Memory for object and object-location after lesions to the ventromedial prefrontal cortex in humans

Iwona Szatkowska[1], Anna Grabowska[1] and Olga Szymańska[2]

[1]Nencki Institute of Experimental Biology, Department of Neurophysiology, 3 Pasteur St., 02-093 Warsaw, [2]Warsaw University of Medicine, Department of Neurosurgery, 1a Banach St., 02-097 Warsaw, Poland

Abstract. The aim of the present study was to investigate the effect of small unilateral lesions to the ventromedial portion of the prefrontal cortex on two memory functions: memory for objects and memory for object locations. Patients, who had undergone surgery of the anterior communicating artery aneurysm, and normal control subjects, participated in the study. The patients were subdivided into two groups: with and without unilateral resection of the gyrus rectus. Subjects were presented with two memory tests, that required remembering either simultaneously presented visual stimuli (object memory test; OMT) or locations of the stimuli (location memory test; LMT). In the OMT, patients with resection of the gyrus rectus were impaired in comparison to patients without resection and normal control subjects. In the LMT, the three groups did not differ from each other. Our results suggest that the ventromedial prefrontal cortex is specifically involved in memory for objects.

The correspondence should be addressed to I. Szatkowska, Email: iwona@nencki.gov.pl

Key words: ACoA aneurysm, gyrus rectus, orbitofrontal cortex, damage, patient

INTRODUCTION

In recent years, substantial evidence has accumulated for the critical role of the prefrontal cortex in memory functions. Studies in nonhuman primates have shown that, within the prefrontal cortex, two separate systems could be identified for visual objects memory and visual location memory that are functionally and anatomically distinct. They are associated with the inferior (or more ventral) and with the superior (or more dorsal) lateral areas, respectively (Goldman-Rakic 1995, Wilson et al. 1987).

An important question is whether functional segregation applies to the human prefrontal cortex as well. Positron emission tomography (PET) studies (Courtney et al. 1996, 1998) suggest that the human lateral prefrontal cortex shows a high similarity to the monkey's lateral prefrontal cortex in that object memory occupies the more ventral area, whereas location memory the more dorsal part (but see Owen 1997, and D`Esposito et al. 1998, for different opinions). This conclusion was derived from finding that retention of information concerning the identity of face stimuli activated the right inferior and mid-prefrontal cortex whereas retention of information about the location of the same face stimuli activated an area of the superior frontal sulcus.

It is worth noting that studies revealing the functional differentiation of the prefrontal cortex have mainly dealt with its lateral parts: dorsal or ventral. Little is known of what specific memory functions are subserved by the areas located in the ventromedial rather than in the ventrolateral region. Bachevalier and Mishkin (1986) found that, in monkeys, lesion to the ventromedial portion of the prefrontal cortex (including the orbital cortex, gyrus rectus, subcallosal cortex and anterior cingulate gyrus) impaired object recognition memory measured by delayed non-matching-to-sample tasks whereas dorso-lateral lesions affected spatial delayed responses. This data suggests that the ventromedial cortex in monkeys shows a high similarity to the ventrolateral part in that they are both engaged in retention of object rather than spatial information. It remains unknown, however, whether this also holds true for the human brain because most of the clinical research that has dealt with the role of the ventromedial prefrontal cortex in memory were performed on subjects with relatively large lesions. The effects of damage to the ventral portion of the prefrontal cortex were often investigated in patients who underwent rupture and repair of the an-

eurysm of the anterior communicating artery (ACoA). In most cases, the lesions were rather large due to infarction in the territory of the ACoA and they extended posteriorly, involving the basal forebrain region (Alexander and Freeman 1984, Drumm et al. 1993, Łuria 1976, Petrides 2000). Patients with such lesions are impaired in remembering both object features and the spatial context in which objects occurred (Talland et al. 1967, Volpe and Hirst 1983) but it is difficult to attribute specific memory deficits to particular structures. In the present study, we could be much more precise because we had the cooperation of patients in whom brain damage was limited to the ventromedial prefrontal cortex (posterior part of the gyrus rectus) either in the left or right hemisphere.

