A. Montoya
M. Pelletier
A. M. Achim
S. Lal
M. Lepage

Prefrontal dysfunction in schizophrenia: implication in associative recognition

Brain Imaging Group
McGill University, Montreal (Canada)
Douglas Hospital Research Centre
Verdun, Quebec (Canada)

Objective. We used an event related functional magnetic resonance imaging (fMRI) method to examine the neural basis of associative recognition memory deficit in schizophrenia.

Methods. Fifteen people with schizophrenia and 18 healthy control subjects were scanned with fMRI while performing a memory task (coding and recognition) of visual objects. During coding, the subjects studied items and pairs of items. During recovery, the subjects had to recognize items (old/new decisions) and recognize associations (intact/rearranged decisions). The study design was based on a random effect model and the fMRI analysis was restricted to correct items only.

Results. At the behavioral level, both groups performed equally well on item recognition, whereas people with schizophrenia demonstrated poorer performance on associative recognition. At the brain level, comparison between associative and item recognition tasks revealed greater left dorsolateral prefrontal and right inferior prefrontal activations in the control group relative to the schizophrenia group.

Conclusions. The findings of this fMRI study suggest the prefrontal cortex as the basis for the selective memory deficit for associative recognition obsevered in schizophrenia.

Key words:
Schizophrenia. Episodic memory. Recognition. Associations. Functional magnetic resonance imaging. Prefrontal dysfunction.

Actas Esp Psiquiatr 2007;35(3):176-181

Disfunción prefrontal en esquizofrenia: implicación en el reconocimiento de asociaciones

Objetivo. En este estudio empleamos la resonancia magnetica funcional (RMf) para examinar los sustratos neurales del déficit de memoria para el reconocimiento de asociaciones en esquizofrenia.

Métodos. Quince pacientes con diagnóstico de esquizofrenia y 18 sujetos control sanos fueron sometidos a RMf mientras realizaban una prueba de memoria (codificación y reconocimiento) de objetos visuales. Durante la codificación los sujetos estudiaron ítems y pares de ítems. Durante la recuperación los sujetos tenían que reconocer ítems (decisiones entre ítems nuevos/estudiados) o reconocer asociaciones (decisiones entre pares intactos/reacomodados). El diseño del estudio fue basado en un modelo de efecto aleatorio y el análisis de la RMf fue restringido únicamente a las respuestas correctas.

Resultados. A nivel del desempeño, el rendimiento de ambos grupos fue similar durante el reconocimiento de ítems, mientras que durante el reconocimiento de asociaciones los pacientes con esquizofrenia mostraron un rendimiento inferior. A nivel cerebral el contraste entre el reconocimiento de ítems y el reconocimiento de asociaciones demostró una mayor activación predominantemente a nivel de la corteza prefrontal dorsal izquierda y prefrontal inferior derecha en el grupo control en relación al grupo de pacientes.

Conclusiones. Los hallazgos de este estudio de RMF sugieren que una disfunción de la corteza prefrontal pudiera ser la responsable del déficit selectivo de memoria para el reconocimiento de asociaciones observado en pacientes con esquizofrenia.

Key words:
Esquizofrenia. Memoria episódica. Reconocimiento. Asociaciones. Resonancia magnética funcional. Disfunción prefrontal.

INTRODUCTION

Cognitive alterations are a central part of schizophrenia and adversely affect the course and prognosis of the disease[1]. Even though schizophrenia is associated to a wide spectrum of cognitive dysfunctions, memory deficits are especially noticeable[2]. Based on the present neurobiological and

Correspondence:
Alonso Montoya
Douglas Hospital Research Centre – FBC1
6875 boul. La Salle
Verdun, Quebec
H4H 1R3, CANADA
Correo electrónico: alonso_montoya@lilly.com

psychological knowledge, memory cannot be referred to as a single psychological function, since there is clear evidence on the disassociation of memory that is well supported by neuroanatomical and neurofunctional studies[3,4]. The most currently admitted memory disassociation is that of declarative and non-declarative memory[5].

Declarative memory deficit, especially in episodic memory, is the most consistent and outstanding in patients with schizophrenia[2]. However, the severity of the deficit, reflected in performance in episode memory tasks, varies considerably from one task to another. This suggests the possibility of very specific alterations in the declarative memory processes of patients with schizophrenia[6].

