Basal ganglia involvement in memory-guided movement sequencing

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The basal ganglia (BG) are thought to play a critical role in motor planning and movement sequencing. While electrophysiological and imaging studies have shown that the dorso-lateral prefrontal cortex (DLPFC) is involved in working memory (WM), the involvement of the BG in this process is not well understood. We used a motor sequencing task to investigate the differential role of BG nuclei in memory-guided movement. Significant activation was observed in the DLPFC and posterior putamen and globus pallidus (GP), with a trend in the caudate and no differences in the anterior putamen. We then investigated the effect of BG outflow on thalamic activation using functional connectivity analysis. Activation in the posterior putamen + GP was found to be correlated with thalamic activation only in the hemisphere contralateral to movement. These results provide the first fMRI evidence that the BG may modulate activity in the thalamus during working memory-guided movement sequencing. Our findings suggest that the BG activation may reflect increased motor sequencing demands during the memory-guided movement condition and, specifically, that the posterior putamen and GP may play a role in maintenance of representations in WM in a manner that contributes to planning and temporal organization of motor sequencing. *NeuroReport* 11:3641–3645 © 2000 Lippincott Williams & Wilkins.

Key words: Basal ganglia; Caudate; DLPFC; fMRI; Motor sequencing; Putamen; Working memory

INTRODUCTION

The basal ganglia (BG) play an essential role in adaptive behavior in general and movement initiation, control and sequencing in particular. Although the BG have been primarily thought to be involved in motor functions, researchers have argued that the BG may play a more direct role in supporting cognitive operations [1–3]. This argument has been supported by a number of studies which have noted a profile of cognitive performance deficits in patients with BG disease [4–6]. BG-related cognitive dysfunction might result from a number of factors, including deficits in the allocation of attention resources, the maintenance of representations in working memory, the temporal organization of behavior, planning, or the self-elaboration of internal strategies, which resemble dysfunctions of processes that are commonly considered to be controlled by the frontal lobes [5].

In the present study we investigated the role of various BG nuclei in supporting cognitive operations by examining its involvement in working memory-guided movement sequencing. Electrophysiological studies in primates have examined the role of the BG in memory-guided movement but there have been no such studies in humans to date. Mushiake and Strick [7] investigated the activity of globus pallidus (GP) neurons in Macaque monkeys during sequential reaching tasks with and without memory requirements and reported that several GP neurons were preferentially active during working memory-guided movement. Electrophysiological studies have also found memory-contingent neurons in the substantia nigra during visual and saccade responses [8,9]. However, the precise role played by the striatum in visuo-spatial WM is still not well understood, as some electrophysiological studies have found delay related neuronal activity in the caudate [10,11] while others have failed to find any such activity in the caudate or anterior putamen [12]. Levy *et al.* [13] examined the role of the monkey caudate in spatial and non-spatial WM tasks using PET imaging and found that the caudate head was active during spatial WM and the caudate tail was active during nonspatial WM. Other electrophysiological studies have suggested that the caudate and putamen nuclei of the BG primarily perform an integrative role in binding sensory inputs to motor response [14]. Kermadi and Joseph [15] have reported that neurons in the caudate appear to play a role in the construction, but not storage of spatial sequencing.

To date, no imaging studies have examined the differential activation of BG nuclei in the context of memory-guided movements. Although, in principle, functional magnetic resonance imaging (fMRI) provides adequate resolution to image the basal ganglia at the spatial scale of the individual nuclei, activating these nuclei with fMRI has

proven to be difficult. In this study we investigated the differential role of various BG nuclei during memory-guided movement sequencing and the effect of BG outflow on thalamic activation. We modified a motor sequencing task, which we had previously shown to reliably activate the BG [16], to include a delay component and investigated activation related to WM in the DLPFC, which is commonly activated by the executive component of WM tasks [17–19], and various nuclei of the BG. Previous studies that have investigated BG function have mainly used purely motor tasks which activate the motor output regions of the BG [20–22]. Our memory-guided movement sequencing task was analogous to those used in electrophysiological studies [7].