The aim of the present study was to investigate whether the ventromedial portion of the prefrontal cortex plays a role in memory functions. Additionally, we were interested whether this role would be limited exclusively to object memory, or it would be related both to memory for objects and memory for object locations.

METHODS

Subjects

PATIENTS

Twenty-one patients after surgery of ACoA aneurysm participated in the study. They were operated with ligation of the aneurysmal neck. During surgery for the ACoA aneurysm, partial resection of the gyrus rectus is frequently performed to facilitate exposure of the aneurysm. In other cases, the operation does not involve removal of neural tissue. Our patients, thus, constituted two groups: one with resection of the posterior 1/4 quarter of the gyrus rectus (GR+) and one without this resection (GR-). All patients were very similar in both patterns of their disease and the medical treatment they received. The comparison of the two groups offered the opportunity to test the effects of such small lesions on brain functions. As the resection was performed either on the left or right side, the GR+ group was further subdivided into two subgroups: left (LGR+) and right (RGR+). The sizes of the left- and right-sided lesions were very similar (1 cm diameter) because of the standard procedure used in such operations.

Patients were selected from a large sample of brain-damaged subjects who had undergone an opera-

Table I

Patients' characteristics

	Sex		Age (years)		Education (years)		Time after operation (years)	
	M	F	Mean	Range	Mean	Range	Mean	Range
RGR+	5	1	40.2	27-49	11.0	8-13	4.6	3-7
LGR+	5	1	45.6	41-50	11.3	8-16	5.0	4-8
GR-	5	4	38.7	24-53	14.0	10-17	5.0	2-7

RGR+, patients with partial resection of the right gyrus rectus; LGR+, patients with partial resection of the left gyrus rectus; GR- , patients without resection of the gyrus rectus.

tion of the ACoA aneurysm at the Department of Neurosurgery of the Warsaw University of Medicine. High attention was devoted to careful selection of patients. Only patients who fulfilled the following criteria were included: no CT evidence of cerebral damage due to factors other than the operation; no evidence for clinical or angiographic post-hemorrhagic vasospasm; no gross memory loss as revealed by performance on memory subtests of WAIS-R (Wechsler Adult Intelligence Scale, Revised) (Brzeziński et al. 1996) and by neuropsychological examination; no plegias or other neurological impairments; no aphasia symptoms; no other diagnoses likely to affect cognition (e.g., psychiatric disease, alcoholism or drug abuse); not older than 55 years. The patients were characterized by normal intellectual functions as measured with WAIS-R. All patients were right handed. All of them consented to enter the study.

Table I presents data about the sociodemographic and clinical characteristics of patients.

CONTROL SUBJECTS

Fourteen right-handed individuals (9 men and 5 women) served as control subjects. They were matched as much as possible to the patients with respect of their age, education and intelligence (as measured by WAIS-R). None had any history of trauma affecting the central nervous system.

Procedure

Subjects were presented with two recognition memory tests that required remembering either visual stimuli *per se* (OMT - object memory test), or the locations of simultaneously presented stimuli (LMT - location memory test). Object and location memory tests used equivalent (similar) stimuli. They differed only in terms of the information that subjects were instructed to retain, namely the identity or the location of the stimuli.

