Clustering and switching in semantic fluency: predictors of the development of Alzheimer’s disease

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SUMMARY

Objective The aims of the study are twofold: (1) to compare semantic fluency, clustering and switching performance among subjects with memory complaints, patients with Alzheimer Disease (AD), and healthy controls; and (2) to examine the clinical utility of the clustering/switching scoring system in the prediction of incident AD in subjects with memory complaints.

Methods A semantic fluency task was used to compare thirty eight subjects with memory complaints, forty two AD patients and twenty five healthy controls on the total number of words generated, clustering and switching performance. Subjects with memory complaints were followed-up for a maximum period of two years and re-evaluated. They remained in the memory complaints group (twenty eight subjects) or were defined as probable AD (ten subjects).

Results AD patients generated fewer correct words ($p < 0.001$) and showed a reduction in clustering ($p = 0.008$) and switching ($p < 0.001$). Subjects with memory complaints showed a significant reduction in correct words ($p < 0.001$) and clustering performance ($p = 0.008$) compared to controls. In the first evaluation, the subgroup of patients who converted to AD at follow up produced less correct words ($p < 0.01$) and smaller clusters ($p = 0.007$) than the subgroup who did not become demented. There were no differences in switching between these two subgroups. AD development was better predicted by cluster size than by the total number of words generated or by switching.

Conclusions Subjects with memory complaints and AD patients have an alteration in both qualitative and quantitative aspects of semantic fluency. A clustering analysis could enhance the reliability of early AD diagnosis. Copyright © 2008 John Wiley & Sons, Ltd.

INTRODUCTION

Patients with Alzheimer’s disease (AD) exhibit an important deficit in both, semantic and phonemic fluency, although several studies have suggested that semantic fluency is disproportionately impaired (Cerhan et al., 2002; Canning et al., 2004; Henry et al., 2004; Taylor et al., 2005). In fact, impairments on semantically related test, such as semantic fluency, not only have been shown to be more sensitive and specific in differentiating patients with AD from normal elderly persons (Canning et al., 2004) but may also exist prior to the clinical AD diagnosis (Vogel et al., 2005).

An analysis of the sequences of generated words revealed that two different but complementary cognitive strategies are used in the fluency task: clustering (words produced inside the same subcategory) and switching (ability to change subcategory). These concepts were defined by TROYER et al. (1997) and TROYER (2000) and used to investigate fluency performance in different pathologies (TROYER et al., 1998; HO et al., 2002; CANNING et al., 2004; BOZIKAS

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et al., 2005), including AD (Troster et al., 1998; Epker et al., 1999; Gomez and White, 2006).

An analysis of switching and clustering in AD patients reveals impairments in both components compared to healthy controls (Troyer et al., 1997; Gomez and White, 2006). These patients also show a reduction in mean cluster size and greater number of switches than Parkinson’s disease (PD) patients (Troster et al., 1998; Epker et al., 1999). However, the AD patients show a similar clustering performance than demented PD patients, suggesting that a greater cognitive impairment may result in a greater reduction in fluency performance, regardless of the dementia type (Epker et al., 1999).

Even so, research in this area has not been extensive and has been limited to cross-sectional designs. To our knowledge, no longitudinal studies have investigated the use of different clustering and switching scores to discriminate AD from other pathologies. The present study had two aims: (1) to compare semantic fluency performance and clustering and switching performance among subjects with memory complaints, patients with AD and healthy controls; and (2) to examine the clinical utility of this scoring system in the prediction of incident Alzheimer’s disease after 2 years in a sample of subjects with memory complaints.

MATERIALS AND METHODS

Subjects

All participants had been referred from the neurology service of the Hospital Clinic i Provincial de Barcelona (Spain). Subjects of memory complaints and control group have been involved in previous research carried out in this hospital (Guarch et al., 2004). All subjects were native Spanish speakers.

We conducted a cross-sectional and a longitudinal study (see Figure 1). The cross-sectional study sample comprised a total of 105 subjects, distributed in three groups: subjects with memory complaints, AD patients and healthy controls. The memory complaints group comprised 38 subjects who consulted the neurology service of their own will. All of them presented subjective feelings of memory loss in everyday activities that had no negative impact on their social and working lives. The defining characteristic of the group was their own awareness of memory loss. The AD group consisted of 42 patients, who had a medical diagnosis of probable AD according to the NINCDS-ADRDA diagnostic criteria (McKhann et al., 1984). The control group comprised 25 healthy subjects, relatives or companions of the patients at the time of the examination. The sample for the longitudinal study consisted of the 38 subjects with memory complaints, who were followed-up for a maximum period of 2 years.

