Parallel visuomotor processing in the split brain: cortico-subcortical interactions

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Summary

We tested nine patients with callosal pathology in a simple reaction time task with and without redundant targets in the same or opposite visual hemifield. Four patients showed large facilitation (redundancy gain) in the presence of a redundant target, exceeding probability summation models (neural summation). Five patients showed redundancy gain not exceeding probability models. Violation of probability models was not associated with a specific type of callosal lesion. Neural summation, which probably occurs at collicular level, may be modulated by cortical activity. To test this hypothesis, we used functional MRI. During detection of redundant simultaneous targets, activations in the extrastriate cortex were observed in a patient with callosal agenesis and redundancy gain violating probability models, but not in a patient with callosal agenesis and redundancy gain not exceeding probability models. We conclude that cortical activity in the extrastriate cortex may be a modulating factor in the magnitude of the redundancy gain during parallel visuomotor transforms.

Introduction

Parallel sensorimotor processing, which is critical for efficient behaviour dealing with the multitude of stimuli in the surrounding world, can be investigated effectively by redundancy gain tasks (Todd, 1912). Redundancy gain occurs when reaction times (RT) to multiple copies of the same stimulus are faster than RTs to a single stimulus. This phenomenon has been explained traditionally according to two contrasting models: probability summation and neural co-activation (Miller, 1982). Probability summation assumes that redundancy gain occurs because of the summation of the independent probabilities of detecting each stimulus, such that a response can be initiated by the fastest channel. The upper limit of probability summation for a given number of identical stimuli can be computed by using the responses to single stimuli. When this limit is exceeded, the violation of probability models can be explained only by neural co-activation (Miller, 1982, 1986). Paradoxically, when simple (detection) RTs to two flashes of light presented in the two visual fields were compared with RT to a single flash in the visual field ipsilateral to the response hand, the redundancy

gain was found to be bigger in a split-brain patient than in normal subjects. Moreover, the redundancy gain observed in normal subjects could be accounted for by probability summation, whereas the redundancy gain observed in the split-brain patient could be accounted for only by neural co-activation (Reuter-Lorenz *et al.*, 1995). Even more paradoxically, the split-brain patient had 'visual extinction', and was not verbally aware of the presence of a redundant target facilitating the detection of the perceived stimulus (Reuter-Lorenz *et al.*, 1995). Similarly, the redundancy gain observed in right brain-damaged patients without visual extinction could be accounted for by probability summation, whereas the redundancy gain observed in right brain-damaged patients with visual extinction could be accounted for only by neural co-activation (Marzi *et al.*, 1996).

In a recent study, split-brain patients showing redundancy gain exceeding probability models when tested with stimuli and background of different luminance were also tested in the condition of equiluminance between stimuli and background (Corballis, 1998). Under this condition, the

redundancy gain in these patients was diminished and did not violate probability models. This was taken to suggest that neural co-activation occurs at a collicular level (Corballis, 1998), in keeping with animal data (Stein and Meredith, 1993). Experimental data in animals, however, suggest that specific cortex–midbrain interactions are essential to parallel sensorimotor processing (Wallace and Stein, 1994; Wilkinson *et al.*, 1996; Stein, 1998). In fact, the removal of the cortex around the anterior ectosylvian sulcus eliminates parallel multisensory processing in superior colliculus neurons in the cat (Wallace and Stein, 1994). In a later study, the reversible deactivation of the anterior ectosylvian sulcus produced a reversible deficit in parallel multisensory processing in superior colliculus neurons in the cat (Wilkinson *et al.*, 1996). In keeping with the animal data, the redundancy gain recently observed in hemispherectomy patients (in which cortex–midbrain interactions are reduced because of the lack of one hemisphere) was extremely small (Tomaiuolo *et al.*, 1997), even though the patients had preserved superior colliculi. However, the study with stimuli equiluminant to the background failed to show modulation of redundancy gain in a patient with callosal agenesis: a violation of probability models was observed in both the equiluminant and the non-equiluminant condition (Corballis, 1998). Thus, it is possible that differences in redundancy gain between patients are due to the complex interactions of midbrain and cortical structures in parallel visuomotor transforms. In fact, among the patients showing neural summation tested by Reuter-Lorenz and colleagues (Reuter-Lorenz *et al.*, 1995), Marzi and colleagues (Marzi *et al.*, 1996) and Corballis and colleagues (Corballis *et al.*, 1998), there is no common anatomical or neuro-psychological denominator. Cortical influence on collicular activity may be a way to unify seemingly disparate behaviours.

In this paper, we report data from two experiments that are relevant to these issues. In the first experiment, chronometric evidence in nine patients with callosal pathology confirmed that redundancy gain violating probability models is not associated with a specific type of callosal lesion. In the second experiment, using functional MRI (fMRI), different patterns of cortical activity during parallel visuomotor transforms were observed in patients with different types of redundancy gain. These data suggest that different patterns of cortical activity may modulate collicular activity differently, resulting in different types of facilitation during parallel visuomotor transforms.

Experiment 1: behavioural study
Methods
Subjects
Nine patients with different callosal pathology were studied. Two patients (L.B. and N.G.) had complete commissurotomy (Bogen *et al.*, 1988). Two patients (D.T. and G.C.) had complete callosotomy and three patients (B.M., J.P. and D.W.) had anterior callosal section. The partial callosotomy

in D.W. has been described previously (Iacoboni *et al.*, 1994). Finally, two patients (M.M. and J.L.) were born with callosal agenesis (Iacoboni *et al.*, 2000). All subjects gave written informed consent to participation in the study, which was carried out according to the ethics guidelines of the UCLA Institutional Review Board.

Apparatus and procedure
Subjects were seated in a dimly lit room at a distance of 57 cm from a Macintosh computer monitor, with the chin in a chinrest and the eyes aligned with the fixation cross that was presented throughout the experiment. The software program MacProbe was used to present stimuli and to record RT. Software characteristics are described elsewhere (Zaidel and Iacoboni, 1996). Stimuli consisted of black flashes on a grey background, subtending 1° of visual angle. They were presented for 50 ms, and were presented 500–2500 ms after a warning tone of 1000 Hz lasting 100 ms. Retinal eccentricity was 5° to the left or right of the vertical meridian and 5° above or below the horizontal meridian. Four frames at these locations were presented throughout the experiment. Light flashes were presented one in each visual hemifield ('between' condition), two in the same visual hemifield ('within' condition) or as one stimulus alone ('single' condition).

