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Phonological and semantic fluencies are mediated by different regions of the prefrontal cortex

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Abstract. Verbal phonological and semantic fluencies were investigated in 24 patients with unilateral prefrontal lesions and 10 normal control subjects. Lesions were limited to small areas within either the dorsolateral (Brodmann's area 46/9) or ventromedial (posterior part of the gyrus rectus) cortices. In a phonological fluency task, patients with lesions to the left dorsolateral region were impaired. In semantic fluency, not only the left dorsolateral group but also the two right frontal damaged groups performed worse than the control group. In agreement with previous studies, our results show that the phonological fluency is mediated by the left dorsolateral prefrontal cortex. In contrast to this, performance on the semantic fluency task depends on a wider portion of the prefrontal cortex involving the left and right dorsolateral and the right ventromedial areas.

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Verbal fluency is typically measured by the quantity of words produced within a time limit and usually within a restricted category. The verbal fluency task was first introduced as a means of evaluating the overall productivity in brain damaged subjects (Thurstone 1938, Hécaen and Albert 1978). Nowadays, it is regarded as a frontal lobe test as patients with frontal localization of damage are especially impaired in that task (Lezak 1995). Two types of verbal fluency tests are used in which words are elicited according to either a phonological criterion (words beginning with a given letter) or a semantic criterion (items belonging to a specific semantic category, e. g. names of animals). Although both phonological and semantic fluency require an access to lexical memory and retrieval of lexical items following the instruction given to the subject, it is possible to distinguish between search strategies according to the phonological or semantic nature of the considered task. In the phonological fluency task, one has to suppress the ordinary way of retrieving words from memory according to their meaning (Perret 1974, Birri and Perret 1985, Ahola et al. 1996). Such a task forces the subject to use a search strategy based mainly on lexical representations. In contrast, the semantic fluency task requires first an exploration of the conceptual knowledge and, then, a search strategy according to semantic category.

An important question is which specific brain regions are engaged in phonological and semantic fluency tasks. Clinical data based on performance of patients with unilateral brain lesions has usually pointed to the involvement of the left dorsolateral prefrontal cortex in phonological fluency (Ramier and Hécaen 1970, Perret 1974, Janowsky et al. 1989, Martin et al. 1990, Stuss et al. 1998). Data on specific regions engaged in semantic fluency is less consistent. Although semantic fluency has been frequently linked to different areas in the left hemisphere (dorsolateral prefrontal and temporal) (Martin et al. 1990, Saykin et al. 1995, Troster et al. 1995, Stuss et al. 1998), several authors have demonstrated that the right hemisphere areas might also add to this function (Boller 1968, Joannette and Goulet 1986, Joannette et al. 1988, Laine 1988, Stuss et al. 1998).

Most clinical studies have concentrated on verbal fluency deficits after lesions to the dorsolateral part of the prefrontal cortex. Little is known, however, as to the effect of ventromedial prefrontal lesions. The majority of studies investigating the role of the ventromedial part of the prefrontal cortex were performed in patients who underwent rupture and repair of the anterior communicating artery (ACoA) aneurysm. Various deficits were described, including short-term and long-term memory along with a number of behavioral changes typical of frontal lobe disorders, including verbal fluency deficits (Diamond et al. 1997, Beeckmans et al. 1998, Bottger et al. 1998, Mavaddat et al. 1999, Ptak and Schnider 1999, ThomasAnterion et al. 1996). In most studies, however, lesions were rather large and included not only a large portion of the prefrontal cortex but also basal forebrain structures. It was difficult, therefore, to attribute the observed deficits to particular frontal areas. Still less is known whether left and right ventromedial prefrontal areas are functionally equivalent or not (Alexander and Freeman 1984, Owen et al. 1995) because lesions were either bilateral or the authors did not search for a possible dissociation between the effects of the left- and right--hemispheric lesions. These limitations prevented a firm conclusion as to the exact loci of damage responsible for the deficits that were found. To avoid these difficulties in the present study, we investigated a highly selected group of patients with lesions to the ventromedial portion of the prefrontal cortex who had no brain damage except a partial resection of the gyrus rectus either in the left or in the right hemispheres.

It is worth noting that, in the majority of clinical studies, lesions were limited to either dorsolateral or ventromedial regions of the prefrontal cortex. This precluded the direct comparison of the effects of different lesions. Our study addressed this issue by studying phonological and semantic fluency in patients with damage to dorsolateral and ventromedial portions of the prefrontal cortex.

Four groups of patients participated in the study: Patients with left dorsolateral prefrontal lesions (LDL group - 6 subjects); right dorsolateral prefrontal lesions (RDL group - 6 subjects); left ventromedial prefrontal lesion (LVM group - 6 subjects); and right ventromedial prefrontal lesions (RVM group - 6 subjects). The LDL group and RDL group encompassed patients who underwent surgery to remove a tumor localized in either hemisphere (Brodmann's area 46/9). In all cases, the size of lesion was comparable (about 3 cm diameter). The LVM group and RVM group was constituted by patients who have undergone surgery of the ACoA aneurysm together with a resection of the posterior 1/4 of the gyrus rectus. The left- and right--sided lesions were very similar (1cm diameter) because of the standard procedure used in such operations.

