The neural consequences of conflict between intention and the senses

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Summary

Normal sensorimotor states involve integration of intention, action and sensory feedback. An example is the congruence between motor intention and sensory experience (both proprioceptive and visual) when we move a limb through space. Such goal-directed action necessitates a mechanism that monitors sensorimotor inputs to ensure that motor outputs are congruent with current intentions. Monitoring in this sense is usually implicit and automatic but becomes conscious whenever there is a mismatch between expected and realized sensorimotor states. To investigate how the latter type of monitoring is achieved we conducted three fully factorial functional neuroimaging experiments using PET measures of relative regional cerebral blood flow with healthy volunteers. In the first experiment subjects were asked to perform Luria's bimanual co-ordination task which involves either in-phase (conditions 1 and 3) or out-of-phase (conditions 2 and 4) bimanual movements (factor one), while looking towards their left hand. In half of the conditions (conditions 3 and 4) a mirror was used that altered visual feedback (factor two) by replacing their left hand with the mirror image of their right hand. Hence (in the critical condition 4) subjects saw in-phase movements despite performing out-of-phase movements. This mismatch between intention, proprioception and visual feedback engendered cognitive conflict. The main effect of out-of-phase movements was associated with increased neural activity in posterior parietal cortex (PPC) bilaterally [Brodmann area (BA) 40, extending into BA 7] and dorsolateral prefrontal cortex (DLPFC) bilaterally (BA 9/46). The main effect of the mirror showed increased neural activity in right DLPFC (BA 9/46) and right superior PPC (BA 7) only. Analysis of the critical interaction revealed that the mismatch condition led to a specific activation in the right DLPFC alone (BA 9/46). Study 2, using an identical experimental set-up but manipulating visual feedback from the right hand (instead of the left), subsequently demonstrated that this right DLPFC activation was independent of the hand attended. Finally, study 3 removed the motor intentional component by moving the subjects' hand passively, thus engendering a mismatch between proprioception and vision only. Activation in the right lateral prefrontal cortex was now more ventral than in studies 1 or 2 (BA 44/45). A direct comparison of studies 1 and 3 (which both manipulated visual feedback from the left hand) confirmed that a ventral right lateral prefrontal region is primarily activated by discrepancies between signals from sensory systems, while a more dorsal area in right lateral prefrontal cortex is activated when actions must be maintained in the face of a conflict between intention and sensory outcome.

Keywords: prefrontal cortex; sensorimotor integration; PET; monitoring; Luria's bimanual co-ordination task

Abbreviations: BA = Brodmann area; DLPFC = dorsolateral prefrontal cortex; PPC = posterior parietal cortex; rCBF = regional cerebral blood flow; SPM = statistical parametric map

Introduction

To achieve goals we continually modify our behaviour on the basis of current perceptual experience. This flexibility is a central facet of higher order cognition. Keeping track of congruence between our intentions and their sensorimotor consequences also enables us to distinguish between events produced by our own actions or by the environment acting upon us (Frith, 1992). These integrative processes require monitoring of internal representations in relation to incoming sensorimotor feedback (von Helmholtz, 1867; von Holst and Mittelstaedt, 1950; Wolpert *et al.*, 1995; Miall and Wolpert, 1996; Jeannerod, 1997). The match between intended and realized movements is usually achieved automatically without awareness of the component processes (Jeannerod, 1997). By contrast, novel tasks or situations which produce conflict or incongruence between intentions and sensorimotor consequences, or between sensory modalities, involve awareness of sensory feedback and conscious control of action (Wolpert *et al.*, 1995). Such explicit monitoring then becomes a crucial constituent in the governance of our conscious behaviour and can be seen as a process whereby an internal model of self-generated action is checked against an actual state of affairs, and updated accordingly (Picton and Stuss, 1994; Wolpert *et al.*, 1995; Jeannerod, 1997).

Neurophysiological evidence implicates prefrontal cortex as a key structure of this 'perception–action cycle' with respect to active monitoring (Fuster, 1993). Neuropsychology provides complementary evidence where frontal damage leads to gross deficits in the planning and regulation of behaviour; in particular, patients with prefrontal cortex damage have problems with the flexible maintenance of appropriate behaviour in novel or conflicting situations (Luria, 1966, 1969; Shallice, 1988; Stuss *et al.*, 1994*b*; Knight and Grabowecky, 1995; Shallice and Burgess, 1996; Stuss *et al.*, 1997).

Here we describe three consecutively performed functional neuroimaging studies in normal volunteers, using PET, that address which brain regions are involved in actively monitoring the match between current motor intention, sensory feedback and sensorimotor integration. Study 1 demanded maintenance of paced hand movements in the context of visual feedback which could be misleading (Fig. 1). The task (Luria's bimanual co-ordination task) required subjects to open and close their hands repetitively, either in-phase (conditions 1 and 3) or out-of-phase (conditions 2 and 4) with each other (factor one, *movement type*), while looking towards their left hand in all conditions. This task has classically been used to assess the effects of prefrontal damage in neurological patients. In half of the conditions (conditions 3 and 4) a mirror was used to manipulate visual feedback from their left hand (factor two, *visual feedback*), by showing a reflection of the right hand in the place of the left hand (non-veridical visual feedback), so that in the critical condition 4 visual feedback was rendered non-veridical *and* incongruent: both the volunteer's intention and the

proprioceptive feedback indicated out-of-phase hand movements, while the visual feedback (i.e. the mirror image reflecting the right hand) showed in-phase hand movements. Accordingly, this condition produces cognitive conflict. This conflict refers to the subjective feeling which results from a mismatch between vision and both intention and/or another sensory feedback (Rock and Victor, 1964; Ramachandran and Rogers-Ramachandran, 1996).

To address potential ambiguities in the interpretation of study 1, two further experiments were subsequently carried out. Study 2 was performed to control for laterality effects of which hand was observed, by using an identical (fully factorial) experimental set-up, except that the mirror was now reversed and therefore the mirror image of the subjects' left hand replaced the subjects' right hand (in the non-veridical visual feedback conditions 3 and 4). Throughout all conditions subjects now attended to their right hand (or in conditions 3 and 4 the mirror image of their left hand replacing it). In the critical condition, this again resulted in a cognitive conflict situation where visual feedback was non-veridical and incongruent with proprioception and intention: both the volunteers' intention and the proprioceptive feedback indicated out-of-phase hand movements, while the visual feedback (i.e. the mirror image reflecting the left hand) showed in-phase hand movements.

Activations specifically elicited by the critical conditions of studies 1 and 2 (i.e. condition 4 with non-veridical, incongruent visual feedback) might result from monitoring a mismatch between an intended act and visual feedback while maintaining the correct action throughout, or alternatively might simply reflect a mismatch between vision and proprioception. A third study was finally performed to distinguish between these two possibilities. In another fully factorial experiment, subjects rested their hands on bars that were *passively* moved (factor 1) either in-phase (conditions 1 and 3) or out-of-phase (conditions 2 and 4). This removed the intentional motor (manual) component of the task while visual and proprioceptive feedback was maintained. As in the previous experiments, visual feedback (factor 2) was again manipulated using a mirror in conditions 3 and 4 to render visual feedback non-veridical. As in study 1, subjects were asked to observe their left hand (or the mirror image of their right hand replacing it on the left) in all conditions. In the critical condition, the mirror image of their right hand showed in-phase (passive) movements when out-of-phase (passive) movements were performed by the machine. Accordingly, in condition 4, visual feedback was non-veridical *and* incongruent with proprioception. Again, this critical condition produced subjective conflict but the crucial point of study 3 is that the non-veridical incongruent visual feedback was now produced without subjects making self-generated movements of the hands. Hence, in the critical condition only vision and proprioception conflicted, not vision and intention.
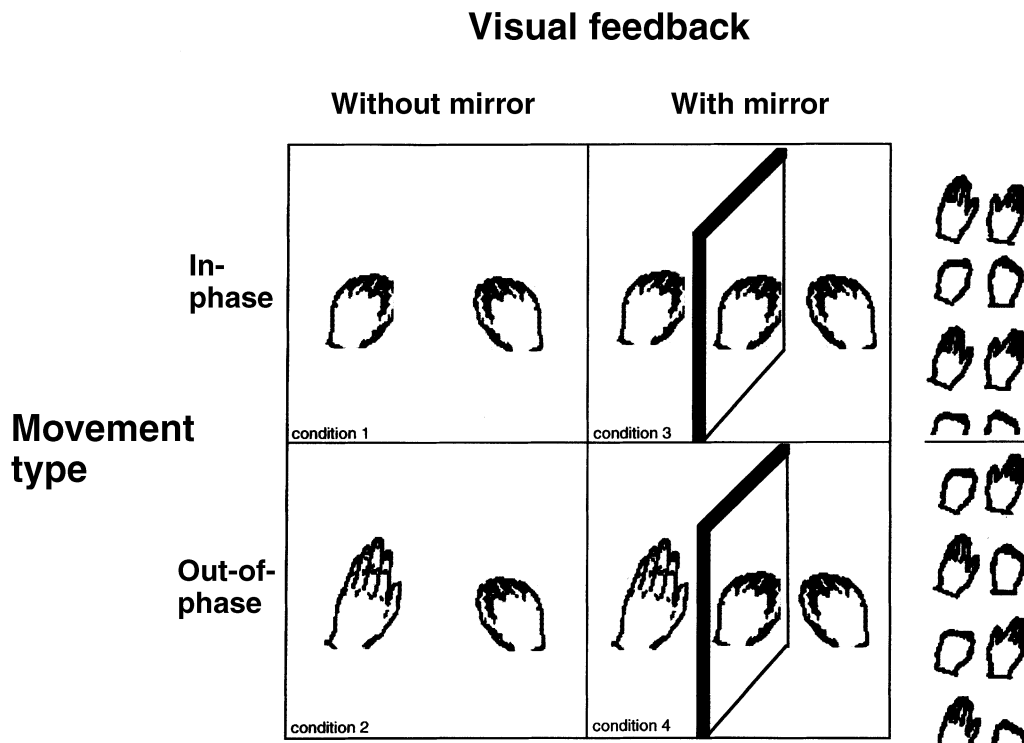
Visual feedback