Subjects received 16 blocks of 45 trials each, 15 trials per condition. To minimize attentional components, before each block subjects were told to attend and respond to light flashes presented in one of the four frames. The order of attended frames was counterbalanced across blocks. A response panel was placed at the midline and used for manual responses. When D.T. was tested, the response panel was not available and the computer keyboard was used instead. Responses were performed with the index finger only. The use of the right or of the left index finger for motor responses and of the four attended locations was counterbalanced across blocks. The subject's task was to respond as fast as possible after detection of the stimulus presented at the attended location.

Data analysis
RTs of <140 ms were considered anticipatory errors, whereas RTs of >600 ms were considered attentional errors. When anticipatory and attentional errors occurred, a trial was added automatically, such that there was the same number of trials for every experimental condition. The median RT was used as the descriptive statistic in each condition in each response hand. The redundancy gain for the within condition in each response hand was computed by subtracting the median RT in the within condition from the median RT in the single condition, in both cases only for attended ipsilateral visual hemifield targets. The redundancy gain for the between condition in each response hand was computed by subtracting the median RT in the between condition from the median RT in the single condition, in both cases only for attended

ipsilateral visual hemifield targets. Interhemispheric conduction delays were computed by subtracting the median RT of the two uncrossed single conditions (left visual hemifield and left hand; right visual hemifield and right hand) from the two crossed single conditions (left visual hemifield and right hand; right visual hemifield and left hand) and dividing this difference by 2 (Poffenberger, 1912; Iacoboni and Zaidel, 1995).

To test whether the redundancy gain for the within and between conditions in each response hand violated probability models, we used the following logic: let P_{S1} be the probability of responding to a first stimulus and P_{S2} be the probability of responding to another stimulus, in a given time T. What probability models assume is that the probability P_{S1S2} of responding to redundant stimuli by time T is produced by the first arriving process (P_{S1} or P_{S2}). Whether P_{S1} and P_{S2} are independent (Meijers and Eijkman, 1977) or are not (Duncan, 1980), all probability models predict that

$$P(_{S1S2}) \leqslant P_{S1} + P_{S2} \qquad (1)$$

(Miller, 1982)

Inequality 1 creates an upper boundary to the facilitation occurring during detection of redundant targets for any time T [although, empirically, this generally occurs only at small values of T; see discussion on this issue in Miller (1982)]. This method has been used in recent studies on split-brain patients (Reuter-Lorenz *et al.*, 1995) and stroke patients (Marzi *et al.*, 1996). The study on the effect of equiluminance on split-brain patients, in contrast, has adopted the assumption of complete independence between P_{S1} and P_{S2} (Corballis, 1998). This assumption generates a slightly different way of calculating violation of probability models. The assumption of complete independence between P_{S1} and P_{S2} may be reasonable for stimuli presented in the two opposite visual hemifields in a patient with complete commissurotomy. In our study, however, it was difficult to assume complete independence between the two processes in the within condition, especially given the known anatomical connectedness of the cerebral cortex, where, according to detailed quantitative anatomical studies, each synapse is no more than three or four synapses away from any other synapse (Braitenberg and Schuz, 1991). Thus, we preferred to use inequality 1 to test probability models. Inequality 1 is also more satisfactory in that it does not require extra assumptions.

Empirically, we proceeded as follows. We first ranked ordered RT in each block in each condition. With the cumulative distribution functions (CDFs) of the RTs thus obtained, we computed an average 15-point CDF for each condition for each hand. This was done simply by averaging, across blocks, all the RTs at each point of the rank order. This approach has the desirable property of not being contaminated by practice effects or by differences in overall RT between blocks that may be due to fatigue or boredom (Ratcliff, 1979). Fatigue is especially a factor of concern when patients with serious neurological disorders, who are often receiving multiple anti-epileptic treatments, are tested.

However, it must be noted that this approach may bias the results towards the rejection of race-model inequality.

We then summed the CDFs for the ipsilateral and contralateral single condition, and the CDFs for the upper and lower locations of the visual field ipsilateral to the responding hand in the single condition. These summed CDFs were compared, respectively, with the CDFs of the between condition and of the within condition in the ipsilateral visual field in each response hand (as shown in Figs 3 and 4). When these CDFs are plotted, as in Figs 3 and 4, probability models require that CDFs of the between condition be everywhere to the right of the summed CDFs for the ipsilateral and contralateral single condition trials. Also, probability models require that CDFs of the within condition in the ipsilateral visual field be everywhere to the right of the summed CDFs for the upper and lower locations of the visual field ipsilateral to the responding hand in the single condition trial (Miller, 1982).

Results

The total percentage of errors was 3.4%, ranging from 0.8 to 5.1% in individual patients. Redundancy gains for the between and within conditions at each response hand in our nine patients are summarized in Fig. 1. As the figure shows, redundancy gains may be quite variable in the same patient. For instance, patient D.T. had a much larger redundancy gain when he responded with the right hand than with the left hand. The opposite pattern was observed in patient M.M. Patient N.G. had a much larger redundancy gain for the between conditions than for the within conditions. A similar pattern was observed in L.B., although less dramatically than in N.G. Some patients, such as J.P. and D.W., showed practically no facilitation.

When the data were analysed to test inequality 1, in five patients there was no violation of probability models (Fig. 2). In contrast, in four patients a violation of probability models was observed in one, two, or even all four conditions (Fig. 3). The presence or absence of violation of probability models was not associated with specific callosal pathology. For instance, the redundancy gain of acallosal patient J.L. violated probability models, whereas the redundancy gain of the other acallosal patient M.M. did not. Also, the redundancy gain of the complete callosotomy patient G.C. violated probability models, whereas the redundancy gain of the other complete callosotomy patient, D.T., did not. Redundancy gains violating probability summation, however, were found to be associated with long interhemispheric conduction delays, the critical transition occurring around 15 ms (Fig. 4).

