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PATTERNS OF WORD-LIST GENERATION IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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Abstract

Patients with amnesic mild cognitive impairment (aMCI) have been described as exhibiting greater impairment on tests of category fluency than letter fluency. This has been offered as evidence that this condition represents pre-clinical Alzheimer's disease (AD). We hypothesized that this pattern of differential impairment is dependent on the specific semantic categories and initial letters selected, and is not specific to AD and aMCI. A total of 40 cognitively normal older adults, 74 MCI patients—25 “amnesic single domain” (aMCI), 27 “amnesic multiple domain”, and 22 non-amnesic—and 29 AD patients were tested with multiple forms of semantic-category and initial-letter fluency tasks. The pattern of deficits within and across groups was highly dependent on the specific categories and letters chosen. Overall, aMCI patients did not demonstrate greater impairment in category than letter fluency. In fact, the level and pattern of their performance resembled that of cognitively normal older adults much more than AD patients. MCI patients with deficits in multiple cognitive domains performed most like AD patients. These findings indicate that verbal fluency performance is highly influenced by the specific tasks used, and impairment on semantic fluency is not characteristic of pure amnesic MCI.

Keywords

Verbal fluency; Mild cognitive impairment; Alzheimer's disease.

INTRODUCTION

Tests of “verbal fluency” require the rapid generation of (usually spoken) words, typically constrained by semantic category or initial letter. Impairments in both “category fluency” and “letter fluency” are ubiquitous among patients with dementia (Barr & Brandt, 1996; Rosser & Hodges, 1994; Suhr & Jones, 1998; Troyer, Moscovitch, & Winocur, 1998).

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Patients with Alzheimer's disease (AD) are often described as more impaired on category fluency than letter fluency tasks (Cerhan, Ivnik, Smith, Tangalos, Petersen, & Boeve, 2002; Martin & Fedio, 1983; Monsch, Bondi, Butters, Salmon, Katzman, & Thal, 1992; Salmon, Heindel, & Lange, 1999), a differential deficit that was supported by a meta-analysis of 153 published studies (Henry, Crawford, & Phillips, 2004). In addition several studies have reported that the greater vulnerability of category fluency than letter fluency is unique to AD and is not seen in patients with subcortical dementias (e.g., Monsch et al., 1994; Rosser & Hodges, 1994), but this is not always the case (Barr & Brandt, 1996; Suhr & Jones, 1998).

Several research groups have reported a selective category fluency deficit in patients with mild cognitive impairment (MCI), a clinical entity thought in many cases to be transitional between normal aging and AD (Morris et al., 2001; Petersen, 2003). Murphy, Rich, and Troyer (2006) reported that elderly patients with isolated memory impairments (amnesic MCI) were impaired in generating lists of animals (category fluency), but were unimpaired in generating words beginning with the letter F (letter fluency). Although the normal control participants in their study produced more words on the category task than the letter task, amnesic MCI patients performed similarly on both, resulting in relatively impaired category fluency. Murphy and colleagues interpreted their findings as consistent with the notion that amnesic MCI represents pre-clinical AD (Murphy et al., 2006). Adlam and colleagues (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006) reported similar results: category fluency for living things (animals, birds, and fruits) and man-made objects (household items, tools, and vehicles) was impaired in amnesic MCI, while fluency for the letters F, A, and S was not.

One potential limitation of previous research on fluency impairments in aMCI is the failure to equate category and letter fluency tasks for difficulty. It is entirely conceivable that different patterns of fluency performance may be obtained depending on the specific letters and semantic categories chosen. Although Murphy and colleagues write that "one can manipulate the difficulty levels by choosing different categories and letters ..., but this does not tend to change the pattern of fluency performance (Bayles et al., 1989)" (2007, p. 573), they do not test this assertion. Therefore, the possibility remains that the apparent differential deficit in semantic fluency in aMCI is artifactual.

The aims of our present study are to determine: (1) whether the greater impairment in category than letter fluency among older adults with cognitive impairment is dependent on the specific semantic class and initial letter used, and (2) whether there are patterns of fluency performance that are specific to AD and pure amnesic MCI, or whether they can also be found in non-amnesic MCI patients. To our knowledge, no study to date has examined verbal fluency performance in different subtypes of MCI, despite recent evidence suggesting that these subtypes may have different outcomes (Lopez et al., 2006; Winblad et al., 2004).

