Structural Brain Correlates of Verbal and Nonverbal Fluency Measures in Alzheimer's Disease

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The ability to generate verbal or nonverbal material rapidly according to specified rules, as is demanded in fluency tasks, is commonly impaired in patients with frontal lobe lesions (Baldo & Shimamura, 1998; Baldo & Shimamura, 1998). More recent brain imaging work using functional magnetic resonance imaging (fMRI) and positron emission tomography protocols suggests that verbal fluency produces activation of the frontal lobes, particularly the prefrontal cortex in the language dominant hemisphere (Frith, Friston, Liddle, & Frackowiak, 1991; Parks et al., 1988; Phelps, Hyder, Blamire, & Shulman, 1997; Pujol et al., 1996). The active search and retrieval of information necessary for adequate performance on fluency tasks are believed to be primarily mediated by the frontal lobes (Baldo & Shimamura, 1998).

The majority of studies investigating brain correlates of fluency performance have involved patients with focal lesions; fewer studies have investigated the brain-behavior correlates of fluency performance in patients with widespread or multifocal brain dysfunction. Although fluency performance is generally deficient in degenerative disorders such as Alzheimer's disease (AD), it is not yet known whether these deficits are related to specific brain regions or instead are reflective of more diffuse dysfunction. Fluency ability can be assessed with verbal—phonological (i.e., letters of the alphabet) and semantic (i.e., categories such as animals or objects)—and nonverbal (i.e., design) tasks. Both verbal and nonverbal fluency abilities are impaired in AD (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Fama et al., 1998; A. Martin & Fedio, 1983; Mickanin, Grossman, Onishi, Auriacombe, & Clark, 1994; Monsch et al., 1992; Rossor & Hodges, 1994). Within the verbal domain, semantic fluency has been reported to be even more impaired than phonological fluency on average (Butters et al., 1987). The relatively greater deficit in semantic fluency has been...
interpreted as evidence of a breakdown in semantic structure in AD, which is consistent with the associated neuropathology of the neocortical temporal area. Nonverbal fluency can be as impaired as semantic fluency in AD patients (Fama et al., 1998). Differences in the severity and pattern of impairment among different fluency tasks have provided information about the underlying neural and processing mechanisms involved in dementing conditions (Butters et al., 1987; Monsch et al., 1994; Rosser & Hodges, 1994).

Studies on individuals with focal lesions reveal that fluency deficits are not restricted to patients with frontal lobe impairment and can accompany more posterior lesions (Bolter, Long, & Wagner, 1983; Jones-Gotman & Milner, 1977; Miceli, Caltagirone, Gainotti, Masullo, & Silveri, 1981; Newcombe, 1969; Pendleton, Heaton, Lehman, & Hulihan, 1982; Stuss et al., 1998). Pendleton et al. (1982) reported that participants with documented frontal lesions and those with nonfrONTAL and diffuse lesions performed significantly worse than control participants on a verbal fluency task, with no difference in performance between patient groups with the two different lesion sites. On a nonverbal fluency task, Jones-Gotman and Milner (1977) reported that although the greatest impairment occurred in participants with right frontal lesions, participants with right nonfronal lesions were also impaired on this task. Thus, fluency tasks are sensitive to frontal lobe dysfunction, yet their specificity and utility in the localization of brain dysfunction remains unresolved (cf. Monsch et al., 1992).

Laterality of a lesion can influence fluency performance. Deficits on verbal fluency tasks are more strongly associated with left- than right-hemisphere lesions, whereas deficits on nonverbal or design fluency tasks are more strongly associated with right- than left-hemisphere lesions (Benton, 1968; Jones-Gotman & Milner, 1977; Lee, Strauss, McLoskey, Loring, & Drane, 1996; Miceli et al., 1981; Milner, 1964; Ramier & Hecaen, 1970; Ruff, 1988; Ruff, Allen, Farrow, Niemann, & Wylie, 1994). These findings were based on patients with surgical resections or relatively large space-occupying lesions. Despite evidence for material-specific processing and hemispheric laterality, right-hemisphere lesions can influence efficiency in verbal fluency performance (Joanette & Goulet, 1986; R. C. Martin, Loring, Meador, & Lee, 1990), and left-hemisphere lesions can influence efficiency in nonverbal fluency performance (Jones-Gotman & Milner, 1977). Joanette and Goulet (1986) found an association between right-hemisphere dysfunction and semantic but not phonological fluency deficits in 35 individuals who suffered unilateral vascular based lesions to the right hemisphere, and R. C. Martin et al. (1990) found an association between right-hemisphere dysfunction and both semantic and phonological fluency performance in 32 patients with unilateral temporal lobe epilepsy, 15 patients with left-hemisphere focus, and 17 patients with right-hemisphere focus. More recently, Baldo and Shimamura (1998) observed that patients with right as well as those with left MRI-documented unilateral lesions performed significantly worse than control participants on semantic and phonological fluency tasks. Additionally, Parks et al. (1988) reported activation of the left and right frontal and temporal lobes in normal participants when performing verbal fluency tasks, providing further evidence for right-hemisphere influence on verbal fluency performance.