Discussion

The chronometric results showed no clear-cut relationship between redundancy gain as described by descriptive statistics (subtraction of median RT of redundant target conditions from single target conditions) and as tested by inequality 1.
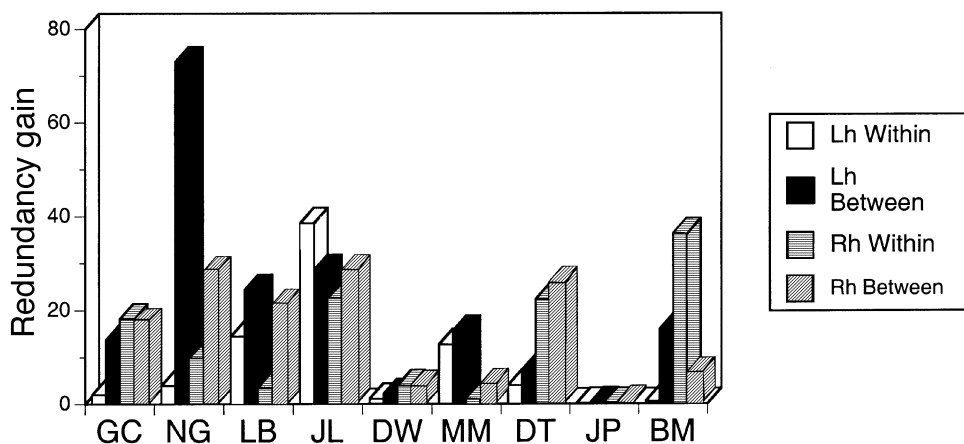
Fig. 1 Redundancy gains (in ms) in all four experimental conditions in all patients. Within = two light stimuli presented in the same visual hemifield; Between = two light stimuli presented one in each visual hemifield; Lh = response with left index finger; Rh = response with right index finger.
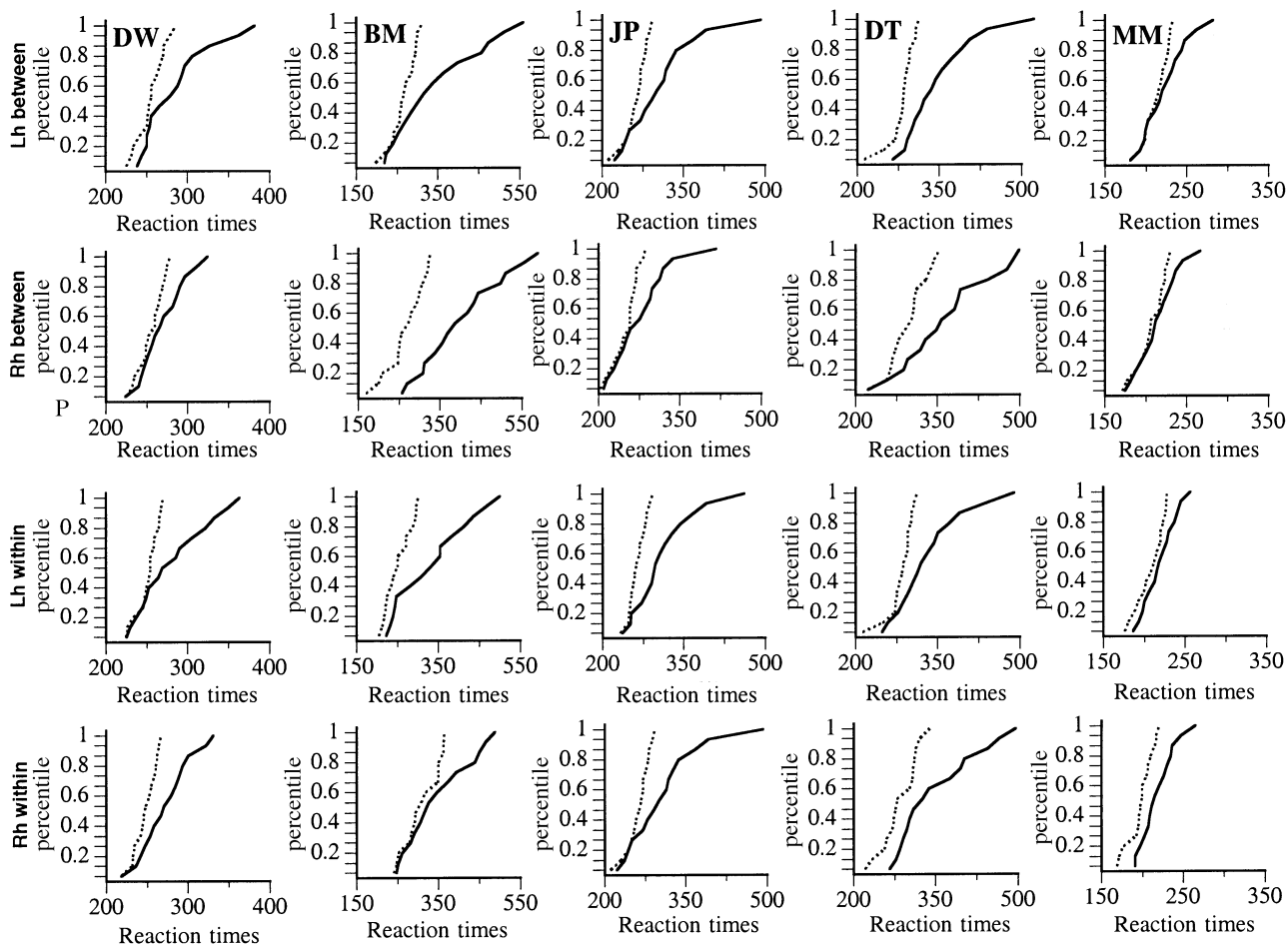

Fig. 2 Cumulative distribution functions of RT to double stimuli across the visual fields (continuous lines) and of the upper limit of probability summation (dotted lines). When the continuous line is to the left of the dotted line, statistical models are violated. No violation occurs in these five patients.

