Saccadic eye movement and working memory deficits following damage to human prefrontal cortex

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Abstract—A patient with a lesion confined largely to the right inferior frontal gyrus was found to be impaired on tests of spatial working memory and executive functioning. By contrast, his pattern recognition was good. The patient’s selective impairments are consistent with the view that prefrontal cortex contributes to processes involved in spatial working memory. The patient was also tested on a range of oculomotor paradigms, some of which required the temporary suppression of a saccadic response. He was unable to suppress making contra- or ipsilesional reflexive glances to peripheral stimuli on the “anti-saccade” paradigm, but his performance improved on delayed saccade, memory-guided saccade and fixation tasks. Although reflexive glances were observed under these conditions they occurred more frequently in response to contralesional stimuli than ipsilesional ones. Furthermore, the patient had no difficulty in performing anti-point movements with his ipsilesional hand. Thus, his inability to suppress reflexive glances on the anti-saccade task is not due to a generalised problem of “distractibility”. The patient’s deficits are discussed in terms of models of anti-saccade generation and are related to recent findings regarding the role of prefrontal cortex in working memory and visual attention. © 1998 Elsevier Science Ltd. All rights reserved.

Key Words: anti-saccade; frontal lobe; attention; distractibility.

Introduction

Saccadic eye movements are rapid movements of the eyes that bring stimuli of interest onto the foveal region for detailed processing. In recent years the neural structures involved in the generation of saccades have become increasing well documented [11, 46, 47, 50, 64, 73, 74, 76] and studies of saccades have proved to be an influential method of studying cognitive functions such as visual attention [10, 39, 81] and working memory [19–21, 67]. The frontal lobe is one region where neuronal discharges appear to be closely related to the generation of saccades [22] and damage to the frontal lobe results in specific deficits in saccadic eye movements [26, 32, 58]. It was argued by Holmes (1938) that a primary role of the frontal lobes is the voluntary suppression of reflexive ocular behaviour so that: “reaction to vision is no longer con-

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fined by the fatality of a reflex” (p.112). Consistent with this view, damage to the frontal lobe can result in an increase in oculomotor distractibility on tasks that require the voluntary suppression of a saccade [26, 58, 64, 66].

One particular oculomotor task found to be sensitive to frontal lobe impairments is the anti-saccade paradigm. In this task, subjects are instructed to make saccades in the direction opposite to a briefly presented peripheral target [27, 28]. The anti-saccade paradigm was first used to study patients with unilateral frontal lobe damage by Guitton et al., (1985) who contrasted performance with that of a control group with temporal lobe ablations. Subjects with frontal lobe lesions were found to have high error rates on the anti-saccade task and made many reflexive glances to the target, while patients with temporal lobe lesions were not impaired. Similarly, Pierrot-Deseilligny et al. [64] reported high anti-saccade error rates in patients with prefrontal lesions and low error rates in patients with parietal damage. High anti-saccade error rates have also been reported in a patient with visual neglect following a right frontal lesion although these reflexive glances occurred predominantly for con-
restricted to the frontal eye fields or the parietal lobe, while cases with damage to the prefrontal cortex region while cases with damage restricted to the frontal eye fields (FEF), although this view has since been questioned following investigations of patients with more focal brain damage [64]. Pierrot-Deseilligny, et al. reported that high anti-saccade error rates were observed in patients with damage to the prefrontal cortex region while cases with damage restricted to the frontal eye fields or the parietal lobe had low error rates. Rivaud et al. [66] examined a small number of cases with frontal eye field damage and found that anti-saccade error rates were low. Frontal eye field damage did, however, result in a bilateral increase in saccade latency under conditions in which the central fixation stimulus remained on throughout the trial (overlap condition). Thus, these latter studies attributed a role in disengagement from fixation to the frontal eye fields and suppression of reflexive glances to the prefrontal cortex. Positron emission tomography (PET) studies have provided converging evidence for a role of both the frontal eye fields and dorsolateral prefrontal cortex [49, 56] in the generation of anti-saccades.

The functional basis of erroneous saccades, to, rather than away from, the target in the anti-saccade paradigm (so-called pro-saccade errors) is a further issue that remains to be resolved. Hallett and Adams (1980) proposed that pro-saccade errors in normal subjects were related to the time required to programme a saccade compared to the time to initiate a stop signal. The assumption is that the onset of the peripheral target automatically triggers the programming of a saccade to that location. In the anti-saccade condition a second cancellation signal must be programmed to cancel the reflexive glance. Hallett and Adams suggested that if on some trials the saccade programme is completed before the cancellation signal is generated, then a reflexive saccade to the target will result. A similar argument was advanced by Guittion et al. [26] to account for the high error rates observed in patients with frontal lobe damage. Specifically, they proposed that frontal lobe damage could lead to an increase in the time required to programme the cancellation signal. If the cancellation signal is sufficiently delayed then the saccade program may be initiated before the cancellation signal is produced.

Roberts et al. [67] provided an alternative explanation of anti-saccade errors by relating them to working memory processes. They noted that tasks considered to be sensitive probes of frontal lobe impairments such as the Wisconsin card sort test [44], Stroop task [59] and the anti-saccade paradigm [26] all require a prepotent response to be suppressed (e.g. reading colour rather than the word in the Stroop task). For the subject to be able to inhibit the prepotent response the task instructions must be maintained “on-line” throughout the experiment and any fluctuations in this memory component could result in errors. In experimental studies with normal human subjects Roberts et al. demonstrated that anti-saccade error rates increased bilaterally when a secondary task designed to load working memory was performed. The secondary task had no effect on reflexive saccade latency and tasks considered to have a lower working memory load did not influence anti-saccade error rates. This finding appears consistent with the working memory hypothesis that suppressing prepotent responses requires the ability to maintain one’s goals and plans on-line. A further possibility is that the working memory burden in the anti-saccade task may be specifically related to the process of holding “on-line” the spatial position of the target, suppressing a response to it and manipulating it to code the inverse response (cf. [21]).

The working memory explanation of anti-saccade impairments is appealing because responses considered to be correlates of working memory processes have been demonstrated in rhesus monkeys [25] and human subjects (e.g. [52, 62]). Furthermore, lesions of prefrontal cortex produce deficits on working memory tasks in monkey [23, 60, 71]. Frontal lesions in man also produce deficits on tasks which are thought to require working memory [51, 54, 63] but, to date, patients with large lesions have been studied and localisation of working memory deficits has not been possible.