METHOD

Participants

The Johns Hopkins University Institutional Review Board reviewed and approved this study, and all participants (and their proxies, where applicable) gave written informed consent. Patients with AD were enrolled in the Johns Hopkins Alzheimer's Disease Research Center (ADRC). They received the diagnosis of AD in a clinical consensus conference where all available history and test results were reviewed. MCI participants and normal control participants were also recruited from the ADRC, as well as from physician referrals, community lectures, and advertisements. The diagnosis of MCI was made either by a consensus team or by an experienced neurologist, neuropsychiatrist, or

neuropsychologist. Volunteers were excluded from study participation if they had a history of psychotic illness or neurological disorder other than AD.

Procedure

Every participant was required to have a family member or close friend available to be interviewed for a Clinical Dementia Rating (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982). All participants were administered the following tests to determine group membership: Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), Logical Memory subtest (story A) of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1981), a 30-item version of the Boston Naming Test (Goodglass & Kaplan, 1983), clock drawing to request, Controlled Oral Word Association Test (COWAT) (Spreen & Benton, 1969), and word list generation for semantic categories. For the COWAT, participants were asked to say as many different words as possible that begin with the letter F, A, or S, with 60 seconds allowed for each trial. Participants were instructed not to say proper names or variations of the same word root (e.g., swim, swimming, swam). Such responses were not counted in scoring. For the category fluency task, participants were asked to say as many different words as possible from the categories animals and then vegetables, with 60 seconds allowed for each trial. Participants were also administered the 15-item version of the Geriatric Depression Scale (Yesavage et al., 1982).

NC group

To be eligible for the study, neurologically and cognitively normal older adults had to obtain a total CDR score of 0, indicating no cognitive impairment. They also had to perform at or above the 20th percentile for age and education on the MMSE (Bravo & Hébert, 1997); score above -1.5 standard deviations for age and education (according to published norms) on the Boston Naming Test, clock drawing, and letter and category fluency; and score above -1.5 standard deviations for education on Logical Memory delayed recall.

MCI groups

Participants were diagnosed with MCI according to the Mayo Clinic criteria (Petersen, 2004). Specifically, each participant (or collateral of the participant) reported substantial decline in memory and/or another cognitive domain, obtained an overall CDR score of 0.5, indicating questionable dementia, and performed normally (at or above the 20th percentile for age and education) on the MMSE. In addition, the 25 participants with amnesic single-domain MCI demonstrated performance at or below -1.5 standard deviations for education on WMS-R Logical Memory delayed recall. Of these pure amnesic participants, 12 were recruited from the ADRC and physician referrals, and 13 were recruited from the community. The 27 participants with multiple-domain amnesic MCI (18 from the ADRC/physician referrals and 9 from the community) additionally performed at or below -1.5 standard deviations for age and education on at least one additional test. The 22 patients with non-amnesic MCI (8 from the ADRC/physician referrals and 14 from the community) performed normally on Logical Memory delayed recall but performed at or below -1.5 standard deviations for age and education on one or more of the non-memory tests described above.

AD group

A total of 29 participants met NINCDS-ADRDA criteria for probable AD (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984). They included 21 participants with an overall CDR score of 1, indicating mild dementia, and eight participants with a CDR of 2, indicating moderate dementia. The tests described previously were used to determine the presence of impairments in multiple areas of cognition.

Statistical analyses

Three analyses of covariance (ANCOVA) were computed. Sex was included as a covariate in the models because of the preponderance of women in the normal elderly group and of men in the two amnesic groups, and because women often outperform men on verbal fluency tasks (Bolla, Gray, Resnick, Galante, & Kawas, 1998; Loonstra, Tarlow, & Sellers, 2001). To replicate the analysis of Murphy et al. (2006), we first compared the number of legitimate words produced for the letter F to the number of correct words produced for the category *animals*. Next, we compared total legitimate words produced for the letter S to those produced for the category *vegetables*. In these analyses, total words generated were analyzed using a 5 group (healthy adult, pure amnesic MCI, amnesic multiple domain MCI, non-amnesic MCI, AD) by 2 fluency task (letter, category) repeated-measures model. Our third ANCOVA model pooled over initial letters and over categories. We *z*-transformed the sum of legitimate words generated on the three letter trials and the sum of the words given on the two category trials based on performance of the healthy adult group. These *z*-scores were subjected to a 4 group (pure amnesic MCI, multiple domain amnesic MCI, non-amnesic MCI, AD) by 2 fluency task (letter, category) repeated-measures ANCOVA. Bonferroni adjustments were used for all post-hoc tests.