MATERIALS AND METHODS

Subjects: Ten healthy right-handed subjects (six men and four women; ages 20–35 years) participated in the study after the study was explained to each and written informed consent was obtained. The human subjects committee at Stanford University and the Palo Alto VA Health Care System approved this protocol. No subject had more than 1 mm of head motion in any axis during the scan.

Experimental design: The tasks consisted of alternating epochs of motor sequencing with and without WM demands. Trials (8 s each) were presented using a blocked-design with five trials per block and six blocks of each condition (12 blocks total) presented in an ABAB... paradigm. Brief instructions preceded each block. Motor sequencing involving finger movements do not elicit reliable fMRI activation of the BG; we therefore designed a task, involving arm movements, which reliably activated the caudate, putamen and GP [16]. In both task conditions, subjects rested the closed fist of their right hand on the base of a palm-shaped keypad. Movement consisted of touching, with thumb and forefinger pinched together, one of four locations 15 cm away from the base and returning to the base position. Subjects practiced the task briefly for 2 min 40 s (four epochs) 30 min before the scan and were monitored visually during the scan to verify consistent task performance. Numbers between 1 and 4 were presented binaurally and subjects made arm movements to corresponding locations on the keypad. In the memory-guided (experimental) condition, subjects heard three numbers in succession and had to respond with the arm movements after a 3.5 s delay. In the control condition, numbers were presented with an ISI of 1.5 s and subjects moved their arm immediately after each number was presented (Fig. 1). The number of movements and auditory stimuli were balanced across conditions.

Data acquisition: Images were acquired on a conventional 1.5 T GE (Milwaukee, WI) scanner using a quadrature whole head coil. Twelve axial slices (6 mm thick, 0 mm skip), roughly extending −20 to +52 mm relative to the anterior commissure, were imaged with a temporal resolution of 4 s at 120 time points using a T2*-weighted gradient echo spiral pulse sequence (TR = 1000 ms, TE = 40 ms, flip angle = 40° and 4 interleaves) [23]. The field of view was 310 mm and the effective inplane spatial resolution was 4.35 mm.

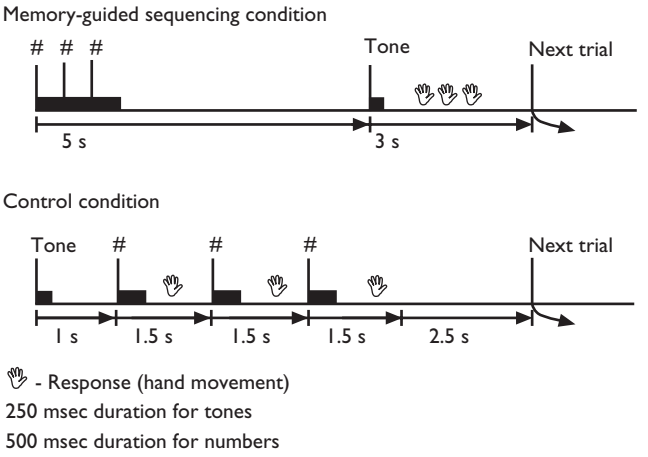

Fig. 1. Schematic diagram of task design. In the working memory (experimental) condition, subjects had to remember the numbers for 3.5 s before making a response, while in the non-working memory (control) condition, subjects responded immediately after hearing each number. The number of stimuli and movements were balanced across the two conditions.

Data analysis: Images were corrected for movement using least square minimization, normalized to stereotaxic Talairach coordinates [24], resampled every 2 mm using sinc interpolation and smoothed with a 4 mm Gaussian kernel. Statistical analysis was performed on individual subject data to determine which voxels showed significantly greater activation during the memory-guided, compared to the control condition. The general linear model and the theory of Gaussian random fields as implemented in SPM96 were used to analyze the fMRI data. This method implements a multivariate regression analysis and corrects for temporal and spatial autocorrelations in the fMRI data [25]. For each subject, voxel-wise *t*-statistics were computed and normalized to Z scores to provide a statistical measure of activation that is independent of sample size.

