



Response channel activation and the lateral prefrontal cortex

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Abstract—The role of lateral prefrontal cortex in transducing perception into action was studied in 10 patients with chronic, unilateral lesions. They identified colors in the center of a visual display, while a flanking, distractor color was presented simultaneously in either the ipsilesional or contralesional field. The flanker could be either the same color as the target, or incompatible with the correct response. The effects of compatible and incompatible flankers on reaction time (RT) served as a measure of response channel activation by the flanker. Flankers in the contralesional field influenced RT less than did those in the ipsilesional field. These results suggest that the lateral prefrontal cortex is involved in maintaining stimulus–response channels. Copyright © 1996 Elsevier Science Ltd

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Introduction

Consider a simple task in which one is given a pile of red and green items (say M&M candies), and asked to sort them by color: “Pick up the red ones with your right hand, and pick up the green ones with your left hand”. At first you may need to think about this rule before you pick up an item. With a little practice, however, you become quite skilful at the task. Now, in this task, the stimulus response pairing is arbitrary and can be temporary. You could be asked, the next day, to reverse the rule, “red with the left hand and green with the right”. With a little practice, this task, too, would become effortless. Presumably, this automatization occurs because a stimulus–response channel is maintained in working memory so that red is directly linked to one motor response and green to another.

The current study investigated the contribution of lateral prefrontal cortex to maintaining task specific stimulus–response channels. To measure response channel activation by visual stimuli, a flanker interference paradigm was used [3]. The subjects’ task was to respond to a small color patch in the center of a display by pressing one key for red and another key for green. On each trial,

a larger flanking color patch that subjects were instructed to ignore, was presented to one side of the target in either the contralesional or the ipsilesional field. The flanker could be either compatible with the correct response or incompatible (specifying a competing response). In this type of ‘flanker’ paradigm, normal subjects are quicker to respond to a target when the flanker is compatible rather than incompatible with the correct response. Because subjects are to ignore the flankers, these effects are attributed to automatic response channel activation by the flanker [5]. When the flanker activates the same response channel as the required response, performance is facilitated; but when the flanker activates a response channel incompatible with the correct response, interference slows performance. If the prefrontal cortex is required for maintaining the representation for stimulus–response pairs in working memory, and if this cortical region is damaged on one side, then flankers presented to the contralesional field should produce less response channel activation and, thus, a smaller effect of the contralesional flankers on reaction-time responses to the target.

Experiment 1: Central Report Task

Subjects

Ten patients with lesions involving inferior lateral prefrontal cortex (see Table 1 and Fig. 1), and 12 neuro-

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Table 1. Clinical information for each patient

| Patient | Age/sex | Lesion | Hemisphere | Vintage (years) | Volume (cm ³) | Clinical |
|---------|---------|--------|------------|-----------------|---------------------------|----------|
| AA | 25 F | Stroke | L | 0.5 | 59 | |
| AL | 61 F | Stroke | L | 10 | 51 | A |
| EB | 76 F | Stroke | R | 10 | 17 | |
| JC | 65 M | Stroke | L | 5 | 103 | A, H |
| JD | 64 M | Stroke | L | 13 | 31 | A |
| LS | 62 F | Tumor | L | 14 | 28 | MG |
| MG | 29 M | AVM | R | 9 | 25 | |
| MI | 69 F | Stroke | L | 9 | 70 | A, H |
| MM | 67 M | Stroke | R | 5 | 52 | |
| RT | 73M | Stroke | L | 9 | 39 | A |

Vintage refers to the number of years since the stroke, or since surgical resection. MG, meningioma; AVM, arteriovenous malformation; A, aphasia; H, hemiparesis.

logically normal control subjects participated after giving oral and written informed consent. The control subjects included eight men and four women, ranging in age from 54 to 76 (mean = 64, S.D. 7). The patients included five men and five women, ranging in age from 25 to 76 (mean = 59, S.D. = 16). The two groups did not differ significantly in age [t (d.f. 20) = 1.19, $P > 0.24$].

Patients were selected on the basis of a single, chronic, unilateral lesion restricted to lateral prefrontal cortex and underlying structures. All were right-handed, and the lesion was due to a stroke in all, except two patients. The lesion had occurred at least 5 years prior to testing, except for patient AA who had had a stroke related to a migraine attack 6 months earlier. All patients were functioning independently, and most had previously participated in behavioral studies. None had any history of drug or alcohol dependency, or mental illness. None had any clinical sign of visual field defect, extinction or neglect, or any oculomotor impairment evident on neurologic examination. Lesion location was verified in all patients by a CT scan or MRI. Lesion areas were reconstructed onto axial templates drawn from an atlas [2]. Individual reconstructions were then computed from the axial sections [4].