From the point of view of neurocognitive research in schizophrenia, identification of the altered memory processes and its neural correlates is very important. Studies performed in the scope of declarative memory (episodic), with the same patient sample and comparing memory for items (words, objects, etc., individually) versus associative memory (associated pairs, or relation memory, etc.), have consistently reported that the patients with schizophrenia have inferior performances in associative memory[7]. This suggests that the processes inherent to associative recognition could be more affected.

Investigations in cognitive psychology suggest that different memory processes participate in item and associative memory[8-10]. This concept has been reinforced by the findings of recent functional neuroimaging studies conducted in healthy controls, in which it was consistently demonstrated that there was better activity in the prefrontal regions during associative recognition than during item recognition[11-14].

Based on the results described, it is feasible to suggest the possibility that an abnormal functioning on the prefrontal level could be involved in the selective memory alteration in the associative recognition found in patients with schizophrenia. In the present study, we have used a neuroimaging technique, the functional magnetic resonance imaging (fMRI), to examine the neural bases of the alteration in associative recognition in schizophrenia.

METHOD

Fifteen patients diagnosed of schizophrenia participated in the study. Their ages ranged from 18 to 50 years (mean age of 34 years), 67% of them being males. The patients were diagnosed by clinical psychiatrists based on DSM-IV diagnostic criteria for which the semistructured clinical interview (SCID) was applied. In general, they were chronic patients, with a mean disease duration of 10.3 (SD ± 7.3) years, who were clinically stable at the time of the initial evaluation. Except for one patient, all had been receiving treatment with antipsychotics (12 with second generation antipsychotics, 3 with conventional ones, and 4 were receiving a combination of both). The mean dose of antipsychotics received was equivalent to 453 mg/day of chlorpromazine[15]. One patient was also receiving low doses of an anticholinergic agent (benztropine). A group of 18 healthy control subjects was used and was paired for age, schooling, gender and right hand manual preference.

All the participants were informed on the study procedure and gave their written consent. The study was approved by the Ethics Committee of the Hospital Douglas and the Montreal Neurological Institute.

Experimental memory test for item and associative recognition

We administered a recognition memory test that we designed in our laboratory and that has been previously reported[11]. The test stimuli consisted in images of simple objects (animals, fruits, furniture, etc.) consecutively presented on the screen of a personal computer, whether in pairs (two different images), or as duplicate items (two identical images) and a pair of abstract images (basal). The test consisted in the presentation of a stimulus for 2.5 seconds, followed by a fixation cross presented for 4 seconds (fig. 1).

The participants were scanned during four functional series (scanners), altering the coding and recognition phases of the test. In this article, only the results of the recognition test analysis will be reported and the analysis and the results of the coding phase will be reported separately. During each coding phase, 90 stimuli (30 items, 30 pairs and 30 basal images) were presented consecutively. The subjects had to memorize the images and indicate if it was an image of pairs or of items using the computer mouse. No type of response was required when a basal image appeared.

During the recovery phase, some of the images were regrouped and 15 new images were grouped (15 original items, 15 new items, 15 intact pairs, 15 rearranged pairs and 30 basal images). The subjects had to recognize if the images presented had been previously studied or if they were new images, or if the images presented were paired in the same way in which they were originally presented (intact pairs) or forming new pairs (rearranged pairs). Once again, the appearance of a basal image did not require any type of response. The use of this type of recognition (of associations) does not only depend on the memory processes that make it possible to identify an image as new or not but also depends significantly on the contextual characteristics (as site or time) at the time of the original presentation (coding), which represents the use of the associative memory processes[20]. Prior to the experimental phase within the scanner, the subjects perform an exercise with a short test version in order to assure that they have correctly understood the instructions.