For instance, patient B.M. had, in the within condition for right-hand responses, a redundancy gain that was twice as great as the facilitation seen in the between condition for right-hand responses in patient G.C., as measured by descriptive statistics. However, inequality 1 was violated in G.C. for right-hand responses in the between condition but not in B.M. for right-hand responses in the within condition. To understand how this is possible, one must keep in mind that
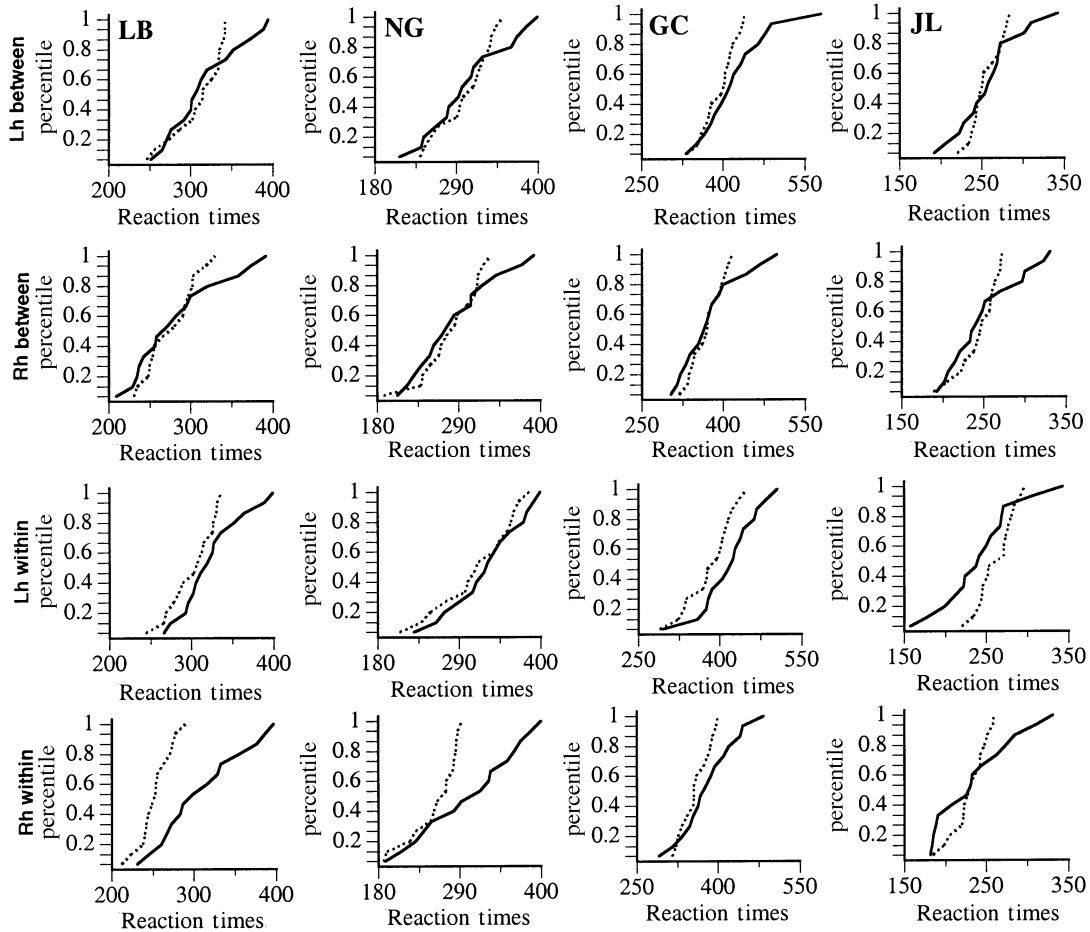
Fig. 3 Cumulative distribution functions of RT to double stimuli across the visual fields (continuous lines) and of the upper limit of probability summation (dotted lines). When the continuous line is to the left of the dotted line, statistical models are violated. Violation occurs in one or more conditions in these four patients.
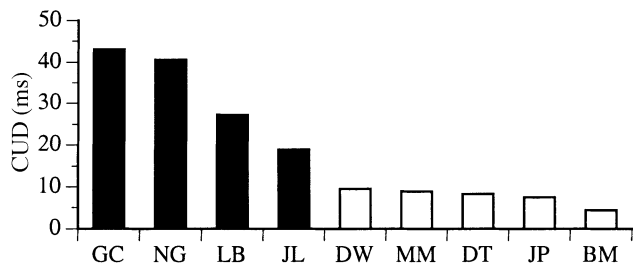

Fig. 4 The conduction delay (CUD) in the nine patients studied here. Black bars represent patients showing violation of probability summation models. White bars represent patients in which probability summation models are not violated. Patients with large redundancy gain violating probability summation have interhemispheric conduction delay >15 ms, whereas patients with small redundancy gain not violating probability summation have interhemispheric conduction delay <15 ms.

the use of inequality 1 makes race models more likely to be violated for small values of *T*. Thus, while the median RT is sampling the central part of the distribution of RT, violation of race models based on inequality 1 depends largely on the early part of the RT distribution.

The data of the first experiment seem to suggest that interhemispheric conduction delay is a critical parameter that determines a transition from redundancy gain compatible with statistical facilitation to redundancy gain violating probability models, as shown in Fig. 4. In keeping with this, patient G.C., who was the one showing violation of probability models only when responding with the right hand, also had a much longer transmission delay during right-hand responses (73 ms) than during left-hand responses (13 ms). One could speculate that the association observed between long interhemispheric conduction delays and violation of inequality 1 may be determined by the lack of synchronization between visual areas of the two hemispheres. Callosal fibres are critical structures for interhemispheric synchronization of neuronal activity (Engel *et al.*, 1991; Munk *et al.*, 1995). Synchronization seems a powerful stimulus–response binding mechanism (Konig and Engel, 1995; Engel *et al.*, 1997; Roelfsema *et al.*, 1997). Further, neuronal synchronization is best achieved among distant neuronal systems that are reciprocally connected in the presence of oscillatory firing patterns (Konig *et al.*, 1995). Specifically, reciprocal coupling of oscillating systems is best established if the conduction delays between the systems do not exceed one-third of the

cycle time (Engel *et al.*, 1991, 1992; Konig and Schillen, 1991; Konig *et al.*, 1995, 1996). Given that oscillatory firing patterns in the cerebral cortex are generally seen in the gamma band (30–70 Hz), a long interhemispheric conduction delay would interfere with interhemispheric synchronization. In fact, an interhemispheric conduction delay of >15 ms would interfere even with the slowest oscillation cycles.

Thus, the chain of events would go like this. (i) In a brain with an interhemispheric conduction delay <15 ms, when two stimuli are presented in the two visual hemifields the activity in the extrastriate cortex becomes synchronized. The two extrastriate cortices then input synchronously to the colliculus. (ii) In a brain with interhemispheric conduction delay >15 ms, when two stimuli are presented in the two visual hemifields, the activity in the extrastriate cortex cannot become synchronized because of the intrinsic properties of oscillating systems cited above. The extrastriate cortex is an oscillating system in that cortical activity oscillates in the gamma band. Thus, given that activity in the two extrastriate cortices is not synchronous, cortical input to the colliculus arrives independently from the two sides of the brain, resulting in a bigger cortical input summed over time. (iii) This bigger cortical input over time on the colliculus feeds back to the extrastriate cortex, speeding up responses and producing the activations that are observed. Note that the extrastriate cortex inputs to the premotor cortex, which has bilateral motor control [each premotor cortex controls both hands, as repeatedly shown in neuroimaging and neurophysiological studies (Passingham, 1993; Roland, 1993)]. So, regardless of which side becomes activated, one can see the behavioural effect on both hands.