ROI analysis: Regions of interest (ROIs) were constructed based upon known neuroanatomical landmarks [26] and guided by the Talairach atlas [24] for caudate head, anterior putamen, posterior putamen and GP, and DLPFC (BA 9/46). We also examined activation in the thalamus since it is the primary target of BG output. Given the limited spatial resolution of the fMRI scan we did not attempt to differentiate activation in the various thalamic nuclei. The anterior commissure was used to demarcate anterior and posterior putamen and GP. Separate left and right hemisphere ROIs were constructed for each region. The percentage of voxels activated above a threshold of $Z > 1.645$ ($p < 0.05$) within each ROI was determined for each subject. Regional differences in activation were examined using ANOVA.

RESULTS

Activation across subjects: Although nearly every subject activated the basal ganglia and thalamus, the inter-subject variability in activation of individual voxels was high. Thus, individual voxels activated by different subjects showed little overlap and no single voxel was activated by more than five of 10 subjects. Figure 2 shows a composite

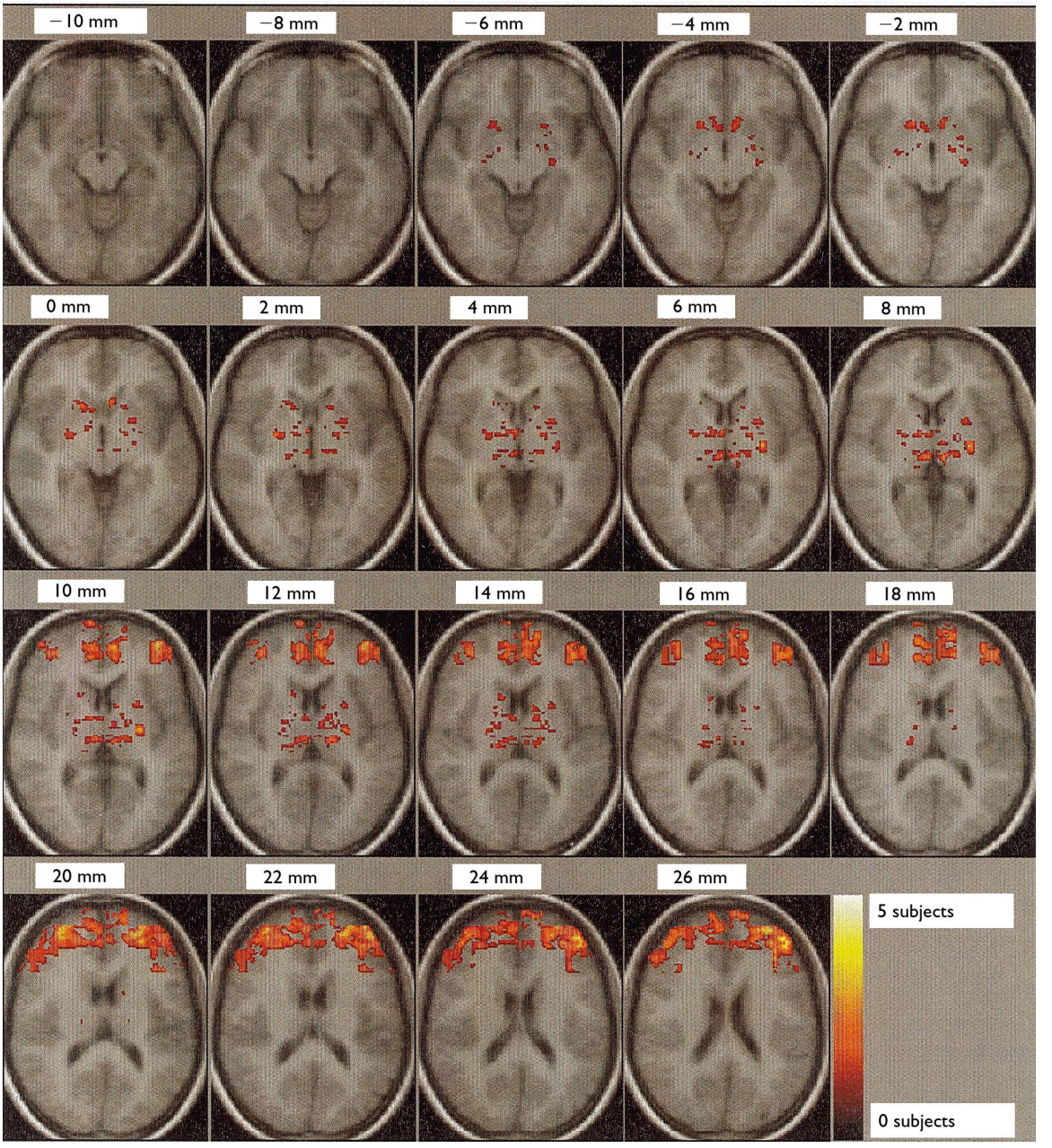

Fig. 2. Composite map of activation across 10 subjects in the dorsolateral prefrontal cortex, basal ganglia, and thalamus during the memory-guided compared to a non-working-memory guided movement sequencing task. The number of subjects who showed significant activation ($Z > 1.65$, $p < 0.05$) in each voxel was computed and displayed according to the adjoining scale. The precise voxels activated by each subject in the basal ganglia and thalamus were quite variable. Six of 10 subjects activated the caudate, six of 10 activated the anterior putamen, nine of 10 activated the posterior putamen + globus pallidus and nine of 10 activated the thalamus. All 10 subjects activated the dorsolateral prefrontal cortex. This map is shown for illustrative purposes only. Statistical analysis of activation across subjects was conducted using an ANOVA on the percentage of voxels activated by each subject in each region of interest.