Category-specific deficits occur where, within the semantic domain for example, an individual may be impaired in naming exemplars from particular semantic categories (animate objects, such as animals) but unimpaired for other semantic categories (inanimate objects, such as tools; see Devlin, Gonnerman, Andersen, & Seidenberg, 1998; Farah & McClelland, 1991; Silveri, Daniele, Giustolisi, & Gainotti, 1991; Warrington & McCarthy, 1987; Warrington & Shallice, 1984, for reviews). Whether differences in performance between semantic categories reflect the workings of relatively independent brain systems is not yet clear. It has been hypothesized that the ability to generate names of animals may be more reliant on the ability to associate from one animal to another on the basis of perceptual features (e.g., what the animal looks or feels like), whereas the ability to generate names of inanimate objects may be more reliant on the ability to associate from functional features (e.g., what an object is used for; see Devlin et al., 1998, for a review). Additionally, the perceptual information used to generate exemplars to animate categories may be mediated by the temporal-limbic regions, whereas functional information used to generate exemplars to inanimate categories may be mediated by the frontal-parietal regions (Damasio, Grabowski, Tanel, Hichwa, & Damasio, 1996; A. Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; A. Martin, Wiggs, Ungerleider, & Haxby, 1996; Mummery, Patterson, Hodges, & Wise, 1996; Perani et al., 1995; Silveri et al., 1991).

Whether category-specific deficits noted in AD are due to impairment in specific anatomical regions (e.g., knowledge of animals associated with temporal regions; knowledge of nonanimate objects associated with frontal and parietal regions) or rather a function of the nature of the representation of semantic knowledge (e.g., exemplars associated by perceptual features being more interrelated than exemplars associated by functional features) has been debated (cf. Garrard, Patterson, Watson, & Hodges, 1998; Gonnerman, Andersen, Devlin, Kempler, & Seidenberg, 1997). Thus, different semantic category tasks may be reflective of the integrity of different neural pathways.

In this study, we investigated whether the verbal and nonverbal fluency abilities of patients with AD were selectively associated with the volumes of regional cortical and hippocampal volumes. On the basis of previous research, we tested the following hypotheses: (a) that scores on semantic, phonological, and nonverbal fluency tests would be related to frontal lobe gray matter volumes because of the production and retrieval processes required for these tasks; (b) that semantic fluency would be related to gray matter volumes of the temporal lobe of both hemispheres; (c) that nonverbal fluency performance would be related to parietal lobe gray matter volumes because of the visuospatial component of the task; (d) that the verbal fluency tasks would be more strongly associated with left-hemisphere volumes and that the nonverbal fluency tasks would show a stronger association with right-hemisphere volumes; and (e) that although hippocampal abnormalities are a hallmark feature of AD and
MRI AND FLUENCY IN AD

are related to disease severity and explicit memory performance in AD (see Cahn et al., 1998; Fama et al., 1997), fluency performance would not be related to hippocampal volumes.

