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Research report

Perseverations in Alzheimer's disease: Memory slips?

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ABSTRACT

Previous studies of verbal fluency tasks reported higher rates of repeated responses in Alzheimer's disease (AD) compared to elderly controls. The present investigation aimed at determining if perseverations are caused by word retrieval deficits or working memory deficits, both of which are commonly observed in AD. Based on current theories of lexical processing and working memory, we derived specific predictions concerning the lag between the first occurrence of a word and its repetition. With word retrieval deficits, repetitions are expected to be progressively less frequent at greater lags; conversely, with working memory deficits, repetitions should occur especially after long lags. These predictions were tested analyzing the performance of 392 AD individuals in verbal fluency tasks. The finding of lags that were significantly longer than would be expected by chance is consistent with the hypothesis that perseverations are primarily caused by working memory deficits. Specifically, we propose that perseverations stem from an impairment affecting the working memory mechanisms that control response monitoring. We also investigated the relationship between perseverations and other cognitive deficits observed in AD. We discuss the implications of our findings for understanding the nature of perseverations, the effects of working memory deficits in AD, and the neural correlates of working memory components.

1. Introduction

When people are involved in effortful memory searches, they need to retrieve items that meet specific characteristics, while avoiding retrieving the same item repeatedly (Benjamin, 2003). Memory theories assume that this form of voluntarily controlled retrieval is supported by a component of working memory commonly referred to as the central executive after Baddeley and Hitch (1974). The central executive is supposed to involve frontal cortical regions (e.g., Baddeley, 2002; Curtis and D'Esposito, 2003; Fuster, 1997; Miyake et al., 2000; Moscovitch and Winocour, 1992; Roberts et al., 1998; Smith and Jonides, 1999) and, like other components of working memory, operates under limited resources (Baddeley and Hitch, 1974; Baddeley, 2003). The central executive is assumed to regulate both memory encoding and retrieval

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processes interfacing with an associative memory system where information is stored. The functions related to memory that have been assigned to the central executive include (a) devising cues and retrieval strategies; (b) organizing information made available from associative memory; and (c) ensuring that only information compatible with the task at hand is retrieved and that repeated responses are avoided (Baddeley, 2003; Engle, 2002; Ericsson and Kintsch, 1995; Gathercole, 2007; Moscovitch, 1992; Norman and Shallice, 1986).

Fluency tasks, in which participants generate words starting with specific letters or from specific semantic categories (e.g., animals), illustrate the characteristic features of an effortful memory search. Essential to the task is the ability to monitor that responses are from the correct set and are not repetitions. Therefore, good performance on the fluency task relies on retrieval strategies that are under the control of the central executive. Given such features, fluency tasks provide a research model for investigating strategic retrieval and, more generally, memory processing related to the central executive.

Prior research has linked verbal fluency tasks to central executive processing. For example, Rosen and Engle (1997) showed that participants who scored high on measures of working memory capacity generated significantly more animal names relative to participants with comparatively lower working memory capacity scores. High working memory capacity was also associated with generating larger clusters of semantically related words, as when, in the animal fluency task, participants start by producing a number of farm animals and then quickly switch to different clusters – from cats, to fish, to birds (Rosen and Engle, 1997). Large clusters and short inter-cluster intervals are viewed as markers of efficient memory retrieval, further suggesting that central executive mechanisms appear to play a significant role in efficient memory retrievals. Other studies adopted a complementary approach, examining the effect on verbal fluency tasks of concurrent tasks that are known to interfere with central executive processing (Moscovitch, 1994; Troyer et al., 1997). As expected, the number of generated words was reduced with the interference tasks. In addition, studies that examined the cognitive correlates of verbal fluency found that measures of working memory capacity were significant predictors of total scores on verbal fluency tasks (Fisk and Sharp, 2004; Fournier-Vincente et al., 2008; Hedden et al., 2005) or measures of clustering and switching (Unsworth et al., 2011), further supporting the role of central executive processing in the verbal fluency task.

As discussed above, one hypothesized role of the central executive in verbal fluency is the prevention of repeatedly retrieving the same item, that is the prevention of what are typically referred to as perseverations. If so, one anticipates finding a relationship between perseverations on verbal fluency tasks and central executive processing ability. Although perseverations typically have very low incidences in tasks conducted with normal adults, their frequencies increased significantly in experimental conditions that, crucially, are specifically taxing for working memory. Rosen and Engle (1997; Exp. 4) observed a significant increase of perseverative responses using a tracking digit task that reduced working memory capacity. This effect of concurrent task on rate of perseveration was especially pronounced in low-span participants. Similar effects on perseveration rates were found by Azuma (2004) using a concurrent memory task.

