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Neural activity during attention shifts between object features

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To investigate the neural mechanisms involved in shifting attention we used positron emission tomography to examine regional cerebral blood flow (rCBF) during a task that demands shifting attention between color and shape. Significant activation was observed in the right dorsal prefrontal cortex and parieto-occipital cortex at all frequencies of attention shifts. The frequency of shifts between categories correlated significantly with rCBF in the rostral part of the supplementary motor area and the left precuneus, whereas the number of successive correct responses correlated with rCBF in the orbitofrontal cortex and the caudate nucleus. This study suggests that several prefrontal regions may participate in the processes of shifting attention in different ways. *NeuroReport* **9: 2633–2638 © 1998 Rapid Science Ltd.**

Key words: Attention; Cerebral blood flow; Prefrontal; Presupplementary motor area; Shift; Supplementary motor area

Introduction

Damage to prefrontal regions of the human brain can cause characteristic cognitive or affective deficits. Dorsolateral prefrontal damage tends to impair such abilities as planning and monitoring of information,[1] while patients with orbitofrontal lesions show altered emotion or socially inappropriate behavior.[2] The ability to shift cognitive set, which is traditionally assessed using the Wisconsin Card Sorting Test (WCST), is also impaired by frontal lobe lesions.[3] Patients with frontal lobe damage frequently continue to sort cards according to a previous rule, even when the rule has clearly been changed (e.g., from color to shape). However, this test is not always differentially sensitive to frontal lobe dysfunction, and diffuse or non-frontal brain damage can produce similar deficits.[4,5] Although attention set shift is a core component of the WCST, it is a complex task that includes several other cognitive processes, such as rule learning and concept formation. Therefore, it is not clear whether the deficit on the WCST in non-frontal patients is qualitatively equal to that in frontal patients.

Recently, several neuroimaging procedures, such as positron emission tomography (PET) and functional magnetic resonance imaging, have been used to determine neural substrata corresponding to a variety of human cognitive process. Previous PET studies have shown that neural activity is increased in the dorsolateral and ventral prefrontal, inferior parietal, and occipital cortices and the cerebellum during the WCST.[6,7] Since it is a complex task, it is somewhat difficult to analyze the relationship between the cognitive processes involved in the WCST and the brain area activated during the task. Therefore, to further investigate the neural mechanisms involved in shifting attention set, we developed a simplified card sort task that requires shifting attention between only two categories (color and shape), and examined regional cerebral blood flow (rCBF) during the task using PET. The number of attention shifts between categories was varied on successive scans, therefore we were able to estimate the relationship between the changes in neural activity in particular brain regions and the number of attention shifts.

Subjects and Methods

Subjects: We studied six right-handed male volunteers (age 22–26 years). Written consent was obtained after the nature of the study had been fully explained. Approval for the experiments was given by the Ethics Committee at Fukui Medical School.

Experimental design: The rCBF was examined while the subjects performed a Weigl-type card sort task.[8] A set of cards with color figures (Fig. 1A) was presented on a monitor placed 50 cm in front of the subject using a Macprobe (Aristometrics, Castro Valley, CA, USA) on a Power Macintosh (Apple Computer Inc., Cupertino, CA, USA). We deliberately selected ambiguous colors and shapes so that the subject would not be able to name them easily. The subjects had to match a test card to one of the two target cards according to color or shape. The stimulus was displayed on the monitor until the subject responded (or 2 s maximum), and the subject selected an answer by pushing the left or right button with his right index and middle fingers (e.g. by color, Fig. 1A-1). The answer and the reaction time (RT) between the onset of stimulus and the response were recorded. A green circle or red X appeared at the center of the monitor for 600 ms to indicate whether each response was correct or incorrect, then all cards disappeared, and the next set of cards was presented immediately afterward. After a prescribed number of successive correct responses to one category, the rule was changed without warning (sorting by color became incorrect, Fig. 1A-2), and the subject had to shift the sorting criterion to another category (by shape, Fig. 1A-3). Sixty-four sets of stimuli were presented in a session. To prevent the subject counting the presentation series to solve the task, the number of successive correct responses within each session swayed between the mean ± 1. The mean number of successive correct responses varied between 16, 10, 6 and 2, which resulted in attention being shifted 2.1 ± 0.3, 3.1 ± 0.3, 4.3 ± 0.5 and 9.8 ± 0.9 times during a scan, respectively (mean ± s.d.). To minimize the effect of rule learning and differences in problem-solving strategy among the subjects, we fully instructed the subjects as to the rules of the task, and before the PET scan, we trained them until they could perform the task without difficulty.