One might think that this chain of events is too complex for simple RTs to lateralized flashes. Recent neurophysiological studies, however, suggest that this chain of events is compatible with the complex spatiotemporal dynamics of cortical activation during simple reaction times to lateralized flashes. In fact, electrical scalp recordings during simple reaction times to lateralized flashes (Saron *et al.*, 2000) have shown that what occurs is as follows. (i) There is an initial visual activation that occurs contralaterally to the stimulus <100 ms after stimulus presentation. (ii) There is an ipsilateral visual activation that occurs <150 ms after stimulus presentation. (iii) Depending upon the speed of the RTs, from the fastest to the slowest, there is (a) contralateral first and then bilateral motor activation, (b) bilateral motor activation, and (c) ipsilateral first and then bilateral motor activation (here, contralateral ad ipsilateral is related to the side of the response hand). (iv) Before response initiation, it is possible to observe in visual areas further contralateral and ipsilateral activations that are probably due to re-entrant signal from other cortical areas or from subcortical nuclei.

The association of long interhemispheric delays and the violation of race models, however, may simply be the result of using inequality 1 rather than equations that do not relax the assumption of stochastic independence (Corballis, 1998), as we explained in Methods in this section. More important,

we feel, is the issue of variability in chronometric estimates of interhemispheric conduction delays. This variability is quite large (Forster and Corballis, 1998; Iacoboni and Zaidel, 2000). Some of the patients tested in our first experiment have been tested repeatedly in our laboratory, and we have a good sense of the variability of chronometric estimates of interhemispheric delays in these patients. The data collected in the first experiment fit well with previous observations on the same patients. Some other patients, however, have been tested only once and we have no way of knowing the extent of the variability of chronometric estimates of interhemispheric delays in these patients. Thus, the association between neural summation and long interhemispheric conduction delays must be tested further in future studies.

The data of the first experiment do not support any relationship between violation of probability models and the type of callosal pathology. In fact, the four patients showing violation of inequality 1 in one or more conditions include two patients with complete commissurotomy, one patient with complete callosotomy and one patient with callosal agenesis. The five patients not showing violation of inequality 1 in any condition include three patients with anterior callosotomy, one patient with complete callosotomy and one patient with callosal agenesis. This is in keeping with previously published data on this paradigm in neurological patients (Reuter-Lorenz *et al.*, 1995; Marzi *et al.*, 1996; Corballis, 1998), in which no common anatomical denominator was observed.

The most likely site of neural summation is, as we said in the Introduction, the superior colliculus. Animal data suggest that the neuronal activity that subserves multisensory integration at the collicular level is heavily modulated by posterior cortical regions (Stein, 1998). Thus, differences in cortical activity in patients with and without neural summation may be a unifying explanation of seemingly different parallel visuomotor behaviours. To test this hypothesis, we performed the second experiment.

Experiment 2: fMRI
Methods
Subjects

The acallosal patients J.L. and M.M. were selected for the imaging study. These were the only two patients that fitted the three selection criteria that we adopted for our imaging study: (i) different parallel visuomotor transforms (J.L. has a large redundancy gain and violation of statistical models in all conditions; M.M. has small redundancy gain in all conditions and no violation of race inequality); (ii) the same anatomical status (J.L. and M.M. are both acallosal patients with similar colpocephaly, i.e. the ventricular enlargement often associated with callosal agenesis); (iii) no drug treatment that might affect cerebral blood flow in an uncontrolled fashion.
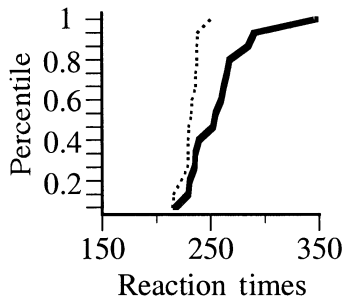
Fig. 5 Cumulative distribution functions of RT to double asynchronous stimuli across the visual fields (continuous line) and of the upper limit of probability summation (dotted line). When the continuous line is to the left of the dotted line, statistical models are violated. No violation occurs in J.L. under this condition.

Behavioural paradigm

The main interpretational limitation in an imaging study of redundancy gain is that, if one compares the brain activity while detecting two stimuli versus the brain activity while detecting a single stimulus, any observed difference in brain activity could be related to the unbalanced sensory input. To circumvent this problem, we tested whether the asynchronous presentation of redundant stimuli could be used as a control condition in the imaging study. In fact, we have evidence that in normal subjects the asynchronous presentation of double stimuli yields slower RTs than the simultaneous presentation of double stimuli (Iacoboni *et al.*, 1998*a*). Also, the asynchronous presentation of double stimuli affected the redundancy gain in the patient described by Reuter-Lorenz and colleagues (Reuter-Lorenz *et al.*, 1995). So, before the imaging study was planned, we performed two behavioural sessions with J.L. and M.M. that were identical to the previous sessions described above, except that redundant stimuli were presented with a stimulus onset asynchrony (SOA) of 30 ms. The first stimulus presented was always the attended one. To test whether probability models are violated during detection of asynchronous stimuli, inequality 1 must be modified. In asynchronous presentation, processes P_{S1} and P_{S2} do not start at the same time, and completion times must be corrected for the SOA. Thus, assuming that P_{S1} is the sensorimotor process related to responding to the first stimulus and P_{S2} is the sensorimotor process related to responding to the second stimulus, an inequality that can be applied in these cases is:

$$P(RT_{S1S2}) \leqslant P(RT_{S1}) + P(RT_{S2} - SOA) \qquad (2)$$

(Miller, 1986).

Thus, inequality 2 was used to test probability models in this experiment.

For right-hand responses to asynchronous stimuli, the redundancy gain in M.M. was 11.2 ms in the between condition and 11.5 ms in the within condition. For left-hand responses to asynchronous stimuli, the redundancy gain in M.M. was 7.4 ms in the between condition and 2 ms in the within condition. For right-hand responses to asynchronous

stimuli, the redundancy gain in J.L. was 1 ms in the between condition and 4 ms in the within condition. For left-hand responses to asynchronous stimuli, the redundancy gain in J.L. was 2.1 ms in the between condition and 1.6 ms in the within condition.

When inequality 2 was applied to the data obtained from J.L. and M.M., no violation of probability models was observed (Fig. 5). Because of this result, we considered the detection of redundant asynchronous stimuli an optimal control condition for our imaging study on redundancy gain, in that redundant asynchronous targets did not produce the paradoxical facilitation observed in J.L. during the detection of simultaneous redundant targets, and allowed the balancing of sensory inputs between the two detection tasks for simultaneous and asynchronous redundant targets.