Individuals diagnosed with Alzheimer's disease (AD) demonstrate an abnormal increase of perseverative responses in verbal fluency tasks (Bayles et al., 2004; Marczinski and Kertesz, 2006; Pekkala et al., 2008; Shindler et al., 1984), with the rate of perseverations increasing as a function of the severity of cognitive decline in AD (Pekkala et al., 2008). In light of the experimental results discussed above, it would seem reasonable to attribute the pathological incidence of perseverative responses in AD to a deterioration of central executive processes. However, pathological rates of perseveration in individuals with AD in the context of the verbal fluency task may reflect some other cognitive impairment associated with the disease. AD may result in the degeneration of a variety of cognitive functions such as memory, language, and visuospatial abilities. Increased perseverations in verbal fluency may be attributed to one of these other deficits. Specifically, a multitude of findings in aphasia have shown that acquired language impairments can result in noticeable word repetitions in spontaneous speech or in the naming tasks routinely used to evaluate word production. These word repetitions are generally attributed to an impairment in the ability to activate the target lexical item (Ackerman and Ellis, 2007; Caccappolo-van Vliet et al., 2003; Cohen and Dehaene, 1998; Dell et al., 1997; Hirsh, 1996; Lee et al., 2009; Martin and Dell, 2004, 2007; Martin et al., 1998; Moses et al., 2007). Under current accounts of word production, the word that is selected for production is (typically) the most activated one. In normal conditions, the most activated word corresponds to the target word that a speaker aims to produce, but in pathological conditions individuals may fail to strongly activate the target item. Recently produced words are assumed to remain relatively activated after production, even in the unimpaired system. Therefore, when target words do not reach sufficiently high activation levels, recently produced items are plausible candidates for selection, and perseveration errors are produced.

The language impairments that are frequently observed in AD typically manifest themselves in word production difficulties (Croot et al., 2000; Cummings et al., 1985; Huff et al., 1986; Price et al., 1993), and therefore may contribute to the perseverations that AD individuals make on verbal fluency tasks. Furthermore, the hypothesis of a contribution of language mechanisms on fluency is also supported by the results of correlational studies that demonstrated that in normal individuals fluency tasks load to language factors corresponding to vocabulary size or word retrieval (Hughes and Bryan, 2002; Unsworth et al., 2011). The goal of the current study is to identify the underlying cause of the perseveration errors produced by AD individuals during verbal fluency tasks: are the errors due to central executive or language processing deficits?

One method for distinguishing these alternative hypotheses is to analyze the temporal characteristics of the perseverations, specifically the distance, either in terms of number of items or time elapsed, between the first instance of the item and its later repetition. Analyses of the word perseverations that aphasics made in word production tasks revealed a precise temporal relationship between the first occurrence of a word and its incorrect repetition: the probability that a word will be repeated decreases as more time elapses since the first occurrence of the word or as the number of intervening words increases (Cohen and Dehaene, 1998; Lee et al., 2009). This result is predicted by the hypothesis that perseverations arise due to a failure to activate the current target item. The activation of recently produced responses is expected to decrease with time or intervening items. As a result, when there is a failure to activate the target, the likelihood of selecting a recently produced item should be greater than the likelihood of selecting a more distantly produced item, leading to a relatively short lag between the first occurrence of the word and its repetition. Following this logic, if the perseverations made by AD individuals on verbal fluency tasks originate from impairments in lexical selection of the same nature as those hypothesized for aphasia, then perseverations in AD and aphasia would both be associated with comparably short lags.

In contrast, if the perseverations made by AD individuals on verbal fluency tasks originate from impairments in central executive processing, then the lag between the first occurrence of the word and its repetition should be relative long. According to this account, perseverations are produced because of a failure to remember that a word has already been generated. As the number of intervening words increases, it should be progressively more difficult to recognize that a word has already been generated, particularly in conditions of central executive impairments. In essence, distinct temporal patterns should appear if perseverations on verbal fluency tasks reflect central executive impairments (*long lags*) or language impairments (*short lags*). The responses of a large group of AD individuals on verbal fluency tasks were analyzed in the present investigation to determine to which of these temporal patterns perseverations conform in AD. Our investigation aimed at defining the role of working memory in perseverations, thus contributing to the identification of the possible effects of working memory impairments in AD. A further objective of our investigation was to determine whether a novel form of perseverations traceable to working memory impairment exists. A specific problem confronted in analyzing perseverations is to establish whether their distribution differs significantly from chance distribution (Cohen and Dehaene, 1998). We used Monte Carlo simulations to determine whether participants produced perseverations at longer or shorter lags greater than would be expected by chance. To anticipate the principal finding of our investigation, repetitions tend to concentrate at longer compared to shorter lags, a finding linking repetitions to working memory deficits in AD. As we discuss in detail in the final section of this article, our finding contributes to characterize the cognitive aspects and neuronal correlates of AD as well as the neurocognitive components of working memory that prevent repetitions in healthy cognitive systems but are plausibly associated with pathological repetition rates in conditions of neuronal degeneration.