Method

Participants

Participants in this study included 32 AD patients (23 men, 9 women) recruited from the Geriatric Psychiatry Rehabilitation Unit and the National Institute of Mental Health Aging Clinical Research Center, both housed at the VA Palo Alto Health Care System in California. All AD patients met the National Institute of Neurological and Communicative Diseases and Stroke and Alzheimer's Disease and Related Disorders Association criteria for possible or probable AD (Khachaturian, 1985; McKhann, Drachman, Folstein, & Katzman, 1984). Normal control participants spanning the adult age range (20-84 years of age) were used as a reference group for the MRI volumetric measures. These participants, or a subset of them, have formed the norms for other studies from our laboratory (Cahn et al., 1998; Fama et al., 1997; Pfefferbaum et al., 1994; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995a). The normal control group was composed of 95 men and 41 women for the axial MRI protocol and 84 men and 28 women for the coronal protocol. The reference group for the fluency measures consisted of 51 normal control participants, spanning the ages of the AD participants (age = 66.7 ± 7.4 years; education = 16.4 ± 2.3 years). The fluency performance of these control participants was used to calculate standardized Z scores for the AD participants that corrected the raw scores for age. These fluency data and group results were reported in a previous article by Fama et al. (1998), which reported a comparison of the pattern of phonological fluency, and 31 semantic fluency. MRI data included in this study, 23 received figural fluency, 32 phonological fluency score was the total number of different correct words produced across the three trials.

Nonverbal Fluency Test

Nonverbal fluency was assessed with the Ruff Figural Fluency Test (RFFT; Ruff, 1988; Ruff, Light, & Evans, 1987), which requires participants to generate as many different designs as possible by using straight lines to connect arrays of five dots. The test consists of five trials, each with a 1-min time limit. The nonverbal fluency score was the total number of correct unique designs summed across the five trials.

Not all participants received all tests. A given participant had to have phonological fluency and at least figural or semantic fluency data along with an MRI scan within 3 months of neuropsychological testing to be included in the study. Of the 32 AD patients with MRI data included in this study, 23 received figural fluency, 32 phonological fluency, and 31 semantic fluency.

MRI Scanning and Quantification

Axial Protocol

Acquisition parameters. Participants were scanned with 1.5T General Electric Signa MRI scanners (Milwaukee, WI). Image acquisition procedures and parameters have been previously described in detail in other studies (see Lim & Pfefferbaum, 1989; Pfefferbaum et al., 1994; Zipursky, Lim, Sullivan, Brown, & Pfefferbaum, 1992). Axial MRI images were 5 mm thick (2.5 mm skip) and were acquired in an oblique plane using a spin-echo sequence (20- and 80-ms echoes), with a 24-cm field of view and a 256 × 256 matrix. Acquisition was gated to every other cardiac cycle for an effective repetition time (TR) of >2,400 ms, with one excitation for each of 256 phase encodes.

All images were stored on magnetic tape and transferred to optical disks for analysis. For each participant, the index slice was identified as the most inferior slice above the level of the orbits, where the anterior horns of the lateral ventricles could be seen bilaterally. Seven consecutive slices, beginning with the section inferior to the index slice and proceeding superiorly, were analyzed for each participant.

Regional divisions and segmentation of images. Each MRI slice was segmented into cerebrospinal fluid (CSF), gray matter, and white matter compartments, using a semiautomated image analysis technique (Lim & Pfefferbaum, 1989; Lim, Zipursky, Watts, & Pfefferbaum, 1992). To separate the cerebral hemispheres, we drew a midline manually on each slice. Additionally, each slice was divided into an inner 55% region (to facilitate quantification of Table 1: Demographics for Alzheimer's Disease Participants

<table>
<thead>
<tr>
<th>Measure</th>
<th>Age (years)</th>
<th>Age of symptom onset (years)</th>
<th>Duration of diagnosis (years)</th>
<th>Education (years)</th>
<th>MMSE</th>
<th>DRS</th>
<th>NART IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>70.9</td>
<td>65.9</td>
<td>5.0</td>
<td>15.0</td>
<td>18.8</td>
<td>108.9</td>
<td>105.7</td>
</tr>
<tr>
<td>SD</td>
<td>6.8</td>
<td>7.7</td>
<td>3.9</td>
<td>3.7</td>
<td>4.1</td>
<td>16.7</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Note. There were 23 male and 9 female participants with Alzheimer's disease. MMSE = Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975); DRS = Dementia Rating Scale (Mattis, 1976, 1988); NART = National Adult Reading Test (Nelson, 1982).
central CSF, which arose primarily but not exclusively from the lateral ventricles) and an outer 45% (to facilitate quantification of the cortical tissue volumes and sulcal CSF; Pfefferbaum et al., 1992).

