research in humans in our laboratory and the results of a large study group of parietal patients (T. Shallice, personal communication) indicate that unilateral SPL lesion in humans results in deficit of online control of hand movement.

Saccade Control
Together with reaching deficits, our study shows for the first time that the bilateral inactivation of the SPL resulted in defective timing of saccades. After target jump, the eye did not interrupt the saccade to the first target, as the hand did, but made 2 consecutive saccades, originally toward the first target’s location and then to the second one. These movements had normal peak velocity and spatial dispersion of their endpoints, in both single- and double-step trials.
However, a delayed onset of the saccade to both the first and second targets was observed, suggesting that, as for the hand, the parietal inactivation impaired the timing of the composition of both the original and new motor commands. This result is consistent with the presence of populations of presaccadic cells whose signals are combined with hand-related information in this segment of the parieto-frontal network (Battaglia-Mayer et al. 2000, 2001; see Caminiti et al. 2010 for a review).

**Role of Parietal Cortex in the Control of Coordinated Hand–Eye Movement**

Studies where healthy subjects “look and point” to visual targets have highlighted a clear temporal coupling between eye and hand movement. A tight correlation between the time of initiation of eye movement (eye RT) and that of hand (hand RT) has been found when looking and reaching toward a common visual target (Herman et al., 1981). Varying degrees of correlations ranging from moderate (Prablanc et al. 1979) to high (Gielen et al. 1984; Neggers and Bekkering 2002) have been reported during reaches with target displacement. The correlation reported by these studies during corrected reaches is significantly different from that observed during direct ones, if the target jumps during RT, and the interval between the first and the second target presentation is greater than 125 ms (Gielen et al. 1984).

Despite the large evidence of a functional link between eye and hand movement, not only in humans, but also in monkeys (Snyder et al. 2002), neuropsychological studies of OA have basically ignored the analysis of the eye movement which naturally leads hand reaching, mostly because patients are usually requested to keep fixation constant while reaching at peripheral targets, a condition believed as necessary to...
Figure 8. Effects of muscimol on timing of saccadic eye movements in the double-step saccade task. (A) Cumulative frequency distributions of RT₁ and RT₂, under control conditions (gray) and after BL-I (black), in both monkeys (Mk1 and Mk2). In all cases, the difference between the 2 conditions was significant (K–S test; *P* < 0.001). (B) Replicas (n. 20) of eye velocity profiles under control condition (gray) and after BL-I (filled black) in Mk1. Gray and black triangles indicate the time of the first target’s presentation under control condition and BL-I, respectively; 0 ms (vertical interrupted line) indicates the time of second target presentation.

Figure 9. Correlation between eye and arm reaction times, before (gray) and after parietal inactivation (black). (A) Eye and hand RTs refer to those recorded during Direct reaches and to those relative to movements toward the first target during Corrected reaches. (B) Correlation between eye RT₁ (time elapsing from the appearance of the second target and the onset of the second saccade toward it) and hand RT₁ (time elapsing from the appearance of the second target and the change in direction of hand trajectory), collected during Corrected reaches. In (A) and (B), eye–hand correlation has been restricted to data sets (Monkey 1, left and right arms; Monkey 2, right arm) that showed a significant increase in hand RTs (see Fig. 5A,B). Correlation coefficient (r) is reported for each linear regression. Asterisk (*) indicates highly significant differences (*P* < 0.001) between intercepts of 2 linear regressions (gray and black lines). For details about linear regression, see Methods.
reveal OA. Since the impairment in eye movements often consists in a short increase in latency of saccade initiation, this cannot be detected without a quantitative control of oculomotor behavior. Furthermore, when impaired eye movements were observed, they have been considered irrelevant for the hand misreaching (Pererin and Vighetto 1988; Baylis and Baylis, 2011). This conviction has been strengthened by the belief of the existence of a parietal “saccade” system, strictly segregated from that dedicated to hand movement, both in humans (Pierrrot-Deseilligny et al. 2004) and monkeys (Andersen et al. 1992), and by the observation that after parietal lesion impairments of eye and hand movement can occur in isolation. However, several neurophysiological studies on humans and monkeys have pointed to the existence of a functional link between eye and hand movement (Battaglia-Mayer et al. 2000; also see Caminiti et al. 2010 for a review) in most cortical areas belonging to PPC, as also shown by the observation that the degree of effector selectivity during reaches and saccades is rather low in different areas of parietal cortex, not only in monkeys, but also in humans (Levy et al. 2007; also see Filimon, 2010 for a review).

A recent study (Gaveau et al. 2008) was aimed at investigating ocular control in OA, testing 2 patients with bilateral parietal lesion in a natural “look and point” paradigm with a target jump. Both subjects exhibited a delayed visual capture, showing an impairment of fast saccade control. This resulted in a modification of the temporal sequence of eye–hand coordination, consisting in a delayed pointing to visual targets. In particular, patient AT showed a marked increase of about 200 ms in eye RTs, followed by a larger increase of hand RT greater than 400 ms. Our observations are in agreement with these results. In fact, it is worth noting that the reported delayed initiation of hand movement in parietal patients can be, at least in part, explained by the elongated eye RTs. However, its value (about 2 times higher relative to eye RT, as reported by Gaveau et al. 2008) points to the existence of a further independent impairment in the hand movement initiations after parietal lesions, as similarly suggested by the significant increase, after parietal inactivation, in the intercepts of the linear regressions that link eye and hand RTs (Fig. 9A). During corrections, our results showed that the elongation of the time necessary to reverse hand movement direction is instead largely influenced by the delayed oculo-motor behavior.

Overall, the behavioral defects observed after reversible inactivation of the SPL seem to be dependent both on the impaired timing of composition of a new motor command, which is reflected in the delayed planning and, as far as the hand is concerned, on an altered shape and length of the hand trajectory, probably resulting from both planning and execution errors. The planning phase of reaching movement is, however, undoubtedly influenced by the associated saccade occurring before the hand movement. Therefore, the impaired fast ocular control, consisting in the elongation of the saccade to the visual target, might be regarded as a potential source of the delayed manual correction after parietal lesions, to be added to a parallel impairment in the control of the hand trajectory. This is not surprising, since both eye and hand reach defects can be expected when considering the functional properties and the cortico-cortical connectivity of the SPL areas silenced by muscimol injection. Areas PE mostly encodes somato-motor information about limb position and movement direction (Lacquaniti et al. 1995; Archambault et al. 2009) and projects directly to motor cortex (Johnson et al. 1996), while its most caudal part (area PEc), in addition to somatosensory information, also receives significant visual and eye-related inputs (Battaglia-Mayer et al. 2001; Marconi et al. 2001; Squatrito et al. 2001; Bakola et al. 2010) and projects to dorso-caudal premotor cortex (PMd/F2; Marconi et al. 2001; Bakola et al. 2010), which in turn projects to motor cortex. In PEc, neural activity is also related, among other functions, to planning of eye–hand movement (Battaglia-Mayer et al. 2001). Therefore, in the functional gradient of the SPL, all information about target localization, eye and hand position, movement direction and speed, as well as preparatory signals coexist and, as previously shown, are combined in a coherent fashion in the global tuning field (Battaglia-Mayer et al. 2000, 2001) of individual neurons. This information is crucial for the utilization of target location signals necessary for reach planning and its continuous update. The collapse of this combinatorial mechanism may result in a cascade of behavioral defects, such as those observed in monkeys after reversible inactivation of these parietal areas, thus providing a “positive image” of OA in humans (Battaglia-Mayer and Caminiti 2002; Caminiti et al. 2010).

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes
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References