Patients were selected from a large sample of brain damaged subjects who have undergone operations at the

Table I

Sociodemographic and clinical characteristics of patients

	Sex		Age (years)		Education	
Group	M	F	Mean	Range	Mean	Range
LDL	4	2	44.8	38-52	11.5	8-16
RDL	6	0	45.2	40-54	10.8	8-16
LVM	5	1	40.2	27-49	11.0	8-13
RVM	5	1	45.6	41-50	11.3	8-16

LDL, patients with lesions to the left dorsolateral prefrontal cortex; RDL, patients with lesions to the right dorsolteral prefrontal cortex; LVM, patients with lesions to the left ventromedial prefrontal cortex; RVM, patients with lesions to the right ventromedial prefrontal cortex.

Department of Neurosurgery of the Warsaw University of Medicine in Poland. Only patients who fulfilled the following criteria were included: not older than 55 years; no plegias or other neurological impairments; no aphasia or psychosis; no CT (computerized tomography) evidence of permanent cerebral damage due to factors other than the operation. Patients were characterized by normal intellectual functions as measured with WAIS (Wechsler Adult Intelligence Scale). All patients were right handed. All of them consented to enter the study. Table I presents data about the sociodemographic and clinical characteristics of the patients.

Ten individuals (6 men and 4 women) served as control subjects. They were matched as much as possible to the patients with respect to their age, education and intelligence (as measured by Wechsler Adult Intelligence Scale - Revised; WAIS-R).

Subjects were required to orally produce the greatest possible number of Polish words with respect to the following two criteria: phonological criterion (words beginning with letter "K") and semantic criterion (words belonging to the semantic class whose superordinate is "ANIMAL"). The time limit for production within each category was 60 s. Subjects were instructed to utter nouns without repeating any one. Numbers of words belonging to each category were analyzed separately for the first 30 s and 60 s.

Fig. 1A illustrates the mean number of words belonging to each category elicited by five groups of subjects in the first 30s. A two-way (group x criterion type) analysis of variance revealed statistically significant effects of

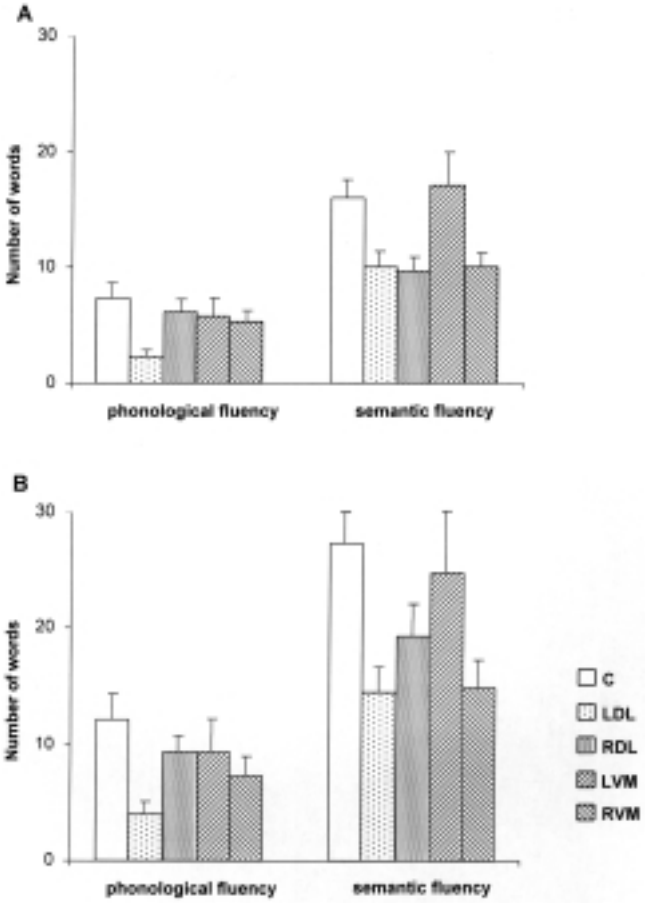

Fig. 1. Performance of brain-damaged and control subjects on phonological and semantic fluency tasks (A, after 30 s; B, after 60 s). C, controls; LDL, left dorsolateral prefrontal lesion; RDL, right dorsolateral prefrontal lesion; LVM, left ventromedial prefrontal lesion; RVM, right ventromedial prefrontal lesion.

group ($F_{4,29} = 5.92$, $P<0.001$), criterion ($F_{1,29} = 200.25$, $P<0.0005$) and the interaction ($F_{4,29} = 7.14$, $P<0.0005$). The post-hoc Neuman-Keul test, performed separately for each criterion data, revealed significant differences across groups for both phonological ($F_{4,29} = 4.41$, $P<0.0067$) and semantic criterion ($F_{4,29} = 6.964$, $P<0.0005$). With phonological criterion, the LDL group differed significantly from all other groups ($P<0.05$), which did not differ from each other. With semantic criterion, LDL, RDL and RVM groups differed significantly from the control group and LVM group ($P<0.05$).