We further analyzed task-specific word frequency effects. We reasoned that the words more frequently generated by our participants were not only words that ‘come to mind’ more easily but also the more probable candidates to perseverate. The reason why frequently generated words are likely to be repeated is twofold. First, high frequency words would typically pop-out every time a further attempt to generate a word is made. Second, previous work has shown that recognition memory is worse for higher frequency words (Gorman, 1961; Benjamin, 2003). Therefore, it should be more difficult to recognize that a high-frequency word has been already generated and consequently it should be less likely that its repetition is blocked. We should note that the prediction of a word frequency effect is not unique to the hypothesis that perseverations stem from a central executive impairments. Nevertheless, this prediction is integral to this hypothesis and its confirmation would strengthen the hypothesis. Finally, we considered measures of attention and inhibition (color-Stroop task), verbal short-term memory (digit span), memory encoding, and lexical processing (picture naming) to obtain a more comprehensive picture of the cognitive abilities that affected word retrieval and erroneous repetitions in our AD sample.

2. Methods

2.1. Participants

Responses from verbal fluency tasks were collected from 392 individuals who were consecutive attendees at the Memory Disorders Center of the Taub Institute, Columbia University. All participants received a diagnosis of AD made by a consultant neurologist on the basis of a detailed medical history and a full neurological evaluation. Diagnoses were supported by neuroimaging data and neuropsychological evaluation that included tests that assess praxis, visuo-spatial functions, memory, language, and executive function. Criteria for inclusion in the study were English as native language and no history of drug or alcohol dependency, seizure disorders, psychiatric illnesses, or prior brain damage. Participants had no concomitant extrapyramidal symptomatology commonly associated with Lewy body disease, or showed behavioral or neuroimaging results suggesting any of the forms of primary progressive aphasia. Furthermore, none of the participants exhibited fluctuating levels of arousal or reported hallucinations. Seventy-seven participants were re-tested one or two times at about 1-year interval (their verbal fluency responses at re-test were also included in the analyses). All participants obtained mini-mental scores above 10/30, so the investigation focused on AD individuals with mild to moderate dementia. On average, participants were 76 years old (SD = 7.7), had 15.2 years of education (SD = 2.9), and received a score of 22.3 (SD = 4.1) on the Mini-Mental Status Examination (MMSE; Folstein et al., 1975). 58.5% of the participants were females. In addition to responses from verbal fluency tasks (see below), the following data were collected from participants: forward digit span (raw score), interference score based on Stroop color naming task, number of correct responses on Boston Naming Test (BNT; Kaplan et al., 1983), and total number of correctly recalled words on the Selective Reminding Test (SRT; Buschke and Fuld, 1974). Analyses that involved these data were based on result sets that varied slightly due to occasional data missing. Compared to age-matched normal controls (Tomaugh and Hubiey, 1997), the performance of AD participants on the picture naming task corresponded to an average z-score of −3.6 (SD = 3.2), and 65% of AD participants had z-scores lower than −3. These results demonstrate widespread and severe word production difficulties in our group of AD participants.

2.2. Verbal fluency tasks

Verbal fluency tasks were included in the test battery that was administered to assess a wide range of cognitive functions in the participants. In two distinct category fluency tasks, participants produced names of animals and vegetables, respectively, whereas in three distinct letter fluency tasks, participants generated words that started with a specific letter (C, F or L). Participants generated as many words as possible within 60 sec, and were explicitly instructed not to repeat words or produce inflectional variants of the same word (e.g., both *cat* and *cats*). Instructions for letter fluency tasks specifically instructed the avoidance of proper names (of people, geographical places, brands, or products). The number of words produced every 10 sec was recorded for the responses in the animal fluency task of 138 participants. A distinction is made in the neuropsychological literature between continuous recurrent perseverations (without words intervening between repetitions) and discontinuous recurrent perseverations (with words intervening between repetitions). These two types of perseverations were jointly analyzed. In a few instances, singular/plural variants of a same noun were produced (e.g., *cat*/*cats*); such responses were scored as repetitions. Incorrect responses (i.e., words not appropriate for a given semantic category or with incorrect word onset) were ignored in the analyses of perseverations, as these analyses were primarily aimed at determining whether the number of intervening words affected perseverations.