image of the number of voxels activated by each subject and captures some of the variability in activation across subjects. Although the precise voxel activated in each subject in the basal ganglia and thalamus were quite variable, six of 10 subjects activated the caudate, six of 10 activated the anterior putamen, nine of 10 activated the posterior putamen + GP and nine of 10 activated the thalamus. All 10 subjects activated the DLPFC. This map is shown for illustrative purposes only. Statistical analysis of activation across subjects was conducted using an ANOVA on the percentage of voxels activated by each subject in each region of interest.

Region of interest analysis: A two-way repeated-measures ANOVA with factors ROI (DLPFC, caudate, anterior putamen, posterior putamen + GP) and hemisphere (left and right) was used to investigate the profile of significant regional differences in activation. There was no ROI ×

hemisphere ($F(3,27) = 0.120$, $p = 0.948$) interaction, or main effect of hemisphere ($F(1,9) = 0.388$, $p = 0.549$), but a significant main effect of ROI was found ($F(3,27) = 3.197$, $p = 0.039$). We compared activation in the memory-guided and control conditions using a two-tailed *t*-test. Significant activation differences were found in the DLPFC ($t(9) = 3.036$, $p = 0.014$) and posterior putamen + GP ($t(9) = 2.545$, $p = 0.031$), but not the caudate ($t(9) = 2.052$, $p = 0.070$) or anterior putamen ($t(9) = 1.700$, $p = 0.122$; Fig. 2). Significant activation was also found in the thalamus ($t(9) = 2.555$, $p = 0.031$). Figure 3 compares activation across subjects in the DLPFC, BG and thalamus.

Basal ganglia and thalamus connectivity analysis: We then investigated the effect of BG outflow on thalamic activation separately in each hemisphere. Left thalamic activation was significantly correlated with left posterior putamen + GP activation (Spearman $R = 0.66$, $p = 0.04$; Fig. 4), but right thalamus activation was not related to right posterior putamen + GP activation (Spearman $R = 0.27$, $p = 0.46$). Activation in the left and right thalami was also significantly correlated (Spearman $R = 0.83$, $p = 0.003$).