RESULTS

Table 1 shows the demographic and clinical characteristics for the five groups of participants. The groups did not differ in mean age, years of education, or score on the Geriatric Depression Scale. Aside from the difference in sex distribution mentioned earlier, the only difference among groups was that AD patients scored significantly lower on the MMSE than all the other groups.

Total number of words (sex-adjusted means) produced by each group for the letter F and the category *animals* are shown in Figure 1 (top). There were significant main effects of group, $F(4, 137)=20.31, p < .001, \eta_p^2=.37$, and task, $F(1, 137)=4.70, p < .05, \eta_p^2=.03$, as well as a group by task interaction, $F(4, 137)=6.24, p < .001, \eta_p^2=.15$. Animal naming was an easier task than F-word naming, and the groups differed in their overall performance. Moreover, the healthy adult and amnesic single-domain MCI groups demonstrated an advantage for animal fluency over F-word fluency, whereas this was not the case for the other three groups.

Total number of words (sex-adjusted means) generated by each group for vegetables and the letter S are shown in Figure 1 (bottom). Again, there were significant main effects of group, $F(4, 137)=20.90, p < .001, \eta_p^2=.38$, and task, $F(1, 137)=10.14, p < .01, \eta_p^2=.07$, but now the group by task interaction was non-significant, $F(4, 137)=1.23, p=.30, \eta_p^2=.03$. All the groups, with the exception of the non-amnesic MCI patients, displayed better performance on the letter task than the category task. More importantly, this difference was greatest in the AD and multiple-domain MCI groups (where no category/letter difference existed for animal naming and F-word naming.)

Z-scores were created for the sum of the three letter trials (FAS) and the sum of the two category trials (animals and vegetables) using the means and standard deviations of the healthy adult group (see Figure 2). A 4×2 repeated measures ANCOVA revealed significant main effects for group, $F(3, 98)=9.06, p < .001, \eta_p^2=.22$, and task, $F(3, 98)=6.30, p < .05, \eta_p^2=.06$, but the group by task interaction fell short of significance, $F(3, 98)=2.20, p=.09, \eta_p^2=.06$. However, examination of each group separately is deemed justifiable based

on our hypotheses. Participants with amnesic single-domain MCI were not more impaired in category than letter fluency. Furthermore, this pure amnesic MCI group performed better than all other groups on category fluency. Both the AD and multiple-domain MCI groups demonstrated disproportionate impairment in category over letter fluency. The non-amnesic participants performed equivalently poorly on the two types of fluency tasks.

DISCUSSION

The data presented here have important implications for the assessment of verbal fluency in mild cognitive impairment. They suggest that the relative sensitivity of letter fluency and category fluency tasks in age-related cognitive impairments depends on the specific letters and categories chosen. First, it is easier for older adults to generate animal names than words beginning with the letter F, but harder for them to generate vegetable names than words beginning with the letter S. As a result, any statements about the selective vulnerability of initial letter and category word-list generation based on a single trial of each (as in Murphy et al., 2006) are suspect. Second, the specific pattern of deficits across patient groups depended on the specific task. Category fluency was worse than letter fluency for the AD and amnesic multiple-domain MCI groups when S-words and vegetables were compared, but no difference existed when F-words and animals were compared. This illustrates the importance of basing conclusions about word-list generation ability on multiple trials of each type, and always considering task difficulty. Converting raw scores to standard scores (e.g., z-scores) based on the performance of appropriately matched normal participants is one way to accomplish this (Barr & Brandt, 1996).

