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**Reduced Cluster Switching in Category Fluency Reveals Cognitive Decline:
A Longitudinal Study¹**

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Abstract. Impairments in semantic fluency tasks are well-established in Alzheimer's disease (AD). These are apparent both in quantitative measures, namely total number of items produced, and qualitative measures, namely the frequency with which AD patients switch between semantic clusters (e.g., from farm animals to African animals). Similar deficits have been seen in quantitative output of individuals who will go on to develop AD or who have been diagnosed with mild cognitive impairment (MCI). However, less research has examined qualitative aspects of fluency performance in these populations. We assessed the fluency performance over time of twelve healthy elderly who went on to be diagnosed with MCI. Over a seven-year period, declines were seen in qualitative measures, specifically the number of cluster switches, but not in total output. The finding that switching between clusters on a semantic fluency task begins to decline up to seven years before diagnosis with MCI indicates that performance on this task may be an important predictor of future cognitive decline in healthy elderly adults.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease affecting a number of cognitive domains, including memory, language and executive function (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; American Psychiatric Association, 1994). It has become clear in recent years that individuals with AD manifest cognitive deficits across a number of tasks even prior to meeting diagnostic criteria for probable AD (e.g., Flicker, Ferris, & Reisberg, 1991; Hodges & Patterson, 1995; Jacobs et al., 1995), and interest in early identification of individuals who will develop AD has surged.

Recently, Petersen et al. (1999) developed a set of criteria to identify individuals with mild cognitive impairment: subjective and objective memory impairment, generally preserved other cognitive function and absence of dementia, and no other neurological or psychiatric explanations for the memory impairment. MCI was found by Petersen et al. and a number of subsequent studies to constitute a significant risk factor for dementia, with around 15% of individuals meeting criteria for MCI developing probable AD per annum, versus 1-2% in the healthy elderly population (Chertkow, 2002). However, a significant proportion of MCI individuals remain undemented. Recent recommendations for revised MCI criteria include the criterion that the patient should show either impaired performance on cognitive tasks in the context of self and/or informant report of decline, or decline over time on objective cognitive tasks (Winblad et al., 2004). These criteria should assist in identifying those individuals who show cognitive decline from a high baseline, thus appearing unimpaired on cognitive testing.

One area in which deficits are often reported in pre-clinical AD is on lexical-semantic tasks such as verbal fluency (for a review of language performance in MCI and pre-clinical AD, see Taler & Phillips, in press). In verbal fluency tasks, participants must name as many items as possible that conform to a given criterion within a certain time limit (typically one minute). The criterion may either be semantic (e.g., animals) or phonemic (e.g., words beginning with the letter F). Both semantic and letter fluency tasks impose significant demands on executive function, since participants must organize verbal retrieval and recall, initiate responses, and monitor prior responses, as well as inhibiting inappropriate responses (Henry et al., 2004). However, unlike letter fluency, semantic fluency requires that participants

retrieve semantic extensions of a superordinate term. This task requires intact semantic associations within the mental lexicon (Rohrer, Salmon, Wixted, & Paulsen, 1999).

There exists a great deal of research demonstrating impairments in verbal fluency tasks in AD, and a recent meta-analysis (Henry, Crawford, & Phillips, 2004) indicated that, while both letter and semantic fluency are impaired in AD, the impairment is more severe in semantic than in letter fluency. This disparity is in part due to the degradation in semantic knowledge that occurs in AD; however, impairments in object naming are also less severe than those in semantic fluency, suggesting that deficits in executive function that affect semantic search may also play a role. The research to date indicates that declines in verbal fluency performance are also seen in MCI, particularly in category fluency (for a review, see Taler & Phillips, 2007). Similarly, deficits in semantic fluency have been observed in individuals at risk for AD, either because they are carrying the APOE-4 allele or due to a family history of the disease (Miller, Rogers, Siddartha, & Small, 2005).

The vast majority of research to date has analyzed category fluency scores without examining more closely the qualitative aspects of category fluency performance in these populations. Troyer, Moscovitch, Winocur, Leach and Freedman (1998) were the first to report qualitative alterations in verbal fluency performance in AD. They focused on aspects of semantic search, analyzing the number of semantic clusters (groups of semantically or phonemically related items) and the number of switches from one category to another that occur in AD patients' output on this task. They found that AD patients produced smaller clusters on both letter and semantic fluency, and fewer switches on semantic fluency than healthy control participants. Subsequent research has confirmed this finding and indicated that that clustering and switching variables can discriminate between very mild AD and healthy elderly (Gomez & White, 2006).

The present study extends previous research on semantic fluency performance in pre-clinical AD, examining alterations in performance over time. We report on quantitative and qualitative aspects of semantic fluency performance in healthy control participants who remain cognitively intact as well as a group who were subsequently diagnosed with MCI. Participants were assessed annually and their performance over time was analyzed.