OBJECT MEMORY TEST
(OMT)
/   \
VERBAL   NONVERBAL
SESSION   SESSION
(max. 9 trials)   (max. 9 trials)

LOCATION MEMORY TEST
(LMT)
/   \
VERBAL   NONVERBAL
SESSION   SESSION
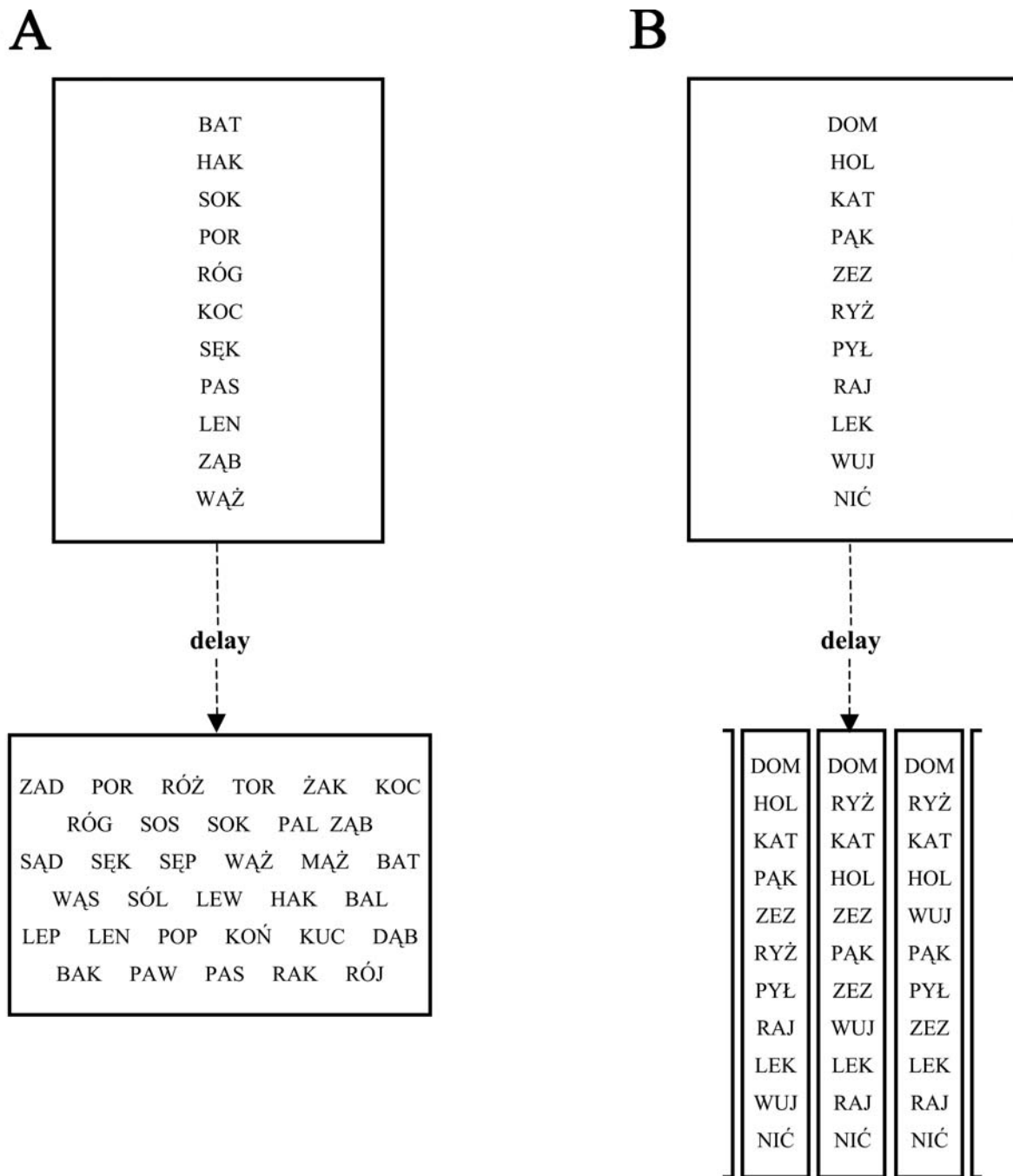(max. 9 trials)   (max. 9 trials)

Fig. 1. Experimental paradigm.