The images were divided according to anatomical landmarks and a priori geometric rules in an effort to achieve standardized regional divisions of the brain images. The cortical tissue measure (the outer 45% of each image) was divided into six anatomically and geometrically defined regions of interest, which roughly correspond to lobar anatomy. The regions did not fully volume the cortical lobes after which they were named but provided a reliable basis for dividing cortical sections (Zipursky et al., 1992). To form these divisions, we divided each MRJ slice into four regions by three coronal planes, which passed through the most anterior extreme of the genu of the corpus callosum, the most posterior extreme of the splenium of the corpus callosum, and midway between them. The first plane established a boundary for the prefrontal region. From these quadrants and slices, we devised six cortical regions, defined as follows:

- **Prefrontal** — the most anterior quadrant of all seven slices;
- **Frontal** — the anterior middle quadrant of Slices 3-7;
- **Anterior superior temporal** — the anterior middle quadrant of Slices 1 and 2, which included the anterior superior temporal gyrus and the most posterior extents of the frontal lobes at the level of the superior temporal gyrus;
- **Posterior superior temporal** — the posterior middle quadrant of Slices 1 and 2, which included the posterior superior temporal gyrus and the anterior extents of the parietal lobes just above the superior temporal gyrus;
- **Anterior parietal** — the posterior middle quadrant of Slices 3-7; and
- **Posterior parietal-occipital** — the most posterior quadrant of Slices 3-7, which also included much of the occipital lobes (see Figure I).

**Coronal Protocol**

A detailed description of the acquisition methods, anatomical borders, and reliability of measurement technique used in our laboratory to examine the temporal lobes and hippocampus has been reported previously (Sullivan et al., 1995a; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995b). A summary of the acquisition parameters and regional divisions and segmentation of images is presented below.

**Acquisition parameters.** With this protocol, 22 contiguous 3-mm thick coronal images were acquired using a multiecho, flow-compensated cardiac-gated pulse sequence (echo time \(TE = 40, 80\) ms; effective TR = 2,800 ms) with field of view equal to 24 cm, number of excitations (NEX) = 1, and a 256 X 256 matrix. The plane of image acquisition was oriented perpendicular to the anterior commissure—posterior commissure line. Image acquisition was specifically designed to encompass temporal-limbic structures, beginning 6 mm anterior to the anterior commissure and extending 66 mm posteriorly. Hippocampal tissue could not be adequately segmented into gray matter and white matter compartments, and, therefore, its volume reflected total tissue (i.e., pixels represented gray matter plus white matter). The hippocampus was outlined on each consecutive slice on each side of the brain, and the volumes were derived by adding the areas of each measured slice.

**Regional divisions and segmentation of images.** The anterior limit of the hippocampal measurement began where hippocampal tissue was clearly distinguished from amygdala, coinciding with the appearance of the digitations of Ammon's horn and consistent with the location of the pes hippocampus. This initial slice usually coincided with the visualization of ventricular temporal horn CSF over the digitations. Because the boundary between the subiculum and the amygdala cannot be distinguished at the medial aspect of the hippocampal formation at this slice level, we drew a line from the most medial point of the subiculum to the most medial aspect of the temporal horn, thereby excluding amygdala from the measure. The posterior limit corresponded to the posterior temporal lobe image, as detailed below. This measure predominantly included portions of the head and body of the hippocampus, with exclusion...
of the most anterior portion of the pes (where it could not be
distinguished from the amygdala) and the most posterior portion
of the hippocampus (the ascending tail). The medial hippocampal
boundary included the regional outline at the choroidal fissure. The
inferior boundary was formed by, but did not include, the white
matter of the parahippocampal gyrus. The fornix was not included
in posterior slices unless it was inextricably embedded within the
hippocampal structure. In the absence of histological confirmation,
this measure presumably included hippocampal fields CA1 to CA4,
the dentate gyrus, and portions of the subiculum (Amaral &
Insausti, 1990; see Figure 2).