Apparatus

The experiments were conducted in a sound attenuated chamber using an IBM compatible personal computer connected to a NEC Multisync video graphics array (VGA) stimulus monitor. The timing of the visual displays was synchronized with the 60-Hz vertical synchronization of the computer monitor. Button-press response latencies were timed to the nearest millisecond by setting the 8253 chip of the computer to millisecond ticks. Responses were made on a two-button Gravis joystick connected to the game-port adapter of the computer.

Procedure

Subjects were tested individually in a single session. The video display monitor was positioned at eye level at a viewing distance of 61 cm. Subjects responded to visual signals presented at the center of the screen by pressing one of two adjacent response keys on the table in front of them, using the index and middle fingers of the preferred hand.

The task was to respond to a small color patch (0.5° solid square) in the center of a display by pressing one key for red and another for green. On each trial, a larger flanking color patch (1.5° solid square) was presented to one side (left or right) of the target. The center-to-center distance between the target and flanker was 2°. Subjects were instructed to ignore the flanker. With equal probability, the flanker could be either compatible with the correct response or incompatible (specifying a competing response); and it could occur in the left or the right visual field. The color of the target stimulus, the color of the flanker stimulus, and the field of the flanker were each selected with equal probability, at random, and combined orthogonally. The target stimulus and flanker came on simultaneously, and both remained visible until the subject responded. If no response was made, the trial terminated after 3000 msec. The next trial began 1500 msec after the subject responded. After a practice block of 38 trials, an experimental block of 360 trials was run with a rest period after every 120 trials.

Data analysis

Median RTs were calculated individually for correct responses for each condition, and these were analyzed in a repeated measures 2 × 2 ANOVA with two within factors: field of flanker (contralesional or ipsilesional for the patients; left or right for the control subjects) and flanker compatibility (compatible or incompatible with