Subjects were excluded from both studies if they had had a psychiatric disorder diagnosed by DSM-IV classification, movement disorders, gait disturbance, sphincter incontinence, infarctions, cranial traumatism, drug or alcohol abuse, recent use of psychotropic medication that might affect cognitive functions, other medical conditions such as arterial hypertension, and diabetes or other systemic diseases requiring specific

Figure 1. Flowchart of the sample included in the study.
medical treatment. Controls and subjects with memory complaints were also excluded if they had had symptoms that were compatible with diagnostic criteria for dementia, according to DSM-IV classification (APA, 1994). All subjects were informed of the nature of the study and invited to take part.

Procedure
As described in more detail in Guarch et al. (2004) the evaluation consisted of: (1) brief interview (either with the patient or close relative) to record biographical and sociodemographic data; and (2) administration of a complete neuropsychological battery. The psychologist in charge of the evaluation was unaware of the subjects’ diagnoses at the time of the assessment. In the present study only the semantic fluency test was used.

For the longitudinal study, patients from the memory complaints group were followed-up for 2 years. After consultation of each patient’s neuropsychological, clinical and neurological records, their diagnostic classifications were compared and updated. Patients either remained in the initial group or were defined as probable Alzheimer’s disease. This gave rise to two subgroups: no change in diagnosis (n = 28) and change in diagnosis (n = 10).

Semantic fluency task scoring
All testing was conducted in Spanish. For this task, subjects were requested to produce as many words as possible belonging to the animal’s semantic category.

Two kinds of scoring were applied: (1) the total number of correctly generated words in 60 seconds, excluding intrusions, perseveration and repetitions; and (2) the number of switches, clusters and the mean cluster size. These three indicators were calculated according to the scoring rules defined by Troyer et al. (1997) and Troyer (2000). A cluster consisted of two or more successively generated words belonging to the same semantic subcategory. The subcategories were determined a priori (See Appendix 1). Cluster size was counted from the second word in each cluster (e.g. a three-word cluster was counted as a cluster of two) and the mean cluster size was calculated by summing the size of each cluster and dividing by the number of clusters. Switches were calculated as the number of times a subject changed from one cluster to another, including single words (cluster size = 0). Intrusions, repetitions and perseverations were included in the calculation of clustering and switching. The cluster and switch scores given by three independent observers were used to assess the interobserver reliability.

Statistical analysis
An intraclass correlation coefficient (ICC) was used to measure interobserver reliability. Group differences were analysed with one-way ANOVA and Tukey’s post hoc multiple comparison analysis. Differences between two groups were calculated with independent Student’s t-test. A stepwise logistic regression to determine which variable (total corrected words, cluster size or switching) would better predict the evolution to AD was performed. To assess the clinical relevance of this scoring system, a hierarchical logistic regression analysis was performed to calculate the cumulative contribution of mean cluster size in addition to the total corrected word. The level of statistical significance was set at 0.05. All data were analysed with the statistical package SPSS for Windows version 12.0 (SPSS Inc, Chicago, IL).

RESULTS
Cross-sectional study
There were no significant differences among subjects with memory complaints, AD patients and healthy controls in age, gender and education level (Table 1).

The intraclass correlation coefficient between the three independent observers (ABF, SL, MR) was 0.82 and 0.72 for mean cluster size and number of switches, respectively. The scoring of one of the researchers (ABF) was used in the rest of the analysis.

Descriptive statistics for semantic fluency results are presented in Table 1. AD patients generated significantly fewer correct words (p < 0.001) and showed smaller cluster sizes (p = 0.008) and less switching (p < 0.001) than both, subjects with memory complaints and healthy controls. Subjects with memory complaints also produced significantly less correct words (p < 0.001) and smaller cluster sizes (p = 0.008) than healthy controls. Conversely, there were no significant differences among groups in switching scores.

Longitudinal study
We did not find any statistical differences between memory complaints subgroups in age, gender and education level (Table 2).

Table 2 summarizes the semantic fluency results. In the first evaluation, the number of correct words
(p < 0.01) and the cluster size (p = 0.007) were significantly lower in the subgroup of patients who converted to AD at follow up as compared with subjects who did not become demented. However, there were no significant differences between groups in the switching performance.