Statistical Analysis

The volumes of each brain region of interest in the AD patients
were corrected for variation attributable to intracranial volume (i.e.,
head size) and age through regression analyses described in detail
in previous articles (Mathalon, Sullivan, Rawles, & Pfefferbaum,
1993; Pfefferbaum et al., 1994). Briefly, a correction using a
two-step regression analysis to adjust for normal variation in head
size and age that was based on normal control participants yielded
head size and age-corrected \( Z \) scores. All regional brain measures
were expressed as \( Z \) scores, where the expected mean of the control
participants at any age was 0 ± 1. This correction method allows
for analysis of disease-related changes that are independent of the
known effects of normal aging and head size. For the AD
participants, these head size and age-corrected \( Z \) scores provided
volume estimates relative to that which would be expected for
normal control participants of a particular head size and age. Lower
\( Z \) scores for tissue measures reflect greater abnormality. Fluency
scores were also standardized to allow direct comparisons across
tasks to be made. Raw scores were converted to age-corrected
standardized \( Z \) scores on the basis of data from 51 control
participants because of significant correlations found between age
and semantic \( (r = -0.40) \) and nonverbal \( (r = -0.37) \) fluency in a
similar aged control group (see Fama et al., 1998).

Relationships between the age-corrected standardized fluency
measures and the head size and age-corrected standardized regional,
regional, and laterized (left and right), brain volume
measures were examined with Pearson product-moment correla-
tions. We used a familywise Bonferroni correction (6 correlations
for each fluency measure and bilateral brain volumes and 12
correlations for each fluency measure and laterized brain vol-
umes) when determining whether a correlation was statistically
significant. We interpreted a correlation as being significant if it
reached the \( p \leq .008 \) level for bilateral brain volume correlations
and \( p \leq .004 \) for laterized brain volume correlations. Statistical
trends are reported for correlations at the \( p \leq .05 \) level. Multiple
regression models were used to examine whether the brain volumes
of specific brain regions contributed independently to the predic-
tion of fluency scores after the contributions of other relevant brain
regions were taken into account. Finally, to ensure that the
relationships observed between regional brain volumes and fluency
measures were not due to the influence of gender on these
variables, we used partial correlations as follow-up analyses.

Results

Fluency Performance

When compared with age-appropriate normal control
participants, AD participants were significantly impaired on
all fluency measures (group differences, \( p < .01 \)). Control
group raw scores were as follows: phonological \( (F, A, S) =
41.2 \pm 12.9 \), semantic = 24.1 ± 5.1 (animals = 22.1 ± 4.4,
objects = 26.1 ± 7.3), and nonverbal (figural) = 76.1 ±
21.1 (see Fama et al., 1998). Mean scores on the fluency

Figure 2. Coronal magnetic resonance image of a 42-year-old normal healthy man. The left side
shows an outline of regions of interest—temporal lobes and hippocampi. The right side shows
segmentation of the image into gray matter (dark gray), white matter (light gray), and cerebrospinal
fluid (black).
tasks for the AD group were as follows: phonological (F, A, S) = 19.9 ± 10.9, semantic = 8.3 ± 4.4 (animals = 8.2 ± 4.4, objects = 8.4 ± 4.9), and nonverbal (figural) = 25.3 ± 12.3. All three fluency scores were significantly correlated with the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), a measure of dementia severity (phonological $r = .40$, $p < .01$; semantic $r = .53$, $p < .01$; nonverbal $r = .44$, $p < .05$). None of the raw fluency scores was significantly correlated with age, years of education, or years since diagnosis. Age-corrected Z scores for the AD group indicated greater than 1.5 to 3 SD deficits in fluency scores: phonological (F, A, S) = -1.7 ± 0.85, semantic = -2.8 ± 0.86 (animals = -3.2 ± 1.1, objects = -2.4 ± 0.78), and nonverbal (figural) = -2.4 ± 0.82.

MRI Volume Abnormalities

Head size and age-corrected Z scores indicated that the AD group had almost 0.5 to 1.5 SD deficits in gray matter volume present throughout the cortex (see Figure 3; Z scores: prefrontal = -0.53 ± 1.2, frontal = -0.79 ± 0.93, anterior superior temporal = -0.74 ± 0.96, posterior superior temporal = -0.97 ± 0.88, anterior parietal = -0.76 ± 0.94, and posterior parietal-occipital = -0.38 ± 1.1; total cortical = -0.87 ± 1.2 SD from the expected mean). In addition, the hippocampus was abnormally small in volume bilaterally (Z scores for left = -0.77 ± 1.1, right = -0.70 ± 1.3; also see Cahn et al., 1998; Fama et al., 1997).