DISCUSSION

The motor sequencing task used in the present study has been previously shown to activate the caudate, anterior putamen, and the posterior putamen + GP [16]. The current study compared activation between motor sequencing conditions with and without WM demands. Consistent with previous imaging studies [18,19], we observed significant activation of the left and right DLPFC. In addition, significant activation was detected in the posterior putamen + GP, with a trend toward significant activation in the caudate. No significant activation was detected in the anterior putamen. There were no significant hemispheric differences in activation, suggesting that the overall activation is not entirely due to increased motor demands during the memory-guided task. It should be noted that the motor components of the task were balanced across the WM and non-WM conditions. Our results provide the first evidence for posterior putamen + GP involvement during working memory-guided movement sequencing in humans. These results are in agreement with electrophysiological studies in primates [7] which have indicated that GP activation is modulated by memory requirements during motor sequencing.

In addition to significant activation in the BG, we found increased activation in the thalamus. Furthermore, thalamic activation was found to be correlated with posterior puta-

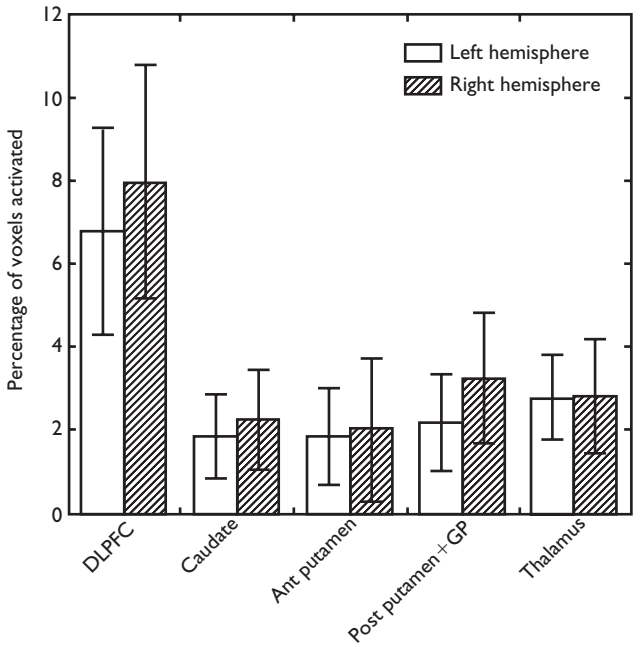

Fig. 3. Mean and S.E. of activation in the dorsolateral prefrontal cortex, basal ganglia and thalamus regions of interest (ROI) during the memory-guided minus the control condition. The percentage of voxels within each ROI activated by each subject above a threshold of $Z > 1.65$ ($p < 0.05$) was calculated used as the measure of activation.