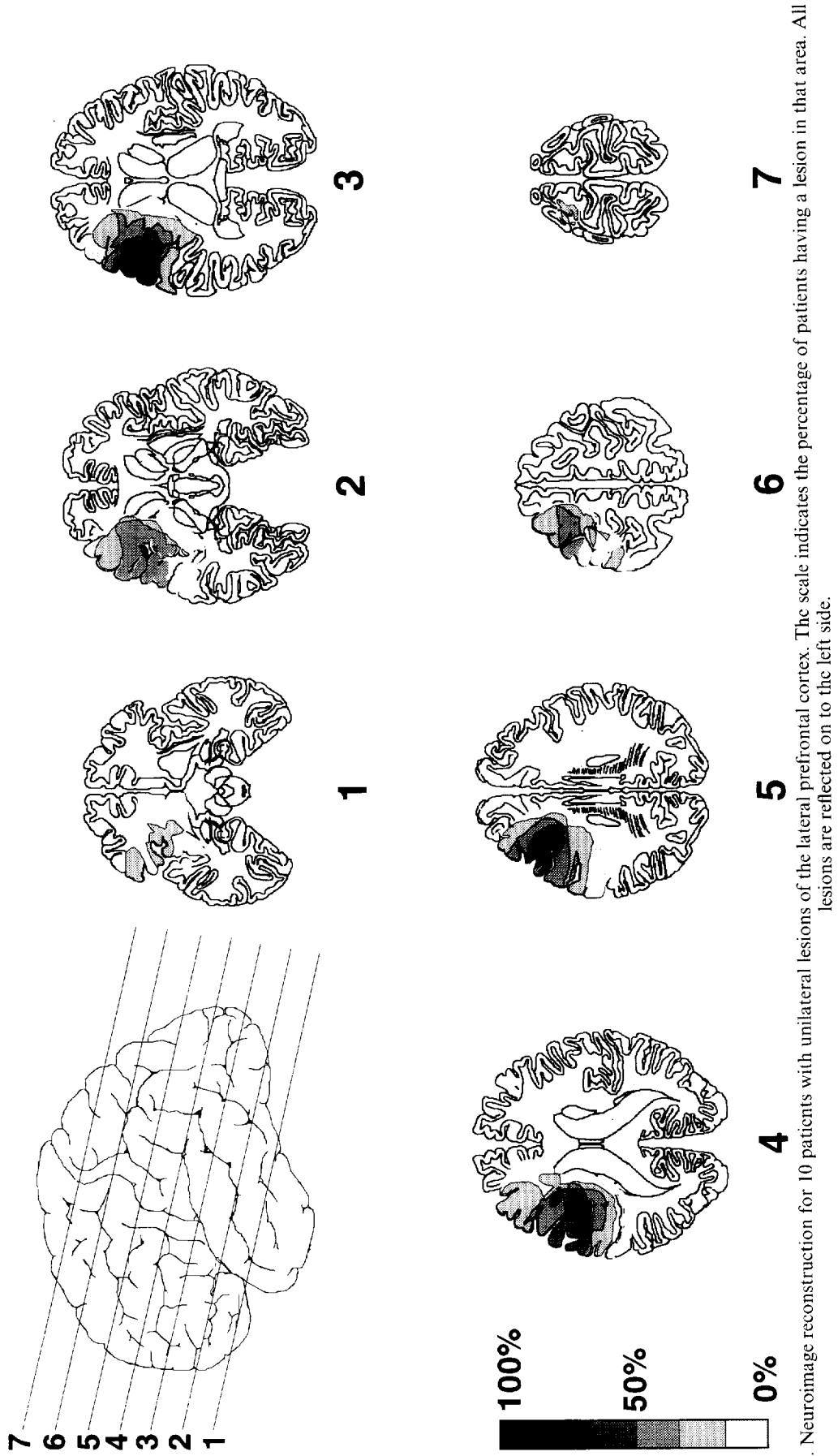


Fig. 1. Neuroimage reconstruction for 10 patients with unilateral lesions of the lateral prefrontal cortex. The scale indicates the percentage of patients having a lesion in that area. All lesions are reflected on to the left side.

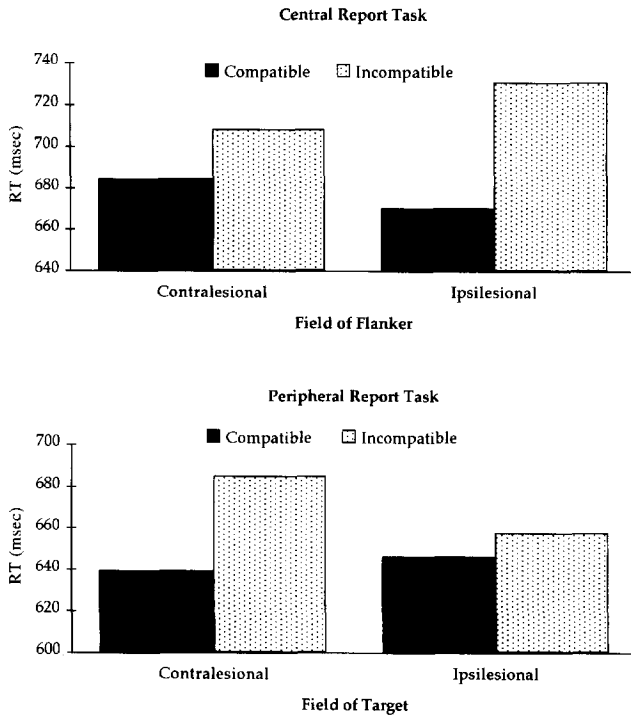


Fig. 2. The mean of the median reaction times (msec) for each of the patients is shown for: Central report task (Experiment 1) (top); and Peripheral report task (Experiment 2) (bottom).

the correct response). Control and patient data were analyzed separately.

Results

Control subjects. Error rates averaged less than 3%. RTs to targets, displayed with incompatible flankers (512 msec), were significantly slower [$F(1,11)=43.8$, $P<0.0001$] than RTs to targets displayed with compatible flankers (464 msec). There was no main effect of field of flanker, and the field of flanker did not interact with flanker compatibility [$F(1,11)<1$ for both].

Patients. Errors occurred in less than 5% of trials. Figure 2 (top) shows the mean of median RTs for compatible and incompatible flankers presented in the contralesional and ipsilesional fields. Flankers in the ipsilesional field produced a significantly greater effect on RTs to the target than did contralesional flankers [$F(1,9)=8.5$, $P<0.02$]. Table 2 shows the flanker compatibility effect (RT for incompatible minus RT for compatible flanker) for each patient for ipsilesional (mean=60.4 msec) and contralesional (mean=23.5 msec) flankers. There was a significant compatibility effect of the flanker when it was presented in the ipsilesional field ($t=-4.005$, $d.f.=9$, $P<0.005$), but not when the flanker was presented in the contralesional field ($t=-1.3$, $d.f.=9$, $P>0.15$). No other main effects or interactions approached significance.