The control task was a simple literal matching task, in which one of the targets was identical to the test card (Fig. 1B). The parameters of stimulus presentation and feedback were the same as in the card sort task.

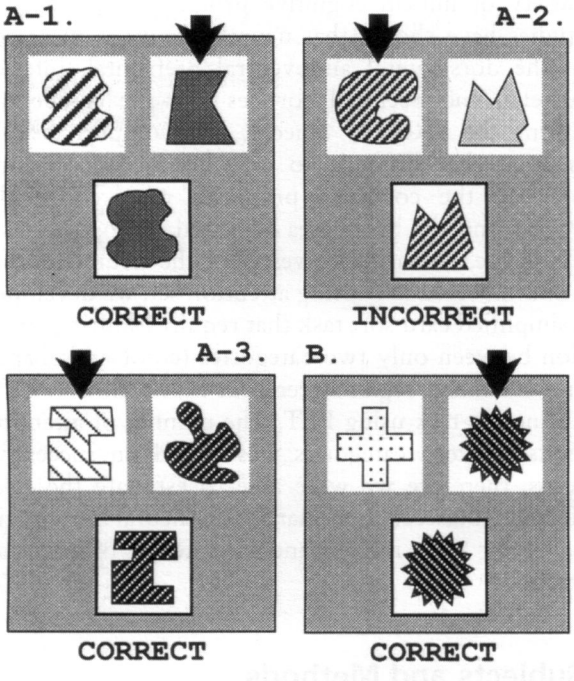

FIG. 1. Scheme of the tasks. (**A-1**–**A-3**). The Weigl-type card sort task. The upper two cards are target cards, and the lower one is a test card. The subject's answers are indicated by thick arrows. (A-1) The subject matches the test card to the target by color, and it is correct. (A-2) After a prescribed number of cards is sorted by color, the feedback response becomes incorrect. (A-3) The subject has to shift the sorting rule from color to shape to yield correct answers. (**B**) The simple literal matching task used as a control.

PET data acquisition: The tasks were started 15 s before injection of $H_2{}^{15}O$ and continued throughout the scanning. Each subject was scanned twice for control and each level of attention shift frequency (10 scans total). The rCBF was measured using a General Electric Advance tomograph (GE-YMS, Tokyo, Japan) with the interslice septa retracted. This scanner acquires 35 slices with an interslice spacing of 4.25 mm. Each subject received 370 MBq $H_2{}^{15}O$ for each scan, and the data were collected for 60 s following the first detection of an increase in cerebral radioactivity.[9] The images were reconstructed into 128 × 128 pixels (2.0 × 2.0 mm size) with Hanning filters, giving final transaxial and axial resolutions of 6 and 10 mm full-width at half-maximum, respectively.

Data analysis: Each response of the subjects was classified as the (successive) correct response, proper shift response, and the error. The RT for the proper shift responses and that for the successive correct responses were used for analysis, and the RT for the errors were excluded from analysis.

The PET data were analyzed with SPM95 (Wellcome Department of Cognitive Neurology, London, UK).[10] The images were realigned to correct for head motion, and transformed into a standard stereotactic anatomical space.[11] PET images were then smoothed with a 16 mm gaussian filter to reduce the variance due to individual anatomical variability. The resulting voxel size was 2 × 2 × 4 mm. Thereafter, the effect of differences in global CBF across scans or subjects was removed using analysis of covariance. This process generated a condition-specific adjusted mean