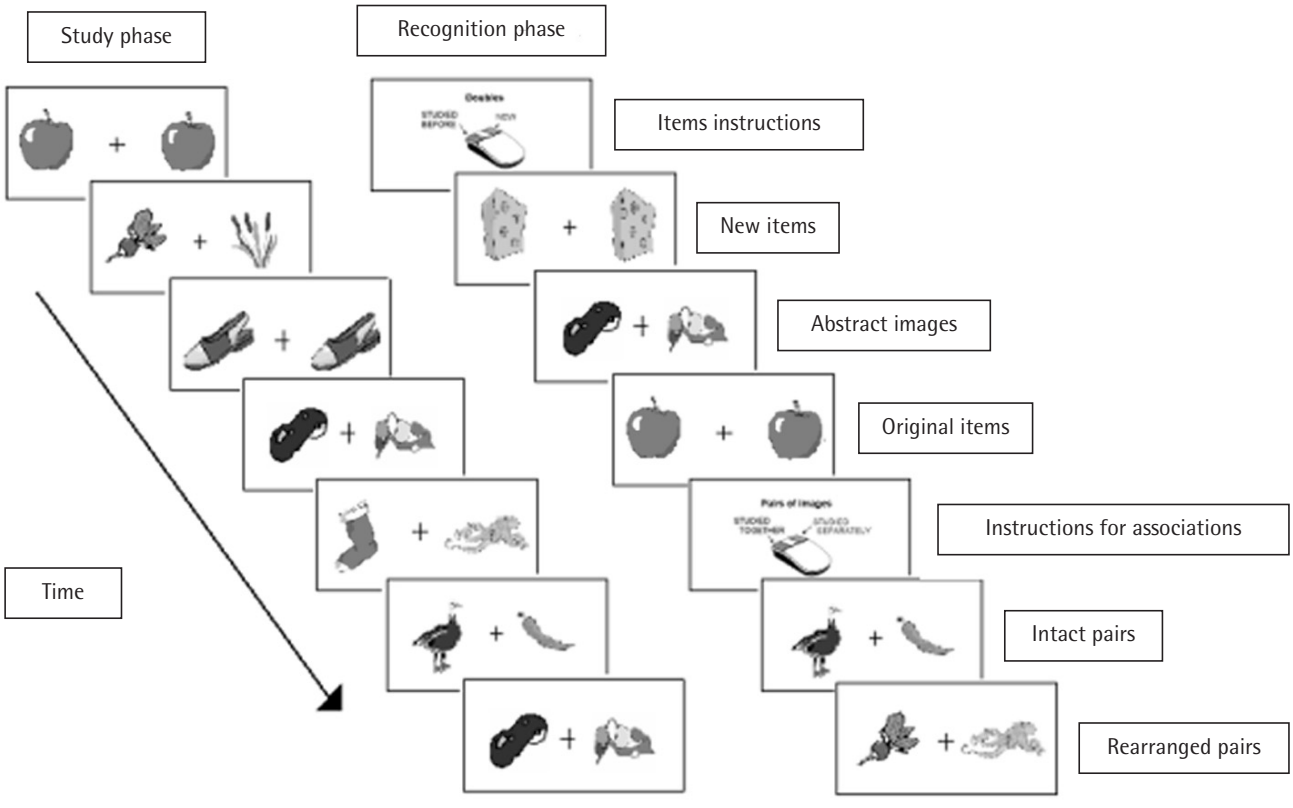

Figure 1 *Representation of the memory test of recognition for items and associations.*

Acquisition and analysis of fMRI images

The functional imaging sessions were conducted in the Neurological Institute of Montreal in a scanner of 1.5 T (Siemens Sonata). Each session began with the acquisition of a high resolution T1 image used for anatomical localization and its functional series consisted in the acquisition of 230 T2 images, performed parallelly to the anterioposterior commissural level, with BOLD contrasts (blood oxygenation level-dependent) (TR: 3,000 ms; TE: 50 ms; 25 slices, 2 × 2 × 5 mm voxels).

The functional images were analyzed with the software for a general statistical analysis of fMRI data[16] described in detail in[17] and only including the correct answers of the recognition test.

Briefly, the T2 images were co-recorded and realigned at the fifth image of the first functional series and especially transformed with a Kernell Gausiana (fwhm) of 6 mm, using preestablished parameters[16]. Normalization to the standard spatial template was done with the MNI_305 template[1].

The statistical mapping for the contrast of interest was calculated for each group with a random effect model and only those voxels that showed statistically significant activations were examined. In this way, the activations reported in the following had a p-value level less than 0.001 in the control group (t [17] = 3.65) or in the group of patients with schizophrenia (t [14] = 3.78). Given the limited number of voxels examined with this procedure, the statistical threshold to find differences between the groups was established at a p-value less than 0.01 (t [31] = 2.46). Only those groupings over five voxels are reported.