Imaging

We performed fMRI on J.L. and M.M. with a GE 3.0 T scanner with ANMR upgrade using an echo-planar T_2*-weighted gradient echo sequence [TR (repetition time) = 2.5 s; TE (echo time) = 40 ms; flip angle = 80°; 64 × 64 matrix; 16 axial slices; 3.125 mm in-plane resolution; 4 mm thickness; skip 1 mm]. Each subject had one fMRI scan of 4 min. Task conditions were (i) detection of double simultaneous lateralized flashes in both visual fields and (ii) detection of double asynchronous (30 ms) lateralized flashes in both visual fields. The software MacProbe was used for stimulus presentation and recording the responses (Zaidel and Iacoboni, 1996). The fMRI unit was equipped with a stimulation and response recording environment controlled by a Macintosh computer system. Visual stimuli were provided with a magnet-compatible Resonance Technology 3D Visual Stimulation device. A magnet-compatible electrostatic pointing device was used. This device is based upon an ALPSGlide Point (Alps Electronics, San Jose, Calif., USA) with multiple response buttons that is connected to a remote stimulus display and response computers via a twisted-pair differential line driver that passes through the MR scanner filter panel and then to the Macintosh ADB port.

In each trial there was a random time window of 1500 ms for stimulus presentation. The purpose of this was to avoid anticipation of responses in this detection task, in which no response selection is required. The random time windows and the variable RT at each trial were compensated by the computer to obtain a fixed total trial time of 2.5 s. Presentation of asynchronous and simultaneous stimuli were alternated in blocks of 30 s, for a total of 12 trials per block (2.5 s per trial) and a total of four blocks per type of presentation. To minimize attentional components, the subjects were instructed to respond to flashes presented at the upper right frame. In the case of double asynchronous flashes, the stimulus presented at the attended location was always the first to be presented. Subjects responded with their right hand and were not told that redundant stimuli were either asynchronous or simultaneous. When interviewed after the fMRI scan, both

J.L. and M.M. reported that they did not notice any difference between asynchronous and simultaneous stimuli.

Images were co-registered using automated image registration (AIR) (Woods *et al.*, 1998). Global normalization was applied (Mazziotta *et al.*, 1985). A contrast analysis was performed using the normalized signal intensity in each voxel as the dependent variable and with blocks (one to four), type of presentation (asynchronous, simultaneous) and brain volumes per block (one to twelve) as between-voxel effects (Woods *et al.*, 1996). Statistical thresholds, estimating variance separately for each voxel, were adjusted for multiple spatial comparisons comprising the whole brain in the field of view as the search region of interest (Worsley *et al.*, 1996). This is the approach we typically use in our imaging studies (Iacoboni *et al.*, 1996, 1997, 1998b). Functional images were finally co-registered with T$_1$-weighted anatom-

ical images of the patients' brains for the localization of functional activations.

Results

In J.L., the median RT to redundant simultaneous stimuli was 23 ms faster ($P = 0.005$, two-tailed unpaired t test) than to redundant asynchronous stimuli. In M.M., the median RT to redundant simultaneous stimuli was not significantly faster (10 ms, $P = 0.266$, two-tailed unpaired t test) than to redundant asynchronous stimuli. Inequalities 1 and 2 could not obviously be tested, given that no responses to single flashes were made during the imaging session. A significant change in signal intensity between the detection of simultaneous redundant targets and of asynchronous redundant targets ($t = 6.72$, $P < 0.05$ corrected for multiple
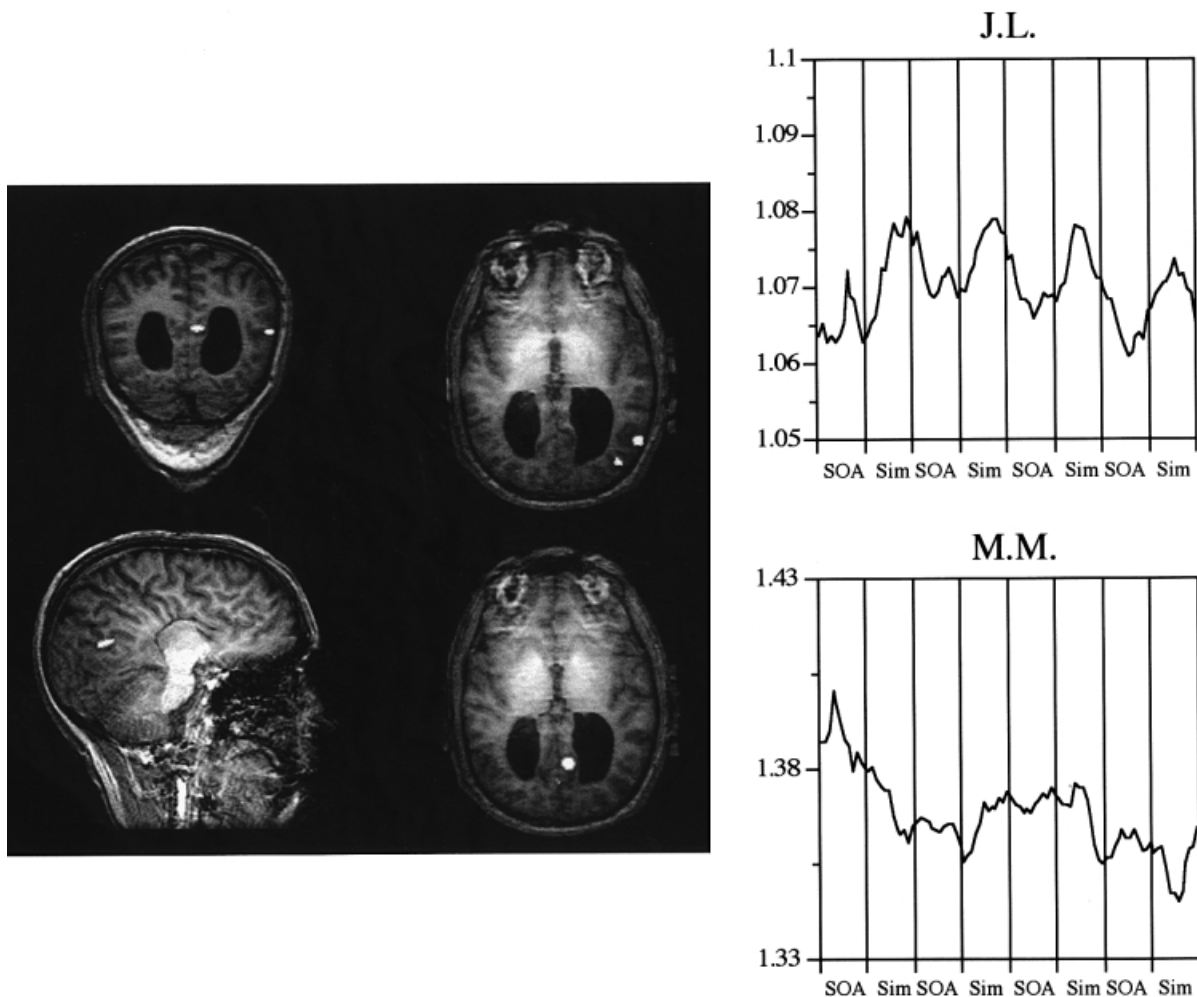