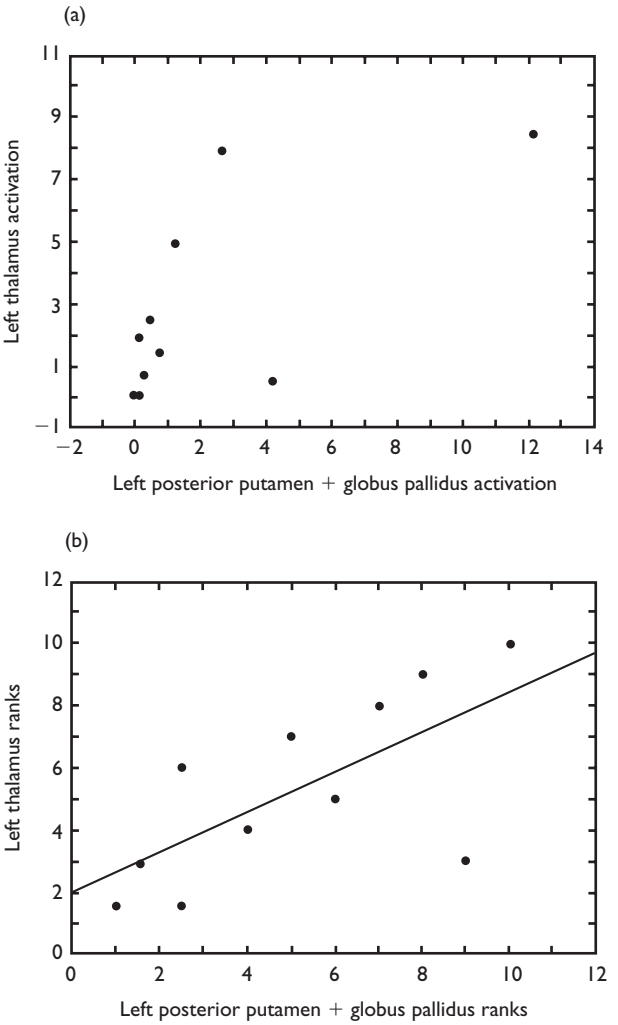

Fig. 4. Relationship between posterior putamen + globus pallidus and thalamus activation. (**a**) Scatterplot of left posterior putamen + globus pallidus and left thalamus activation. (**b**) Scatterplot of the same activation after rank ordering to correct for outliers and non-normal distribution, corresponding to the use of a non-parametric Spearman correlation. The activations were significantly correlated ($p < 0.05$; Spearman correlation). The percentage of voxels activated by each subject in each ROI was used as the measure of activation.

men + GP activation in the left but not the right hemisphere. The increase in thalamic activation contralateral to the movement may therefore be related to increased motor coordination demands during the memory condition. Our results provide the first fMRI evidence that thalamic activation may be related to BG outflow and further suggest that the thalamic input from the BG is increased during working memory-guided movement. These activations may be related to the additional motor sequencing demands that are present during the memory-guided, but not the control condition. Given recent neuroanatomical evidence for interhemispheric thalamic connectivity [27,28] we also investigated the relationship between left and right thalamic activation. A significant relation between left and right thalamic activation was found suggesting that the left hemisphere (contralateral to movement) basal ganglia outflow may play a role in the bilateral integration of motor planning systems via inter-thalamic cross-talk.

While electrophysiological studies have specifically investigated the role of the BG in memory operations in the context of movement sequencing, imaging studies in humans have focused on its role in WM tasks in general. These studies have suggested that the caudate head plays a role in visuo-spatial [29,30] but not verbal working memory tasks [18,29]. However, Owen *et al*. [31] have reported deficits in GP activation, but not caudate or putamen, in Parkinson's patients during spatial WM. Within the context of movement sequencing, Menon *et al*. [16] compared BG activation during externally and self-paced sequences of arm movements and reported a dissociation in anterior and posterior putamen and GP activation. They found that both externally paced and self-paced movements activated the posterior putamen+GP but only the externally paced movements activated the anterior caudate and putamen. Based on these results, as well as animal [32] and imaging studies, they suggest that the anterior caudate and putamen may be involved in sensory to motor stimulus-response mapping and the posterior putamen and GP may be involved in the motor response itself.

In the present study, stimulus-response associations were completely balanced across the two conditions. Thus, statistically significant differences were not found in the caudate and anterior putamen. Elliott and Dolan [30] have noted that caudate activation is not modulated by increase in WM delay and several electrophysiological studies have failed to find delay related activation in the caudate [12]. However, significant activation was detected in the posterior putamen + GP which together receive sensorimotor input and send output to the sensorimotor cortex via the thalamus [1,33]. Given the lack of evidence, from both neuroimaging [30] and electrophysiological studies [12,15], of delay specific modulation of activation in the BG, our results suggest that the observed activation may reflect increased motor sequencing demands during the memory-guided movement condition. Since motor sequencing alone has been shown to activate more extensive regions of the BG [16], the present results suggest that the posterior putamen + GP may be specifically involved in the construction, but not the storage of movement sequences.

CONCLUSION

Taken together, our findings are compatible with the hypothesis that the BG plays a role in maintenance of representations in working memory in a manner that contributes to planning and temporal organization of motor sequencing. More broadly, our findings suggest that the BG supports operations that could contribute to planning of action. Given the neuroanatomical projections between the BG and DLPFC via the thalamus [34], the BG may also exert a modulatory influence on the DLPFC and contribute to adaptive behavior. Our findings also suggest that the paradigm developed in the present study can be used to investigate cognitive and motor abnormalities in disorders such as ADHD, Parkinson's disease and schizophrenia, in which BG output is known to be disrupted [31,35].