RESULTS

In regards to the performance in the experimental memory tests for recognition, a different performance was observed in the groups depending on the type of test used. Analysis of variance (ANOVA) and accuracy of the responses showed a tendency towards an X group interaction test (F [1,31] = 3.02; p = 0,09). In regards to the item recognition test, the post-hoc analysis showed no differences in the statistically significant group (t [30] = 0.34; n.s.). However, in the associative recognition test, the performance in the group of patients with schizophrenia was inferior to that of the control group and this difference was statistically significant (t [30] = 1.86; p < 0,05). The results of the comparisons between the items and associative tests are shown in figure 2A.

On the brain level, the contrast between the items and associative tests revealed several regions with a greater ac-

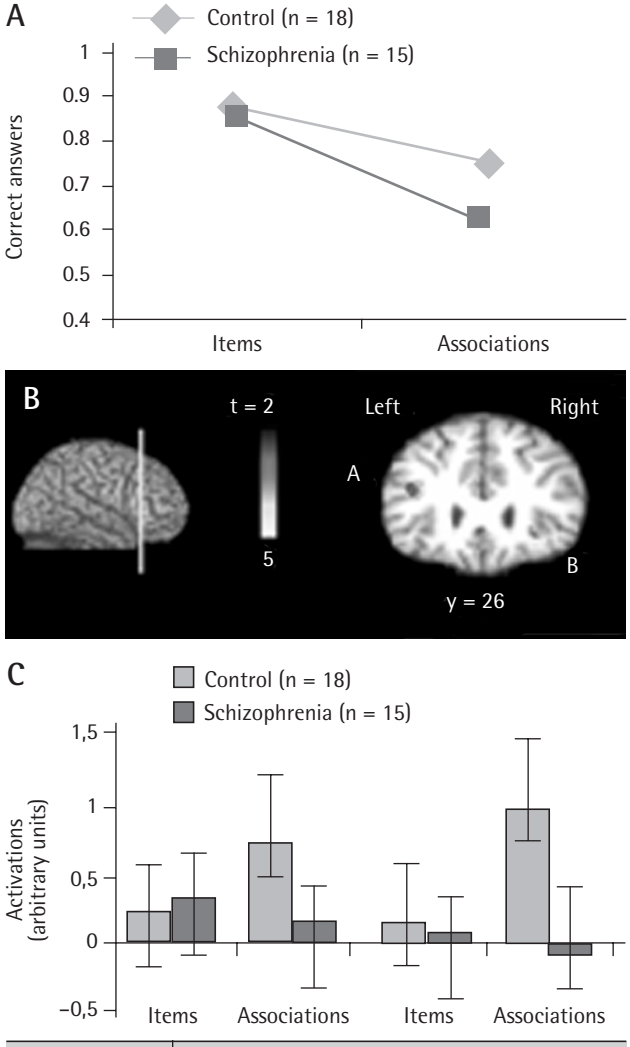

Figure 2 **(A)** *Represents the performance of the control group and group with schizophrenia in the item and associative recognition memory tests.* **(B)** *Represents the results of the analysis of the fMRI images on the X group interaction recognition tests. The yellow line over the tridimensional reconstruction of the MRI represents the site of the cutoff presented to the right.* **(C)** *Shows the estimation of parameters of each recognition condition in both groups.*

tivation in the control group in comparison with the patient group. Figure 2B shows two of these regions, one corresponding to the dorsolateral gyrus of the left side (-40, 28, 20) and the other to the interior frontal gyrus of the right side (28, 26, -4). Figure 2C shows the estimation of the parameters of these two regions. Some other voxels that showed a significantly greater activation in the control group were found in the right side medial frontal gyrus (2, 18, 48), lobulus quadrangularis (-30, -50, 48), right superior parietal lobe (-28, -64, 46) and left one (34, -74, 52), right lingula (4,-76, 16) and the cingulum gyrus (4,-38, 26) (table 2).