Finally, a logistic regression was used to assess which variable would better predict the development of AD. The cluster size was the only predictive variable, while the other two were excluded as they were not statistically significant (Table 3). In the hierarchical analysis the introduction of total corrected word in the first block yielded an $R^2 = 0.13$ (p = 0.022) which increased to 0.292 (p = 0.005) when the mean cluster size was introduced in the second block.

**DISCUSSION**

Our findings provide support for the hypothesis that subjects with memory complaints and AD patients have impairment in both qualitative and quantitative aspects of semantic fluency. Both groups showed a significant reduction in the number of words generated and the mean cluster size, while AD patients also showed alterations in the ability to switch between semantic subcategories.

Our results replicate earlier reports showing that semantic fluency, the mean cluster size, and the number of switches are useful in discriminating between AD patients and different pathologies (Troyer et al.)

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**Table 1.** Comparison between Alzheimer’s disease patients, subjects with memory complaints and healthy controls: demographic characteristics and semantic fluency-related variables

<table>
<thead>
<tr>
<th></th>
<th>AD Group (n = 42)</th>
<th>MCG (n = 38)</th>
<th>Controls (n = 25)</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>$X^2$</td>
</tr>
<tr>
<td>Gender (male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (64)</td>
<td>24 (63.2)</td>
<td>12 (48)</td>
<td>1.97</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.57 (7.73)</td>
<td>67.76 (8.11)</td>
<td>64.20 (9.51)</td>
<td>2.28</td>
</tr>
<tr>
<td>Education (years)</td>
<td>5.64 (3.57)</td>
<td>7.37 (4.84)</td>
<td>6.48 (4.49)</td>
<td>1.61</td>
</tr>
<tr>
<td>TWG$^1$</td>
<td>7.33 (4.41)</td>
<td>15.79 (7.27)</td>
<td>21.80 (4.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCS$^2$</td>
<td>1.73 (1.50)</td>
<td>2.07 (1.13)</td>
<td>2.73 (0.86)</td>
<td>5.02</td>
</tr>
<tr>
<td>Switches</td>
<td>2.64 (2.41)</td>
<td>4.74 (2.67)</td>
<td>5.16 (1.67)</td>
<td>11.72</td>
</tr>
</tbody>
</table>

$^1$ = Total words generated.  
$^2$ = Mean cluster size.

**Table 2.** Comparison between the memory complaints subgroups: demographic characteristics and semantic fluency-related variables

<table>
<thead>
<tr>
<th></th>
<th>No change in diagnosis (n = 28)</th>
<th>Change in diagnosis (n = 10)</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>$X^2$</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>16 (57.14)</td>
<td>8 (80)</td>
<td>3.39</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.93 (8.41)</td>
<td>70.10 (7.10)</td>
<td>-1.06</td>
</tr>
<tr>
<td>Education (years)</td>
<td>7.82 (4.86)</td>
<td>6.10 (4.79)</td>
<td>0.96</td>
</tr>
<tr>
<td>TWG$^1$</td>
<td>17.50 (7.29)</td>
<td>11 (4.59)</td>
<td>2.60</td>
</tr>
<tr>
<td>MCS$^2$</td>
<td>2.36 (1.12)</td>
<td>1.26 (0.72)</td>
<td>2.84</td>
</tr>
<tr>
<td>Switches</td>
<td>4.93 (2.86)</td>
<td>4.20 (2.09)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

$^1$ = Total words generated.  
$^2$ = Mean cluster size.

**Table 3.** Logistic regression: total words generated, mean cluster size and number of switches

<table>
<thead>
<tr>
<th>Variable</th>
<th>B (df.1)</th>
<th>Exp (B)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWG$^1$</td>
<td>2.37</td>
<td>—</td>
<td>0.12</td>
</tr>
<tr>
<td>MCS$^2$</td>
<td>-1.57</td>
<td>0.20</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of switches</td>
<td>2.27</td>
<td>—</td>
<td>0.13</td>
</tr>
</tbody>
</table>

$^1$ = Total words generated.  
$^2$ = Mean cluster size.
The reduction in the number of elements inside semantic subcategories observed in AD patients can be explained by the disorganization of the semantic store (Hodges et al., 1992) and the loss of semantic hierarchy (Martin and Fedio, 1983) present in patients diagnosed as AD. These results are congruent with previous studies which have suggested that the significant alteration in semantic fluency found in AD reflects a degradation of the semantic store and not a reduction in retrieval speed (Henry et al., 2004). Conversely, the reduced number of switches found in our AD group could be explained by an alteration in the executive functions involved in switching performance, such as mental flexibility and search strategies (Troyer et al., 1997). This could be because of the disruption of the frontal-subcortical circuits that characterize middle and advanced stages of the disease (Pantel et al., 2004).