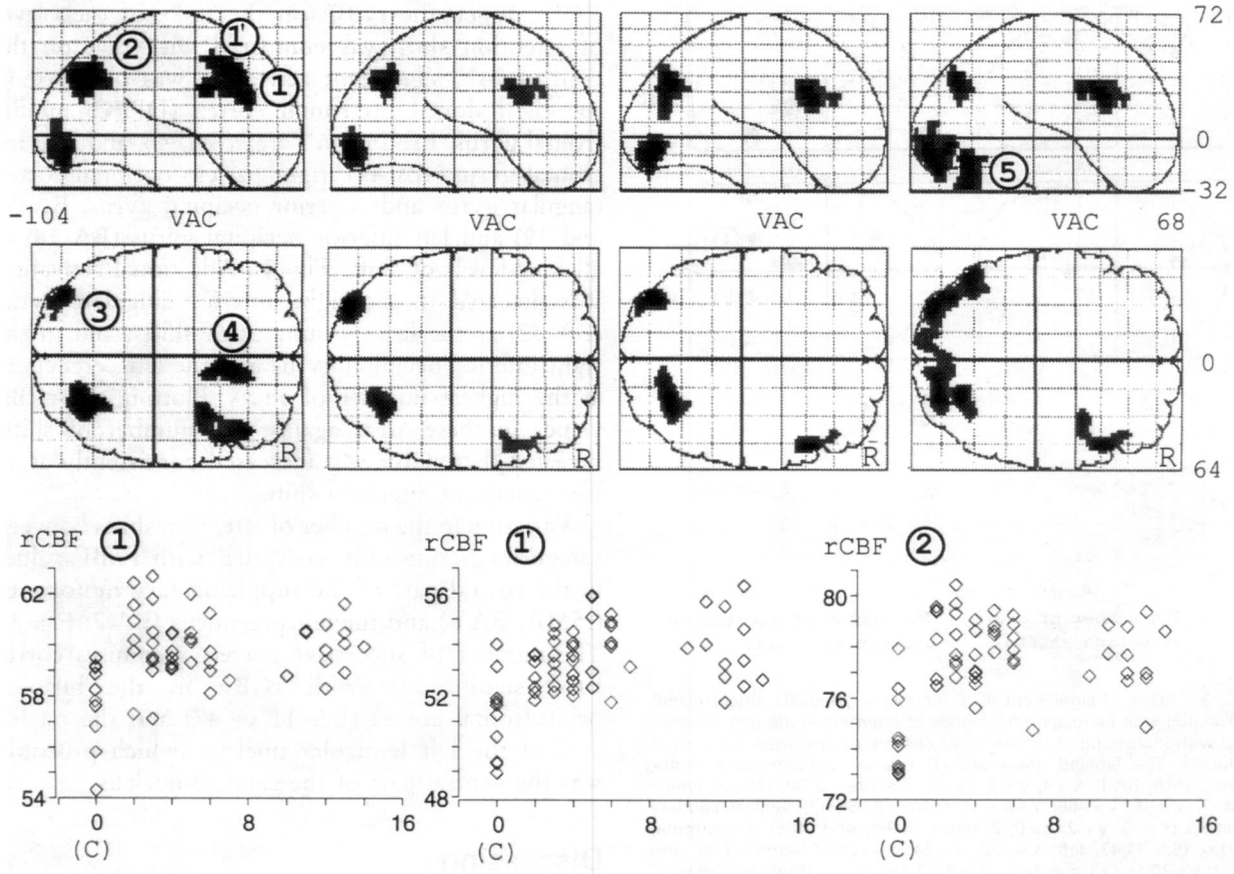

FIG. 2 Cerebral activation during the card sort task compared with the control task. Upper two rows: Areas of significant rCBF increases ($p < 0.05$, corrected for multiple comparisons) are shown as sagittal and transverse projections of the brain. From left to right, we showed rCBF increases in tasks with frequencies of attention shifts of 2.1 ± 0.3, 3.1 ± 0.3, 4.3 ± 0.5 and 9.8 ± 0.9 during a scan. The labeled areas are: (1) right middle frontal gyrus (Brodmann's area (BA) 46, Talairach's coordinates of x = 44, y = 30, z = 24), (1′) right inferior frontal gyrus (BA 44, x = 52, y = 16, z = 24), (2) right parieto-occipital cortex (BA 39 and 19, x = 24, y = –74, z = 32), (3) left inferior occipital gyrus (BA 18, x = –34, y = –92, z = –8), (4) right anterior cingulate gyrus (BA 32, x = 10, y = 24, z = 36), and (5) left cerebellum (x = –42, y = –66, z = –28). VAC, vertical plane through the anterior commissure; R, right. Lowest row: Representative plotting of the rCBF (ml/dl/min, y axis) in the labeled areas 1, 1′ and 2 against frequency of attention shifts (x axis). C, the control task.

rCBF value (50 ml/dl/min) and an associated adjusted error variance for each voxel; this allowed us to make comparisons of the mean CBF distributions across all sets of conditions and subjects.