Table 1 **Demographic and clinical data**

Demographic characteristic	Patients with schizophrenia (n = 15)			Healthy control subjects (n = 18)			Analysis (p)
	Mean	SD	Range	Mean	SD	Range	
Age	34.0	8.4	20-50	28.9	9.5	20-50	p = 0.118
Schooling	14.6	3.6	10-22	16.1	2.9	12-22	p = 0.191
Schooling of parents	12.4	2.7	8-17	12.7	2.7	9-17	p = 0.754
	N		%	N		%	
Gender							
Masculine	10		67	10		56	p = 0.530
Feminine	5		33	8		44	
Language							
English	4		27	5		28	p = 0.945
French	11		73	13		72	
Manual preference							
Right-handed	14		93	18		100	p = 0.334
Left-handed	1		7	0		0	
Clinical characteristics	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	
Duration of disease (years)	10.3	7.3	2-25				
PANSS							
Positive symtoms	11.3	3.0	8-18				
Negative symptoms	10.0	3.1	7-17				
General psychopathology	24.1	5.3	17-37				
Abnormal movements scale	2.2	4.3	0-16	0.0	0.0	0-0	
Global functioning scale	66.8	8.7	55-81	85.5	6.6	70-91	p < 0.001
	N		%				
Clinical subtype, schizphrenia							
Paranoid	12		80				
Residual	1		6.6				
Undifferentiated	2		13.3				

DISCUSSION

The objective of this study was to examine the neural correlates of memory deficit for associative recognition in patients with schizophrenia. The contrasts made between item recognition and associative recognition tests revealed

Table 2 Areas of greater activation on contrasting recognition of items and recognition of associations

Peak	X	y	z	Hemisphere	Region	AB
Interaction: control > schizophrenia						
2.87	−40	28	20	Left	Dorsolateral frontal gyrus	46
3.22	−30	−50	48	Left	Lobulus quadrangularis	7
2.90	−28	−64	46	Left	Superior parietal lobule	7
3.41	28	26	−4	Right	Inferior frontal gyrus	47
3.05	2	18	48	Right	Medial frontal gyrus	8
3.63	4	−38	26	Right	Cingulum gyrus	31
2.88	30	−58	48	Right	Superior parietal lobule	7
3.66	34	−74	52	Right	Superior parietal lobule	7
3.10	4	−76	−16	Right	Lingula	18
Interaction: schizphrenia > control						
No significant activations were identified.						

a greater activation in several brain regions, predominately prefrontal (left dorsolateral and right inferior regions) in the control group versus the group of schizophrenic patients.

These results are consistent with the findings reported in previous studies. In a recent meta-analysis study that synthesized the data of 23 neuroimaging studies that had examined associative recognition memory in schizophrenia, Achim et al. (2005) reported that the most important brain region that differentiated the control subjects from patients with schizophrenia was exactly a greater left prefrontal activation[19].

Evidence derived from neurocognitive and neuropsychological studies indicate that the associative recognition depends on, as a fundamental mechanism, a conscious recovery of the information to perform recognition judgments[20], and previous neuroimaging studies have demonstrated that the prefrontal cortex is involved in this process[21]. Thus, as Danion has suggested[7], when there is poor or deficient conscious recovery, there is greater difficulty to combine and recover the different aspects of a memory events. Another possibility, that is consistent with our results, would be that the patients with schizophrenia have a greater difficulty monitoring the information recovered to guide the recognition judgments. It is also known that such a process depends on the adequate functioning of the dorsal lateral prefrontal cortex[17].

One important characteristic of the present work is its design, which makes it possible to overcome some of the methodological limitations of previous studies. In the analysis of functional images, we have used the design related to the event (in comparison with the designs in the block commonly used), which has allowed us to compare the neural activity among the groups during the correct answers in the recognition tests. Although the patients with schizophrenia had an average of more mistakes than the controls, only the correct answers were included in the analysis. This approach provides greater analytic advantages versus other strategies, such as design and blocks, in which the errors are considered in the analysis[22].

Furthermore, in our study, a more controlled manipulation of the memory processes has been used on making direct contrasts between items and associations using the same stimulus. Previous studies that have examined the neural correlates of recovery in episodic memory have contrasted recognition of stimuli (whether items or associations) versus basal stimuli, a method that is not the most favorable one to reveal neuronal correlates of a specific process.