In monkey, localisation has been far more precise and there is even evidence for regional specialisation within prefrontal cortex. One view contends that dorsolateral prefrontal cortex (DLPFC) situated in and dorsal to the principal sulcus has a special role in spatial working memory, whereas ventrolateral prefrontal cortex (VLPFC) situated ventral to the principal sulcus has a role in the non-spatial mnemonic processing of objects [23, 85]. However, one recent electrophysiological study has demonstrated spatial- and object-related responses in both DLPFC and VLPFC [65]. Indeed, some cells in both these regions appear to respond in both spatial- and object-memory tasks.

An alternative view, proposed by Petrides [60] is that there are two stages of working memory processing in the prefrontal cortex: the first stage is in VLPFC which, it is suggested, is involved in various “executive processes” [1] including those which require judgements to be made on stimuli held in short-term memory and active retrieval of information held in long-term stores. The second stage is in DLPFC which, it is proposed, has a critical role only when high-level planning involving monitoring of self- and externally-generated responses is required.

In man, it is proposed that the VLPFC resides in the inferior frontal gyrus (Brodmann’s areas 45 and 47), whereas DLPFC is located in the middle frontal gyrus (Brodmann’s areas 46 and 9). Petrides’ [60] proposes that the most severe impairments in executive processing within working memory occur after VLPFC lesions, and
that these affect both spatial and non-spatial working memory. He contends that lesions of DLPFC also lead to impairments on both spatial and non-spatial tasks but only when they require manipulation or monitoring of information in working memory. Evidence in favour of such a dichotomy has also been provided by lesion studies [71] and in PET studies using human subjects [53].

In this study we present a detailed investigation of a patient who suffered infarction of the right ventrolateral frontal lobe who had profound impairments on tasks of working memory and executive function. The patient’s reflexive saccadic eye movements were normal but he was unable to suppress reflexive glances to peripheral targets in the anti-saccade situation. By contrast, when he was asked verbally to report the required direction, or to make an anti-pointing movement with his ipsilesional hand his performance was flawless. Furthermore, a reduction in the frequency of his reflexive glances was observed in other oculomotor paradigms that involve the suppression of a response. The patient made less reflexive glances to stimuli during delayed-saccade, memory-guided saccade and maintain fixation paradigms. These findings demonstrate that high error rates on the anti-saccade paradigm may not reflect a generalised problem of “distractibility” and shows that the patient was able to voluntarily control his reflexive glances under other conditions. This is the first demonstration of working memory deficits and an impairment in the ability to generate anti-saccades in the same subject. The significance of this finding and the role of ventrolateral frontal lobe regions in working memory, distractibility and the selection of targets for saccadic eye movements is discussed.

Case description

The patient was a 62-year-old right-handed hypertensive male who presented with sudden-onset left-sided weakness. On initial examination, he was found to have a left-sided hemiplegia. Visual fields were full to confrontation but he was considered to have left-sided neglect. There was no visual extinction to confrontation, although he did show left-sided extinction on simultaneous tactile stimulation. There has been little change in the patient’s hemiparesis 14 months following stroke. However, his left-sided visual neglect slowly improved. Five weeks after stroke onset he scored only 34/60 on the Mesulam shape cancellation task [43], finding targets only on the right side of the search array; line bisection on the Rivermead line bisection task [84] and drawing of objects such as clocks was normal. Three months after stroke and at subsequent testing sessions thereafter, he scored 60/60 on the Mesulam shape cancellation task and continued to perform well on line bisection and drawing tasks. The patient’s neglect appeared to have spontaneously recovered and there was no evidence of residual neglect on subsequent formal tests, or when performing everyday activities such as eating, washing, or dressing.

A CT scan performed within 2 days of admission to hospital demonstrated a right middle cerebral artery territory infarct, largely involving the frontal lobe but extending caudally to the anterior parietal lobe. A MRI scan performed two months after stroke onset demonstrates that within the frontal lobe the infarct is confined almost entirely to the inferior frontal gyrus and ventral precentral gyrus. Figure 1 shows four coronal sections extending from the most rostral (anterior) aspect of the lesion (Fig. 1c) to the caudal (posterior) frontal lobe (Fig. 1f). Comparison with the atlases of Talairach and Tournoux [77] and Damasio [9] shows that the infarct extends along the inferior frontal gyrus from a region which corresponds to Brodmann’s areas 45 and 47, through area 44 to ventral area 6. The lesion appears largely to spare the middle frontal gyrus (including Brodmann’s areas 46 and 9) but does extend to involve the ventral aspect of this gyrus (Fig 1d and 1e). Thus the infarct is confined largely to VLPFC (Brodmann’s areas 45 and 47) and ventral premotor cortex (Brodmann’s areas 44 and 6) but does encroach on DLPFC and is also likely to involve white matter fibres passing to and from this region. It should be noted that the lesion did not encroach on the region now considered to be the frontal eye fields, which is located at the junction of the superior frontal sulcus and the precentral sulcus [57].

Neuropsychological assessment

A detailed neuropsychological assessment was performed three months after stroke concurrently with the oculomotor testing. The patient was alert and orientated in time and place and scored 20/20 on a subset of the mini mental state examination [13]. His predicted pre-morbid IQ score on the New Adult Reading Test was 110 [48]. Phonological fluency was found to be within the normal range: he produced a mean of eleven words beginning with “B” or “F” per min (25th percentile). Cognitive estimation [49] was within the normal range (10th percentile). The patient’s performance on the Stroop test [78] was poor with his score being less than the second percentile. The patient also scored poorly (0.1 percentile) on the Hayling Sentence Completion Test [4] which measures the ability to inhibit a prepotent response by completing sentences with nonsense words rather than selecting the most appropriate word to end the sentence.

Tests of memory and problem solving from the CANTAB (Cambridge Automated Neuropsychological Test Battery: Cambridge Cognition, U.K.) [14, 51] were performed 14 weeks post-stroke. The CANTAB tests were administered using a laptop computer and touch screen and included an assessment of spatial span using a test analogous to the Corsi block-tapping test [45]. In this test the subject is required to observe and subsequently recall a sequence of blocks that change colour. Each trial begins with nine white boxes presented in fixed locations on the monitor screen. Initially, two of the boxes change colour,
Fig. 1. **a**: T2-weighted magnetic resonance axial image demonstrating a right hemisphere infarct, confined largely to the frontal lobe. **b**: T1-weighted sagittal image showing the level of coronal sections numbered 1–25. **c–f**: Coronal T1-weighted images corresponding to sections 21–18 respectively in **b**. These sections demonstrate that the lesion extends along the inferior frontal gyrus but does not encroach upon the ventral aspect of the middle frontal gyrus.
one after the other, in a predetermined sequence. The end of the sequence is indicated by a tone. Subjects are then asked to point to the boxes in the order in which they changed colour. The patient obtained a spatial span score of four which is at the low end of the normal range (10th percentile). When tested one year later his spatial span score was five (50th percentile).