Pooled across the three initial letters and two semantic categories used in this study, patients with amnesic single-domain MCI did not display a differential deficit in category fluency. Thus, our findings contradict those of Murphy et al. (2006) and Adlam et al. (2006), but are consistent with those of Nutter-Upham et al. (2008). Not only were the pure amnesic MCI patients equivalently impaired on the two types of word-generation task, they were the most minimally impaired group overall (see Figure 2). This makes it difficult to support the conclusion that elderly patients with isolated memory impairments are on a cognitive and neuropathological trajectory toward Alzheimer's disease. In fact, we found that memory-disordered elderly who also had other deficits (amnesic multiple-domain MCI) most resembled AD patients, as they too demonstrated a greater impairment in category than letter fluency. This leads us to hypothesize that these patients have more severe or widespread degenerative brain change than the subtype with memory impairment only. This hypothesis is consistent with several observations that multiple-domain MCI patients are more likely to convert to dementia at follow-up than are pure amnesic MCI patients (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006; Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005; Tabert, Manly, Liu et al., 2006). Our non-amnesic MCI group performed about 1.5 standard deviations below average on both category and letter fluency, with no difference in the magnitude of deficits. This fluency pattern is sometimes associated with forms of dementia other than AD (Rascovsky, Salmon, Hansen, Thal, & Galasko, 2007; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006).

This study, like most other studies of MCI, is limited by the fact that the diagnosis and subtyping of MCI are not independent of neuropsychological test results (Lopez et al., 2006). Three participants in this study earned their MCI diagnoses by having isolated impairments in verbal fluency (classified as non-amnesic MCI). However, when these participants were removed from the analyses, the overall pattern of performance of the non-amnesic group did not change. In other words, if category and letter fluency were removed from the group of tests defining subtypes of MCI, our conclusions would remain the same.

Differences in the performance of our pure amnesic MCI participants and those of Murphy et al. (2006) and Adlam et al. (2006) may be due to differences in operational criteria for MCI. Methods of diagnosis and classification of mild cognitive impairment continue to vary from study to study. There remains no consensus on the specific tests to be used for defining subtypes, the number or proportion of impaired tests performances necessary, and the level of impairments necessary (Gauthier et al., 2006; Winblad et al., 2004). Finally, it is worth mentioning explicitly that all these data are cross-sectional, and we therefore make no assumption that any MCI subtype represents preclinical Alzheimer's disease. Only longitudinal follow-up will allow us to determine the utility of verbal fluency performance patterns for the early diagnosis of dementia. These issues notwithstanding, we find no evidence that pure amnesic MCI is more similar to AD than to neurologically healthy adults in their verbal fluency performance.

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Figure 1.

Top: Total F-words and animals (adjusted for sex) produced by the participant groups.

Bottom: Total S-words and vegetables (adjusted for sex) produced by the participant groups.

Error bars represent 95% confidence interval. NC = Normal controls; MCI = Mild Cognitive Impairment.

Figure 2. Z-scores (adjusted for sex) for letter and category fluency in the patient groups. The performance of the normal control group was used for comparison. Error bars represent 95% confidence interval. NC = Normal controls; MCI = Mild Cognitive Impairment.

Table 1

Demographic and clinical characteristics of the participant groups

	Normal controls (<i>n</i> = 40)	Anesthetic single domain MCI (<i>n</i> = 25)	Anesthetic multiple domain MCI (<i>n</i> = 27)	Non-amnesic MCI (<i>n</i> = 22)	Alzheimer's disease (<i>n</i> = 29)
Age, years	74.57 (5.73)	74.72 (5.35)	78.07 (6.91)	77.31 (6.78)	76.34 (5.78)
Sex, men:women *	16:24	18:7	19:8	10:12	15:14
Education, years	15.65 (2.64)	15.71 (2.59)	15.74 (2.61)	15.41 (2.21)	15.38 (3.35)
Mini-mental state examination, score (<i>SE</i>) **	29.15 (0.15)	28.32 (0.22)	28.40 (0.21)	28.31 (0.27)	21.52 (0.56)
Geriatric depression scale, score (<i>SE</i>)	1.18 (0.35)	1.83 (0.40)	2.59 (0.47)	1.79 (0.42)	1.21 (0.27)

Data are means (*SD*), except where noted.*
 $p < .05$.**
 $p < .001$, AD < all other groups.