Some limitations of the present study should be taken into account when interpreting its results. In the first place, although most of the patients who participated in the study had a chronic disease, all of them had mild symptoms. Thus, it is possible that some of our results cannot be generalized to patients with symptoms having greater severity. On the other hand, the patients were compared to the control group in terms of personal schooling level, but not in regards to the schooling of their parents, currently considered as a more adequate measure of general intellectual capacity. In addition, when the accuracy of the responses in name recognition test was examined, only a tendency towards interaction between groups was observed, reducing the specificity of the finding.

Finally, except in one case, all the patients received antipsychotic drugs during the conduction of the study, although in a secondary analysis, no correlation was found between global performance of recognition memory and the mean dose of antipsychotics. Thus, the possible effect of the use of antipsychotics in the results of memory should be taken into account.

In summary, the results of the present study show that there is a selective memory deficit in the associative recognition in patients with schizophrenia and the results also suggest that a prefrontal cortex dysfunction may be responsible for the selective memory disorder.

ACKNOWLEDGEMENTS

The study received help from CIHR and FRSQ granted to Martin Lepage and Alonso Montoya.

REFERENCES

1. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321-30.
2. Aleman A, Hijman R, de Haan EH, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry 1999;156:1358-66.
3. Tulving E. Memory systems and the brain. Clin Neuropharmacol 1992;15(Suppl. 1)Pt A:327A-328A.
4. Weiss AP, Heckers S. Neuroimaging of declarative memory in schizophrenia. Scand J Psychol 2001;42:239-50.
5. Tulving E. Multiple memory systems and consciousness. Hum Neurobiol 1987;6:67-80.
6. Pelletier M, Achim AM, Montoya A, Lal S, Lepage M. Cognitive and clinical moderators of recognition memory in schizophrenia: a meta-analysis. Schizophr Res 2005;74:233-52.
7. Danion JM, Rizzo L, Bruant A. Functional mechanisms underlying impaired recognition memory and conscious awareness in patients with schizophrenia. Arch Gen Psychiatry 1999;56:639-44.
8. Hockley WE. Recognition memory for item and associative information: a comparison of forgetting rates. En: Hockley WE, Lewandowsky S, editores. Relating theory and data: essays on human memory in honor of Bennet B. Murdock. Hillsdale: Lawrence Erlbaum Associates, 1991; p. 227-48.
9. Hockley WE, Cristi C. Tests of the separate retrieval of item and associative information using a frequency-judgment task. Mem Cogn 1996;24:796-811.
10. Westerman DL. The role of familiarity in item recognition, associative recognition, and plurality recognition on self-paced and speeded tests. J Exper Psychol: Learn Mem Perform 2001;27:723-32.
11. Achim AM, Lepage M. Neural correlates of memory for items and for associations: an event-related functional magnetic resonance imaging study. J Cogn Neurosci 2005;17:652-67.
12. Lepage M, Brodeur M, Bourgouin P. Prefrontal cortex contribution to associative recognition memory in humans: an event-related functional magnetic resonance imaging study. Neurosci Lett 2003;46:73-6.
13. Rugg MD, Fletcher PC, Chua PM, Dolan RJ. The role of the prefrontal cortex in recognition memory and memory for source: an fMRI study. Neuroimage 1999;10:520-9.
14. Rugg MD, Henson RN, Robb WG. Neural correlates of retrieval processing in the prefrontal cortex during recognition and exclusion tasks. Neuropsychologia 2003;41:40-52.
15. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003;64:663-7.
16. Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, et al. A general statistical analysis for fMRI data. Neuroimage 2002;15:1-15.
17. Achim AM, Lepage M. Dorsolateral prefrontal cortex involvement in memory post-retrieval monitoring revealed in both item and associative recognition tests. Neuroimage 2005;24:1113-21.
18. Cocosco CA, Zijdenbos AP, Evans AC. A fully automatic and robust brain MRI tissue classification method. Med Image Anal 2003;7:513-27.
19. Achim AM, Lepage M. A meta-analysis of episodic memory related activation in schizophrenia. Br J Psychiatry 2005;187:500-9.
20. Yonelinas AP. The nature of recollection and familiarity: a review of 30 years of research. J Mem Lang 2002;46:441-517.
21. Henson RN, Rugg MD, Shallice T, Josephs O, Dolan RJ. Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. J Neurosci 1999; 19:3962-72.
22. Price CJ, Friston KJ. Scanning patients with tasks they can perform. Hum Brain Mapp 1999;8:102-8.