Spatial working memory was also assessed using the CANTAB battery. This task tests a subject’s ability to retain information regarding memory for previously visited locations. The subject is required to search through a number of coloured boxes presented on the touch screen. He is instructed to look for blue tokens by touching the boxes which “open” to reveal their contents. On any one trial only a single token is hidden in one of the boxes. Once found, the next token is “hidden” by the computer programme. The critical instruction to the subject is that once a token has been found within a particular box, that box will not be used to hide a token again. Performance is measured according to three indices, two relating to errors and a third measured as a search strategy. “Between-search” errors occur when a subject mistakenly returns to a box in which a token has been found. “Within-search” errors occur when a subject returns to a box that has been opened and shown to be empty earlier in the same trial. Owen et al. [51] have found that an efficient method for completing the task is to follow a predetermined search sequence, always starting with a particular box. Evidence for the use of a strategy of this sort is obtained by monitoring the number of search sequences that start with a novel box in the more difficult six and eight box problems. The patient was found to be impaired on the spatial working memory test and made 106 between-search errors and obtained a strategy score of 38, which equate to scores below the first percentile and in the 50th percentile, respectively [14].

A dissociation was revealed between the patient’s performance on the spatial recognition and pattern recognition sub-tests. On the spatial recognition task five squares are presented sequentially in different locations around the screen. Subsequently, in the recognition phase, each square is presented again paired with a square occupying a novel location. The subject is asked to touch the location they have previously seen a square appear in. On this test, the patient scored 13/20, which is at the low end of normal for his age and IQ ( > 10th percentile). By contrast, his performance on the pattern recognition memory test was good. In the pattern recognition task the subject is presented with a series of twelve abstract patterns on the monitor screen and is instructed to remember them. After a 5 s delay, each pattern, paired with a novel pattern, is presented in reverse order and the subject is instructed to touch the pattern they have previously seen. On this test, the patient scored 22/24, corresponding to the 30th percentile.

The patient was also found to be impaired on the tests of executive function included in the CANTAB battery. On a modified version of the Tower of London task [75] which requires the subject to move coloured balls between vertical ‘stockings’ to establish a goal position, he was able to negotiate only the most simple of problems and the test was therefore abandoned after only the first five trials. He was next assessed on the ID/ED shift test. This requires the subject to learn a series of two-alternative forced-choice discriminations using feedback provided by the computer. The task is composed of nine stages presented in the same fixed order, starting with simple discrimination and its reversal for stimuli varying in just one dimension (e.g. two different white line configurations). A second alternative dimension is then introduced (purple filled shapes) and compound discrimination and reversal are tested. Successful completion requires that the subject continues to respond to the previously relevant dimension whilst ignoring the presence of the new irrelevant dimension. At the intradimensional shift (IDS) stage, novel exemplars of each of the two dimensions are introduced and the subject must continue to respond to one of the two exemplars from the previously relevant dimension. Following another reversal, the extradimensional shift (EDS) and its reversal are presented, again using novel exemplars of each stimulus dimension. In order to succeed at this stage the subjects must shift “response set” to the previously irrelevant dimension, whilst ignoring the previously relevant dimension. This stage is akin to a change in category in the Wisconsin Card Sorting Test. The patient failed to pass the ID shift stage and his performance was below the first percentile.

Method

Oculomotor paradigms

Apparatus and procedure. Stimuli were generated by a Macintosh IICi computer using Superlab software and were displayed on a 14” colour VDU monitor. Head movements were restrained by a chin rest. Horizontal eye movements were recorded at a rate of 250 Hz using a video based eye tracker (SensoMotoric Instruments, GmbH). The subjects eye position was displayed in real time on a second VDU monitor (visible to the operator only) which enabled the experimenter to check that the subject was following the instructions on a trial by trial basis. Saccades were detected on line using a velocity (>11°/s) criterion and written to disk for later analysis.

Stimuli. The stimuli used in each paradigm were identical but the timing and instructions varied across paradigms. At the start of each trial a fixation cross (which subtended 0.5° visual angle) was presented in the centre of the screen for a random foreperiod. Targets were black squares (0.5°) which were presented randomly at eccentricities of 4° and 8° left and right of fixation along a horizontal axis. The patient was tested on a range of oculomotor paradigms performed from 3–15 months after stroke. In the final testing session a manual pointing tasks was performed in addition to the oculomotor paradigms. The different paradigms are described below and the stimulus timing sequence is shown schematically in Fig. 2.
**Reflexive saccades**

**Overlap and gap conditions.** In the overlap and gap conditions reflexive saccades were made to targets that appeared unilaterally to the left and right of the fixation cross. Each trial started with the onset of the fixation cross in the centre of the VDU screen. In the overlap condition targets appeared following a random fixation foreperiod (1000–1200 ms) and the fixation cross remained on throughout the trial. In the gap condition the fixation cross went off 200 ms before the onset of the target (+ 200 ms gap) following a random foreperiod (800–1000 ms). In both conditions targets were presented for 800 ms and an inter-trial interval of 2 s occurred between trials. The instructions were as follows: “Please look at the cross when it appears in the centre of the screen. A small square will then appear to the left or right of fixation and you should move your eyes as quickly as possible to that square. On some trials two squares will appear and you are free to move your eyes to either one”. There were 90 trials in a block (15 for each target eccentricity).

**Voluntary saccades**

**Anti-saccades.** In the anti-saccade task saccades were to be made away from the peripheral targets into the opposite (non-target) hemifield. Targets were presented unilaterally to the left and right of fixation (overlap condition). The instructions emphasised that eye movements should be made to the location opposite to the target. The instructions were as follows: “Please look at the cross when it appears in the centre of the screen. Targets will then appear to either the left or right of the cross as before. Try to move your eyes as quickly as possible in the direction away from the target, to the mirror image location”. Each block contained 60 trials (15 for each target eccentricity).

**Delayed-saccades.** In the delayed-saccade paradigm eye movements were made to peripheral targets following a fixed delay period. At the start of each trial the fixation cross appeared and targets appeared following a random fixation foreperiod (1000–1200 ms). A delay period of 1000 ms then occurred during which time eye movements had to be suppressed. The offset of fixation after the delay served as a “go” signal to initiate an eye movement. The instructions were as follows: “Please look at the cross when it appears in the centre of the screen. A small square will then appear but you should not make an eye movement until the cross goes off. The signal to move your eyes to
the target is the cross going off and so you must delay your eye movements for about 1 s”. There were 60 trials in each block.