REFERENCES

1. Alexander GE, DeLong MR and Strick PL. *Annu Rev Neurosci* **9**, 357–381 (1986).
2. Graybiel AM. *Schizophr Bull* **23**, 459–469 (1997).
3. Graybiel AM. *Neurobiol Learn Mem* **70**, 119–136 (1998).
4. Owen AM, Iddon JL, Hodges JR *et al. Neuropsychologia* **35**, 519–532 (1997).
5. Dubois B and Pillon B. *J Neurol* **244**, 2–8 (1997).
6. Stebbins GT, Gabrieli JD, Masciari F *et al. Neuropsychologia* **37**, 503–510 (1999).
7. Mushiake H and Strick PL. *J Neurophysiol* **74**, 2754–2758 (1995).
8. Hikosaka O and Wurtz RH. *J Neurophysiol* **49**, 1285–1301 (1983).
9. Hikosaka O, Sakamoto M and Miyashita, N. *Exp Brain Res* **95**, 457–472 (1993).
10. Hikosaka O, Sakamoto M and Usui S. *J Neurophysiol* **61**, 780–798 (1989).
11. Hikosaka O and Sakamoto M. *Brain Dev* **8**, 454–461 (1986).
12. Rolls ET. *Rev Neurol (Paris)* **150**, 648–660 (1994).
13. Levy R, Friedman HR, Davachi L *et al. J Neurosci* **17**, 3870–3882 (1997).
14. Lidsky TI, Manetto C and Schneider JS. *Brain Res* **356**, 133–1346 (1985).
15. Kermadi I and Joseph JP. *J Neurophysiol* **74**, 911–933 (1995).
16. Menon V, Glover GH and Pfefferbaum A. *Neuroreport* **9**, 1567–1573 (1998).
17. Romo R, Brody CD, Hernandez A *et al. Nature* **399**, 470–473 (1999).
18. Smith EE and Jonides J. *Science* **283**, 1657–1661 (1999).
19. D'Esposito M, Detre JA, Alsop DC *et al. Nature* **378**, 279–281 (1995).
20. Lehericy S, van de Moortele PF, Lobel E *et al. Ann Neurol* **44**, 398–404 (1998).
21. Reichenbach JR, Feiwell R, Kuppusamy K *et al. Magn Reson Imaging* **16**, 281–287 (1998).
22. Bucher SF, Seelos KC, Stehling M *et al. Neurology* **45**, 180–182 (1995).
23. Glover GH and Lai S. *Magn Reson Med* **39**, 361–368 (1998).
24. Talairach J and Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain.* New York: Thieme; 1998.
25. Friston KJ, Ashburner J, Frith CD *et al. Hum Brain Mapp* **2**, 165–189 (1995).
26. Duvernoy H. *The Human Brain: Surface, Three-Dimensional Sectional Anatomy*. New York: Springer-Verlag; 1991.
27. Pare D and Steriade M. *Neurosci Lett* **154**, 96–100 (1993).
28. Raos V and Bentivoglio M. *J Comp Neurol* **332**, 145–154 (1993).
29. Postle BR and D'Esposito M. *Brain Res Cogn Brain Res* **8**, 107–115 (1999).
30. Elliott R and Dolan RJ. *J Neurosci* **19**, 5066–5073 (1999).
31. Owen AM, Doyon J, Dagher A *et al. Brain* **121**, 949–965 (1998).
32. McDonald RJ and White NM. *Behav Neurosci* **107**, 3–22 (1993).
33. Parent A and Hazrati LN. *Brain Res Brain Res Rev* **20**, 91–127 (1995).
34. Middleton FA and Strick PL. *Science* **266**, 458–461 (1994).
35. Marie RM, Barre L, Dupuy B *et al. Neurosci Lett* **260**, 77–80 (1999).

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