With respect to 60s period, similar results were obtained (Fig. 1B). A two-way analysis of variance showed significant effects of group ($F_{4,29} = 6.22$, $P<0.001$), criterion ($F_{1,29} = 259.84$, $P<0.0005$) and the interaction ($F_{4,29}$

= 6.23, $P<0.001$). The post-hoc Netic criterion ($F_{4,29}$ = 6.34, $P<0.0009$). With phonologicaluman-Keul tests also revealed significant differences across groups for both phonological ($F_{4,29}$ = 3.84, $P<0.01$) and seman criterion, the LDL group differed from the control group ($P<0.05$). With semantic criterion, LDL, RDL and RVM groups differed from the control group ($P<0.05$), and the RVM group differed from the LVM group ($P<0.05$).

Considerable evidence suggests that women are superior to men in a wide range of skills that require the use of language, including verbal fluency. We were interested, therefore, whether the subjects' sex might have influenced the fluency performance in our study. As the numbers of patients in different damaged groups were very small, we performed the two-way analyses of variance with sex and criterion as factors (pooling data from different groups). Neither for the first 30 s nor for 60 s period, the analyses showed significant effect of sex or the interaction.

Our results showed that, with respect to phonological criterion, patients with LDL lesions were impaired. With respect to semantic criterion, however, not only the LDL group but also the two right-hemisphere damaged groups (RDL, RVM) performed worse than the control group. In keeping with the prediction derived from clinical studies that concerned the role of the left dorsolateral prefrontal cortex in verbal fluency, our results showed that patients with lesions to this region exhibited difficulties in both phonological and semantic fluency tasks. The involvement of this region in both types of verbal fluency was also demonstrated by a PET study (Klein et al. 1995), which showed that the left dorsolateral prefrontal cortex was activated irrespective of whether subjects were required to generate words with phonological or semantic search strategies. Such data is not surprising as both types of verbal fluency tasks engage lexical exploration, which is the left hemisphere domain.

Our finding that the right dorsolateral lesions resulted in selective impairment of semantic fluency also finds support in both clinical (Stuss et al. 1998) and neuroimaging (Cardebat et al. 1996) studies. According to some authors, semantic fluency may challenge language skills at a level where they are strongly connected with higher mental processes that are not exclusively linguistic (Boller 1968, Varley 1995), as, in contrast to phonological fluency, it requires en exploration of conceptual knowledge. Similar remarks have been made with regard to other semantic tasks (e.g. word comprehension task) that were shown to be impaired after right hemisphere lesions (Lesser 1974, Gainotti et al. 1979, 1981).

It cannot be excluded, however, that the dissociation between the effects of left and right dorsolateral lesions on the phonological and semantic fluency may be due to different strategies used by subjects during word production. When generating words, subjects could use both a verbal strategy and a strategy based on visual imagery - the latter being particularly likely in a semantic fluency task. Although we do not have direct evidence supporting the idea of a greater involvement of visual strategies in semantic fluency tasks than in phonological tasks, this assumption seems to fit well the results of two recent PET studies that have shown that the degree and direction of rCBF asymmetry, observed during verbal fluency task, was dependent upon the main search strategy used by the subjects (Lindgren et al. 1997, Elfgren and Risberg 1998). Verbal strategy (e.g. generating the combinations of different syllables or searching for verbal association) resulted in marked flow increases in the left dorsolateral prefrontal areas, whereas visual search strategy (e. g. searching for visual memory representation to find out the words) caused flow increases in the corresponding areas of the right hemisphere.

An interesting finding of our study was that small lesions limited to the right ventromedial cortex also impaired semantic fluency. One might wonder whether this result reflects a more general deficit within either the attentional or memory domain. Such hypotheses seem plausible in light of cytoarchitectonic data showing that the gyrus rectus is morphologically an extension of the cingulate complex (Morecraft et al. 1992) that plays an important role in both attention (Posner 1994, Posner and Rothbart 1998) and memory processing (Damasio et al. 1989). As neuropsychological examination of our patients with ventromedial localization of lesions did not reveal any attentional deficits (as measured by the Letter Cancellation Test, the Trail Making Test, and the Symbol Digit Modalies Test) the attentional deficit hypothesis seems be unlikely.

Let us consider the other possibility that the impairment observed in the RGR+ group was related to memory disorders. A large body of behavioral and anatomical data indicates that, at least in monkeys, the ventromedial prefrontal cortex belongs to a neural system that plays an important role in visual object memory (Voytko 1985, Bachevalier and Mishkin 1986, Bachevalier et al. 1997). Interestingly, we have recently found that patients with resection of the right gyrus rectus also showed deficits in

maintaining information about visual objects (paper in preparation). The precise role of the ventromedial prefrontal cortex in the semantic fluency task, however, has yet to be determined.

In conclusion, our data shows that phonological and semantic fluencies have different neuronal basis, the former being supported by the left dorsolateral prefrontal cortex and the later by a wider prefrontal region including both the left and right dorsolateral and the right ventromedial cortices. Thus, it provides further evidence that the prefrontal cortex is a complex structure compound of several functionally differentiated areas.

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