Brain regions responsible for word retrieval, speech production and deficient word-fluency in elderly people: A PET activation study

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ABSTRACT

A PET (positron emission tomography) activation study using word-fluency tasks was administered to identify the network for word retrieval and speech production, and to explore mechanisms for word finding difficulty observed in elderly people. It was found that the left anterior insula, as opposed to Broca’s area, left premotor area, the anterior cingulate gyrus, thalamus, basal ganglia, midbrain and cerebellum constitute the network for speech production. In semantic processing for word retrieval of proper names, the left anterior temporal lobe and frontal pole (BA 10) were activated. As for the animate and inanimate name retrieval, and the syllable fluency the same areas, viz., the left inferoposterior temporal lobe (BA 37) and left inferior frontal lobe (Broca’s area), were activated.

In elderly people an activated area was generally small, and those regions activated in young people were sometimes inactive. However, an great, stable and diffuse activation was also observed. The latter may reflect an effort to compensate for deficient word retrieval. These are possible sources of word finding difficulty in the elderly.

INTRODUCTION

Recent PET activation studies revealed that brain regions other than classical language areas, i.e., Broca’s and Wernicke’s areas, associate with word information processing (Damasio and Damasio, 1992). Mummery et al. (1996) adopted word-fluency tasks for animate and inanimate objects, and letters (letter fluency: speaking as many words beginning with a given letter as possible). The authors found that the left and right medial temporal lobes associated with retrieval of animate names, the left temporo-occipito-parietal junction with retrieval of inanimate object names, and the left inferior frontal lobe, with letter (or phoneme) fluency.

Damasio et al. (1996) administered picture naming of animals, tools and famous persons’ faces, and showed that the left temporo-parietal region was activated in tool picture naming, left inferior temporal gyrus just prior to the tool area in animate picture naming, and left and right temporal poles in naming of famous persons’ pictures. They hypothesize that in the left temporal pole precise perceptual semantic information is processed (Tranel et al., 1997).

More recently, Tempini et al. (1998), using same/different judgment tasks for pictures and names of famous and non-famous persons, revealed that the left anterior middle temporal gyrus (BA 21) and left angular gyrus (BA 39) were responsible for same/different judgment for pictures and names of famous persons. Those areas are shown to relate to semantic information processing in the previous studies (Vandenberghe et al., 1996; Price et al., 1997). Among others, Tempini et al. (1998) demonstrated that the region inherent to processing of faces of famous people was the left anterior middle temporal gyrus.

In Experiment 1 of the present study, we performed a PET activation study using word-fluency tasks to identify networks in the brain for word retrieval from semantic categories and syllables, as well as for speech production. In Experiment 2 the word-fluency tasks were conducted with the elderly people to compare their brain activation patterns with those of young subjects, and to elucidate mechanisms causing word finding difficulty widely seen in elderly people.

EXPERIMENT 1
METHOD

Subjects
Subjects were 12 young normal male volunteers with handedness scores of 100 measured by the Edinburgh Handedness Inventory (Oldfield, 1971). All were paid to participate, and their ages ranged from 21 to 35 years. None of them has a history of neurological and psychiatric disorders, as well as alcohol and drug abuse. Informed consent in written form was obtained from all subjects prior to the experiment.

Tasks and Procedure
The subject performed four word-fluency tasks and the rest task. The four word-fluency tasks were the syllable fluency task (Syllable hereafter) in which the subject was required to speak aloud as many words which begin with a given syllable like /ka/ as possible, and three semantic fluency tasks in which the subject was required to utter aloud as many words as possible in a pre-specified semantic category such as politicians. Three semantic categories were proper names (Proper), animate objects (Animate) and inanimate objects (Inanimate).

The subject lay in a supine position with their eyes masked, and their heads were fixed with a plastic foam headholder. The subject underwent repeated cerebral blood flow (CBF) measurements during a 120 s task or rest. In the resting state the subject was instructed to empty his mind. On the word-fluency task the subject was instructed to produce overtly as many appropriate words as possible based on a given semantic category or monosyllable presented to the subject through earphones.

PET scanning
A Shimadzu HEADTOME IV PET camera (Iida, et al., 1989) operating in the 2D mode was used. A small catheter was inserted into the right radial artery for blood sampling. The task and a 120 s emission scan started at the same time. The images were reconstructed with a Ramp filter convoluted with a Butterworth filter (cutoff frequency = 8 mm, and order = 2), which provided a spatial resolution of 7.5 mm FWHM. The arterial radioactivity was monitored with a beta detector equipped with a plastic scintillator, and was used as the input function with delay and dispersion correction (Iida, et al., 1989), from which the look-up table was computed with the partition coefficient of water being set to unity (Herscovitch, and Raichle, 1985).

Analysis of Individual Data
The scanned data were analyzed with statistical parametric mapping (SPM96: software from the Wellcome Department of Cognitive Neurology, London, UK; Friston, et al., 1995) implemented in Matlab (Mathworks Inc. Sherborn MA, USA).