Memory-guided saccades. The memory-guided saccade paradigm was similar to the delayed paradigm, but targets were flashed briefly for 100 ms so that saccades were directed to a remembered location. At the start of each trial the fixation cross appeared for a random fixation foreperiod (1000–1260 ms) following which targets appeared for a duration of 100 ms. A delay period of 1000 ms then occurred after which the fixation cross went off which acted as the go signal to initiate an eye movement. The instructions were as follows: “Please look at the cross when it appears in the centre of the screen. A target will then appear for a short period of time. You should make an eye movement to the remembered location only when the cross goes off. The signal to move your eyes to the target is the cross going off which means that you should delay making an eye movement for about 1 s”. There were 60 trials in each block.

Fixation task. In the fixation task the stimuli and timing sequence was identical to that used in the overlap condition and only the instructions were changed. Targets therefore appeared unilaterally left and right of the fixation cross, but the instructions were that eye movements should not be made and gaze should be directed to the cross throughout each trial. The instructions were: “Please look at the cross when it appears in the centre of the screen. A target will then appear for a short period of time. You should move your eyes to the target when it appears in the centre of the screen. Small squares will again appear to the left or right of the cross, but you must not move your eyes away from the cross. Try to look at the cross without moving your eyes and ignore the small squares”. There were 60 trials (15 for each eccentricity) in a block.

At the start of each block a minimum of 20 practice trials were given to ensure that the task instructions had been understood. The experimenter could view each eye movement on line and gave feedback on a trial by trial basis during the practice session. Feedback was not given during the experimental block which was performed only when it was clear that the patient understood the nature of the task.

Pro and anti pointing paradigms

Apparatus. The patient’s pointing movements (ipsilesional hand) were recorded using a MacReflex 3D infrared motion analysis system (50 Hz). Small hemispherical markers were placed on the patient’s wrist and on the finger nail of the index finger which were tracked by infrared video cameras. The data was stored on disk for later off-line analysis. Movement onset and offset were defined using a threshold criterion of 25 cm/s and the time taken to initiate a movement (RT) calculated. The VDU was tilted 90° backwards so that it was positioned level with the desktop for the pointing task.

Stimuli and procedure

In this condition the patient was instructed to make pointing movements (pro and anti) with the index finger of his right (ipsilesional) hand. The stimuli and timing sequence were identical to those described above for the overlap eye movement paradigm. The fixation cross appeared at the start of each trial and the patient was instructed to place the index finger on the cross. Once the patient had placed his finger on the start position the experimenter pressed a key which initiated the trial and triggered recording by the MacReflex system. This procedure was adopted to ensure that the patient’s hand was at the starting position at the beginning of each trial.

On each trial a target appeared unilaterally to the left and right of the fixation cross. In the first block the patient was asked to point to the target (pro-pointing) and in the second block he was asked point to the location opposite to the target (anti-pointing). The instructions were as follows: “Please place your finger over the fixation cross when it appears. A small square will then appear to the left or right of fixation and you should point to (away from it as quickly as possible)”. No instructions were given regarding eye movements during the pro- and anti-pointing trials and the subject was therefore free to move his eyes as desired. There were 60 trials in each block (15 trials for each target eccentricity) and the patient completed two blocks.

Results

The patient completed four testing sessions performed some 3–15 months after stroke. He had no problem in complying with the demands of oculomotor recording procedures and appeared to be co-operative and well motivated. As a result few records (<5% of total) were discarded because of artefacts resulting from gross head movements, blinks or inaccurate fixation.

Overlap, gap and anti-saccade latency

In the first eye movement session the patient made reflexive saccades in the overlap and gap conditions and completed a block of anti-saccades in a fixation overlap condition. The latency for the two target eccentricities were collapsed and the resulting mean latency is displayed in Fig. 3. It is important to note that in the anti-saccade condition the patient always made prosaccades to the target and the latency shown in Fig. 3 is, therefore, of these erroneous pro-saccade errors. Mean reflexive saccade latency in the overlap condition was 202 ms (SD = 50) for contralesional saccades and 180 ms (SD = 29) for ipsilesional saccades (t(42) = 1.6, P > 0.5, two-tailed). Saccade latency was dramatically reduced in the gap condition with a mean of 128 ms (SD = 27) for contralesional saccades and 134 ms (SD = 36) for ipsilesional saccades. A “gap effect” (overlap latency—gap latency) of 62 ms was obtained and saccade latency was significantly reduced in the gap condition compared to that in the overlap condition (t(88) = 7.68, P < 0.01, two-tailed). There was no directional asymmetry in the latency of saccades in either the gap, or anti-saccade conditions. Mean latency of pro-saccade errors made in the anti-saccade condition (162 ms) was, however, significantly faster than his reflexive saccade latency (193 ms) obtained under similar fixation overlap conditions (t(83) = 3.25, P < 0.01, two-tailed).

Overlap, gap and anti-saccade gain

The gain (saccade amplitude/target amplitude) of primary saccades made in the overlap, gap and anti-saccade conditions are shown in Fig. 4. It can be seen that the gain
Fig. 2. Mean latency of reflexive saccades made under gap and overlap conditions and for pro-saccade errors on the anti-saccade task (overlap condition). It is important to note that for anti-saccades the patient was unable to suppress making reflexive glances to the target and so there were no correct responses (see text). The data for contralesional and ipsilesional saccade directions is shown separately.

Fig. 3. Gain of reflexive saccades (gap and overlap conditions) and anti-saccades made to targets appearing in the left and right hemifields. The data for the two target eccentricities has been collapsed.

of saccades made to contralesional targets was reduced indicating a slight undershoot of the target while ipsilesional saccade gain reveals a tendency to overshoot ipsilesional target locations. In each condition the accuracy requirements of the task was low, but a consistent trend of contralesional undershoot and ipsilesional overshoot was observed. There was no suggestion, however, of multiple saccades being made to reach the contralesional target and the primary amplitude of contralesional saccades appeared normal.
Single and bilateral target latency

In one block of trials eye movements were made to targets that appeared either unilaterally left or right of fixation, or bilaterally and simultaneously in both hemifields. Mean saccade latency obtained in this block is shown in Fig. 4. The latency of saccades made to unilateral contralesional targets was 195 ms (SD = 57) and to unilateral ipsilesional targets was 217 ms (SD = 90). On bilateral target trials the patient was free to choose either one of the bilateral targets to make a saccade towards. The patient appeared to have a bias for making saccades in the ipsilesional direction and he chose the ipsilesional target on 85% of bilateral target trials. When questioned he reported seeing both bilateral targets and so the ipsilesional bias cannot be attributed to contralesional extinction of targets presented in the left hemifield. The latency of ipsilesional saccades from bilateral trials was 314 ms (SD = 117) which is 97 ms greater than for ipsilesional saccades made to unilateral targets ($t(37) = 3.3, P < 0.01$, two-tailed).