Our design did not include a 'neutral' flanker condition, i.e. a flanker which did not code for either possible response (e.g. blue). We could not, therefore,

Table 2. Flanker effects (msec) (RT for incompatible minus RT for compatible flanker) in the central report (Experiment 1), and peripheral report (Experiment 2) tasks for each patient, as well as means (S.E. in parentheses)

| Patient | Central report task | | Peripheral report task | |
|---------|-----------------------|-------------------------|------------------------|------------------------|
| | Ipsi-lesional flanker | Contra-lesional flanker | Ipsi-lesional target | Contra-lesional target |
| AA | -7 | 13 | -2 | 32 |
| AL | -5 | -54 | -5 | 49 |
| CI | 136 | 113 | -3 | 68 |
| EB | 119 | 60 | 18 | 74 |
| JC | 64 | 2 | 35 | 57 |
| JD | 88 | 40 | 36 | 40 |
| LS | 84 | -30 | 5 | 59 |
| MG | 45 | 2 | 21 | 72 |
| MM | 33 | 45 | 5 | -18 |
| RT | 47 | 44 | 5 | 22 |
| Mean | 60.4 (15.1) | 23.5 (15.1) | 11.5 (4.8) | 45.5 (8.9) |

estimate the relative contributions to the flanker compatibility effects that were due to facilitation by compatible flankers or to interference from incompatible flankers. However, as shown in Fig. 2, faster RTs from compatible flankers in the ipsilesional compared to contralesional field, and slower RTs from incompatible flankers in the ipsilesional compared to contralesional field, both appeared to contribute to the difference in flanker effects between the two fields.

Experiment 2: Peripheral Report Task

Experiment 1 showed that visual information contralesional to the patients' focus of attention (the target stimulus in the center) was less effective in activating response channels. These results are consistent with a role of the prefrontal cortex in maintaining stimulus-response channels. An alternative explanation is that the lesions of the prefrontal cortex decrease flanker effects because they reduce perceptual processing of the flanker stimuli. That is, a contralesional flanker may not influence responses to the target simply because it is not sufficiently perceived by the time the subject responds to the central target.

None of the patients in this study had any clinical signs of hemianopia, neglect or extinction; and none had any difficulty in naming the peripheral flanker stimuli when asked to do so. Moreover, we have shown previously that patients with hemispatial neglect show preserved flanker effects from contralesional flankers [1]. Thus, flanker activation of stimulus-response channels does not appear to require attention to, or awareness of, the flanker. Nevertheless, to exclude a perceptual impairment as the basis for decreased stimulus-response channel activation by contralesional flankers in the first experiment, we examined directly the perception of contralesional stimuli in a

second experiment. In Experiment 2, subjects were instructed to respond to the color of the flanking peripheral stimulus while ignoring the color of the central stimulus. By reversing the roles of target and distractor from those used in Experiment 1, we could ensure that the distractor was perceptually processed (since it was at the center) and could determine if there was any asymmetry in perceptual processing for contralesional and ipsilesional target stimuli.

Subjects

The same patients and control subjects tested in Experiment 1 participated in the second experiment.

Procedure

The display, stimuli and apparatus were identical to Experiment 1. The only change was in the instructions: subjects were asked to ignore the central stimulus (which had been the target in Experiment 1), and to make a choice key press response based on the color of the peripheral stimulus (which had been the flanker distractor in Experiment 1).

Results

Control subjects. Errors occurred in less than 3% of the trials. Mean RT was longer [$F(1,11)=36.7$, $P<0.0001$] when the central stimulus was incompatible with the peripheral target (464 msec), than when the central stimulus was compatible with the target (448 msec). There were no other significant main effects or interactions.

Patients. Errors occurred in less than 4% of the trials. As shown in Fig. 2 (bottom), the mean RTs to respond to peripheral targets in the contralesional field were not slower than to those in the ipsilesional field [$F(1,9)=0.79$]. Incompatible central distractors produced longer mean RTs than did compatible central distractors [$F(1,9)=26.8$, $P<0.001$]. As in Experiment 1, there was a significant interaction between field and flanker compatibility [$F(1,9)=13.8$, $P<0.005$]. Figure 2 (bottom) shows that when the central distractor was contralesional to the peripheral target, less flanker interference was generated than when it was ipsilesional to the peripheral target. Table 2 shows the effect of central distractor compatibility for each patient for ipsilesional (mean = 11.5 msec) and contralesional (mean = 45.5 msec) targets.