3. Results

Analyses were based on the responses from 489 administrations of the semantic and letter fluency tasks. The average number of correct words in the letter fluency tasks was 9.9, which was significantly greater than the average number of correct words in the semantic fluency tasks [8.1; F (1, 489) = 69.7, $p < .0001$]. Number of correct words varied across onset letters [F (2, 982) = 9.6, $p < .0001$], a finding explained by fewer L-onset words than C-onset words [mean: 5.1 *vs* 5.4; t (491) = 2.7, $p = .006$] or F-onset words [mean = 5.5; t (491) = 4.5, $p < .0001$]. This finding mirrors the distribution in the English language; as revealed by counts of the words listed in CELEX (Baayen et al., 1993), L-onset words are more sparsely represented. While our results align with those of several prior AD investigations that recorded fewer words in semantic compared to letter fluency (Barr and Brandt, 1996; Butters et al., 1987; Capitani et al., 2009; Crossley et al., 1997; Monsch et al., 1994; Troyer et al., 1998), the effect of set size we observed with letter categories replicates prior findings that highlighted the relevance of set size in AD performance (Diaz et al., 2003). Total number of correctly produced words in verbal fluency tasks was significantly correlated with MMSE scores [$r = .39$, t (471) = 9.2, $p < .0001$] and education [$r = .13$, t (479) = 2.86, $p = .002$], but not with age [$r = -.04$, t (479) < 1]. A model composed of participants' scores on Stroop interference, picture naming, total recall on SRT, and digit span that was used to predict the total number of correct responses in verbal fluency tasks yielded a R^2 equal to .28 [F (4, 393) = 39, $p < .0001$].

Perseverations account for 1–3% of the responses produced by normal elders on fluency tasks (Albert and Sandson, 1986; Bayles et al., 2004; Bayles et al., 1993; Foldi et al., 2003; Henry and Phillips, 2006; Kozora and Cullum, 1995; Pekkala et al., 2008; Ramage et al., 1999; Troster et al., 1989). Perseverations occurred, on average, in 9.5% of the responses (SD = 7.7; range = 0–47%). Perseveration rates were above the 1–3% range of normal elders for 74% of our participants and were related to MMSE scores [$r = -.21$, t (471) = 4.5, $p < .0001$] and age [$r = .10$, t (479) = 2.14, $p = .03$], but not to education [$r = -.02$, t (479) < 1]. When entered in a multiple regression as predictors of perseveration rates, scores of Stroop interference, picture naming, total recall on SRT, and digit span yielded a R^2 of .03 [F (4, 393) = 3.5, $p < .007$]. Of these scores, only picture naming accuracy rates correlated significantly with perseveration rates [$r = -.20$, t (396) = −3.6, $p = .0003$]. Perseverations were made with similar frequencies in semantic and letter categories [means: 7.9% *vs* 8.7%; F (1, 489) = 2.98, $p > .05$].

3.1. Lag analyses

A further set of analyses evaluated the lag between the first occurrence of the word in a response and its subsequent repetition. For the first analysis, lag is defined by the number of intervening items. Consider the animal fluency responses produced by one of the participants: "Cat; Dog; Tiger; Leopard; Mouse; Rat; Squirrel; Lion; Tiger," with the perseverated word "Tiger." We will call the first instance of "Tiger" *the source* and the repetition, *the perseveration*. For this error, the perseveration occurs at a lag of five, as there are five items between the source and perseveration. A lag of 0 (an immediate repetition) is the shortest possible lag. For this response, a lag of 5 is the longest possible lag, as only six words were produced following the production of the source. Indeed, the longest possible lag will always be when the perseveration is produced as the final word in the sequence. Aggregating perseverations across all participants and fluency tasks, we asked: do perseverations appear at short lags as would be predicted by a lexical activation deficit account of perseveration in verbal fluency? Or do perseverations appear at relatively long lags as would be predicted by the working memory deficit account?