A

BAT
HAK
SOK
POR
RÓG
KOC
SĘK
PAS
LEN
ZĄB
WĄŻ

delay

ZAD POR RÓŻ TOR ŻAK KOC
RÓG SOS SOK PAL ZĄB
SĄD SĘK SĘP WĄŻ MĄŻ BAT
WĄS SÓL LEW HAK BAL
LEP LEN POP KOŃ KUC DĄB
BAK PAW PAS RAK RÓJ

B

DOM
HOL
KAT
PĄK
ZEZ
RYŻ
PYŁ
RAJ
LEK
WUJ
NIĆ

delay

DOM	DOM	DOM
HOL	RYŻ	RYŻ
KAT	KAT	KAT
PĄK	HOL	HOL
ZEZ	ZEZ	WUJ
RYŻ	PĄK	PĄK
PYŁ	ZEZ	PYŁ
RAJ	WUJ	ZEZ
LEK	LEK	LEK
WUJ	RAJ	RAJ
NIĆ	NIĆ	NIĆ

Fig. 2. The sequence of events in a single trial of the object memory test (A) and location memory test (B).

The test material consisted of verbal stimuli (3-letter Polish words) and nonverbal stimuli (Kanji characters). Both the object- and location-memory tests consisted of two experimental sessions – verbal and nonverbal (Fig. 1). The order of the tests and sessions was counterbalanced within each group. For both sessions, the procedure was the same. In the single trial, stimuli (verbal or nonverbal) were presented on a test card for 60 s and, after a delay of about 5 s, a response card was exposed (Fig. 2). The task of the subject was to recognize either the previously presented stimuli or their spatial arrangement. Trials were repeated until the subject reached the criterion of two consecutive 100% correct performances. The intertrial interval was approximately 90 s. Participant was not informed about the number of errors committed. The session was interrupted if the subject
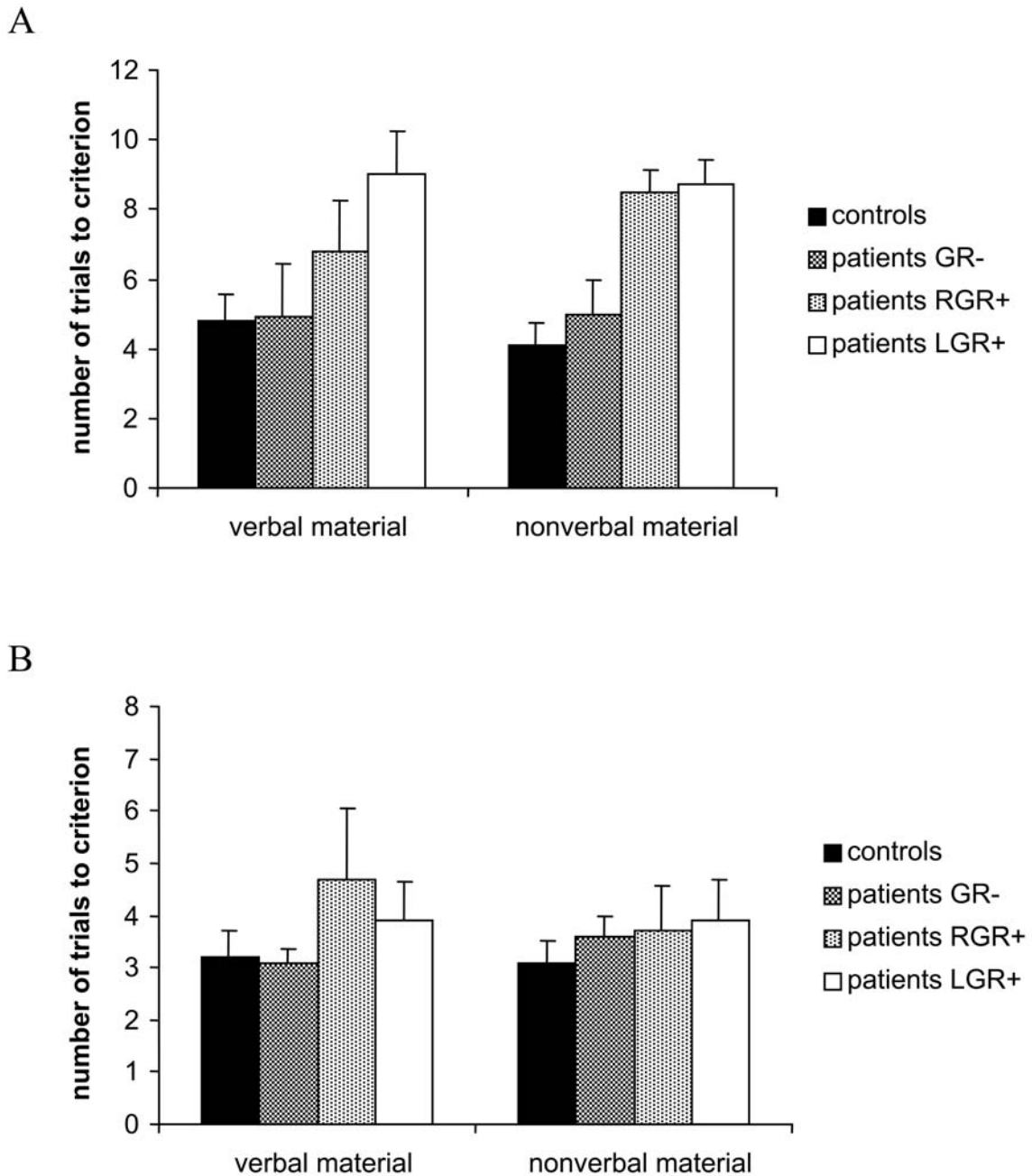
Fig. 3. Performance of four groups of subjects (controls, patients GR-, patients RGR+, patients LGR+) on the verbal and non-verbal sessions in the object memory test (A) and location memory test (B). The bars represent S.D.