Two statistical analyses were performed. First, the main effects of test conditions (each shift level *vs* control) were estimated. The mean rCBF was calculated separately for each of the main effects for each voxel, and comparisons of the means were made using t-statistics and then transformed into normally distributed Z-statistics, yielding a statistical map (SPM{Z}) for each contrast. The level of significance was set at $p < 0.05$, corrected for multiple non-independent comparisons. Second, significant co-variation of rCBF with the frequency of attention shifts in each session and significant co-variation of rCBF with the mean number of successive correct responses were assessed. The significance level was set at $p < 0.001$ without correction.

Results

Behavioral performances: The subjects performed well in all the tasks and made few errors (Table 1). The numbers of errors were comparable among different levels of shift frequency ($F = 1.16$, $p = 0.35$, analysis of variance (ANOVA)). The RT in the control task was significantly faster than that in the attention shift task (515 ± 108 ms *vs* 709 ± 222 ms, respectively, $F = 553.9$, $p < 0.001$). The RT for the shift responses were slower than that for the successive correct responses in all shift frequencies, and the RT for the correct responses tended to be slower at higher frequencies. Two-way ANOVA revealed significant effects of both the shift frequency ($F = 3.25$, $p = 0.02$) and the response type (RT for the shift responses *vs* that for the correct responses ($F = 22.1$, $p < 0.001$) without no significant interaction ($p = 0.60$). *Post-hoc* test with Bonferroni's

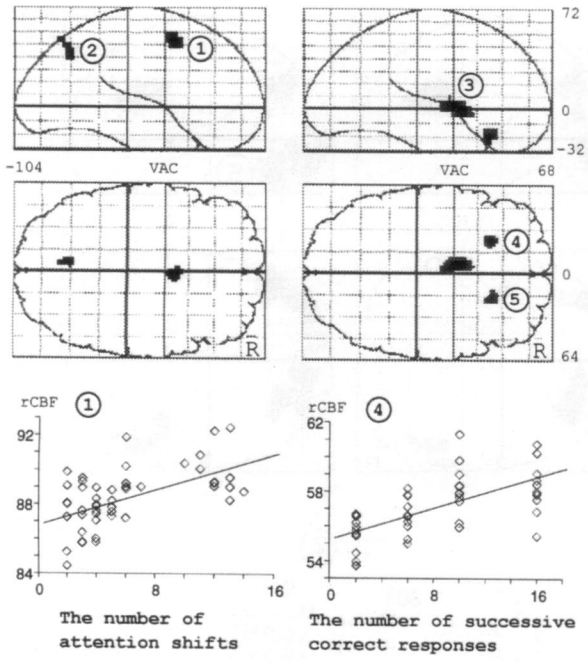

FIG. 3. Areas of significant rCBF increases ($p < 0.001$, uncorrected) correlated with increasing frequency of attention shifts (left column) and with increasing numbers of successive correct responses (right column). The labeled areas are (1) rostral supplementary motor area (rSMA, BA 6, x = 4, y = 4, z = 48, Z score = 3.74), (2) precuneus (BA 7, x = –4, y = –66, z = 40, Z score = 3.46), (3) ventral caudate nucleus (x = –6, y = 2, z = 0, Z score = 4.90), and (4)(5) orbitofrontal cortex (BA 11/47, left; x = –22, y = 24, z = –20, Z score = 4.60, and right; x = 20, y = 26, z = –16, Z score = 3.48). The scattergrams of rCBF (ml/dl/min) in the rSMA (lower left) and the left orbitofrontal cortex (lower right) are also shown.

correction showed that the RT for the shift responses was significantly slower than that for the correct responses at the low shift frequency.

To reveal the effects of practice in making responses, especially during a long succession of correct responses, we examined the time effects on the RT during the task with the lowest shift frequency. The time effects within a session (early, middle and late phases in a session) and that within a successive correct response series (except for the shift responses) were evaluated with repeated two-way ANOVA. There was no significant effects of time on the RT within the session ($F = 0.75$, $p = 0.48$) or within the correct response series ($F = 1.44$, $p = 0.12$).

PET: When the rCBF on the tasks of each level of attention shift was compared with that on the control task, significant activation was observed in the right dorsal prefrontal cortex (DPFC; middle frontal gyrus, Brodmann's area (BA) 46, and inferior frontal gyrus, BA 44), right parieto-occipital cortex (angular gyrus and superior occipital gyrus, BA 39 and 19) and left inferior occipital gyrus (BA 18) at all four levels of shift (Fig. 2). Additional activation was detected in the right anterior cingulate gyrus (BA 32) at the lowest number of shifts, and in the right inferior occipital gyrus and the left cerebellum at the highest number of shifts. Plotting the rCBF values in these areas against the number of shifts revealed that rCBF was increased consistently at all frequencies of attention shifts.