Fig. 1 Experimental design of study 1 (bimanual *active* movement task). Each box represents an experimental condition. Columns 1 and 2 show the conditions without and with the mirror (visual feedback). Rows 1 and 2 show the conditions with in-phase and out-of-phase bimanual *active* movements (movement type). For each of the bimanual *active* movement conditions, we show a representative sequence of hand positions (on the right hand side of the figure). In the without-mirror conditions, subjects looked at their left hand. In the with-mirror conditions, the mirror obscured the real left hand, and subjects accordingly looked at the mirror reflection of their right hand (on the left). Thus, in the out-of-phase condition with the mirror only, there was an incongruence between intention, out-of-phase proprioceptive and in-phase visual feedback. In study 2, the design was identical with the exception that subjects viewed either their real right hand or the mirror reflection of their left hand.

While studies 1 and 2 (in the critical conflict condition 4) emphasize the intentional component of monitoring (in that subjects continued to act against the incongruence of vision with respect to intention and proprioception), study 3 stresses (again in the critical conflict condition 4) receptive aspects of monitoring (attending to incongruence between visual and proprioceptive feedback). Finally, direct comparison of the three studies should reveal whether there are areas differentially activated by the specific monitoring demands.

Material and methods
Subjects
A total of 23 subjects were studied (study 1, $n = 10$; study 2, $n = 6$; study 3, $n = 7$). All subjects were healthy right-handed male volunteers (aged 20–63 years) with no history, current or past, of neurological or psychiatric illness. Informed consent was obtained from all subjects prior to participation. The study involved administration of 4.5 mSv effective dose equivalent of radioactivity per subject. Permission to administer radioactivity was obtained from the ARSAC (Administration of Radioactive Substances Advisory Committee of the Department of Health of the UK). The study was approved by the local ethics committee of the

National Hospital for Neurology and Neurosurgery (London, UK).

Study 1
In our first study we measured brain activity while volunteers performed Luria's bimanual co-ordination tasks (Fig. 1), traditionally used to assess the effects of prefrontal damage in neurological patients (Luria, 1969). In a fully factorial design, subjects were instructed to make simple, paced (1 Hz) repetitive hand movements that involved opening and closing their two hands either in-phase (conditions 1 and 3) or out-of-phase (conditions 2 and 4). Thus, in-phase versus out-of-phase movements yielded factor 1. As a second factor, the subjects' visual feedback was rendered non-veridical: visual feedback of their left hand was manipulated by using a mirror (in conditions 3 and 4, as opposed to conditions 1 and 2 without a mirror) that obscured direct vision of their left hand and replaced it with a reflected image of their right hand on the left. Subjects ($n = 10$) were told to observe their left hand (real or 'virtual') during all these conditions. During the in-phase movements of condition 3 there are potentially increased attentional demands, as subjects were required to match an actual limb position of the obscured

left hand with the mirror image of the right hand that mimics it visually (to produce a 'virtual hand' on the left). More importantly, during *out-of-phase* bimanual movements (condition 4) the mirror provides misleading (non-veridical, incongruent) visual feedback indicative of *in-phase* hand movements which consequently engenders conflict with the intended out-of-phase movements. Subjects were instructed to persist with the out-of-phase motor co-ordination task in this condition despite the non-veridical, incongruent visual feedback. Accordingly, the factors in experiment 1 were *movement type* (two levels: in-phase and out-of-phase) and *visual feedback* (two levels: with and without the mirror). Each combination of levels was repeated three times on 10 subjects ($n = 120$).

The critical condition of this experimental design is condition 4 in which non-veridical incongruent visual feedback (indicating in-phase movements, when out-of-phase movements actually took place) maximizes the demands on the monitoring systems. During the generation of action, it is known that subjects tend to rely more on vision than proprioception when the two information sources conflict ('visual capture') (Rock and Victor, 1964; Ramachandran and Rogers-Ramachandran, 1996). The specific effect of non-veridical incongruent visual feedback on the neural activity due to monitoring and maintaining the out-of-phase bimanual movements in the face of conflicting visual feedback should be indicated by the interaction term [(out-of-phase bimanual movements with mirror – in-phase bimanual movements with mirror) – (out-of-phase bimanual movements without mirror – in-phase bimanual movements without mirror)]. Any main effects due to *visual feedback* and *movement type* per se are controlled for by our use of a fully factorial design when testing for the effect of the critical conflict condition.

Study 2

Study 2 was explicitly performed to address any effect of hand observed on the neural activity elicited in the critical condition 4 of experiment 1 (as assessed by the interaction term). Therefore, in the second study the mirror was put on the other side of the box, thus obscuring the right hand and replacing it with a mirror image of the left hand on the right side. Subjects were now instructed to look at their right hand (or the reflected image of the left hand); in all other respects the conditions of study 1 and 2 were identical. Each combination of levels was repeated three times on 6 subjects ($n = 72$). Therefore, in experiment 2, the critical condition in which conflict was engendered due to non-veridical incongruent visual feedback (indicating in-phase movements when out-of-phase movements actually took place) was again condition 4.

Study 3

Study 3 was performed to remove the intentional motor component from the conflict produced in the critical condition

4 of experiments 1 and 2. In this third experiment, which again used a fully factorial design, seven subjects rested their hands around bars. Subjects did not apply active grip. Rather, their hands were held lightly in place by Velcro bands. This configuration of hand shape was constant throughout the experiment. Only the position of the hands in space changed (in the different conditions). The bars around which subjects rested their hands were moved *passively* at a constant speed by an electrically driven motor either in-phase (conditions 1 and 3) or out-of-phase (conditions 2 and 4), to yield the first factor of *movement type*. By in-phase movements, we here refer to conditions in which the left-hand bar moved left (away from the midline and away from the right hand bar) while the right hand bar moved right (away from the midline and away from the left hand bar), followed by the left hand bar moving right (toward the midline and the right hand) while the right hand bar moved left (toward the midline and the left hand bar). By out-of-phase movements, we here refer to conditions in which both the left hand bar and the right hand bar moved alternately left and right together, with a constant distance between each other. This experimental set-up explicitly removed the intentional motor (manual) component of the task, leaving all other components as before. As in the previous experiments, *visual feedback* was again manipulated (factor 2) using a mirror in conditions 3 and 4 only, thus rendering visual feedback non-veridical. Subjects were instructed to observe their left hand (or the reflection of their right hand on the left) throughout all conditions (as in study 1). This led to a non-veridical incongruence between visual and proprioceptive feedback in condition 4 only. The mirror image of the right hand in place of the left hand showed in-phase (passive) movements when out-of-phase (passive) movements were actually performed by the machine. Accordingly, non-veridical incongruent visual feedback (incongruent with the veridical proprioceptive feedback, which again resulted in conflict) was now produced without subjects having to make any self-generated movements. Thus, the conflict now concerned a mismatch between vision and proprioception only, with no role for motor intention unlike in the previous two studies. Each combination of levels was repeated three times on 7 subjects ($n = 84$).

To maintain identical auditory stimulation across all three studies, a metronome was played synchronous to the passive movements at 1 Hz, as with the active movements in experiments 1 and 2, where it served as the pacing signal. Compliance with the instructions was verified at all times. The order of scans was counter-balanced across subjects to control for possible time effects.

Rating of the conflict

After an initial familiarization procedure with the scanning environment and the task, subjects were introduced to the mirror conditions. Subjects were presented with both mirror conditions, the one with congruent non-veridical visual

feedback, and the one with incongruent non-veridical visual feedback. The latter condition typically produced a relatively strong feeling of cognitive conflict. Following each PET scan, all subjects were asked to rate the strangeness/peculiarity of their experience while they had been doing each task, on a scale ranging from 0–9 (0 meaning not at all peculiar or strange and 9 meaning extremely peculiar or strange). This provided our measure of psychological conflict.

Performance during scanning was scrutinized via on-line video. All subjects were well able to follow the task instructions in all conditions. No switching to in-phase movements was observed during out-of-phase movement conditions (without mirror and with mirror) in the *active* tasks (studies 1 and 2). No subjective measurement of task difficulty was taken in studies 1 and 2 as all subjects had been fully familiarized with the tasks prior to PET scanning and were able to perform the task without any obvious difficulty. In future work it would be pertinent to conduct similar experiments in which on-line measures of motor performance (including latencies and trajectories) were taken.

PET scanning

Relative regional cerebral blood flow (rCBF) was measured by recording the regional distribution of cerebral radioactivity following the intravenous injection of ^{15}O-labelled water (^{15}O is a positron emitter with a half-life of 2.1 min). The PET measurements were carried out using a Siemens/CPS ECAT EXACT HR+ (model 962) PET scanner (CTI Inc., Knoxville, Tenn., USA) with a total axial field of view of 155 mm covering the whole brain. Data were acquired in 3D mode with inter-detector collimating septa removed and a Neuro-Insert installed to limit the acceptance of events originating from out-of-field-of-view activity (i.e. from the whole body).