Anti-saccade error rates

The most dramatic finding observed during this series of experiments was that the patient was unable to suppress making reflexive saccades to the target in the anti-saccade paradigm (Table 1). During the first session of anti-saccades (12 weeks post lesion) it was found that the patient made reflexive glances to the target (pro-saccade errors) on every trial. An examination of the eye movement records showed that the pro-saccade errors were typically followed by a secondary corrective saccade made into the opposite hemifield to the peripheral stimulus. The percentage of these secondary corrections is also shown in Table 1. (N.B. The frequency of secondary corrections may be an underestimate as corrections made over 1 s following target onset would not be recorded.) In the first session secondary corrections were made on the majority of trials in which a target appeared in the contralesional hemifield but fewer corrections were made with ipsilesional targets. In the following sessions secondary corrections were observed on almost every trial following ipsilesional and contralesional targets. The presence of these secondary corrective saccades shows that the patient had understood the requirements of the anti-saccade task and was actually motivated to perform correctly. His deficit appears, therefore, to reflect an inability to prevent reflexive glances to peripheral stimuli.

As the patient appeared unable to perform the anti-saccade task correctly a number of different steps were taken following the first testing session to ensure that he had understood the task instructions. Prior to the second session of anti-saccades (13 weeks post lesion) the patient was asked to verbally report the direction in which eye movements were to be made. He was found to be able to verbally report the correct direction (i.e. that opposite to the target onset) on almost every trial. Eye movements were then recorded and he again made pro-saccade errors on every trial. Prior to the third anti-saccade session (14 weeks post lesion) the patient was asked to point (using

![Saccade direction](image-url)

Fig. 5. Mean latency of reflexive saccades observed when targets appeared unilaterally left or right of fixation, or when targets appeared bilaterally and simultaneously in both hemifields. The patient typically made saccades to the target in the right visual field under bilateral target conditions. A fixation overlap condition was used.
Table 1. The percentage of pro-saccade errors and secondary corrective saccades observed in the anti-saccade paradigm on a number of separate testing sessions performed 12–60 weeks post stroke. The number of weeks which had elapsed following the stroke is shown in parentheses

| Testing session | Prosaccade errors | Secondary corrections | | | |
|-----------------|-------------------|-----------------------|------------------|---------------|
|                 | Target hemi-field | Contralesional | Ipsilesional | Contralesional | Ipsilesional |
| Session 1 (12 weeks) | 100 | 100 | 85 | 60 |
| Session 2 (13 weeks) | 100 | 100 | 87 | 100 |
| Session 3 (14 weeks) | 100 | 100 | 100 | 100 |
| Session 4 (60 weeks) | 100 | 100 | 90 | 96 |

the index finger of his right hand) in the anti-direction. As the pointing movements made it difficult to record eye movements the experimenter observed the direction of eye movements while standing behind the VDU screen. This technique has been shown to be a reasonably reliable way of assessing eye movements [40]. The patient made correct anti-pointing movements on every trial. Observation of his eye movements indicated that pro-saccades were first made to the target (pro-saccade error) which were then followed by secondary corrective saccades before the anti-pointing movement was initiated. Eye movements were recorded on a separate block of anti-saccades and the patient again made pro-saccade errors on every trial.

Anti-saccades and anti-pointing (1 year post stroke)

A final session of anti-saccades and anti-pointing was performed over one year (60 weeks) post stroke. The anti-saccade error rates are shown in Table 1 and the patient made bi-directional pro-saccade errors on 100% of trials. Secondary, corrective saccades were observed on the majority of trials indicating that he had understood the nature of the task. The patient’s ability to suppress reflexive glances in the anti-saccade condition had not spontaneously improved. The patient’s pro- and anti-pointing movements were also recorded on the same day using the MacRelex system. In contrast to his poor performance on the anti-saccade task the patient performed the anti-pointing task without error. The reaction times to initiate the pro- and anti-pointing movements are shown in Fig. 6. The latency of secondary corrective saccades obtained (from the separate block of anti-saccades) are also shown and it can be seen that the anti-pointing movements were initiated after secondary corrective saccades (in the anti-direction) had been made. The patient made no errors in the anti-pointing task showing that he understood the nature of the task.

Memory-guided, delayed saccades and maintain fixation conditions

Error rates. The patient’s eye movements were recorded in the memory-guided, delayed-saccade and maintain fixation paradigms, a further block of anti-saccades was also performed to provide a comparable measure of the patient’s performance on that day. In the memory-guided and delayed saccade conditions eye movements made to the target during the delay period were classified as errors. In the maintain fixation task any saccades made to the targets were classed as errors. The error rates for each condition are shown in Table 2. The patient’s ability to inhibit his reflexive saccades can be seen to vary across conditions, the lowest error rates being observed in the maintain fixation tasks and the greatest number in the anti-saccade condition. A reduction in error rates is also shown for the memory-guided and delayed-saccade paradigms compared to the anti-saccade condition.

A directional asymmetry in the patient’s error rates is revealed in the memory-guided, delayed-saccade and fixation task with more saccades being made to targets in the contralesional hemi-field. The frequency of ipsilesional errors was especially low (7%) in the fixation task. It is important to realise that the same stimulus sequence was displayed in the anti-saccade and maintain fixation tasks and the only difference between the two conditions were the instructions. The frequency of pro-saccade errors in the block of anti-saccades was significantly greater than was observed in the memory-guided ($\chi^2(1) = 32.5, P < 0.01$), delayed ($\chi^2(1) = 105, P < 0.01$), and maintain fixation ($\chi^2(1) = 113, P < 0.01$) conditions. Reflexive saccade error rates were significantly greater in the memory-guided condition than in the maintain fixation task ($\chi^2(1) = 9.3, P < 0.01$), but there was no difference between error rates in the delayed-saccade and fixation task ($\chi^2(1) = 1.65, P > 0.05$).

Saccade latency

The mean latency of erroneous saccades made in the delayed-saccade, memory-guided saccade, anti-saccade and maintain fixation task are shown in Fig. 7a. The latency of pro-saccade errors made on the anti-saccade task appears shorter than the latency of erroneous saccades made during the memory-guided paradigm and fixation task. The longest latency was observed for errors
Fig. 6. Mean reaction times and error bars (1 SEM) for pro- and anti-pointing responses made in the ipsilesional and contralesional direction. The mean latency of secondary corrective saccadic eye movements made in a separate block of anti-saccades are also shown.