Anatomical Normalization
The images were realigned and normalized into the standardized stereotactic space (Talairach and Tourmou, 1988) using linear and nonlinear transformations to match the images to a standardized template from the Montreal Neurological Institute. Anatomically normalized images were smoothed with a Gaussian filter of 15 mm FWHM in the x, y, and z axes.

Statistical Analysis
After specifying the design matrix, the condition, subject, and covariate effects were assessed based on the general linear model at each and every voxel. The design matrix included global CBF as a confounding covariate. To test hypotheses about regionally specific condition effects, the estimates were compared using linear contrasts. The resulting set of voxel values for each contrast constitute a statistical parametric map of the t-statistic SPM{t}, which, in turn, was transformed to SPM{Z} based on the unit normal distribution. To calculate the statistical inferences of set-level, cluster-level, and voxel-level (Friston et al., 1996), SPM96 was used. SPM{Z} was thresholded at Z > 3.09 and p < 0.001 with uncorrection for multiple comparison (Friston et al., 1994; Friston et al., 1995).

RESULT & DISCUSSION

1. Network for Overt Speech Production
In the four word-fluency tasks the subjects overtly produced words, whereas in the rest state they silently lay on the bed. Thus significantly higher activation areas in the word-fluency tasks than in the rest state constitute the network for overt speech production. The activated areas in the four word-fluency tasks are similar, although Proper shows smaller activations (Fig. 1). These include the left anterior insula, left premotor cortex, anterior cingulate, thalamus, midbrain, basal ganglia, and cerebellum. The primary motor cortex was not activated due probably to the narrow field of view (FOV) of the PET camera. Activation of the pons was not clear.

Dronkers (1996) inspected CT or MRI images of patients with apraxia of speech (or disorder of motor programming of speech), and found that the patients commonly had damage to the left anterior insula as opposed to Broca’s area. Wise et al. (1999) did a PET activation study and showed the activation of
the same area during articulation. In addition, they also found participation of the left and right sensorimotor cortices, dorsal brainstem, and cerebellum. In our study a further activation of the thalamus, basal ganglia and anterior cingulate was observed. Results of those studies suggest that the left anterior insula, left and right sensorimotor cortices, basal ganglia, thalamus, cerebellum, midbrain, and anterior cingulate gyrus constitute the neural network for speaking aloud words.

2. Areas Specific to Each Word-fluency Task

Activated regions specific to word retrieval of a given category can be obtained by comparing an activation pattern of a category with that of a different category.

**Proper Names**

Areas more highly activated in Proper than in Animate (P > A), Inanimate (P > I) and Syllable (P > S) are shown in Fig. 2. Although the left temporal lobe did not show activation in comparison with Animate, a lower threshold, e.g., a smaller voxel size of 200, revealed activity. Therefore, regions specific to the proper name retrieval are the most anterior medial frontal lobe (BA 11, 10, 9) and left anterior temporal lobe (BA 21, 22). It has been shown that the former associates with decision making and emotional information processing (e.g., Damasio et al., 1996), and the latter with semantics (e.g., Tempini et al., 1998), suggesting that processing of semantic information derived from categories of proper names like politicians, actresses and so on may automatically evoke emotion.

**Animate Objects**

Retrieval of names of animate objects shows significantly higher activation in the left inferoposterior temporal lobe (BA 37), left and right inferior frontal lobes (BA 44, 45), and right caudate nucleus when compared with the proper name retrieval (A > P: the left panel of Fig. 3). The frontal region is considered to associate with semantic information processing (c.f., Cappa et al., 1998) and the temporal region associate with lexical processing. In the preceding studies, the area related to semantic information processing for Animate is not consistent (e.g., Mummery et al., 1996; Damasio et al., 1996; Cappa et al., 1998; see also Hillis et al., 1991). When activity in Animate was compared with that in Inanimate (A > I) and Syllable (A > S), there was no significantly higher activity, suggesting that the activation pattern for Animate is similar to that for Inanimate and Syllable.

**Inanimate Objects**

Areas with significantly higher activities in Inanimate than in Proper are shown in the right panel (I > P) of Fig. 3. The activity pattern in the left hemisphere is similar to that for Animate except that the activity in the left posterior temporal lobe expands upwards including the middle temporal gyrus where previous studies repeatedly observed activation for processing semantic information of inanimate objects (e.g., Mummery et al., 1996; Damasio et al., 1996; Cappa et al., 1998; Perani et al., 1999). There is no difference in activation between Inanimate, and Animate (I > A) and Syllable (I > S).