had not reached the criterion up to the 9th trial. In the case of interrupted session, we arbitrary assumed that subject reached the criterion in the 10th trial.

To match the sessions for the level of difficulty, the number of verbal and nonverbal stimuli (11 and 9 items, respectively) was determined in a pilot study. In that study, the test cards contained various numbers (8-12) of stimuli. Subjects obtained similar results in the verbal

and nonverbal session (i.e. they reached the criterion in the 4-5 trial) when the test cards contained 11 verbal and 9 nonverbal stimuli.

In the OMT, all test cards contained the same vertically arranged stimuli, but the order of stimuli varied from trial to trial. Recognition cards contained both the stimuli previously exposed on the test card (1/3 of total number) and novel ones. The stimuli were arranged in

six rows. The content of recognition cards was fixed but the position of the stimuli varied, so that, as far as possible, across the trials, each stimulus would appear in every possible position. The subject's task was to indicate which stimuli were previously presented on the test card.

In the LMT, the test cards were always the same (they contained the same stimuli arranged in the same order). After a delay, subjects were simultaneously shown 16 recognition cards that contained the same stimuli as the test card, but arranged in a different order. Only one of the 16 recognition cards perfectly matched the test card. To avoid recognitions that would relay solely on the first or last item, the stimuli that began and finished each list (card) were always the same. The subject's task was to indicate which recognition card matched the order of stimuli on the test card.

RESULTS

The number of trials to criterion was analyzed. A three-way repeated measures analysis of variance MANOVA with group of subjects (Controls, GR-, LGR+, RGR+), test (OMT, LMT), and stimulus material (verbal, nonverbal) showed a significant main effect of group ($F_{3,31}$=14.64, P<0.0005) and of test ($F_{1,31}$=69.87, P<0.0005). Moreover, the analysis yielded a significant test by group interaction ($F_{3,31}$=6.14, P<0.002) indicating that the differences between groups were mainly associated with one of the two tests. Thus, two-way repeated-measures MANOVA were performed separately for the OMT and the LMT.