Variation in the number of attention shifts between categories significantly co-varied with rCBF values in the rostral part of the supplementary motor area (rSMA, BA 6) and the left precuneus (BA 7; Fig. 3). The number of successive correct responses correlated significantly with rCBF in the bilateral orbitofrontal cortex (BA 11 or 47) and the medial area of the left lenticular nucleus, which probably was the ventral part of the caudate nucleus.

Discussion

We planned the task used in this study to extract the neural substrata for shifting attention set, while minimizing the effects of other cognitive processes. The results in this study suggest that several sets of brain regions participate in the process of shifting attention set in different ways.

The DPFC, parieto-occipital cortex and inferior occipital gyrus were activated consistently by the attention shift task. These areas are among the areas activated by the WCST in a previous study,[6] which suggests that our simplification of the WCST was successful. The major difference between results of the two studies is in the laterality of DPFC activation. During the WCST, the DPFC was activated bilaterally and the activation was somewhat left-dominant, whereas DPFC activation in this study was in the right hemisphere. This is as expected because

Table 1. Behavioral performances in the attention shift task.

Number of shifts during a PET scan	2.1 ± 0.3	3.1 ± 0.3	4.3 ± 0.5	9.8 ± 0.9
Number of errors	1.5 ± 0.8	0.8 ± 1.6	1.7 ± 1.0	0.7 ± 0.8
RT for the correct reponses (ms)	677 ± 212*	683 ± 206**	709 ± 227	733 ± 231
RT for the proper shift reponses (ms)	762 ± 223[a]	731 ± 195	776 ± 232[b]	773 ± 235[c]

Values are mean ± s.d.; RT = reaction time
*Significantly shorter than a, b, and c ($p < 0.05$, after Bonferroni's correction).
**Significantly shorter than b and c ($p < 0.05$, after Bonferroni's correction).

we deliberately designed the task to exclude the verbalization of the target's feature, which may be easier in the WCST.

Since the DPFC is postulated as a critical area to complete attention set shift,[12] we expected that the rCBF in this area may increase in proportion to the number of shifts. Therefore, the consistent activation in the DPFC and parieto-occipital cortex even at the lowest number of attention shifts was somewhat surprising. Owen *et al.*[13,14] showed that the mid-dorsolateral frontal cortex is only recruited in working memory tasks when active manipulation or 'monitoring' of the information is required. During the attention shift task, the subjects had to compare the stimulus information with information (i.e. correct category) assimilated from the previous trial to respond correctly. Since the amount of information in the stimulus and interstimulus interval were identical in the attention shift task irrespective of the attention shift frequency, the cognitive load for monitoring of the information may be unchanging in all shift frequencies. This may cause the consistent rCBF increase in the DPFC and parieto-occipital area during the shift task. Alternatively, we cannot exclude a possibility that the rCBF in these areas was saturated at shift frequencies more than 2 per scan. The rCBF in the primary motor area shows sigmoid-shaped increase against rate change of the contralateral finger movement.[15] Similarly, if the rCBF in the DPFC may increase rapidly at the shift frequency less than 2 per scan and then reach a plateau, we cannot detect it in the present analysis.

The rSMA and left precuneus showed a positive correlation of rCBF with the number of attention shifts between categories. The rSMA was situated anterior to the vertical plane through the anterior commissure, and probably corresponds to the presupplementary motor area in the monkey.[16] The rSMA in humans is activated during random or willed action.[17] Matsuzawa and Tanji[16] showed that the rSMA works in shifting the target of future reach, and concluded that this area plays a dominant role in changing motor plans. The rSMA activation that we observed when the frequency of attention shifts increased may indicate a close relationship between the area and the execution of an attention shift, and suggests that the rSMA plays a role in nonmotor aspects of shifting behavior. Although the importance of the medial parietal area in shifting attention in space is well known, recent studies suggest that this area is also activated by attention to object features.[18,19] Fink *et al.* reported similar activation of the SMA and medial parietal area in switching attention between local and global levels of complex visual figures,[20] and the similarity of results between the two studies may indicate that the performance of these tasks involves a common execution component of shifting attention.