Correlations With Bilateral Brain Volumes

No brain–behavior correlation reached statistical significance when overall semantic fluency scores were examined (see Table 2). When animal and object scores were analyzed separately, there was a trend toward a relationship between object fluency Z scores and bilateral gray matter volume Z scores of the frontal ($r = .43$, $p = .015$) and the posterior superior temporal ($r = .40$, $p = .026$) regions (see Figure 4). As the scatterplots indicate, there was 1 AD patient who did not show a deficit on object fluency (Z score = 0). Post hoc analyses with this participant removed indicated that although the nature of the relationship between these brain volumes and object fluency scores remained positive, the significance level of these correlations dropped (frontal $r = .33$, $p < .08$, posterior superior temporal $r = .33$, $p < .08$). Animal fluency scores did not significantly correlate with any of the bilateral brain volumes measured.

To test whether the correlations between animal fluency and object fluency were significantly different from one

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Semantic*</th>
<th>Animals</th>
<th>Objects</th>
<th>Phonological</th>
<th>Nonverbal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 31)</td>
<td>(n = 31)</td>
<td>(n = 31)</td>
<td>(n = 32)</td>
<td>(n = 23)</td>
</tr>
<tr>
<td>Frontal</td>
<td>.31</td>
<td>.19</td>
<td>.43*</td>
<td>-.07</td>
<td>.57**</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>.27</td>
<td>.17</td>
<td>.35</td>
<td>.04</td>
<td>.28</td>
</tr>
<tr>
<td>Anterior superior temporal</td>
<td>.27</td>
<td>.18</td>
<td>.35</td>
<td>-1.01</td>
<td>.49*</td>
</tr>
<tr>
<td>Posterior superior temporal</td>
<td>.26</td>
<td>.13</td>
<td>.40*</td>
<td>.03</td>
<td>.41</td>
</tr>
<tr>
<td>Anterior parietal</td>
<td>.15</td>
<td>.09</td>
<td>.20</td>
<td>-.10</td>
<td>.42*</td>
</tr>
<tr>
<td>Posterior parietal-occipital</td>
<td>.12</td>
<td>.07</td>
<td>.17</td>
<td>-.02</td>
<td>.18</td>
</tr>
<tr>
<td>Total cortical</td>
<td>.26</td>
<td>.15</td>
<td>.37*</td>
<td>.02</td>
<td>.38</td>
</tr>
</tbody>
</table>

*Semantic refers to animals plus objects.

*p < .05. **p < .008.
another, we calculated t values using Fisher z transformations. The correlation between posterior superior temporal volume and object fluency was significantly greater than the correlation between the same brain region and animal fluency, t(30) = 2.2, p < .05. The difference between the correlations for total cortical volume and object and animal fluency scores approached significance, t(30) = 1.7, p < .10.

Phonological fluency scores were not significantly correlated with any bilateral brain volume measured.

Nonverbal fluency scores were significantly correlated with frontal lobe volumes (r = .57, p = .005), and statistical trends were noted with the bilateral volume of the anterior superior temporal (r = .49, p = .018) and anterior parietal (r = .42, p = .048) regions (see Figure 5). A multiple regression analysis indicated that the incremental proportion of variance in nonverbal fluency accounted for by the frontal gray matter volume, after accounting for the contributions of the anterior superior temporal and anterior parietal volumes of gray matter, approached significance (p < .06). Neither of the two nonfrontal regions made significant unique contributions to nonverbal fluency performance after the other regions were accounted for (see Table 3). To establish that the nonverbal fluency scores were not simply reflective of generalized gray matter volume loss, we performed a multiple regression that predicted nonverbal fluency performance from both frontal gray matter and total cortical gray matter. Frontal (p < .02) but not total cortical gray matter (p = .33) volume made a significant independent contribution to the prediction of nonverbal fluency scores.