For each measurement of relative rCBF, 9 mCi of $H_2^{15}O$ was given intravenously as a slow bolus over 20 s. Twelve consecutive PET scans were collected, each beginning with a 30 s background scan before the delivery of the slow bolus. Emission data were thereafter collected sequentially over 90 s after tracer arrival in the brain, and were corrected for background activity. This process was repeated for each emission scan with 8 min between scans to allow adequate decay of radioactivity. All emission scan data were corrected for the effects of radiation attenuation (e.g. by the skull) by means of a transmission scan taken prior to the first relative rCBF measurement. The corrected data were reconstructed into 63 transverse planes (separation 2.4 mm) and into 128×128 pixels (size 2.1 mm) by 3D filtered back-projection using a Hann filter of cut-off frequency 0.5 cycles per pixel, and applying a scatter correction. The resolution of the images was 6 mm (at full width half maximum).

MRI

In a separate session, an MRI image of each subject's brain was obtained: (i) to exclude the possibility of morphological/ pathological abnormalities and (ii) for stereotactic normalization into the standard anatomical space (see below). This was performed with a 2 Tesla system (VISION, Siemens AG, Germany) using a 3D T_1- weighted imaging technique producing 108 transaxial slices ($1 \times 1 \times 1.5$ mm), which gave high grey to white matter contrast.

Image processing

All calculations and image manipulations were performed on a SPARC workstation (SUN Computers). ANALYZE and PROMATLAB software (MATHWORKS Inc., USA) were used to calculate and display images. Statistical parametric mapping software (SPM96; Wellcome Department of Cognitive Neurology, London, UK) was used for image realignment, image normalization, smoothing and to create statistical maps of significant relative rCBF (Friston *et al.*, 1995*a, b*)

Realignment, transformation and smoothing of PET images

Using SPM96 software all PET scans were realigned to the first emission scan to correct for head movement. A mean relative rCBF image was created for each subject and edited to remove counts representing blood flow to the skull or scalp. Each individual's MRI and PET mean image (serving as a template for the individual PET images) were then transformed into a standard stereotactic anatomical space using linear proportions and a non-linear sampling algorithm (Friston *et al.*, 1995*a*). The PET images were thereafter filtered using a low-pass Gaussian filter (resulting in an image resolution of 12 mm) to reduce the variance due to individual anatomical variability and to improve signal-to-noise ratio (Friston *et al.*, 1995*b*). The resulting pixel size in stereotactic space was 2×2 mm with an interplane distance of 4 mm. Data were thereafter expressed in terms of standard stereotactic coordinates in the *x*-, *y*- and *z*-axes (as defined in Table 1).

Statistical analysis

Following stereotactic normalization, statistical analysis was performed. For each experiment (studies 1–3), the main effects of experimental factors (i.e. movement type, visual feedback) and their interaction were estimated separately on a pixel-by-pixel basis using SPM96 (Friston *et al.*, 1995*b*). Differences in global CBF, within and between subjects, were removed by treating global activity as the covariate (Friston *et al.*, 1995*b*). This removed systematic state-dependent differences in global blood flow associated with the different conditions, which can obscure task-related regional alterations in activity. For each pixel in stereotactic space, the ANCOVA (analysis of covariance) generated a

Table 1 *Brain activity associated with Luria's bimanual movement tasks and non-veridical visual feedback*

Region	Side	Coordinates			Z-score
		x	y	z	
(A) Main effect: out-of-phase versus in-phase hand movements					
(C2 + C4) > (C1 + C3)					
Dorsolateral prefrontal cortex[1] (BA 9/46)*	R	44	22	32	4.4
	L	–50	18	48	3.5
Lateral inferior posterior parietal cortex[2] (BA 40)	R	50	–54	38	4.6
	L	–52	–44	42	4.1
Cerebellar hemisphere[3]	L	–30	–66	-42	4.1
(B) Main effect: modulation of visual feedback by mirror (C3 + C4) > (C2 + C1)					
Dorsolateral prefrontal cortex[4] (BA 9/46)*	R	42	16	36	3.8
Superior posterior parietal cortex[5] (BA 7)	R	32	–68	54	3.6
(C) Interaction: effect of modulation of visual feedback on activations greater for					
out-of-phase than in-phase hand movements (C4 – C3) > (C2 – C1)					
Dorsolateral prefrontal cortex (BA 9/46)	R	42	14	42	3.8

Coordinates (in standard stereotactic space as defined by Talairach and Tournoux, 1988) refer to maximally activated foci as indicated by the highest Z-score within an area of activation associated with (**A**) out-of-phase hand movements, (**B**) modulation of visual feedback by the mirror, and (**C**) the effect of modulation of visual feedback on activations being greater for out-of-phase than in-phase hand movements. x = distance (mm) to right (+) or left (–) of the mid-sagittal (interhemispheric) line; y = distance anterior (+) or posterior (-) to vertical plane (VAC) through the anterior commissure (AC); z = distance above (+) or below (–) the intercommissural (AC–PC) line. For each anatomical location, an estimate of the BA is given in parentheses, which is based on the stereotactic atlas (Talairach and Tournoux, 1988) and the group mean MRI. *The right DLPFC shows a main effect of *movement type* and *visual feedback* but also a strong interaction. R = right, L = left. Numbers in superscript refer to Fig. 2. A1 = *active* in-phase hand movements, without mirror; A2 = *active* out-of-phase hand movements, without mirror; A3 = *active* in-phase hand movements, with mirror; A4 = *active* out-of-phase hand movements, with mirror.

condition-specific adjusted mean rCBF value (arbitrarily adjusted to 50 ml/100 ml/min) and an associated adjusted error variance (Friston *et al.*, 1995*b*). This allowed the planned comparisons of the mean blood flow distributions across all sets of conditions. For each pixel, across all subjects and all scans, the mean relative rCBF values were calculated separately for each of the main effects. Comparisons of the means were made using the *t* statistic and thereafter transformed into normally distributed *Z* statistics. The resulting set of *Z*-values constituted a statistical parametric map (SPM{Z} map) (Friston *et al.*, 1995*b*).

In study 1, the data were analysed for the two main effects (movement type, visual feedback) and their interaction; these comparisons were intended to identify those cortical areas concerned with the properties in question (i.e. out-of-phase versus in-phase movements, visual feedback with mirror versus visual feedback without mirror) and to assess the specific effects of non-veridical incongruent visual feedback (via the interaction term) when it conflicted with the intended out-of-phase movements by producing the visual impression of in-phase movements in the critical condition 4. The level of significance was set at $P < 0.001$ (uncorrected for multiple comparisons). This is appropriate because region specific a priori predictions were made for fist opening and closure, bimanual co-ordination and eye-hand co-ordination (e.g. Fink *et al.*, 1997*b*; Jeannerod, 1997; Sadato *et al.*, 1997) and monitoring (von Helmholtz, 1867; von Holst and Mittelstaedt, 1950; Picton and Stuss, 1994; Wolpert *et al.*, 1995; Miall and Wolpert, 1996).

Studies 2 and 3 were performed to address explicitly the functional meaning of a specific activation in right prefrontal cortex that was observed in the interaction term of study 1 (i.e. the neural activity associated with the condition 4 in which conflict was engendered). As subjects in study 1 had been looking at their left hand (or the mirror image of the right hand replacing it) in all conditions, the question arose as to whether the laterality of the prefrontal activation observed in study 1 might reflect the side of the observed hand. Study 2 addressed the effect of hand observed on the neural activity elicited in the conflict condition. The level of significance was now set to $P < 0.01$; this lowered threshold was accepted because study 2 is in effect a replication of study 1 where we only tested the specificity of right prefrontal cortex activation for the conflict situation (i.e. the interaction). Study 3 was performed to address the contribution of self-generated intentional action in relation to incongruent visual and proprioceptive feedback in monitoring, by now using *passive* rather than *active* movements. As a differential neural response depending on specific task demands (i.e. the change from *active* to *passive* movements) was likely, the anatomical a priori hypothesis of right prefrontal activation with conflict was less well defined now, as in study 2. Therefore, the level of significance in this experiment was set back to the more rigorous level of $P < 0.001$ (uncorrected for multiple comparisons), as in study 1.

To assess hemispheric asymmetries in rCBF responses, any hemisphere × condition interactions were identified using SPM96. This did not require correction because these regions

were identified on the basis of the (independent) main effects or interaction terms.

Although our block ANCOVA removed random effects due to subjects, it did not remove all subject-specific effects and therefore does not constitute a random-effects model. Accordingly, for between group comparisons (study 1 versus study 3) we ensured the appropriateness of our fixed effects model by testing explicitly for subject × contrast interaction effects. This analysis demonstrated that no such effects were significant (all *P*-values being > 0.05).

Localization of activations

The stereotactic coordinates of the pixels of local maximum significant changes in relative rCBF were determined within areas of significant relative rCBF change associated with the different tasks. The anatomical localization of these local maxima was assessed by reference to the standard stereotactic atlas of Talairach and Tournoux (1988), and validation of this method of localization was obtained by superimposition of the SPM{Z}-maps on the group mean MRI calculated after each individual's MRI had been stereotactically transformed into the same standard stereotactic space (Friston *et al.*, 1995*a*).