Although the rCBF in the orbitofrontal cortex and the caudate nucleus show a correlation with the number of successive correct responses, the role of these areas in the present task is unclear. Although the activation was seen in the basal ganglia, it is unlikely to indicate practice effects in making the serial correct responses, because the analysis of the RT showed no practice effects during the attention shift task. One explanation is that the orbitofrontal area may work to maintain attention set to a particular dimension under the presence of competing visual input. Earlier lesion studies in monkeys and humans that showed that the maintenance of attention set can be disturbed by the orbitofrontal lesions[21,22] may support this view. Alternatively, orbitofrontal activation may relate to information processing in stimulus–reward association. The emotional learning of stimulus–reward association is impaired by orbitofrontal lesions.[12,23] Since an increasing number of successive correct responses resulted in an increase in reward (green circle) and a reduction in punishment (red X), the orbitofrontal cortex and the ventral caudate, which receives the projections from the orbitofrontal area,[24] may play a role in the emotional process related to reward in the present task.

Conclusion

This study provides evidence that several regions in the prefrontal cortex and related brain areas may participate in information processing during the attention shift task in different ways. We speculate that the DPFC and parieto-occipital area take part in manipulation and monitoring of the information within working memory, and that the rSMA plays a role in the execution of attention shifts. To confirm this view, further investigation of the relationship between neural responses and shifting behavior or other attentional processes is required. Investigation of defects in patients with well-restricted prefrontal lesions will also provide valuable information about the various roles of the prefrontal regions in attentional processes.

References

1. Petrides M. *J Neurosci* **15**, 359–375 (1995).
2. Bechara A, Damasio AR, Damasio H *et al. Cognition* **50**, 7–15 (1994).
3. Milner B. *Arch Neurol* **9**, 90–100 (1963).
4. Anderson SW, Damasio H, Jones RD *et al. J Clin Exp Neuropsychol* **13**, 909–922 (1991).
5. Grafman J, Jonas B and Salazar A. *Percept Mot Skills* **71**, 1120–1122 (1990).
6. Nagahama Y, Fukuyama H, Yamauchi H *et al. Brain* **119**, 1667–1675 (1996).
7. Berman KF, Ostrem JL, Randolph C *et al. Neuropsychologia* **33**, 1027–1046 (1995).
8. Grant DA and Berg EA. *J Exp Psychol* **38**, 404–411 (1948).

9. Sadato N, Carson RE, Daube-Witherspoon ME *et al. J Cerebr Blood Flow Metab* **17**, 732–739 (1997).
10. Friston KJ, Holmes AP, Worsley KJ *et al. Hum Brain Mapp* **2**, 189–210 (1995).
11. Talairach J and Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: An Approach to Cerebral Imaging*. Stuttgart: Georg Thieme Verlag, 1988.
12. Dias R, Robbins TW and Roberts AC. *Nature* **380**, 69–72 (1996).
13. Owen AM, Evans AC and Petrides M. *Cerebr Cortex* **6**, 31–38 (1996).
14. Owen AM, Morris RG, Sahakian BJ *et al. Brain* **119**, 1597–1615 (1996).
15. Sadato N, Ibanez V, Deiber M-P *et al. J Cerebr Blood Flow Metab* **16**, 23–33 (1996).
16. Matsuzawa Y and Tanji J. *J Neurophysiol* **76**, 2327–2342 (1996).
17. Deiber M-P, Passingham RE, Colebatch JG *et al. Exp Brain Res* **84**, 393–402 (1991).
18. Corbetta M, Shulman GL, Miezin FM *et al. Science* **270**, 802–805 (1995).
19. Fink GR, Dolan RJ, Halligan PW *et al. Brain* **120**, 2013–2028 (1997).
20. Fink GR, Halligan PW, Marshall JC et al. Brain 120, 1779-1791 (1997).
21. Iversen SD and Mishkin M. *Exp Brain Res* **11**, 376–86 (1970).
22. Stuss DT, Benson DF, Kaplan EF *et al. Neuropsychologia* **21**, 235–48 (1983).
23. Rolls ET, Hornak J, Wade D *et al. J Neurol Neurosurg Psychiatry* **57**, 1518–1524 (1994).
24. Yeterian EH and Pandya DN. *J Comp Neurol* **312**, 43–67 (1991).

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