Fig. 6 (*Left*) Significant changes in signal intensity (white) between detection of simultaneous redundant targets and of asynchronous redundant targets ($P < 0.05$, corrected for multiple spatial comparisons considering the whole brain in the field of view as region of interest) in J.L. Activations are observed in the medial and lateral extrastriate areas. A T$_1$ structural MRI of the patient's brain is used for anatomical localization. fMRIs were co-registered with the structural image using AIR. Colpocephaly (ventricular enlargement), typically associated with callosal agenesis, can be observed in these MRIs. (*Top right*) fMRI time series in activated extrastriate areas in J.L. Task-related activity is clearly visible in this time series. (*Bottom right*) fMRI time series in extrastriate areas in M.M. that were manually drawn and corresponded roughly to the location of the activated areas in J.L. (activation maps did not show reliably activated voxels in M.M.). No task-related activity is visible in M.M.'s extrastriate cortex.

spatial comparisons considering the whole brain in the field of view as region of interest) was observed in the right medial and lateral occipital areas in J.L. but not in M.M. (Fig. 6). In M.M., we also performed a statistical analysis at $P = 0.05$, uncorrected for multiple comparisons, which is the most liberal statistical approach we can reasonable have. This was done in order to test possible trends of activation that did not reach rigorous statistical thresholds. Only isolated voxels were found to be 'active', and no cluster of at least four activated voxels was observed with this approach. This pattern is typical of noise in the imaging data set. Thus, to show the differences between the two patients at the level of cortical activity (given that activation maps failed to show anything at all in M.M.), we plotted the activity of the activated regions in J.L. and of roughly corresponding regions in M.M., drawn manually. The time series in the extrastriate cortex in the two patients are shown in Fig. 6. A clear task-related activity was observed in J.L. but not in M.M.

Discussion

In an activation study in which redundant stimuli were presented either simultaneously or asynchronously, we found that J.L. had reliably shorter RT for simultaneous stimuli and reliable activations in extrastriate areas in the right hemisphere. The other patient, M.M., in contrast, did not show reliable differences in RT and in blood flow (this is why 'activation maps' were not presented for this patient, no activation being detected) between the two tasks. These two patients were selected for the imaging study because of their contrasting performance in parallel visuomotor transforms, their common anatomical status and the absence of pharmacological treatment that may alter cerebral blood flow.

The fMRI data support the hypothesis that, even though neural summation during parallel visuomotor transforms occurs at the collicular level, the cortical modulation of collicular activity is important for neural summation. This provides a unified physiological mechanism of neural summation in patients with different anatomical status. The extrastriate activations in J.L. were lateralized to the right hemisphere, even though the subject was responding with the right hand and was instructed to respond to the right-sided stimulus. This lateralization is consistent with a generally larger violation of probability summation models when patients respond with the left hand (Fig. 2). If our hypothesis on the association of long interhemispheric conduction delays and neural summation is correct, then this lateralization of activation may be explained by asymmetrical conduction delays from one hemisphere to the other, such that the timing of staggered interhemispheric visual input differs in the two hemispheres, producing differential activation due to different types of temporal summation in extrastriate areas. Asymmetries in conduction delays from one hemisphere to the contralateral one have been hypothesized in subjects with an intact corpus callosum (Marzi *et al.*, 1991) but not in acallosal patients. Our fMRI findings might imply

that asymmetrical conduction delay is a general principle of interhemispheric (callosal or extracallosal) pathways.

We cannot exclude, however, that the acallosal patients studied with fMRI here are somewhat different from the surgical patients. Thus, our conclusions may not apply to all cases.

Conclusion

The findings obtained during the behavioural and the imaging study are in agreement with specific predictions drawn from animal models of parallel sensorimotor processing. The behavioural study demonstrated that neural summation is not associated with a specific anatomical status. When two patients, one with and one without neural summation, were studied with fMRI, the cortical pattern of activity in the extrastriate areas differed between them, with task-related activity in the extrastriate cortex of the patient with neural summation and absence of task-related activity in the extrastriate cortex of the patient without neural summation. Taken together, these data suggest that, even though the superior colliculus is the probable site of neural summation during parallel visuomotor transforms, its activity depends critically on cortical modulation. Indeed, additional evidence for extrastriate modulation of redundancy gain has also been provided in the normal brain with electrical scalp recording (Miniussi *et al.*, 1998).

References

Bogen JE, Schultz DH, Vogel PJ. Completeness of callosotomy shown by magnetic resonance imaging in the long term. Arch Neurol 1988; 45: 1203–5.

Braitenberg V, Schuz A. Anatomy of the cortex: statistics and geometry. Studies of brain function, Vol. 18. Berlin: Springer-Verlag; 1991.

Corballis MC. Interhemispheric neural summation in the absence of the corpus callosum. Brain 1998; 121: 1795–807.

Duncan J. The locus of interference in the perception of simultaneous stimuli. Psychol Rev 1980; 87: 272–300.

Engel AK, Konig P, Kreiter AK, Singer W. Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. Science 1991; 252: 1177–9.

Engel AK, Konig P, Kreiter AK, Schillen TB, Singer W. Temporal coding in the visual cortex: new vistas on integration in the nervous system. [Review]. Trends Neurosci 1992; 15: 218–26.

Engel AK, Roelfsema PR, Fries P, Brecht M, Singer W. Role of the temporal domain for response selection and perceptual binding. [Review]. Cereb Cortex 1997; 7: 571–82.