Correlations With Lateralized Brain Volumes

A statistical trend was present between overall semantic fluency scores and volume of the right anterior superior temporal region (r = .37, p = .04; see Table 4). When the animal and object trials were analyzed separately, animal fluency scores were not significantly correlated with any of the lateralized brain volumes measured, but object fluency showed modest correlations with a number of brain regions: gray matter volumes of the left frontal (r = .44, p = .014), right prefrontal (r = .40, p = .025), right frontal (r = .39, p = .032), right anterior superior temporal (r = .42, p = .018), and right posterior superior temporal (r = .42, p = .018) regions (see Figure 6). Post hoc analyses with the AD participant who showed no deficit on this measure removed indicated that the nature of these brain–behavior relationships remained the same; however, significance levels dropped throughout, with only the correlation between object fluency and right posterior superior temporal volumes reaching a statistical trend (r = .36, p < .05): left frontal r = .33, p < .08; right frontal r = .30, p = .11; right prefrontal r = .29, p = .13; right anterior superior temporal r = .29, p = .13.
From Brain Volumes

Multiple Regressions Predicting Nonverbal Fluency Scores From Brain Volumes

<table>
<thead>
<tr>
<th>Dependent measure</th>
<th>Predictors</th>
<th>β</th>
<th>ΔR²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonverbal fluency</td>
<td>Frontal</td>
<td>.708+</td>
<td>.133</td>
</tr>
<tr>
<td></td>
<td>Anterior superior temporal</td>
<td>.173</td>
<td>.020</td>
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<tr>
<td></td>
<td>Anterior parietal</td>
<td>-.406</td>
<td>.048</td>
</tr>
<tr>
<td>Nonverbal fluency</td>
<td>Frontal</td>
<td>.712*</td>
<td>.212</td>
</tr>
<tr>
<td></td>
<td>Overall cortical</td>
<td>-.225</td>
<td>.031</td>
</tr>
</tbody>
</table>

*p < .06.  *p < .05.

Phonological fluency scores were not significantly correlated with any lateralized MRI volume measures.

Nonverbal fluency scores were significantly correlated with gray matter volumes of the right anterior superior temporal region (r = .61, p = .002; see Figure 7). Strong statistical trends were found between nonverbal fluency scores and left frontal (r = .57, p = .005) and right frontal (r = .53, p = .009) volumes. Statistical trends were also noted with right posterior superior temporal (r = .43, p = .043) and left anterior parietal regions (r = .42, p = .045). A multiple regression model predicting nonverbal fluency performance from left frontal and right frontal gray matter volumes indicated that neither region independently contributed to nonverbal fluency scores once the contribution of the other region was taken into account, left frontal t(22) = 1.18, p = .25, right frontal t(22) = 0.42, p = .68. Fisher z calculations indicated that the correlation for nonverbal fluency scores and right posterior superior temporal volumes was significantly greater than the correlation for nonverbal fluency scores and left posterior superior temporal volumes, t(22) = 2.3, p < .05. No differences were found between any other corresponding left and right correlation. Nonverbal, phonological, and semantic fluency scores were not significantly correlated with hippocampal volumes of either hemisphere.

Partial Correlations Examining Gender Influence on Brain–Behavior Relationships

All reported significant correlations between regional brain volumes and fluency scores remained when partial correlations were calculated to control the influence of gender.

Table 4
Fluency—Lateralized Gray Matter Volumes

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Semantic*</th>
<th>Animals</th>
<th>Objects</th>
<th>Phonological</th>
<th>Nonverbal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Frontal</td>
<td>.34</td>
<td>.25</td>
<td>.23</td>
<td>.11</td>
<td>.44*</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>.16</td>
<td>.34</td>
<td>.06</td>
<td>.26</td>
<td>.26</td>
</tr>
<tr>
<td>Anterior superior temporal</td>
<td>.14</td>
<td>.37*</td>
<td>.06</td>
<td>.29</td>
<td>.22</td>
</tr>
<tr>
<td>Posterior superior temporal</td>
<td>.11</td>
<td>.32</td>
<td>.01</td>
<td>.21</td>
<td>.26</td>
</tr>
<tr>
<td>Anterior parietal</td>
<td>.08</td>
<td>.18</td>
<td>.03</td>
<td>.13</td>
<td>.15</td>
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<tr>
<td>Posterior parietal-occipital</td>
<td>.17</td>
<td>.07</td>
<td>.13</td>
<td>.01</td>
<td>.19</td>
</tr>
<tr>
<td>Total cortical</td>
<td>.22</td>
<td>.28</td>
<td>.13</td>
<td>.17</td>
<td>.32</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>.03</td>
<td>.06</td>
<td>.04</td>
<td>.04</td>
<td>.12</td>
</tr>
</tbody>
</table>

*Semantic refers to animals plus objects.