In the OMT (Fig. 3a), a significant main effect of group was obtained ($F_{3,31}$=15.55, P<0.0005). *Post-hoc* analysis (performed with the Newman-Keuls test) revealed that both the LGR+ group and RGR+ group performed below both control and GR- groups (P<0.05). The GR- group did not differ significantly from controls. The main effect of material and the interaction were not statistically significant. However, a more detailed examination of the data presented in Fig. 3a suggests that in patients with resection of the left *gyrus rectus*, the recognition of verbal and nonverbal stimuli was impaired, whereas in patients with resection of the right *gyrus rectus*, mainly recognition of nonverbal material was impaired. These observations were confirmed by *post-hoc* analyses (Newman-Keuls tests) performed separately for each material data. With verbal material, the LGR+ group differed significantly from all other

groups (P<0.05) which did not differ from each other. With nonverbal material, both the LGR+ group and RGR+ group differed significantly from both the GR- and control groups (P<0.05). The two former and the two latter groups did not differ from each other.

The two-way MANOVA performed on the LMT data did not revealed any significant effects (Fig. 3b).

DISCUSSION

Our data showed that partial resection of the gyrus rectus resulted in selective impairment of memory for objects, leaving memory for locations intact. One might suppose that the object-location test was very easy and not sensitive enough to catch any differences between groups of tested subjects. However, subjects reached the criterion on the average on the 4rd trial. Thus, it indicates that performance in the object-location test was far from ceiling effect.

As we have mentioned earlier, focal lesions to the ventromedial prefrontal cortex are rarely investigated in humans. Most human research concerns the effects of relatively large lesions to this region. The only study we are aware of showed that partial removal of the gyrus rectus resulted in a worse short-term memory as measured with the Benton visual retention test (Hŭtter and Gilsbach 1996). This finding is in agreement with the present data and our previous study performed on the same groups of patients that revealed that this area plays a critical role in short-term storage of visual information (Szatkowska et al. 2001).

There is another clinical study suggesting the involvement of ventromedial prefrontal cortex in memory. Bechara et al. (1998) found that patients with more posteriorily placed bilateral lesions showed deficient performance on an analogue of the delayed nonmatching-to-sample test, whereas patients with more anterior lesions were not impaired. This study may be relevant to our research as posterior ventromedial lesions might imply the involvement of the posterior part of the gyrus rectus. However, more extended and more variable localizations of lesions made it difficult to establish in what cases the area of gyrus rectus was damaged.

It is worth noting that neuropsychological studies did not search for the possibility that the ventromedial prefrontal cortex plays a different role in object- and object-location-memory. However, this issue was investigated in monkeys. As noted in the introduction, studies in monkeys indicated that ventromedial prefrontal le-

sions impaired object memory (Bachevalier and Mishkin 1986). Further work in monkeys (Meunier et al. 1997) showed that selective lesions to the orbital and recti gyri severely impaired object memory processes, as evaluated by delayed nonmatching-to-sample and object reversal learning tests. Location memory processes, assessed by spatial delayed response and spatial reversal learning, were not disturbed. Our data is in line with these findings and suggests that the human medial orbitofrontal cortex has a role in object memory similar to that demonstrated in the monkey.

Several behavioural and anatomical data indicate that the ventromedial prefrontal cortex belongs to a complex neural system that mediates object memory. This system involves the medial temporal region. Removal of the medial temporal lobe structures in monkeys severely impairs object memory (Bachevalier and Mishkin 1986, Leonard et al. 1995, Meunier et al. 1993, Suzuki et al. 1993). Clinical research corroborates these findings and suggests that object memory is disturbed after lesions to medial temporal lobe structures (Jones-Gotman 1986, Pigott and Milner 1993). Anatomical studies have demonstrated that the ventromedial prefrontal cortex receives input from those medial temporal cortical areas that have been shown to contribute to object memory (Aggleton et al. 1986, Bachevalier et al. 1997, Russchen et al. 1987). Based on this data, one might predict that the ventromedial prefrontal cortex is specifically involved in memory for objects, but not in memory for the spatial context in which objects appeared. The present findings confirm this view and indicate that in humans, as in monkeys, this region is functionally closely related to medial temporal lobe structures.