Results
Study 1
Psychological ratings
The subjects' ratings of their feeling of peculiarity (10 subjects, 3 repeats per condition, *n* = 30) confirmed that the critical condition 4 in which non-veridical incongruent visual feedback was produced to indicate in-phase movements when out-of-phase movements actually took place indeed engendered conflict. In condition 4, subjects rated their feeling of peculiarity on the scale ranging from 0 to 9 (with 0 meaning not peculiar at all and 9 meaning extremely peculiar) as 3.5 ± 2.6 (mean ± SD), as compared with 1.7 ± 1.76 for condition 3 (with the mirror showing non-veridical congruent visual feedback), 1.0 ± 1.1 for condition 2 (no mirror, out-of phase movements), and 0.8 ± 0.9 for condition 1 (no mirror, in-phase movements).

The main effect of *movement type* (out-of-phase > in-phase) and the main effect of *visual feedback* (mirror in > no mirror) were significant at *P* < 0.001. The crucial *interaction* (out-of-phase, mirror in – in-phase, mirror in > out-of-phase, no mirror – in-phase, no mirror) was also significant (*P* < 0.05).

Neural activations
The main effect of *movement type* (out-of-phase > in-phase) revealed, as expected (Luria, 1969; Freund, 1987), marked differences in rCBF (*P* < 0.001, see Material and methods) associated with out-of-phase hand movements (compared

with in-phase movements) in dorsolateral prefrontal cortex [DLPFC, Brodmann area (BA) 9/46] bilaterally, lateral inferior posterior parietal cortex (PPC, BA 40) bilaterally extending into the superior PPC (BA 7), and in the left cerebellar hemisphere (Table 1A and Fig. 2A). Within the area of activation in the right DLPFC, an interaction was observed with *visual feedback*. The other areas of activation due to *movement type* did not show such an interaction.

The main effect of visual feedback (replacing direct vision of the subjects' left hand by a mirror image of their right hand on the left) showed increased rCBF (*P* < 0.001, compared with the same movements performed without a mirror) in right superior PPC (BA 7; Table 1B, Fig. 2B). A further area of rCBF increase was observed in the right DLPFC (BA 9/46) for this comparison, but is disregarded as a main effect here since this area shows a strong interaction with movement type. The specific effect of conflicting visual feedback (in condition 4 only), derived from the interaction term [i.e. conditions (4–3) > (2–1)], resulted in significantly increased rCBF in right DLPFC alone (*P* < 0.001, BA 9/46; Table 1C, Fig. 3); no further activations were observed in the interaction term thus revealing a highly specific activation. The hemispheric asymmetries observed during the mirror conditions (superior PPC; *P* = 0.004) and in the interaction (DLPFC; *P* < 0.001) were significant (as assessed by a focal test comparing right hemisphere with left hemisphere by inverting the images). The interaction described indicates a specific right hemisphere DLPFC involvement when conflict is engendered and monitoring demands are emphasized because of the mismatch between the executed out-of-phase movements, and the visual feedback indicating in-phase movements, in the critical condition 4 only.
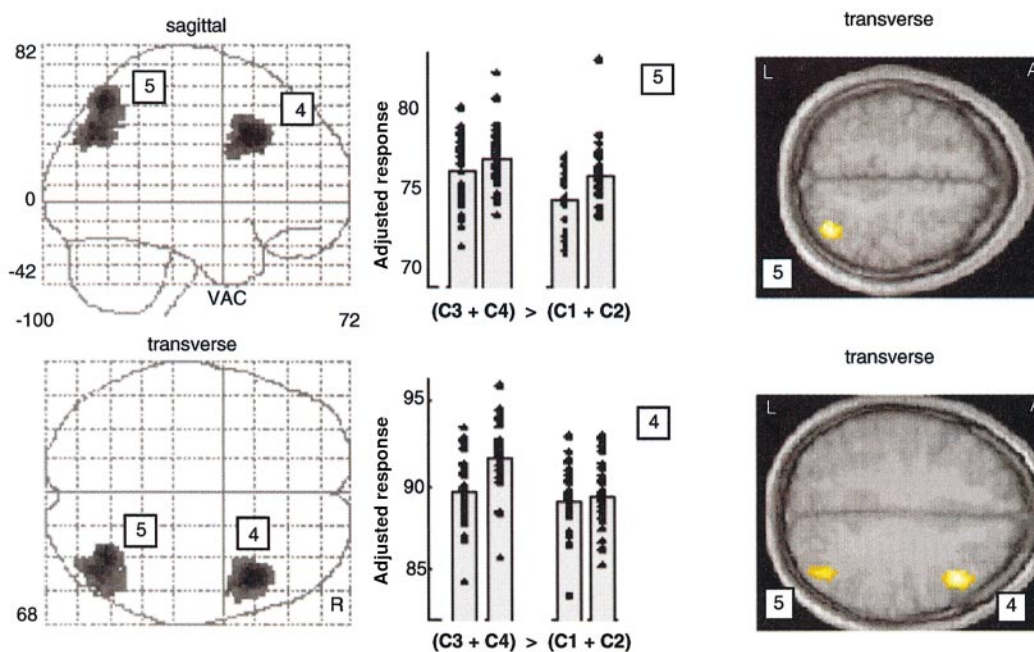
Study 2
To assess whether the hand observed (left hand in study 1) might account for the contralateral activation of right DLPFC when conflict was engendered (as elicited by the interaction term), we conducted the second study with an identical design, except that subjects were now instructed to observe their *right* hand (or a reflection of the left hand replacing the right hand on the right when direct view of the right hand was obscured by the mirror).

Psychological ratings
The subjects' ratings of their feeling of peculiarity (6 subjects, 3 repeats per condition, *n* = 18) confirmed that the critical condition 4 of study 2 again engendered the relevant conflict, as in study 1. In condition 4 (out-of-phase bimanual movements, non-veridical incongruent visual feedback), subjects rated their feeling of peculiarity on the scale ranging from 0–9 (with 0 meaning not peculiar at all and 9 meaning extremely peculiar) as 4.0 ± 2.2, as compared with 1.7 ± 1.6 for condition 3 (in-phase bimanual movements with
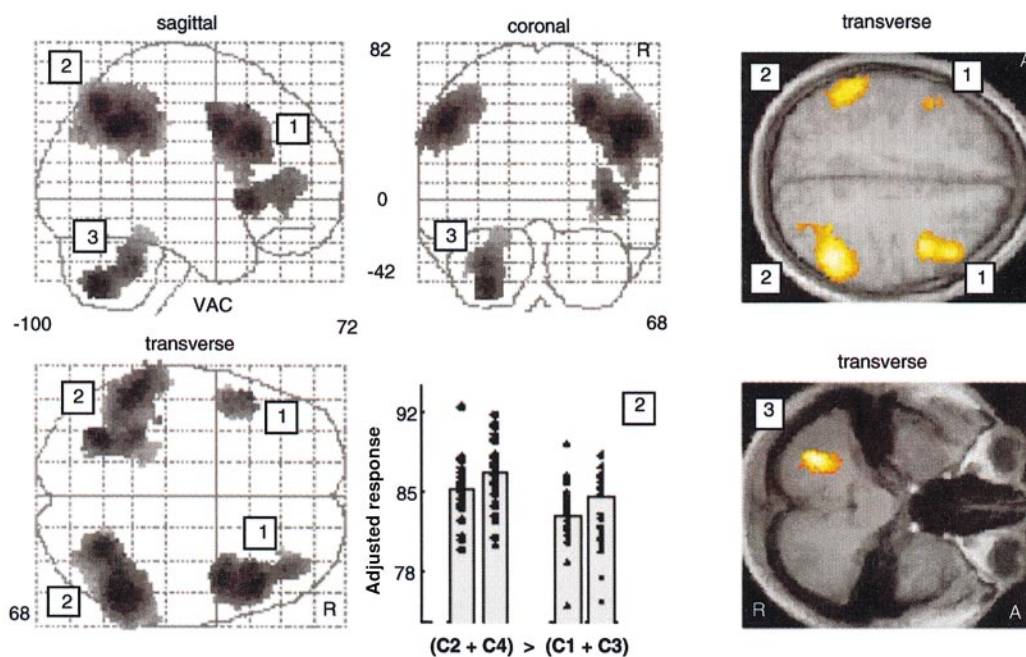
Fig. 2 Relative rCBF increases (study 1, 10 subjects) associated with (**A**) out-of-phase bimanual *active* movements [(C2 + C4) > (C1 + C3)] and (**B**) visual feedback with the mirror [(C3 + C4) > (C1 + C2)]. Areas of significant relative rCBF increases ($P < 0.001$) are shown as through-projections onto representations in standard stereotactic space (Talairach and Tournoux, 1988; Friston *et al.*, 1995a). Sagittal, side view; transverse, view from above; coronal, view from the back. To detail the functional anatomy of the activations and their relationship to underlying anatomy, the respective SPM{*Z*} maps were superimposed upon the group mean MRI, which had been spatially normalized into the same anatomical space (Talairach and Tournoux, 1988; Friston *et al.*, 1995a). The exact coordinates of the local maxima (indicated by numbers in boxes) within the areas of activation, and their *Z* statistics, are given in Table 1A and B. In addition, adjusted mean rCBF (arbitrarily adjusted to a mean of 50 ml/dl/min) and the individual rCBF values per condition are displayed for the respective pixel of maximally significant relative rCBF increase within the area of interest (indicated by the numbers in boxes; for activation 1 the right hemispheric maximum was chosen). R = right, A = anterior, P = posterior, VAC = vertical plane through the anterior commissure; numbers at axes refer to coordinates in standard stereotactic space (Talairach and Tournoux, 1988). C1 = in-phase bimanual *active* movements, without mirror; C2 = out-of-phase bimanual *active* movements, without mirror; C3 = in-phase bimanual *active* movements, with mirror; C4 = out-of-phase bimanual *active* movements, with mirror.
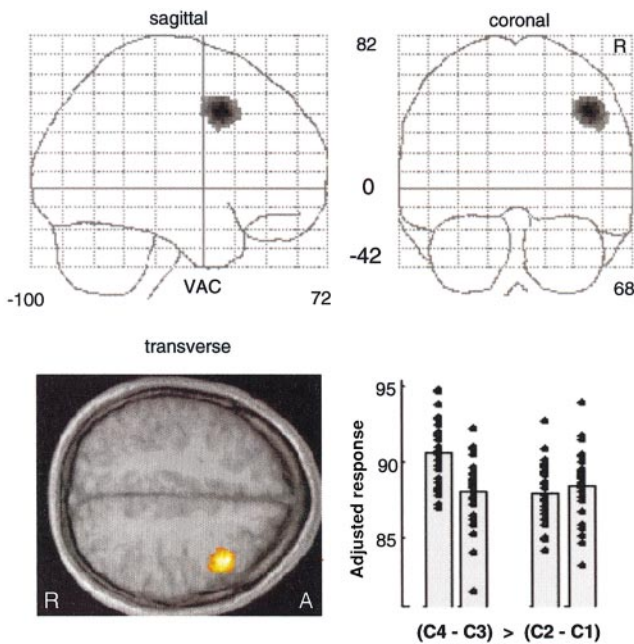
Fig. 3 Interaction of non-veridical/veridical visual feedback on out-of-phase/in-phase hand movements related to neural activity. The region within the right DLPFC where there is a significant relative rCBF increase (study 1, 10 subjects) that reflects an effect of modulation of visual feedback on neural activations greater for *active* out-of-phase than in-phase hand movements [(C4 -C3) >(C2 - C1)]. The exact coordinates of the local maximum within the area of activation in the right DLFPC and the respective *Z* statistic are given in Table 1C. For further details see legend to Fig. 2.