Table 2. Percentages of errors made to contralesional and ipsilesional stimuli in the anti-saccade, delayed-saccade, memory-guided saccade and maintain fixation tasks. All tasks were performed in a single testing session executed 14 weeks after stroke.

<table>
<thead>
<tr>
<th>Saccade paradigm</th>
<th>Target hemifield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contralesional</td>
</tr>
<tr>
<td>Anti-saccade</td>
<td>100</td>
</tr>
<tr>
<td>Memory-guided</td>
<td>71</td>
</tr>
<tr>
<td>Delayed-saccade</td>
<td>50</td>
</tr>
<tr>
<td>Fixation task</td>
<td>50</td>
</tr>
</tbody>
</table>

made in the delayed-saccade paradigm with the maximum latency being observed for ipsilesional erroneous saccades. The latency of correct responses made in the delayed and memory-guided saccade condition is shown in Fig. 7b. It can be seen that the latency of correct saccades was much greater than was obtained on the simple reflexive saccade paradigms. There was also a decrease in the latency of contralesional saccades made in the memory-guided paradigm, but the small numbers of correct responses means that statistical comparisons could not be performed.

Discussion

In this study, we have described a patient with infarction of the right frontal lobe and impairment of spatial working memory, as assessed on the Cambridge Automated Neuropsychological Test Battery (CANTAB). The patient also demonstrated a dramatic impairment on the anti-saccade task, being unable to suppress reflexive glances to peripheral targets. These “pro-saccade errors” were made with equal frequency into both hemifields and were typically followed by a secondary corrective saccade. The presence of corrective saccades indicates that the patient understood the nature of the anti-saccade task and this impression was supported by his ability to verbally report the correct “anti” direction and his perfect performance when making anti-pointing responses. In contrast to his poor performance on the anti-saccade task the patient was able to inhibit, to a variable degree, reflexive glances in delayed, memory-guided and fixation paradigms which also require voluntary suppression of eye movement. Under these conditions he still showed a tendency to make more reflexive glances to contralesional stimuli. The greatest improvement in his performance was observed on the maintain fixation task [58] and it is important to note that the only difference between this condition and the anti-saccade task was the instructions given.
On the basis of his poor performance on the anti-saccade task this subject appears to be an example of a patient who is "confined by the fatality of a reflex" (cf. Holmes, 1938 [32]). On closer examination it is apparent, however, that this is an oversimplification of his distractibility. He was able to maintain fixation on a central cross for more than 1 s in the reflexive saccade paradigms and was able to suppress, to a variable degree, reflexive glances in the memory-guided, delayed and fixation paradigms. Although his performance under these conditions was clearly not normal (because of the number of contralesional errors) he was able to suppress making reflexive
glances to the majority of ipsilesional stimuli. His deficit therefore does not appear to be a loss of voluntary control over his ability to generate saccades, nor does it appear to be a generalised problem of heightened distractibility. For if the patient’s frontal damage had resulted in a complete loss of voluntary control over his eye movements then he would presumably make saccades following any movement, change in illumination, or novel stimulus in his environment. According to this view his saccades would be driven under “bottom-up” control and it is apparent that this is not an adequate description of his performance as he does not complain of problems of fixation (during reading for example) and appears able to function normally in his environment.

Mechanisms underlying pro-saccade error rates

The striking impairment observed in the present study was the patient’s complete inability to suppress reflexive glances in the anti-saccade paradigm. Normal subjects are also known to make some errors in the anti-saccade task and Hallett [27] reported error rates in the range of 7–10%. Hallett’s explanation of anti-saccade errors was based on the time course of processes involved in programming a saccade and those involved in the generation of a cancellation signal. If the saccade programme is completed before the cancellation signal then a reflexive saccade to the target would result. Guitton et al. [26] attributed the high anti-saccade error rates observed in frontal lobe patients to an increase in the time to generate this cancellation signal. If the time required to programme a reflexive saccade to the target is normal but the cancellation signal is delayed then pro-saccade errors would result. The bilateral error rates observed in some of their cases on the anti-saccade task suggests that unilateral frontal lobe damage increases the time required to generate the cancellation signal so that reflexive saccades are never cancelled. This account could also be applied to the performance of our patient who made bidirectional pro-saccades on every trial in the anti-saccade task.

The delayed cancellation signal account cannot, however, easily account for our patient’s performance on the delayed-saccade, memory-guided saccade and maintain fixation paradigms. Under these conditions his performance improved, but in contrast to the anti-saccade task, an asymmetry in error rates was observed with most errors occurring for contralesional stimuli. In the maintain fixation task, for example, he made reflexive glances to contralesional stimuli on 50% of trials, but on only 7% of trials with ipsilesional stimuli. One way in which the delayed cancellation signal could account for this asymmetry in error rates would be if there was a difference in the latency of contralesional and ipsilesional saccades. An increase in the time taken to program ipsilesional saccades would enable more time for a cancellation signal to be generated enabling more ipsilesional reflexive glances to be vetoed. The latency of erroneous saccades is shown in Fig. 7a and although ipsilesional saccade latency is increased for the delayed-saccade task there is no difference, however, in ipsilesional and contralesional-saccade latency in the memory guided and maintain fixation tasks. To account for the reduction in ipsilesional errors on these tasks further assumptions, e.g. the time required to generate a cancellation signal following a contralesional stimulus being greater than for ipsilesional stimuli, would need to be incorporated. Thus, although the delayed cancellation signal hypothesis is appealing it does not provide a parsimonious account of the improvement in the patient’s ability to suppress his reflexive glances on the delayed-saccade, memory-guided saccade and fixation tasks without incorporating additional assumptions.

A different account of anti-saccade errors has been proposed by Henik et al. [31], based on their findings of impairments in exogenous and endogenous saccades in patients with lesions that included the frontal eye fields. They proposed that FEF damage leads to unilateral disinhibition of ipsilesional midbrain structures (e.g. superior colliculus) and that this, in turn, facilitates reflexive glances to contralesional stimuli. Furthermore, anti-saccades made in the contralesional direction following an ipsilesional cue may be impaired as they would be generated by endogenous control processes in the damaged hemisphere. Although appealing, Henik et al.’s account of anti-saccade errors does not seem entirely compatible with the performance of our patient on the different oculomotor paradigms. Firstly, the patient’s lesion did not extend into the region of the precentral sulcus implicated in functional imaging studies as the location human frontal eye fields [57]. Secondly, the pro-saccade errors made by our patient occurred equally frequently in both directions, which is consistent with bidirectional errors observed in other cases [26, 64]. A unilateral disinhibition of midbrain oculomotor structures would also be expected to produce an asymmetry in the latency of reflexive saccades. There was no such evidence of an asymmetry in the latency of reflexive saccades made by our case. Furthermore, under conditions where stimuli appeared bilaterally and simultaneously in both hemifields our patient showed a bias for making saccades to the ipsilesional and not the contralesional stimulus. Thus, our patient’s performance seems inconsistent with the idea of disinhibition of ipsilesional midbrain structures producing a hyperorienting response to contralesional stimuli.