It is important to emphasize that several neuroimaging studies have demonstrated that object memory is mediated by the ventrolateral portion of the prefrontal cortex in humans (Courtney et al. 1996, Frey and Petrides 2000, Haxby et al. 1996, Kohler et al. 1998, Smith and Jonides 1999). It is possible, therefore, that the whole ventral portion of the prefrontal cortex plays a role in object memory but object memory processes may involve relatively sparse changes within the ventromedial region that are difficult to detect with current neuroimaging techniques.

Our results also show that patients with left- and right-side lesions to the gyrus rectus differ with respect to memory for verbal and nonverbal material. Left-hemispheric lesions impaired the memory for both verbal and nonverbal material, whereas right-hemi-

spheric lesions impaired only memory for nonverbal material. Over the past three decades, studies in human subjects have shown that left hemisphere damages result in impairments in verbal memory function, whereas right hemisphere damages disturb memory for nonverbal, visual-spatial material. The lateralization observed in our study is consistent with the general role of the right hemisphere in the processing of visual-spatial information. One might wonder, however, why the impairment of memory for nonverbal stimuli was also observed after lesions to the left hemisphere. It is probably due to the fact that human subjects tend to use verbal strategies to organize and learn a wide variety of stimuli, including nonverbal ones. For example, Kanji characters would show a left- or a right-hemisphere superiority depending on the strategy used by the subject (Sasanuma et al. 1977). Interestingly, our previous study also revealed that the two gyri recti are functionally differentiated (Szatkowska et al. 2000, 2001). Patients with resection of the right gyrus rectus showed deficits in semantic fluency task, as well as in short-term retention of visual images, whereas patients with left–sided lesions were not impaired.

CONCLUSION

Our data shows that the ventromedial portion of the prefrontal cortex is specifically involved in memory for objects, but not for their locations.

REFERENCES

Aggleton J.P., Desimone R., Mishkin M. (1986) The origin, course, and termination of the hippocampothalamic projections in the macaque. J Comp Neurol 243: 409-421.

Alexander M.P., Freeman M. (1984) Amnesia after anterior communicating artery aneurysm rupture. Neurology 34: 752-757.

Bachevalier J., Meunier M., Lu M.X., Ungerleider L.G. (1997) Thalamic and temporal cortex input to medial prefrontal cortex in rhesus monkeys. Exp Brain Res 115: 430-444.

Bachevalier J., Mishkin M. (1986) Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys. Behav Brain Res 20: 249-261.

Bechara A., Damasio H., Tranel D., Anderson S.W. (1998) Dissociation of working memory from decision making within the human prefrontal cortex. J Neurosci 18: 428-437.

Brzeziński J., Gaul M., Hornowska E., Machowski A., Zakrzewska M. (1996) Skala Inteligencji Dawida Wechslera dla Dorosłych. Wersja Zrewidowana WAIS-R (PL). Pracownia Testów Psychologicznych PTP.

Courtney S.M., Ungerleider L.G., Keil K., Haxby J.V. (1996) Object and spatial visual working memory activate separate neural systems in human cortex. Cereb Cortex 6: 39-49.

Courtney S.M., Petit L., Haxby J.V., Ungerleider L.G. (1998) The role of prefrontal cortex in working memory: examining the contents of consciousness. Philos Trans R Soc Lond B 353: 1819-1828.

D'Esposito M., Aguirre G. K., Zarahn E., Ballard D., Shin R.K., Lease J. (1998) Functional MRI studies of spatial and non-spatial working memory. Brain Res Cogn Brain Res 7: 1-13.

Drumm D.A., Greene K.A., Marciano F.F., Prigatano G.P., Spetzler R.F. (1993) Neurobehavioral deficits following rupture of anterior communicating artery (ACoA) aneurysms: The ACoA aneurysm syndrome. BNI Quarterly 9: 2-12.