activations might reflect monitoring a mismatch between self-generated action (i.e. an intended act) and incongruent visual feedback, while having to maintain the correct action despite the non-veridical incongruent, and hence conflicting visual feedback. Alternatively, they may be due only to monitoring of a mismatch between vision and proprioception. These alternative explanations were tested by the passive movements of study 3.

Psychological ratings
The subjects' ratings of their feeling of peculiarity (7 subjects, 3 repeats per condition, $n = 21$) confirmed that the critical condition 4 of study 3 again engendered psychological conflict, as it was in studies 1 and 2. In condition 4 (out-of-phase passive movements, non-veridical incongruent visual feedback), subjects rated their feeling of peculiarity on the scale ranging from 0 to 9 (with 0 meaning not peculiar at all and 9 meaning extremely peculiar) as 5.5 ± 1.9, compared with 1.5 ± 2.0 for condition 3 (out-of-phase passive movements with mirror in but congruent visual and proprioceptive visual feedback), 1.8 ± 2.3 for condition 2 (no mirror, out-of phase *passive* movements), and 1.1 ± 1.2 for condition 1 (no mirror, in-phase *passive* movements).

The *interaction* (out-of-phase passive, mirror in – in-phase passive, mirror in > out-of-phase passive, no mirror – in-phase passive, no mirror) was highly significant ($P < 0.001$).

Neural activations
In study 3 the specific effect of conflicting non-veridical incongruent visual feedback (indicating in-phase *passive* movements when out-of-phase *passive* movements actually took place) as shown by the interaction term [i.e. conditions $(4 - 3) > (2 - 1)$], again resulted in significantly ($P < 0.001$) increased rCBF in right prefrontal cortex only (BA 44/45; $x = 40$, $y = 8$, $z = 22$, Z-score = 4.2). Crucially, however, the area activated for this interaction was now inferior to the activations observed in studies 1 and 2 and extended into BA 44/45, ventral to the inferior frontal sulcus.

mirror in and congruent visual and proprioceptive visual feedback), 1.1 ± 1.0 for condition 2 (no mirror, out-of phase movements), and 1.2 ± 1.0 for condition 1 (no mirror, in-phase movements).

The *interaction* (out-of-phase, mirror in – in-phase, mirror in > out-of-phase, no mirror – in-phase, no mirror) was again significant ($P < 0.01$).

Neural activations
The interaction effect again showed a significant rCBF increase in the *right* DLPFC alone (BA 9/46; $x = 56$, $y = 26$, $z = 34$, Z-score = 2.4, $P = 0.009$). No activation was observed in the left DLPFC. Our conclusion, therefore, is that the increased monitoring engendered by a mismatch between intention, proprioception and visual feedback in condition 4 specifically engages the *right* DLPFC, independent of the hemispace (or bodyspace) to which attention is directed.

Study 3
There are, however, two possible explanations for the observed right hemispheric activations within DLPFC in studies 1 and 2 for the critical conflict situation. These

Study 1 versus study 3
The activations observed within right prefrontal cortex for studies 1 and 3 imply that different anatomical areas are activated depending on the specific monitoring demands of the task, which was active in study 1, but passive in study 3. Study 1 emphasizes the *intentional* component of monitoring a self-generated movement, in that subjects must act against the incongruence of vision with respect to intention and proprioception to maintain the out-of-phase movements in the face of in-phase visual feedback. The area activated lies in right DLPFC above the middle frontal sulcus and includes BA 9/46 (Petrides and Pandya, 1994; Rajkowska and Goldman-Rakic, 1995). By contrast, study 3 (which like study 1 focused attention on the left hand) stressed the
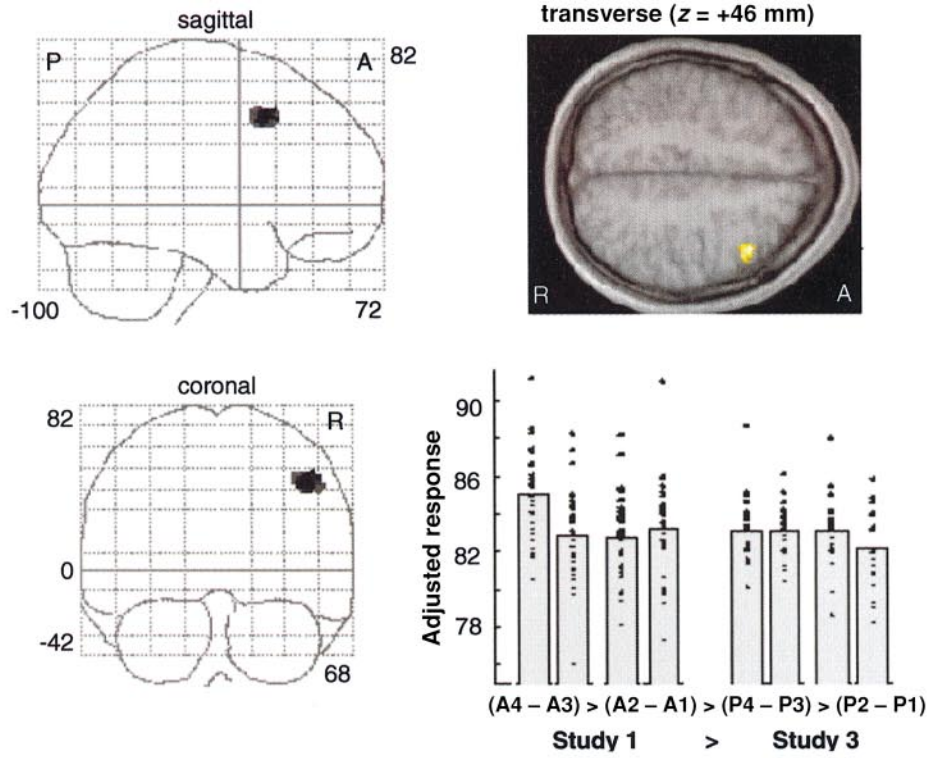
(A) Effect of non-veridical visual feedback in an active movement task (relative to a passive movement task)
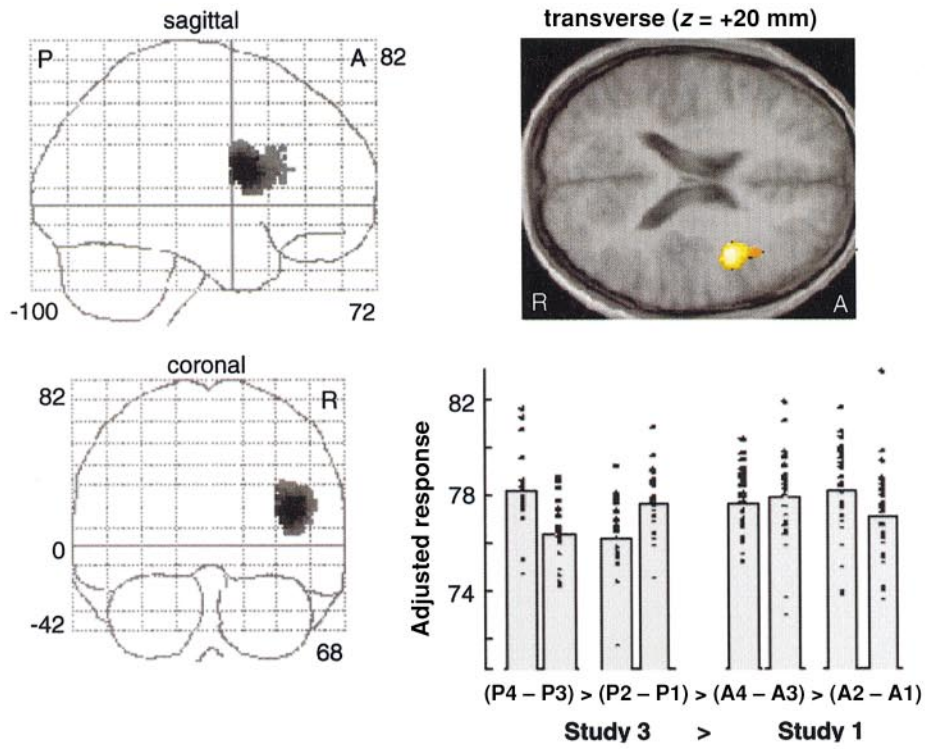
(B) Effect of non-veridical visual feedback in a passive movement task (relative to an active movement task)