Roberts et al. [67] suggested a different account of anti-saccade distractibility based on a deficit of working memory processes. They noted that tasks which are known to be sensitive indicators of frontal lobe damage such as the Stroop test [59], Wisconsin Card Sort [44] and the anti-saccade paradigm [26] share some common features in that the correct response is the opposite to a strong prepotent tendency (e.g. looking at the target in the anti-saccade task). To perform the task correctly subjects must maintain the instructions in memory and apply
them at the appropriate time. Roberts et al. examined the relationship between working memory and anti-saccade errors in normal human subjects using a dual task paradigm. A secondary arithmetic task which was thought to have a high working memory load increased anti-saccade errors, while a secondary shadowing task with a lower memory requirement had less influence on error rates. The authors argued that this indicates that a working memory deficit may contribute to anti-saccade errors. A further explanation, suggested by Roberts et al., is that a decrease in vigilance levels could also account for the differential anti-saccade error rates on their task, although they concluded that their data did not allow them to choose between these two alternatives.

In the present study, our patient’s distractibility error rates varied across the different oculomotor paradigms. Although the patient could not suppress reflexive glances to the target in the anti-saccade task he could do so to a variable degree in the delayed, memory-guided and maintain fixation paradigms. It is possible to argue that the memory load for recollection of instructions in each paradigm was similar and it would therefore be difficult to see how a deficit of working memory for maintaining task instructions on-line could have selectively impaired the patient’s ability to suppress saccades on the anti-saccade task without also impairing his ability to do so on the maintain fixation paradigm. Alternatively, it is possible to argue that the working memory demands are not simply related to keeping the instructions “in mind” but are intricately involved in suppression of prepotent responses [23]. The anti-saccade task requires the subject to hold “on-line” the position of the target, suppressing a response to it and manipulating it to code the inverse response. If an erroneous “pro-saccade” is generated the subject may monitor the error and generate a secondary corrective saccade.

By contrast, the maintain fixation task may produce minimal burdens on working memory because the only requirement is to suppress responses to novel stimuli and there is no active manipulation of information held “on-line”. Between the extremes of the anti-saccade and the fixation task lie the delayed, memory-guided and maintain fixation paradigms. The delayed task is very similar in working memory requirements to the fixation task except that a reflexive saccade to the continuously lit target has to be withheld for a period of time. The memory-guided paradigm may require more active working memory processes since the subject not only has to withhold a saccade for a fixed time but, because the target is briefly flashed, also has to hold “on-line” a representation of its location. It may be argued that this variation in working memory demand is one explanation for the decline in overall error rate from the anti-saccade task (100%), through memory-guided (58%), delayed (38%) and fixation (29%) paradigms. However, it is less easy to explain the selective increase in contralesional errors observed in the delayed, memory-guided and fixation conditions on this basis.

Funahashi et al. [21] have presented evidence to suggest that neurons in monkey DLPFC are not only involved in holding “on-line” the position of a remembered target but also respond when suppression of a response to that target is required in a delayed anti-saccade task. If suppression of responses to stimuli is a key feature of working memory then it is possible to argue that the generation of a cancellation signal is also a function of working memory processes. Since neurons in DLPFC appear predominantly to represent target locations in the contralateral visual field [18], lesions to this region may lead to an impairment in the ability swiftly to generate a cancellation signal and to suppress responses to stimuli presented there. This may account for the contralesional errors on the memory- and delayed-saccade tasks in our patient, but it fails to explain the bilateral failure on the anti-saccade task. It also does not provide an adequate explanation for his perfect performance on the anti-pointing task, although the selective deficit on the anti-saccade paradigm with preserved anti-pointing indicates that distractibility is modality specific. Like the delayed cancellation hypothesis, the working memory account does not provide a simple explanation for our patient’s performance on all the paradigms he was tested on.

The present study has shown that the demands for suppressing a prepotent response may vary across the different oculomotor paradigms used. There are subtle differences in the nature of these tasks which could account for these differences. For example, the signal to initiate a response in the anti-saccade task is the onset of a peripheral stimulus, while in the delayed and memory-guided saccade paradigms the initiate signal is the offset of the fixation stimulus located at the fovea. These apparently minor differences in the oculomotor paradigms had dramatic effects on error rates and we suggest that work should be performed to investigate some of the factors that influence error rates in normal subjects. The prior offset of fixation is known to reduce saccade latency in normal subjects [10, 38, 72, 81] and would according to the cancellation signal hypothesis be expected to increase anti-saccade error rates. Concomitantly, the onset of fixation is known to increase saccade latency [68, 69, 79, 82] and would therefore be expected to reduce error rates. The delayed cancellation signal hypothesis of error rates in patients with frontal lobe lesions may also be tested using the so-called “countermanding task” [29, 30] which attempts to probe the time required to generate a cancellation signal once a saccade has been cued.

**Working memory and prefrontal cortex**

What is the significance of the observations we have made in our patient for the role of human prefrontal cortex in working memory? Investigations of monkey prefrontal cortex have led to the theory that DLPFC has a special role in spatial working memory, while VLPFC has a role in the non-spatial mnemonic processing of objects [23, 85]. An alternative account [61] proposes that
the spatial- and non-spatial distinction fails to capture the difference between these areas. It suggests instead that there are two stages of working memory in prefrontal cortex, the first in VLPFC and the second in DLPFC.

VLPFC, it is proposed, is involved in various “executive processes” [2] including those which require judgements to be made on stimuli held in short-term memory and active retrieval of information from long-term stores. DLPFC, it is suggested, has a critical role only when high-level planning involving monitoring of self- and externally-generated responses is required.

The human homologue of VLPFC is considered to reside in Brodmann’s areas 45 and 47 of the inferior frontal gyrus, whereas DLPFC is thought to be located in Brodmann’s areas 46 and 9 of the middle frontal gyrus. Although it has been demonstrated that working memory deficits occur following frontal lesions it has proven difficult to localise precisely the regions that are involved in these functions. PET and functional MRI (fMRI) have been more useful. A number of studies have demonstrated activation of either DLPFC [3, 30–31] or VLPFC [37] on spatial working memory tasks. Owen et al. [53] have presented PET data in support of the two-stage model of prefrontal cortex in humans. They demonstrated differential activation of DLPFC and VLPFC on spatial tasks, depending upon the demands of the task and the executive processes that are required. It is of particular interest that they found preferential activation of right VLPFC on a spatial span task. By contrast, they report right DLPFC and bilateral VLPFC activation on a spatial working memory task like the CANTAB paradigm we used in this study. A recent meta-analysis of functional imaging studies has demonstrated that activation of dorsolateral frontal regions has consistently been found with both spatial and non-spatial working memory tasks [55]. This provides further support for the view that the lateral frontal cortex is organised according to the nature of the process and not according to the nature of the material [60, 61].