Frey S., Petrides M. (2000) Orbitofrontal cortex: A key prefrontal region for encoding information. Proc Natl Acad Sci U S A 97: 8723-8727.

Goldman-Rakic P.S. (1995) Architecture of the prefrontal cortex and the central executive. Ann NY Acad Sci 769: 71-83.

Haxby J.V., Ungerleider L.G., Horwitz B., Maisog J.M., Rapoport S.I., Grady C.L. (1996) Face encoding and recognition in the human brain. Proc Natl Acad Sci U S A 93: 922-927.

Hűtter B.O., Gilsbach J.M. (1996) Early neuropsychological sequelae of aneurysm surgery and subarachnoid haemorrhage. Acta Neurochir 138: 1370-1379.

Jones-Gotman M. (1986) Memory for designs: The hippocampal contribution. Neuropsychologia 24: 193-203.

Kohler S., Moscovitch M., Wincour G., Houle S., McIntosh A.R. (1998) Networks of domain-specific and general regions involved in episodic memory for spatial location and object identity. Neuropsychologia 36: 129-142.

Leonard B.W., Amaral D.G., Squire L.R., Zola-Morgan S. (1995) Transient memory impairments in monkey with bilateral lesions of the enthorinal cortex. J Neurosci 15: 5637-5659.

Łuria A.R. (1976) The Neuropsychology of memory. Winston and Sons, Washington, p. 255-297.

Meunier M., Bachevalier J., Mishkin M. (1997) Effects of orbital frontal and anterior cingulate lesions on object and spatial memory in rhesus monkeys. Neuropsychologia 35: 999-1015.

Meunier M., Bachevalier J., Mishkin M., Murray E.A. (1993) Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkey. J Neurosci 13: 5418-5432.

Owen A.M. (1997) The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. Eur J Neurosci 9: 1329-1339.

Petrides M. (2000) Frontal lobes and memory. In: Handbook of neuropsychology (Eds. F. Boller and J. Grafman). 2nd ed. Vol. 2. Elsevier, p. 67-84.

Pigott S., Milner B. (1993) Memory for different aspects of complex visual scenes after unilateral temporal- or frontal-lobe resection. Neuropsychologia 31: 1-15.

Russchen F.T., Amaral D.G., Price J.L. (1987) The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey *Macaca fasciularis*. J Comp Neurol 256: 175-210.

Sasanuma S., Itoh M., Mori K., Kobayaschi Y. (1977) Tachistoscopic recognition of Kana and Kanji Words. Neuropsychologia 15: 547-553.

Smith E.E., Jonides J. (1999) Storage and executive processes in the frontal lobes. Science 283: 1657-1661.

Suzuki W.A., Zola-Morgan S., Squire L.R., Amaral D.G. (1993) Lesions of the perirhinal and parahippocampal cortices in the money produce long lasting memory impairments in the visual and tactual modalities. J Neurosci 13: 2430-2451.

Szatkowska I., Grabowska A., Szymańska O. (2000) Phonological and semantic fluencies are mediated by different regions of the prefrontal cortex. Acta Neurobiol Exp 60: 503-508.

Szatkowska I., Grabowska A., Szymańska O. (2001) Evidence for the involvement of the ventro-medial prefrontal cortex in a short-term storage of visual images. NeuroReport 12: 1187-1190.

Talland G.A., Sweet W.H., Ballantine H.T. (1967) Amnestic syndrome with anterior communicating artery aneurysm. J Nerv Ment Dis 1452: 179-192.

Volpe B.T., Hirst W. (1983) Amnesia following the rupture and repair of an anterior communicating artery aneurysm. J Neurol Neurosurg Psychiatry 46: 704-709.

Wilson E.A., O'Scalaidhe S.P., Goldman-Rakic P.S. (1987) Dissociation of object and spatial processing domains in primate prefrontal cortex. Science 260: 1955-1958.