After 2 years, 26% of our patients with memory complaints were diagnosed as AD. In the first evaluation, patients who later developed AD had greater alterations in semantic fluency and in the mean cluster size than patients who did not become demented. However, contrary to expectations, the switching performance was adequate in both subgroups. This result is in contrast with that of Troster et al. (1998), who found a reduction in the number of switches in AD patients. These differences might be explained by the stage of the disease at the time of the assessment. Patients from the Troster study had been diagnosed as probable AD, according to NINCDS-ADRA criteria. In contrast, our patients did not fulfill dementia criteria in the first evaluation, so we can infer that they were in a preclinical stage of the disease. As is known, AD is characterized by regional degenerative changes of the brain which strike the medial temporal lobe structures in the early stages of the disease and cause a generalized brain condition in subsequent stages (Dickerson et al., 2001; Hirono et al., 2001; Pantel et al., 2004). Therefore, the earlier stages are characterized by deficits in the cognitive processes attributed to the medial temporal regions, such as semantic fluency and clustering performance. However, it could be expected that such patients would have preserved the executive functions implicated in switching performance.

Finally, the fact that the mean cluster size was the best predictive variable indicates that a qualitative analysis of semantic fluency might improve diagnostic discrimination, even in early stages of the disease. Palmer et al. (2003) suggested that the presence of a fluency deficit is an AD predictor. Our results not only replicate these findings, but also provide evidence of the utility of clustering assessment in enhancing early diagnostic reliability.

As the incidence of dementia increases (Aupperle, 2006), there is a growing need to determine the diagnostic utility of specific neuropsychological tests, in addition to neuroimaging and genetics dates (Hansson et al., 2007; Matsuda, 2007), in the early diagnosis of Alzheimer’s disease. To our knowledge, this is the first study which assesses qualitative aspects of semantic fluency performance in patients with memory complaints and uses it as a predictor of AD. Nevertheless, there are obvious limitations to our study in terms of the sample size and the fluency score. The sample size in both the AD and memory complaints groups was small, which also explains the low number of patients who developed AD after two years. In addition, we only used one semantic category in the semantic fluency test for potentially predicting AD. For those reasons further research with larger samples, different semantic categories, and an assessment of the qualitative aspects of phonetic fluency is required, in order to replicate and confirm these results.

CONFLICT OF INTEREST

None known.

REFERENCES


APPENDIX 1 EXAMPLES OF SEMANTIC SUBCATEGORIES: FREQUENTLY GENERATED EXAMPLES ARE SUMMARIZED FOR EACH SUBCATEGORY, ALTHOUGH LISTINGS ARE NOT EXHAUSTIVE

GENERAL SUBCATEGORIES

Wild animals:
- African animals, Australian animals, Canines (Except for dog), Artic/Far North animals, Primates, Reptiles/Amphibians.

Water animals
- Fish, Seefood, Artic animals (Except for polar bear), alligator, crocodile...

Farm animals
- Cock, hen, chicken, duck, turkey, cow, donkey, goat, horse, mule, pig, sheep.

Birds
- Farm birds, wild birds.

Pets
- Dog, cat, canary, hamster, guinea pig, parrot, rabbit.

SPECIFIC SUBCATEGORIES

African animals
Lion, tiger, panther, leopard, cheetah, puma, hyena, jackal, lemur, cobra, elephant, giraffe, rhinoceros, zebra, hippopotamus, gazelle, antelope, monkey, chimpanzee, gorilla...

Australian animals
Ostrich, kangaroo, koala, crocodile.

Canines
Dog, wolf, fox, hyena, coyote.

Bovines
Buffalo, cow, sheep, yak.

Felines
Cat, lion, tiger, panther, cheetah, cougar, jaguar, leopard, puma.

Fish
Whale, dolphin, shark, salmon, bass, trout, prawn, lobster.

Seafood
Lobster, prawn, mussel, oyster.

Insects
Butterfly, bee, mosquito, ant, beetle, flea, fly, cockroach.

Primates
Chimpanzee, orangutan, ape, baboon, gibbon, gorilla, human, lemur, monkey.

Reptiles
Crocodile, alligator, snake, lizard, chameleon, iguana, turtle, frog, gecko, salamander, toad, tortoise.

Rodents
Mouse, hamster, chinchilla, beaver, squirrel, guinea pig, hedgehog, marmot, rat.

Artic/Far North animals
Polar bear, penguin, reindeer, seal