Methods

Participants

A total of 29 participants were included in the present study: 17 healthy elderly who remained cognitively intact and 12 healthy elderly who went on to be diagnosed with MCI. All participants were native speakers of English with no neurological or psychiatric history, other than MCI, and were right-handed. The diagnosis of MCI was established according to criteria similar to those proposed by Petersen et al. (1999; 2001). For the healthy elderly who remained unimpaired, average follow-up time was 4.47 years, with an average of 4.12 assessments. In the group who were eventually diagnosed with MCI, the average follow-up time was 4.83 years, with an average of 3.67 assessments. For the MCI group, year 0 was defined as time of diagnosis, and performance in the seven years prior was entered into the analysis. Further details about the participants are provided in Table 1.

	CN Participants – Mean (SD)	CN Participants – Range	CN to MCI Participants – Mean (SD)	CN to MCI Participants – Range
n	17		12	
age	67.59 (8.13)	55-79	72.58 (6.67)	61-81
sex	10 women/7 men		5 women/7 men	
education	15.53 (2.55)	12-20	15.17 (3.49)	8-19
MMSE (/30)*	29.59 (0.62)	28-30	28.33 (1.56)	25-30
BNT (/15)*	14.88 (0.33)	14-15	14.08 (1.24)	11-15
COWA (letter)	39.53 (11.03)	26-66	42.75 (10.81)	26-62

Table 1. Participant characteristics, baseline assessment.

BNT=Boston Naming Test. CN=cognitively normal. COWA=Controlled Oral Word Association.

MCI=mild cognitive impairment. MMSE=Mini-Mental State Examination.

*groups differ at $p < 0.05$

Procedures and Scoring

As part of a larger neuropsychological battery, participants completed a semantic fluency task in which they were asked to name as many animals as they could in one minute. This task was completed at each neuropsychological assessment for a period of up to seven years. For each participant at each assessment, total number of responses, excluding errors and repetitions, was recorded.

In addition to total scores, semantic fluency performance was coded according to switching and clustering. Following the guidelines set out by Troyer, Moscovitch and Winocur (1997), participants' output was scored for total number of times that the participant moved from one semantic subcategory to another (switches) and mean number of items produced in each subcategory (clusters). Clusters included animals that were similar in terms of living environment (e.g., water animals, African animals); zoological categories (e.g., birds, rodents); or human use (e.g., pets, beasts of burden)³. Following Troyer et al., number of switches was coded as [total number of clusters – 1], and cluster size was coded as [total items in cluster – 1].

Results

Figure 1 presents the mean total items generated over time by each group. Those participants who remain cognitively intact appear to increase in total number of items produced, while those who go on to be diagnosed with MCI do not. One-tailed Pearson correlations reveal a borderline positive

³ For a more comprehensive list of categories, see Troyer et al. In our analysis, three additional categories were included: South American animals (e.g., llama, alpaca); equids (e.g., horse, zebra, mule); and nocturnal pests (raccoon, possum, skunk).

correlation between year and total items produced for the healthy CN group ($r=0.17, p<0.08$) but no such correlation for the group who went on to be diagnosed with MCI ($r=-0.16, p>0.15$).

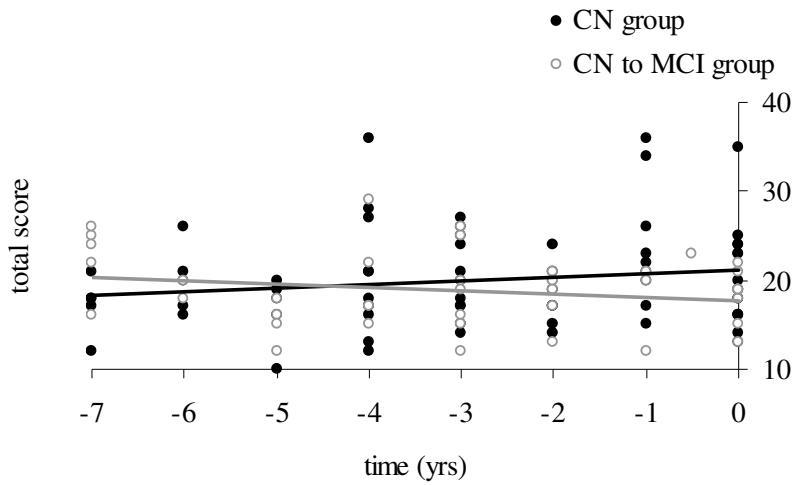


Figure 1. Total number of items generated at each assessment by each participant group. Year 0 = time of diagnosis for converter group. Trend lines represent best linear fit.

In Figure 2, the correlation between number of switches between semantic clusters and year of assessment is shown for each group. One-tailed Pearson correlations reveal a significant negative correlation between year of assessment and number of switches for the CN to MCI group ($r=-0.26, p<0.05$) but not for the group who remained cognitively intact ($r=0.019, p>0.44$).