receptive aspect of monitoring, as entirely *passive* movements now resulted in the incongruence between visual and proprioceptive feedback, without any intentional movements. The area activated within right prefrontal cortex during this passive conflict situation lies ventral to the inferior frontal sulcus and includes BA 44/45 (Petrides and Pandya, 1994).

To evaluate whether the right prefrontal activations for the conflict situations in studies 1 and 3 are indeed anatomically distinct, we directly compared studies 1 and 3 for the critical interaction terms. In view of the anatomically restricted hypothesis (due to the specific activation of right prefrontal cortex in the critical condition 4 of studies 1 and 3) the search volume for these comparisons was limited to prefrontal cortex. Our analysis revealed a significantly greater rCBF increase as a specific outcome of non-veridical incongruent feedback during *active* out-of-phase movements in right DLPFC (for study 1 versus study 3: $x = 42$, $y = 14$, $z = 46$; $P < 0.005$, Z-score = 2.6) and in right mid-ventrolateral prefrontal cortex (for study 3 versus study 1: $x = 40$, $y = 6$, $z = 20$; $P < 0.001$, Z-score = 4.2) with *passive* movements for study 3 (relative to study 1). This analysis confirms that different aspects of monitoring lead to significantly different differential activations within right prefrontal cortex (Fig. 4).

It must be stressed that differences between the two studies (the *active* study 1 and the *passive* study 3) are relative differences. If, for example, one lowered the statistical threshold for the activation seen in the interaction term of study 1 (i.e. the conflict situation), the area of activation due to motor conflict would enlarge and eventually merge with the area of activation observed when emphasis is put on sensory conflict (as in study 3).

Discussion

Luria's bimanual co-ordination task is used clinically to assess aspects of frontal lobe function: patients with frontal lobe disease often demonstrate difficulties in performing (active) out-of-phase bimanual movements or in changing from in-phase to out-of-phase movements (Luria, 1969; McCarthy and Warrington, 1990). In the *active* movement task of study 1, the main effect of movement type delineates the functional basis for bimanual out-of-phase control over and above the neural control of in-phase bimanual co-ordination. In this experiment the actual movements made by each hand individually were equivalent over the PET acquisition epochs for both the in-phase and out-of-phase conditions, thus controlling for the particular muscular changes required etc. Only the relative phase of otherwise identical movements differed. Areas activated in the PPC bilaterally, including the inferior aspect of PPC (BA 40) but extending into the superior posterior aspect of PPC (BA 7), during the co-ordination of out-of-phase bimanual movements are in full agreement with experimental studies that implicate the PPC in the control of limb movement and in hand-eye co-ordination (Andersen, 1995; Their and Andersen, 1996; Andersen *et al.*, 1997; Jeannerod, 1997; Sakata *et al.*, 1997; Snyder *et al.*, 1997). Activation of DLPFC bilaterally during out-of-phase bimanual co-ordination indicates the functional basis that underlies the classical clinical reports of impaired bimanual co-ordination for the Luria out-of-phase task in patients with frontal lobe lesions (Luria, 1966; Luria, 1969; McCarthy and Warrington, 1990). This activation is also consistent with the established functional role of DLPFC in willed action (Frith *et al.*, 1991) complex motor tasks (Frith *et al.*, 1991) and increased motor effort (Dettmers *et al.*, 1995, 1996).

The most parsimonious explanation for the increased neural activity observed as a main effect during the conditions where the mirror produced non-veridical visual feedback in right PPC and right DLPFC is that the 'replacement' of the subjects' left hand by the mirror image of the right hand (thus producing a 'virtual' hand) led to increased attentional demands (for the integration of vision and proprioception) and thereby increased demands on eye-hand co-ordination. Subjects were explicitly asked to match the actual limb position of the obscured hand with the mirror image (virtual hand) that mimicked it visually, so the main effect of the mirror presumably reflects such a requirement.

The critical condition in each of our factorial experiments was condition 4, in which conflicting non-veridical,

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Fig. 4 Relative rCBF increases associated with (**A**) conflicting visual feedback in the bimanual *active* movement tasks [study 1; (A4 – A3) > (A2 – A1)] relative to conflicting visual feedback in the bimanual *passive* movement tasks [study 3; (P4 – P3) > (P2 – P1)], and with (**B**) conflicting visual feedback in the bimanual *passive* movement tasks [study 3; (P4 – P3) > (P2 – P1)] relative to conflicting visual feedback in the bimanual *active* movement tasks [study 1; (A4 – A3) > (A2 – A1)]. Areas of significant relative rCBF increases (A: $P < 0.01$; B: $P < 0.001$) are shown as through-projections onto representations in standard stereotactic space (Talairach and Tournoux, 1988; Friston *et al.*, 1995a). The search volume for these comparisons was limited to the prefrontal cortex (see text). To detail the functional anatomy of the activations and their relationship to underlying anatomy, the respective SPM{Z} maps were superimposed upon the group mean MRI, which had been spatially normalized into the same anatomical space (Talairach and Tournoux, 1988; Friston *et al.*, 1995a). The exact coordinates of the local maxima within the areas of activation and their Z statistics are given in the text. In addition, adjusted mean rCBF (arbitrarily adjusted to a mean of 50 ml/dl/min) and the individual rCBF values per condition are displayed for the respective pixel of maximally significant relative rCBF increase within the area of interest. R = right, A = anterior, P = posterior, numbers at axes refer to coordinates in standard stereotactic space (Talairach and Tournoux, 1988). A1 = in-phase bimanual *active* movements, without mirror; A2 = out-of-phase bimanual *active* movements, without mirror; A3 = in-phase bimanual *active* movements, with mirror; A4 = out-of-phase bimanual *active* movements, with mirror; P1 = in-phase bimanual *passive* movements, without mirror; P2 = out-of-phase bimanual *passive* movements, without mirror; P3 = in-phase bimanual *passive* movements, with mirror; P4 = out-of-phase bimanual *passive* movements with mirror.

incongruent visual feedback produced the visual impression of in-phase movements while out-of-phase movements were actually performed (for both the *active* movement studies 1 and 2, and also the *passive* movement study 3). This condition maximizes psychological conflict, as subjectively rated, and thus imposed differential demands on the monitoring system. The specific neural activations due to the differential aspects of monitoring (which in studies 1 and 2 involved monitoring and maintaining the self-generated intentional action in the face of non-veridical incongruent visual feedback, and in study 3 involved only monitoring of the incongruence of correct proprioception and non-veridical incongruent visual feedback) are elicited by the critical interaction term [conditions (4–3) > (2–1)]. Any main effects of *movement* and *visual feedback* per se (see above) are controlled for by the fully factorial design. There are two crucial findings regarding such monitoring in the present studies. First, the right prefrontal cortex is activated when monitoring demands are increased due to a conflict arising from the non-veridical, incongruent visual feedback. Secondly, differential aspects of monitoring lead to differential activations within the right prefrontal cortex (DLPFC for an *active* task which emphasizes the conflict between the intention and visual and/or proprioceptive feedback, versus ventrolateral prefrontal cortex for a comparable *passive* task emphasising only sensory conflict between vision and proprioception with no role for motor intention). It must be stressed that in order to maximize this distinction between *active* and *passive* tasks it was necessary for the actual handshape in study 3 to remain constant, while alternating between two different forms in the *active* studies 1 and 2. However, the fact that the actual hand shape employed in study 3 was different from either of those used in studies 1 and 2 should not have any effect on the pattern of activations reported here.

Activation of DLPFC has previously been associated with a variety of related functions including complex motor selection (Frith *et al.*, 1991) and effort (Dettmers *et al.*, 1995, 1996), the self-generation of movement (Frith *et al.*, 1991) and also with some aspects of on-line memory (Petrides, 1996; Cohen *et al.*, 1997; Goldman-Rakic, 1997; Courtney *et al.*, 1998). Activation of a more ventral part of prefrontal cortex has been shown in a spatial working memory task where subjects were required to maintain but not manipulate spatial information for brief periods of time (Jonides *et al.*, 1993). In an experiment more similar to ours, Sadato *et al.* (1997) examined bimanual in-phase and out-of-phase abduction/adduction finger movements (Sadato *et al.*, 1997). A comparison of both in-phase and out-of-phase finger movements to rest revealed neural activations in right prefrontal cortex, anterior cingulate cortex, premotor cortex, motor cortex, superior and inferior parietal cortex. The design of their study, however, did not enable them to assign a specific role to the activations observed. In particular, they were unable to distinguish whether the right prefrontal activation reflected sustained attention to motor performance

(Pardo *et al.*, 1991), on-line monitoring of finger position in space, or spatial working memory (Jonides *et al.*, 1993).