Forster B, Corballis MC. Interhemispheric transmission times in the presence and absence of the forebrain commissures: effects of luminance and equiluminance. Neuropsychologia 1998; 36: 925–34.

Iacoboni M, Zaidel E. Channels of the corpus callosum: evidence from simple reaction times to lateralized flashes in the normal and the split brain. Brain 1995; 118: 779–88.

Iacoboni M, Zaidel E. Crossed–uncrossed difference in simple reaction times to lateralized flashes: between- and within-subjects variability. Neuropsychologia. In press 2000.

Iacoboni M, Fried I, Zaidel E. Callosal transmission time before and after partial commissurotomy. Neuroreport 1994; 5: 2521–4.

Iacoboni M, Woods RP, Mazziotta JC. Brain–behavior relationships: evidence from practice effects in spatial stimulus–response compatibility. J Neurophysiol 1996; 76: 321–31.

Iacoboni M, Woods RP, Lenzi GL, Mazziotta JC. Merging of oculomotor and somatomotor space coding in the human right precentral gyrus. Brain 1997; 120: 1635–45.

Iacoboni M, Rayman J, Zaidel E. Contextual facilitation in sensorimotor integration [abstract]. J Int Neuropsychol Soc 1998a; 4: 60–1.

Iacoboni M, Woods RP, Mazziotta JC. Bimodal (auditory and visual) left frontoparietal circuitry for sensorimotor integration and sensorimotor learning. Brain 1998b; 121: 2135–43.

Iacoboni M, Bialik MH, Sicotte N, Zaidel E. Sensorimotor integration in agenesis of the corpus callosum. In: Zaidel E, Iacoboni M, editors. The parallel brain: the cognitive neuroscience of the corpus callosum functions. Cambridge (MA): MIT Press. In press 2000.

Konig P, Engel AK. Correlated firing in sensory-motor systems. [Review]. Curr Opin Neurobiol 1995; 5: 511–9.

Konig P, Schillen TB. Stimulus-dependent assembly formation of oscillatory responses. I. Synchronization. Neural Comput 1991; 3: 155–66.

Konig P, Engel AK, Singer W. Relation between oscillatory activity and long-range synchronization in cat visual cortex. [Review]. Proc Natl Acad Sci USA 1995; 92: 290–4.

Konig P, Engel AK, Singer W. Integrator or coincidence detector? The role of the cortical neuron revisited. Trends Neurosci 1996; 19: 130–7.

Marzi CA, Bisiacchi P, Nicoletti R. Is interhemispheric transfer of visuomotor information asymmetric? Evidence from a meta-analysis. Neuropsychologia 1991; 29: 1163–77.

Marzi CA, Smania N, Martini MC, Gambina G, Tomelleri G, Palamara A, et al. Implicit redundant-targets effect in visual extinction. Neuropsychologia 1996; 34: 9–22.

Mazziotta JC, Huang SC, Phelps ME, Carson RE, MacDonald NS, Mahoney K. A noninvasive positron computed tomography technique using oxygen-15-labeled water for the evaluation of neurobehavioral task batteries. J Cereb Blood Flow Metab 1985; 5: 70–8.

Meijers LM, Eijkman EG. Distributions of simple RT with single and double stimuli. Percept Psychophys 1977; 22: 41–8.

Miller J. Divided attention: evidence for coactivation with redundant signals. Cognit Psychol 1982; 14: 247–79.

Miller J. Timecourse of coactivation in bimodal divided attention. Percept Psychophys 1986; 40: 331–43.

Miniussi C, Girelli M, Marzi CA. Neural site of the redundant target effect: electrophysiological evidence. J Cogn Neurosci 1998; 10: 216–30.

Munk MH, Nowak LG, Nelson JI, Bullier J. Structural basis of cortical synchronization. II. Effects of cortical lesions. J Neurophysiol 1995; 74: 2401–14.

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

Poffenberger A. Reaction time to retinal stimulation with special reference to the time lost in conduction through nervous centers. Arch Psychol 1912; 23: 1–73.

Ratcliff R. Group reaction time distributions and an analysis of distribution statistics. Psychol Bull 1979; 86: 446–61.

Reuter-Lorenz PA, Nozawa G, Gazzaniga MS, Hughes HC. Fate of neglected targets: a chronometric analysis of redundant target effects in the bisected brain. J Exp Psychol: Hum Percept Perform 1995; 21: 211–30.

Roelfsema PR, Engel AK, Konig P, Singer W. Visuomotor integration is associated with zero time-lag synchronization among cortical areas. Nature 1997; 385: 157–61.

Roland PE. Brain activation. New York: Wiley; 1993.

Saron CD, Foxe JJ, Simpson GV and Vaughan HG. Spatiotemporal electrophysiology of interhemispheric visuomotor integration: relations with behavior. In: Zaidel E, Iacoboni M, editors. The parallel brain: the cognitive neuroscience of the corpus callosum. Cambridge (MA): MIT Press. In press 2000.

Stein BE. Neural mechanisms for synthesizing sensory information and producing adaptive behaviors. [Review]. Exp Brain Res 1998; 123: 124–35.

Stein BE, Meredith MA. The merging of the senses. Cambridge (MA): MIT Press; 1993.

Todd JW. Reaction to multiple stimuli. New York: Science Press; 1912.

Tomaiuolo F, Ptito M, Marzi CA, Paus T, Ptito A. Blindsight in hemispherectomized patients as revealed by spatial summation across the vertical meridian. Brain 1997; 120: 795–803.

Wallace MT, Stein BE. Cross-modal synthesis in the midbrain depends on input from cortex. J Neurophysiol 1994; 71: 429–32.

Wilkinson LK, Meredith MA, Stein BE. The role of anterior ectosylvian cortex in cross-modality orientation and approach behavior. Exp Brain Res 1996; 112: 1–10.

Woods RP, Iacoboni M, Grafton ST, Mazziotta JC. Improved analysis of functional activation studies involving within-subject replications using a three-way ANOVA model. In: Myers R, Cunningham V, Bailey D, Jones T, editors. Quantification of brain function using PET. San Diego: Academic Press; 1996. p. 353–8.

Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC. Automated image registration: I. General methods and intrasubject, intramodality validation. J Comput Assist Tomogr 1998; 22: 139–52.

Worsley KJ, Marrett S, Neelin PA, Vandal AC, Friston KJ, Evans AC. A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp 1996; 4: 58–73.

Zaidel E, Iacoboni M. Using a computerized system for behavioral laterality experiments. Brain 1996; 119: 2155–6.