*p < .05.  ***p < .01.  ****p < .004.
did not because of the differences in complexity between the nonverbal and verbal fluency tasks. Although the total semantic score was not associated with frontal lobe volume, there was evidence that object fluency was related to frontal lobe volume. Object fluency, but not animal fluency, showed modest associations with a number of regional brain volumes, namely, left and right frontal, right prefrontal, right anterior superior temporal, and right posterior superior temporal.

Figure 6. Object fluency and bilateral brain volume. Object fluency scores showed modest correlations with a number of lateralized regional brain volumes: right prefrontal, left frontal, right frontal, right anterior superior temporal, and right posterior superior temporal.

Figure 7. Nonverbal fluency and lateralized brain volume. Nonverbal fluency scores were significantly correlated with gray matter volumes of the right anterior superior temporal region. Statistical trends were noted between nonverbal fluency scores and gray matter volumes of the left frontal, right frontal, right posterior superior temporal, and left anterior parietal regions.
posterior superior temporal. This study lends evidence to the notion that generation of animal names is dissociable from generation of object names and that these abilities are subserved, at least in part, by different brain systems (cf. Damasio et al., 1996; A. Martin et al., 1995; Perani et al., 1995; Silveri et al., 1991). It may also be that object fluency denotes a more general category of exemplars than does animal fluency. Thus, the associations between object fluency and frontal regions may reflect the greater need of organization of search for this more general category. Dissociations between semantic fluency categories have been shown with functional imaging studies. Using positron emission tomography, A. Martin et al. (1996) showed that although there was bilateral activation of the ventral temporal lobes and Broca’s area when right-handed participants named animals and tools from pictures; selective activation of the left medial occipital lobe occurred when animals were named, whereas activation of the left prefrontal and left middle temporal gyrius occurred when tools were named.

We, like others (Pasquier, Lebert, Grymonprez, & Petit, 1995; Pendleton et al., 1982; Ruff et al., 1994), did not find significant associations between phonological fluency and integrity of the frontal regions. It may be that phonological fluency is sensitive to generalized brain dysfunction yet not be particularly useful in localization of dysfunction. Failure to find selective relationships between fluency performance and brain volumes may reflect the likelihood that successful fluency performance requires several processing systems subserved by various anterior and posterior brain regions (Borstein, 1986; R. C. Martin et al., 1990). Alternatively, the specific brain regions contributing to the phonological deficit may not have been included in our analyses. Use of imaging protocols using thinner slices or covering the full extent of the brain would provide further opportunity to identify specific regions contributing to performance. Even in instances in which selective brain–behavior relationships are present, we are not proposing that the particular fluency ability is localizable to a specific region. Instead, we believe that these selective relationships indicate the importance of the particular brain region in the successful completion of the specific task.

In conclusion, performance on fluency tests, whether verbal or nonverbal, relies on the efficient generation of exemplars within specific constraints, a process degraded in AD. This study provides evidence that the degradation of nonverbal fluency performance is attributable, at least in part, to structural volume loss in the gray matter of selective cortical areas but not to hippocampal loss. Furthermore, these brain–behavior relationships indicate involvement of both the left and the right hemispheres in the generation of nonverbal and verbal exemplars.

References


MRI AND FLUENCY IN AD


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**Editor Transition for Neuropsychology**

Dr. Laird S. Cermak, Editor for *Neuropsychology* since June 1995, died on November 4, 1999, of complications from a bone marrow transplant. Dr. Cermak prized his work on the journal and continued to devote his time to it throughout his illness.

Associate Editor Patricia B. Sutker, PhD (Departments of Anesthesiology and Neuropsychiatry and Behavioral Science, Texas Tech University School of Medicine), has graciously volunteered to serve as Acting Editor of *Neuropsychology* until a new editor can be appointed. A search for a new editor for the term beginning in 2002 is currently under way and is expected to be completed in March. Manuscripts that Dr. Cermak was handling have been forwarded to Dr. Sutker for final action.

New submissions should continue to be sent in quadruplicate to the Boston office for processing, as follows:

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