By contrast, the structure and sequence of our experiments enables us to identify additional functions to those for which there is already considerable consensus. The present findings demonstrate that prefrontal cortex can be involved in functions (sensory integration, sensorimotor integration) which in the past have been associated with more posterior cortical areas. However, it is consistent with our findings that some sensorimotor transformations required to produce actions under visual guidance are known to employ a route projecting from striate to posterior parietal cortex, and critically from there on to the frontal lobe (Fuster, 1993; Passingham, 1993; Milner and Goodale, 1995; Jeannerod, 1997). Our results suggest that the prefrontal cortex is particularly activated under those conditions which engender conflict and so require supervisory intervention (Shallice and Burgess, 1996).

The crucial question is which cognitive components account for the highly specific right prefrontal activations in our studies. Is this activation due, for example, to the increased *sensory* attentional demands of performing out-of-phase bimanual movements despite incongruent visual feedback? It would seem not, for increased attention to visual input (or other sensory modalities) typically leads to enhanced neural activity in primary and secondary sensory cortices, but not in DLPFC (Corbetta *et al.*, 1990, 1993; Fink *et al.*, 1996; Dolan *et al.*, 1997; Fink *et al.*, 1997*a*, *c*, *d*; Shulman *et al.*, 1997). Likewise, increased demand on *motor* attention is unlikely to account for the observed activations. Such demands typically lead to increased neural activity in the anterior cingulate cortex (Frith *et al.*, 1991) which was not observed in our study. Can the critical activations in our studies be attributed merely to the presence of any conflict in task-performance? Stroop-like tasks, which require subjects to suppress a highly compatible but currently incorrect response, have activated anterior cingulate cortex but not DLPFC (Bench *et al.*, 1993). Unlike Stroop tasks, our studies 1 and 2 involve a conflict between intended actions and their sensory consequences, rather than merely response suppression. Furthermore, no previous study has ever contrasted passive conflict between the senses with conflict between intentions and their sensory outcome, as here (for the contrasts between study 1 and study 3).

Indeed, it is this comparison of studies 1 versus 3 that allows us to demonstrate functional specialization within right prefrontal cortex. In study 1, right DLPFC monitors which motor program is operative, and hence allows subjects to actively maintain the intended out-of-phase bimanual movements despite the non-veridical incongruent visual consequences, which give the appearance of in-phase movements. Such a monitoring role for motor intentions by right DLPFC is consistent with activation of this area in an anti-saccade task in earlier studies (Sweeney *et al.*, 1996). Our results also suggest that the right *mid-ventral* prefrontal cortex monitors the proprioceptive and visual feedback

processed in more posterior regions, and brings to awareness any incongruence between these different types of sensory feedback. It is the additional requirement to act appropriately despite the sensory incongruence that necessitates the involvement of right DLFPC when a self-generated action must be actively performed in the face of such conflicting feedback. We propose that the emphasis on monitoring and maintaining the desired *action* despite conflict with visual feedback (studies 1 and 2), as against the monitoring of the *sensory* incongruence alone (study 3), underlies the differential activations in right prefrontal cortex observed between studies 1 and 3.

The two aspects of monitoring (and their anatomical loci) that we have emphasized are reminiscent of the 'two-level hypothesis' (Petrides, 1996) put forward in the context of working memory tasks in human (Petrides *et al.*, 1993) and non-human primates (Petrides, 1991). This hypothesis proposed that mid-dorsolateral frontal cortex contains a specialized system for monitoring and manipulating information within working memory, whereas mid-ventrolateral frontal cortex is involved in active retrieval of sensory information from posterior cortical association areas. In our studies, we employed manual tasks that have little in common with those previously found to activate right DLPFC, other than the monitoring components themselves. Furthermore, our tasks made minimal demands on working memory in the strict sense of the term, but rather emphasized the engagement of supervisory mechanisms required to register and overcome conflicts between intention and sensory outcome, or between the senses. Our results thus show that the relevant monitoring systems have a domain of operation that extends beyond memory-retrieval or memory-maintenance, as normally construed (Rushworth *et al.*, 1997). The findings we report are nonetheless compatible with an extended view of the functions of working memory. Certainly, the mismatch conditions we employed require that subjects keep a goal or instruction in mind as they attempt to resolve the contradictions between sensory feedback and movement (in experiments 1 and 2). In our study frontal monitoring is needed to detect discrepancies between sensory impressions (as emphasized in experiment 3) and to maintain appropriate movements despite discrepancy between visual feedback and voluntary action (in experiments 1 and 2). The involvement of such processes in a variety of cognitive tasks strongly suggests that these forms of monitoring serve as general supervisory executive processes (Shallice, 1988; Shallice and Burgess, 1996) for which we propose right prefrontal loci.

It is possible that a frontal lobe task, like Luria's bimanual co-ordination task, is monitored in the frontal lobes while a parietal task (e.g. a spatial judgement task) might be monitored in the parietal lobes. We are not aware of any positive evidence for this conjecture and the right prefrontal cortex activation in the critical condition of our passive task (study 3) indicates prefrontal monitoring of a non-frontal (primary) task.

Clinical implications

We now consider the clinical implications of our results. Luria (1969) argued that damage to premotor areas disrupts, above all, the sequencing of different movements as opposed to repetition of the same movement. His bimanual co-ordination tasks were part of the bedside examination of these frontal deficits. The results of experiment 1 confirm and extend the conclusions that Luria drew from lesion-studies. The specific frontal region implicated in the alternating (out-of-phase) manual task is (bilateral) DLFPC, but more posterior areas were equally implicated. The importance of DLFPC in sequential and alternating manual tasks is consistent with the negative findings of Benson and Stuss (1982) in patients with frontal leukotomy. In their study, bilateral lesions that 'primarily involved orbitofrontal white matter and were located medially with little lateral extension' did not impair performance on a range of motor sequencing tasks. The finding (Table 1) that lateral inferior PPC is differentially active during alternating (out-of-phase) hand movements recalls the stress that Liepmann (1908) placed on the spatial control of praxis. Our results show that what Liepmann called 'the space-time plan' is important even in such relatively simple tasks as the alternating asymmetric (out-of-phase) opening and closing of two hands. Luria's bimanual co-ordination tasks should accordingly be useful in the bedside examination of patients with posterior lesions, in addition to their previously demonstrated value in frontal cases. Careful testing may reveal further pertinent qualitative differences in *how* the out-of-phase co-ordination tasks breaks down after damage to different brain regions (McCarthy and Warrington, 1990).

Comparison of the results of experiments 1 and 3 shows that the 'monitoring' capacities of right prefrontal cortex can be anatomically distinguished according to the nature of the inputs thereto. This suggests that clinical testing for behavioural impairments of the 'Supervisory Attentional System' after lesion (Shallice, 1988), including those that lead to perseveration, should investigate a wider range of monitoring and executive functions. In particular, it would be pertinent to deploy the mirror conditions we have used here to investigate alternating (out-of-phase) movements when sensory feedback is non-veridical. It will be particularly interesting to determine whether such future studies of patients will reveal a right hemisphere lateralization of the monitoring functions that are emphasized by the conflict condition of our mirror task, in accordance with the laterality revealed by the functional imaging data in normals. Some previous clinical work has already associated right DLPFC in particular with monitoring the current match between reality and intentions, although primarily within the domain of memory (e.g. Stuss *et al.*, 1994*a*, *b*) rather than sensorimotor integration as emphasised here. We also note that the passive movement mirror condition may be pertinent to the assessment of monitoring functions in patients with somatosensory loss.

Finally, we suggest that the main effect of the modulation of visual feedback by mirror (found in experiment 1) may help to resolve a puzzle in the analysis of visuospatial neglect. Recent studies of neglect have deployed mirror arrangements that reverse the apparent (left–right) position of objects when patients performed visual search tasks (such as cancellation) with a manual response (Tegner and Levander, 1991). The point of comparing cancellation performance in the standard task against cancellation performance in a mirror-reversed situation was to determine whether (for an individual patient) the primary determinant of left neglect was an inability to perceive objects on the left, or an inability to respond motorically to objects on the left. If neglect was purely perceptual, patients with left neglect should cancel those items that appear visually on the right in the reversing mirror, even though these require movements to the left in external space, and they should neglect those items which appear on the left in the mirror, even though these actually lie to the right in external space. Conversely, it was argued that if neglect was determined by (pre-) motor impairment, the patient should fail to move the hand to the left in both the standard and the mirror-reversed condition, and hence would neglect those items which appeared visually to the right in the mirror condition. It has been reported that cases of neglect whose right hemisphere damage extends anteriorly, to include areas such as DLPFC, may be associated with the motor pattern of neglect on the mirror cancellation task. However, this conclusion has recently been criticized (Mattingley and Driver, 1997) on the grounds that the mirror-reversed situation may simply place more demands on frontal monitoring processes, by requiring patients to move their hands in a direction opposite to that which is depicted visually in the mirror. This lack of normal stimulus-response compatibility (Halligan and Marshall, 1989) might in itself lead neglect patients with more anterior lesions to fail the mirror-reversed cancellation task. The present PET results appear to support this proposal, since we found that right DLPFC was specifically activated when normal subjects had to control their hand movements in the face of conflicting visual feedback from a mirror. The fractionation of the neglect syndrome, on the basis of mirror-reversing tasks, may therefore need to be re-examined in the light of our finding that right DLPFC is specifically involved in monitoring conflict between motor intentions and their sensory/perceptual consequences.