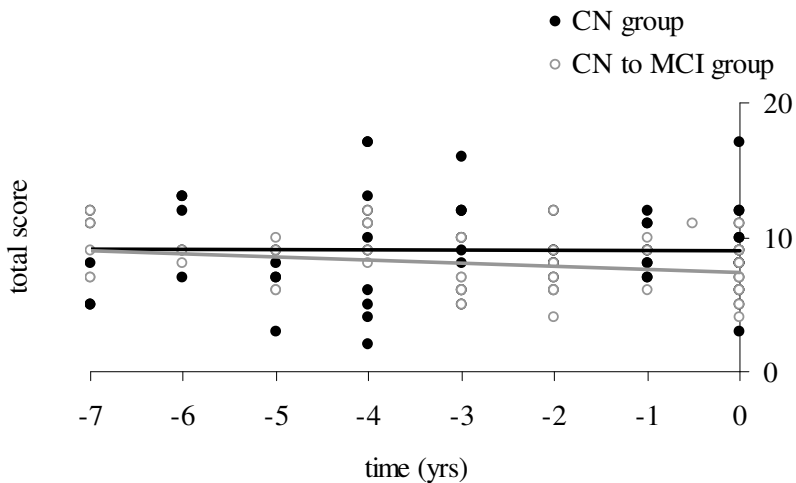


Figure 2. Total number of switches generated at each assessment by each participant group. Year 0 = time of diagnosis for converter group. Trend lines represent best linear fit.

Finally, Figure 3 shows the correlations between average cluster size and year of assessment for each group. No significant correlation was seen between year of assessment and cluster size in either group (CN: $r=-0.13$, $p>0.14$; CN to MCI: $r=0.03$, $p>0.43$).

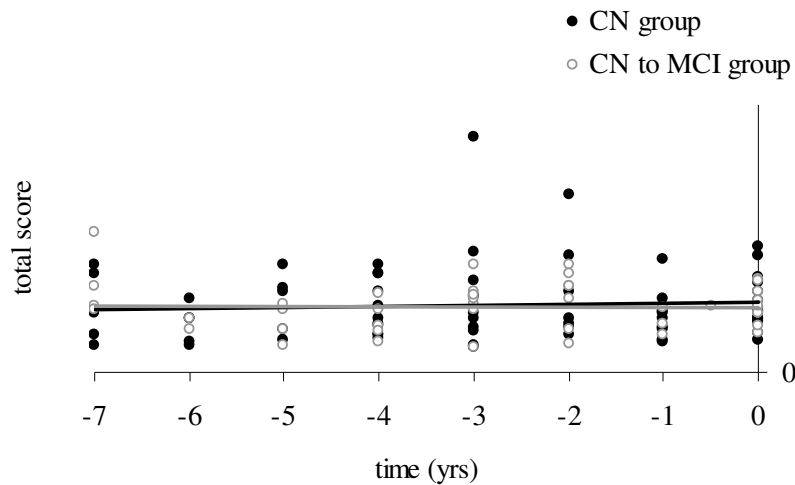


Figure 3. Average size of cluster generated at each assessment by each participant group. Year 0 = time of diagnosis for converter group. Trend lines represent best linear fit.

Discussion

Overall, healthy control participants showed a marginally significant increase in the number of items generated, and no change in the number of cluster switches or cluster size over the course of seven years. In contrast, in the seven years prior to diagnosis, those participants who were eventually diagnosed with MCI showed no change in the number of items generated and a decrease in the number of cluster switches, while the cluster size remained the same.

The results reported here are consistent with previous reports indicating declines in number of cluster switches and stability in cluster size in individuals with a diagnosis of AD (e.g., Troyer et al., 1998). However, to our knowledge, this is the first report to examine the qualitative aspects of category fluency performance longitudinally in a pre-clinical population. The present results indicate that these changes in cluster switching begin much earlier than previously reported, many years prior to the appearance of any objective memory impairment.

That cluster size remains the same suggests that the declines in performance observed here are driven not by impairment in semantic representation per se, but likely by a deficit in executive search within semantic memory. Previous studies of semantic memory in MCI have pointed to similar conclusions (e.g., Duong, Whitehead, Hanratty, & Chertkow, 2006), and the present research indicates that these executive search impairments are a very early marker of cognitive decline in MCI.

It is also of interest that the total number of items produced remains relatively stable in individuals who will be diagnosed MCI, while increasing in healthy control participants. It seems likely that healthy participants are able to recall the tasks included in previous testing sessions, particularly when the same tasks are used over several consecutive annual neuropsychological assessments. These individuals are thus able to benefit from developing strategies over multiple testing sessions. This finding

emphasizes the importance of using alternate versions of tasks such as semantic fluency (for a discussion of the validity of alternate versions of fluency tasks, see Cunje, Molloy, Standish, & Lewis, 2007). Participants who will go on to be diagnosed with MCI, in contrast, are not able to benefit from these practice effects, suggesting deficits in episodic memory. This finding has been reported previously in clinically diagnosed MCI (Cooper, Lacritz, Weiner, Rosenberg, & Cullum, 2004), but to our knowledge this is the first report indicating that declines in practice effects over annual sessions are seen in healthy participants who will go on to develop MCI.

In conclusion, the finding that switching between clusters begins to decline up to seven years prior to diagnosis with MCI has important ramifications for early detection of AD. Semantic fluency is a task that is included in routine neuropsychological evaluations, and as such these data are readily available to the clinician in providing a prognosis for the elderly patient. We thus believe that qualitative as well as quantitative analysis of semantic fluency performance in elderly participants is of great potential value in clinical practice.

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