**Syllable**

The major areas with higher activation in Syllable than in Proper (S > P in Fig. 4) are almost the same as those found in Inanimate, namely, the left posterior temporal lobe and left inferior frontal lobe, although activity in the left sensorimotor area is stronger in Syllable than in Inanimate (S > I). The activation pattern for Syllable is also similar to that for Animate, but the activated area in the left temporal lobe is greater and expands upwards as in Inanimate. Activity in the left inferior frontal lobe is consistent with the study of Mummery et al. (1996), although activity in the left temporal lobe was not seen in their study partly because activity in Syllable was contrasted with that in Animate and Inanimate, the latter two showing an activation pattern similar to that in Syllable.
Results of Experiment 1 revealed two different types of neural systems for word information processing. The first one is the neural system for speaking aloud words, i.e., from planning of speech to execution of articulation. This series of speech act is done by the participation of the left anterior insula, left premotor cortex, basal ganglia, thalamus, cerebellum, midbrain, anterior cingulated cortex. The left motor cortex and pons may participate in the speech production, although their activities were not observed due partly to narrow FOV of the PET camera. The second one is the network for word lexicosemantic processing (and incidental and automatic information processing of emotion). Two networks were identified, one being for retrieval of proper names and the other being for retrieval of common nouns (word fluency for animate and inanimate objects, and syllables). The former consists of the left anterior temporal lobe and anterior frontal lobe, and the latter includes the left posteroinferior temporal lobe and left inferior frontal lobe.

In the next experiment rCBF during word fluency tasks was measured in the elderly people who generally show word finding difficulty. Deficiency of the word fluency depends on semantic categories of words. Deficiency is most evident in proper name fluency (Sakuma et al., 2000). Thus, activities of the lexicosemantic network in the elderly were examined.

**EXPERIMENT 2**

**METHOD**

**Subjects**
All participants took tests for orientation, immediate and delayed story recall, WAIS-R (short-form), and measurement of auditory and visual acuities, as well as self-rating of Geriatric Depression Scale (GDS: Yesavage et al., 1983) and TMIG Index of for a Higher-level Competence (Koyano et al., 1987).

**Tasks and Procedure**
To shorten the time for the experiment, word-fluency tasks for only inanimate objects, proper names and syllables were performed.

**RESULTS AND DISCUSSION**

1. **Proper Name**
Activation greater for Proper than for Inanimate (P > I) and Syllable (P > S) in the elderly subjects is shown in Fig. 5. As can be seen in the figure, higher activity is observed in the frontal pole (BA 10), but not in the left anterior temporal lobe in which activation was seen in the young subjects. The area of the activation is small, and the activation level seems to be unstable since raising the significance level (p < 0.001 for corrected multiple comparison) caused significant activities to no longer
be evident.

2. Inanimate Objects
Regions with greater activation in retrieving inanimate object names than in retrieving proper names in the elderly subjects are shown in the left column of Fig. 6 (I > P). The left and right posteroinferior temporal lobe (BA 37) and right inferior Rolandic region (BA 4, 1, 2, 3) have higher activities. However, the left inferior frontal lobe was not active whereas the same area was active in the young subjects. There is no region with higher activity for Inanimate than that for Syllable, suggesting the activation pattern for Inanimate and for Syllable are similar. This is the case in the young subjects. Activity level is unstable in the elderly subjects, so raising the significance level causes significant activities to disappear.

3. Syllable Fluency
The activation level was high in syllable fluency. Regions showing stronger activities in Syllable than in Proper (S > P) include the left inferior frontal lobe (BA 44, 45), left and right inferior temporal lobes (BA 37), and left and right cerebellum. Activations of the cerebellum were not seen in the young subjects. However, the left pericentral area, which was more active in Syllable than in Animate and Inanimate in the young subjects (see S > A and S > I in Fig. 4), did not show activity in the elderly subjects.

4. Activations Characteristic to the Elderly Subjects
Activations in the elderly subjects are generally unstable. In the proper name fluency, activity in the left anterior temporal lobe is not seen, and in the inanimate name fluency, the left inferior frontal lobe was not activated. Those areas were active in the young subjects.

Unstable activations can be confirmed by raising the statistical significance level. In the present study we adopted a significance level of p < 0.001 for uncorrected multiple comparison. However, for a more strict criteria, e.g., p < 0.001 for corrected multiple comparison, all activities disappeared in the proper name fluency (P > I, P > S), and inanimate name fluency (I > P). This unstable activation may result from decrease in rCBF and/or atrophy of some or all areas of the word retrieval network.

In contrast, the syllable fluency (S > P) revealed large and stable activations, in the sense that the activation pattern showed little change for the above strict criteria. In addition, areas, which were not active in the young subjects, were activated, i.e., the cerebellum. It seems that these reflect an effort to compensate for deficient word retrieval.

We are now undertaking estimation of volume of rCBF during the word fluency tasks in such region as the left inferior frontal lobe, anterior temporal pole, etc. in the young and elderly subjects, as well as investigation into atrophy of the brain of the elderly subjects using VBM (software for detecting areas with atrophy using MRI images of the young and elderly subjects: Wright, et al., 1995; Ashburner, et al., 2000).

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REFERENCES