References

Andersen RA. Encoding of intention and spatial location in the posterior parietal cortex. [Review]. Cereb Cortex 1995; 5: 457–69.

Andersen RA, Snyder LH, Bradley DC, Xing J. Multimodal representation of space in the posterior parietal cortex and its use in planning movements. [Review]. Annu Rev Neurosci 1997; 20: 300–30.

Bench CJ, Frith CD, Grasby PM, Friston KJ, Paulesu E, Frackowiak RS, et al. Investigations of the functional anatomy of attention using the Stroop test. Neuropsychologia 1993; 31: 907–22.

Benson DF, Stuss DT. Motor abilities after frontal leukotomy. Neurology 1982; 32: 1353–7.

Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, et al. Temporal dynamics of brain activation during a working memory task [see comments]. Nature 1997; 386: 604–8. Comment in: Nature 1997; 386: 559–60.

Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE. Attentional modulation of neural processing of shape, color, and velocity in humans. Science 1990; 248: 1556–9.

Corbetta M, Miezin FM, Shulman GL, Petersen SE. A PET study of visuospatial attention. J Neurosci 1993; 13: 1202–26.

Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV. An area specialized for spatial working memory in human frontal cortex. Science 1998; 279: 1347–51.

Dettmers C, Fink GR, Lemon RN, Stephan KM, Passingham RE, Silbersweig DA, et al. Relation between cerebral activity and force in the motor areas of the human brain. J Neurophysiol 1995; 74: 802–15.

Dettmers C, Lemon RN, Stephan KM, Fink GR, Frackowiak RS. Cerebral activation during the exertion of sustained static force in man. Neuroreport 1996; 7: 2103–10.

Dolan RJ, Fink GR, Rolls ET, Booth M, Holmes A, Frackowiak RSJ, et al. How the brain learns to see objects and faces in an impoverished context. Nature 1997; 389: 596–9.

Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RS, Dolan RJ. Where in the brain does visual attention select the forest and the trees? Nature 1996; 382: 626–8.

Fink GR, Dolan RJ, Halligan PW, Marshall JC, Frith CD. Space-based and object-based visual attention: shared and specific neural domains. Brain 1997a; 120: 2013–28.

Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE. Multiple non-primary motor areas in the human cortex. J Neurophysiol 1997b; 77: 2164–74.

Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RS, Dolan RJ. Neural mechanisms involved in the processing of global and local aspects of hierarchically organized visual stimuli. Brain 1997c; 120: 1779–91.

Fink GR, Marshall JC, Halligan PW, Frith CD, Frackowiak RS, Dolan RJ. Hemispheric specialization for global and local processing: the effect of stimulus category. Proc R Soc Lond B Biol Sci 1997d; 264: 487–94.

Freund H-J. Differential effects of cortical lesions in humans. In: Bock G, O'Connor M, Marsh J, editors. Motor areas of the cerebral cortex. Chichester: John Wiley; 1987. p. 269–81.

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

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

Frith CD. The cognitive neuropsychology of schizophrenia. Hove: Lawrence Erlbaum; 1992.

Frith CD, Friston K, Liddle PF, Frackowiak RS. Willed action and the prefrontal cortex in man: a study with PET. Proc R Soc Lond B Biol Sci 1991; 244: 241–6.

Fuster JM. Frontal lobes. [Review]. Curr Opin Neurobiol 1993; 3: 160–5.

Goldman-Rakic PS. Space and time in the mental universe. Nature 1997; 386: 559–60.

Halligan PW, Marshall JC. Perceptual cueing and perceptuo-motor compatibility in visuo-spatial neglect: a single case study. Cogn Neuropsychol 1989; 6: 423–35.

Helmholtz HLF von. Handbuch der physiologischen Optik. Leipzig: L. Voss; 1867.

Jeannerod M. The cognitive neuropsychology of action. Oxford: Blackwell; 1997.

Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA. Spatial working memory in humans as revealed by PET [see comments]. Nature 1993; 363: 623–5. Comment in: Nature 1993; 363: 583–4.

Knight RT, Grabowecky M. Escape from linear time: prefrontal cortex and conscious experience. In: Gazzaniga MS, editor. The cognitive neurosciences. Cambridge (MA): MIT Press; 1995. p. 1357–71.

Liepmann H. Drei Aufsätze aus dem Apraxiegebiet. Berlin: Karger; 1908.

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

Luria AR. Frontal lobe syndromes. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology; Vol. 2. Amsterdam: North-Holland; 1969. p. 725–57.

Mattingley JB, Driver J. Distinguishing sensory and motor deficits after parietal damage: an evaluation of response selection biases in unilateral neglect. In: Thier P, Karnath H-O, editors. Parietal lobe contributions to orientation in 3D space. Berlin: Springer; 1997. p. 309–337.

McCarthy RA, Warrington EK. Cognitive neuropsychology: a clinical introduction. San Diego (CA): Academic Press; 1990.

Miall RC, Wolpert DM. Forward models for physiological motor control. Neural Networks 1996; 9: 1265–79.

Milner AD, Goodale MA. The visual brain in action. Oxford: Oxford University Press; 1995.

Pardo JV, Fox PT, Raichle ME. Localization of a human system for sustained attention by positron emission tomography. Nature 1991; 349: 61–4.

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

Passingham RE. Attention to action. [Review]. Philos Trans R Soc Lond B Biol Sci 1996; 351: 1473–79.

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

Petrides M. Specialized systems for the processing of mnemonic information within the primate frontal cortex. [Review]. Phil Trans Roy Soc Lond B 1996; 351: 1455–1461.

Petrides M, Alivisatos B, Evans AC, Meyer E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc Natl Acad Sci USA 1993; 90: 873–7.

Petrides M, Pandya DN. Comparative architectonic analysis of the human and the macaque frontal cortex. In: Boller F, Spinnler H, Hendler JA, editors. Handbook of Neuropsychology; Vol. 9. Amsterdam: Elsevier; 1994. p. 17–58.

Picton TW, Stuss DT. Neurobiology of conscious experience. [Review]. Curr Opin Neurobiol 1994; 4: 256–65.

Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of area 9 and 46 and relationship to the Talairach Coordinate System. Cereb Cortex 1995; 5: 322–37.

Ramachandran VS, Rogers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. Proc R Soc Lond B Biol Sci 1996; 263: 377–86.

Rock I, Victor J. Vision and touch: an experimentally created conflict between the two senses. Science 1964; 143: 594–6.

Rushworth MF, Nixon PD, Eacott MJ, Passingham RE. Ventral prefrontal cortex is not essential for working memory. J Neurosci 1997; 17: 4829–38.

Sadato N, Yonekura Y, Waki A, Yamada H, Ishii Y. Role of the supplementary motor area and the right premotor cortex in the coordination of bimanual finger movements. J Neurosci 1997; 17: 9967–74.

Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y. The parietal association cortex in depth perception and visual control of hand action [see comments]. [Review] Trends Neurosci 1997; 20: 350–7. Comment in: Trends Neurosci 1998; 21: 63.

Shallice T. From neuropsychology to mental structure. Cambridge: Cambridge University Press; 1988.

Shallice T, Burgess P. The domain of supervisory processes and temporal organization of behaviour. [Review] Philos Trans R Soc Lond B Biol Sci 1996; 351: 1405–12.

Shulman GL, Corbetta M, Buckner RL, Raichle ME, Fiez JA, Miezin FM, et al. Top-down modulation of early sensory cortex. Cereb Cortex 1997; 7: 193–206.

Snyder LH, Batista AP, Andersen RA. Coding of intention in the posterior parietal cortex [see comments]. Nature 1997; 386: 167–70. Comment in: Nature 1997; 386: 122–3.

Stuss DT, Alexander MP, Palumbo CL, Buckle L, Sager L, Pogue J. Organizational strategies in patients with unilateral or bilateral frontal injury in word list learning tasks. Neuropsychology 1994a; 8: 355–73.

Stuss DT, Eskes GA, Foster JK. Experimental neuropsychological studies of frontal lobe functions. In: Boller F, Spinnler H, Hendler JA, editors. Handbook of neuropsychology; Vol. 9. Amsterdam; Elsevier, 1994b. p. 149–85.

Stuss DT, Alexander MP, Benson DF. Frontal lobe functions. In: Trimble MR, Cummings JL, editors. Contemporary behavioral neurology. Boston: Butterworth-Heinemann; 1997. p. 169–87.

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, et al. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J Neurophysiol 1996; 75: 454–68.

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

Tegner R, Levander M. Through a looking glass: a new technique to demonstrate directional hyperkinesia in unilateral neglect. Brain 1991; 114: 1943–51.

Thier P, Andersen RA. Electrical microstimulation suggests two different forms of representation of head-centered space in the intraparietal sulcus of rhesus monkey. Proc Natl Acad Sci USA 1996; 93: 4962–7.

von Holst E, Mittelstaedt H. Das Reafferenzprinzip. Wechselwirkung zwischen Zentralnervensystem und Peripherie. Naturwissenschaften 1950; 37: 464–76.

Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. Science 1995; 269: 1880–2.