The patient described in the present study has a right hemisphere lesion largely of VLPFC (but encroaching upon DLPFC and its connections) and extending into Brodmann’s areas 6 and 44. He was severely impaired on the CANTAB tests of spatial working memory and his performance on the spatial recognition and spatial span test were poor. By comparison, his performance on the pattern recognition subtest was good. His selective impairment on the spatial memory tests is consistent with the functional imaging studies which have implicated both ventral and dorsal prefrontal cortex in spatial working memory. This apparent dissociation between poor performance on the spatial subsets and spared performance on the pattern recognition test is compatible with Petrides’ process model of working memory [61]. Petrides emphasises the distinction between separate processes of active and automatic retrieval in working memory. Active retrieval involves selection and comparison of stimuli held in short- and long-term memory while automatic retrieval involves the triggering of a stored representation. Only the process of active retrieval is thought to require ventrolateral frontal cortex. Our patient performed well on the pattern recognition test which could be explained by automatic retrieval processes being unaffected by the lesion to ventrolateral cortex. Furthermore, his severe deficit on the spatial working memory and poor performance on spatial recognition may reflect impairments to the active retrieval process where retrieval of information is guided by the subjects conscious effort based on specific instructions.

Our patient’s lesion was sufficient also to disrupt the generation of anti-saccades and, to a lesser extent, memory-guided saccades. Sweeney et al. [76] have used PET to study both these types of eye movement and found DLPFC, as well as parietal, activation in both conditions. Our patient’s performance suggests damage to right prefrontal cortex is sufficient to disrupt these types of movement, although not to prevent the generation of corrective secondary movements on the anti-saccade task. Thus, the functional impairments and location of the lesion in the patient we have presented supports some of the claims regarding the localisation of spatial working memory processes and the control of anti- and memory-guided saccades that have arisen from imaging studies.

Until recently, imaging studies have not studied the temporal dynamics of working memory and it has, therefore, proved difficult to distinguish between brain regions that are active only transiently following image presentation from those in which activity is sustained. Two recent fMRI studies have demonstrated sustained prefrontal activation when subjects perform non-spatial working memory tasks [6, 8]. In these investigations, subjects viewed a series of letters or faces presented sequentially at one spatial location. Sustained activity was recorded in DLPFC in both tasks and also in VLPFC in the face task. One other ventrolateral frontal area, caudal (posterior) to VLPFC, was activated bilaterally in both tasks. This region corresponds to Brodmann’s area 44 which is part of Broca’s area in the left hemisphere. The lesion of the patient we have presented also extends to involve the homologue of Broca’s area in the right hemisphere. The role of this region in working memory is unclear [24] but it is interesting that it has also been implicated in attention.

**Role of right ventrolateral frontal lobe**

A number of different types of inattention—spatial and non-spatial—have been described following right frontal lesions. A deficit in vigilance, or the ability to sustain attention, has been reported [70, 83], and PET imaging [56] has demonstrated correlates of sustained attention in Brodmann’s area 44, as well as DLPFC. Lesions of the right ventrolateral frontal lobe, centred on area 44, also result in contralateral visual neglect [33, 35]. It has been suggested that these frontal patients may suffer an
impairment of selecting targets and there is evidence, at least in one case, that ipsilesional non-relevant stimuli (distractors) impede search for contralesional target items [34]. Frontal neglect patients have also recently been found to suffer from a non-spatial disorder of directing attention over time when tested on a rapid serial visual presentation (RSVP) paradigm [36]. This impairment does not appear to be due to difficulty in sustaining attention.

The patient reported here also had contralesional visual neglect at the time of admission. This improved and on standard clinical tests it appeared to have resolved by the time his eye movements and his performance on the CANTAB battery were assessed. On bilateral simultaneous presentation of two targets he nevertheless demonstrated a bias to direct his eyes to the ipsilesional target, even though he could correctly report the presence of both stimuli. This suggests a residual bias to select ipsilesional stimuli in preference to contralesional ones. The patients ipsilesional saccadic latency was dramatically increased under bilateral target conditions and the magnitude of this increase was much greater than is observed in normal subjects [79, 81]. His performance also contrasts with that of patients with unilateral neglect following parietal damage who show no increase in latency with bilateral targets [80]. This suggests that frontal lobe damage may result in a problem of target selection whilst parietal neglect is associated with a hyper-ipsilesional orienting, perhaps reflecting the loss of a normal inhibitory mechanism.

Is there a functional relationship between inability to perform anti-saccades, visual inattention and impairment on working memory tasks? Or does this association arise simply from the close proximity of regions which subserve these functions? Coull et al. [7] have attempted to investigate the relationship between sustained attention and working memory using PET. They report a right ventrolateral frontal focus of activation (centred on Brodmann’s area 44) when subjects were tested on a non-spatial RSVP paradigm which is considered to tax working memory, as well as selective and sustained attention. When the investigators compared activations with those on a sustained attention task, they found the right ventrolateral activation was no longer apparent. One conclusion of these findings is that the right ventrolateral frontal cortex is specialised for sustained or selective attention, and that there may be a very close functional connection between target selection (for example, for reflexive- or anti-saccade control) and working memory processes. Clearly, our understanding of the functional relationship between attention and working memory is in its infancy.

In summary, we have presented a man with an infarct largely confined to the right inferior frontal gyrus who was unable to suppress his reflexive glances on the anti-saccade task. One explanation of his anti-saccade deficit is that it reflects a delay in the production of a cancellation signal that inhibits eye movement. Although this account is appealing it does not easily explain his deficit on other tasks where he made more reflexive glances to stimuli in the contralesional visual field. Furthermore, the finding that the patient was able to suppress saccades under certain situations shows that his problem was not simply one of generalised distractibility. The patient was also impaired on the CANTAB spatial working memory test. Although some investigators have suggested a direct relationship between working memory and suppression of responses on the anti-saccade task, there is no simple working memory account that explains all our patient’s oculomotor behaviour. It is suggested that future studies should investigate more closely the role of both cancellation signals and working memory processes in the control of saccadic eye movements.

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