Discussion

In patients with lesions of lateral prefrontal cortex, both experiments showed that visual information, con-

tralesional to the stimulus to which the patients were responding, failed to activate stimulus–response channels as effectively as ipsilesional information. That is, patients with left hemisphere lesions showed a greater incompatible–compatible difference when the flanker was presented to the left as compared to the right of the target, while the converse was true for patients with right hemisphere lesions. This was the case regardless of whether a target (Experiment 1) or a distractor (Experiment 2) was presented at the initial fixation point.

It seems unlikely that the inefficiency of contralesional flankers in affecting performance in Experiment 1 was due to impaired perception of the flanker. We have recently reported evidence that flanker effects can be activated preattentively by flankers in the contralesional field of patients with visual extinction due to parietal lesions [1]. In that study, flankers in the contralesional field produced compatibility effects as large as those activated by ipsilesional flankers.

The results of Experiment 2 are especially helpful in demonstrating that the reduction of contralesional flanker compatibility effects by prefrontal cortex lesions are attributable to a deficiency of response channel activation rather than to perceptual impairment. At the start of each trial, subjects were fixating the center of the display and did not know on which side the peripheral target would appear. Thus, the center color patch that was the distractor in this experiment was being fixated directly at the time that it and the target appeared. Were flanker compatibility effects only dependent upon perceptual processes activated at the time of stimulus presentation, then no asymmetry for contralesional versus ipsilesional targets would be expected.

In Experiment 2, however, subjects had to first disengage from the distractor and orient to the peripheral target either by making an eye movement or a covert attention shift. In either case, the asymmetry of flanker compatibility effects observed for ipsilesional and contralesional targets indicates that these effects were not contingent solely on perceptual processing of the distractor. Rather, the effects of the distractor did not begin to accrue until the peripheral target was selected for action; and once it was, the compatibility effects of the distractor, like in Experiment 1, were greater when the distractor was ipsilesional to the attended target than when it was contralesional. This observation suggests that stimulus–response channel activation by unattended stimuli operates on an action-centered reference frame [6].

The contrast between our previous observations of preserved contralesional flanker compatibility effects in patients with visual extinction due to parietal lesions [1], and the current observations showing reduced compatibility effects from contralesional flankers in patients with prefrontal cortex lesions without visual extinction, demonstrate that compatibility effects are not contingent upon awareness of the flankers. Rather, the current results implicate the lateral prefrontal cortex in sup-

porting stimulus–response channels for transducing perception into action. They are consistent with a role of prefrontal cortex in holding responses on line which have been activated by preattentive processes. Moreover, the action-based reference frame in which these effects are manifest (Experiment 2) suggests that, as we attend to the business at hand, task-related responses are activated in parallel and held in readiness for subsequent action. The response channels activated by unattended flankers may facilitate subsequent responses to information that is unattended but nearby, i.e. supporting what may be the imminent next response that could be required.

In the current experiments, the stimulus–response pairings were arbitrary and, presumably, the required production rules (press the left button for red, and the right button for green) had to be maintained in working memory. Our results may implicate the prefrontal cortex in holding these kinds of production rules in working memory. If this is the case, then prefrontal cortex lesions may not impair response channel activation under conditions where stimulus–response pairs are not arbitrary, but instead have been overlearned such that no working memory load is present in the task—for example saying the word “red” in response to a red color patch or “green” to a green color patch. We are now conducting experiments to determine whether the prefrontal cortex is involved in maintaining stimulus–response channels in general, or only under the specific circumstances where stimulus–response channels must be maintained in working memory.

We are also now investigating more complex everyday tasks in which more than one production rule must be maintained at the same time. Consider a more complex example of the type of sorting task introduced earlier in which one must sometimes sort not only by color but also, at times, by shape. This kind of task involving

shifting between different stimulus–response rules may require that several response channels be active simultaneously in order to facilitate fast and flexible sequential reactions to the environment, constrained by ongoing goals. These response channels must then compete for activation and execution. We are now directing our attention to understanding the neural mechanisms involved in selection among activated responses, and are exploring the role of frontostriatal circuitry in this selection process.

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