We limited our analyses to items that were repeated a single time in the response; when items are repeated multiple times, it is ambiguous which prior response is the source. We defined six critical response positions: (a) three short lags (the word immediately after the source, with a single intervening word and with two intervening words), and (b) three long lags (the final word, the second-to-last word and the third-to-last word in response). To assure that the perseveration could appear in at most one of the six critical

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response positions, we further limited the first analysis to those cases in which the source word was produced at least six words before the end of the sequence. Across all of the administrations of all of the fluency tasks, a total of 1571 perseveration errors fit these requirements, with 379 of the 489 administrations (78%) containing at least one error of this sort.

A computer program tabulated the percentage of these 1571 perseverations that appeared in each of the six critical positions. These occurrences are illustrated by the bars of the graph in Fig. 1. The fewest perseverations were found at a lag of 0 (2.3%) and few perseverations were observed at either of the other short lags (lag of 1, 3.4%; lag of 2, 8.3%). Many more perseverations were observed at the longer lags (maximum lag, 13.6%; one fewer than the maximum lag, 14.8%; two fewer than the maximum lag, 14.0%). These observed percentages were compared to a measure of chance that assumed that the perseveration had an equal probability of appearing in any position after the source. A distribution of chance values was created using a Monte Carlo simulation. For each run of the Monte Carlo simulation, the set of words following the source was randomly scrambled for each of the 1571 errors. For example, for the animal fluency response: "Cat; Dog; Tiger; Leopard; Mouse; Rat; Squirrel; Lion; Tiger," all of the words after the first occurrence of Tiger (Leopard, Mouse, Rat, Squirrel, Lion and Tiger) were scrambled, such that one run of the Monte Carlo simulation created the chance response "Cat; Dog; Tiger; Rat; Leopard; Tiger; Squirrel; Lion; Mouse," while another run created the chance response "Cat; Dog; Tiger; Squirrel; Leopard; Tiger; Lion; Mouse; Rat."

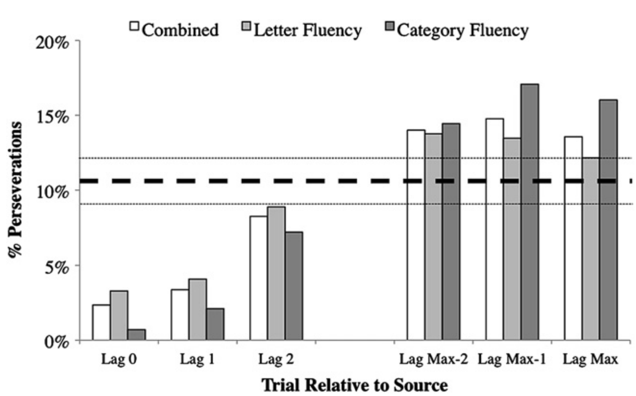

Fig. 1 – Proportion of perseverations that occurred at short lags (0, 1 or 2 intervening words) or long lags (maximum lag, one fewer than the maximum lag, two fewer than the maximum lag) compared to the proportion expected by chance. The white bars show the observed proportions for the two tasks combined, while the light gray bar shows the observed proportions for the letter fluency task and the dark gray bar shows the observed proportion for the semantic fluency task. The thick dotted line shows the proportion expected by chance for the two tasks combined with the thin dotted lines reflecting the 95% confidence interval around the chance mean. Compared to the frequencies expected by chance ($p < .05$), perseverations occurred less often at shorter lags but more often at longer lags in the two tasks combined.

The program then calculated the percentage of the perseverations that appeared in each of the six critical positions in the scrambled data sets. A total of 10,000 runs of the Monte Carlo simulation were carried out creating a distribution that can be used to evaluate whether the observed perseveration rates differed significantly from the perseveration rates expected by chance. The thick dotted line in Fig. 1 shows the average of the 10,000 runs of the simulation. Approximately 10% of the perseverations are expected to appear in each critical position simply due to chance. The thin dotted lines in Fig. 1 show the range of the middle 9500 runs of the Monte Carlo simulation, or the 95% confidence interval. Any observed value outside of that 95% confidence interval differs significantly from chance at an alpha of .05. For all three short lags, the observed percentage fell below this 95% confidence interval, while for all three long lags, the observed percentage fell above this 95% confidence interval. In addition, as shown in Fig. 1, results pattern alike in the semantic and letter fluency tasks. Furthermore, in light of prior results showing a gender effect in the fluency tasks (Bolla et al., 1990; Loonstra et al., 2001), we compared the repetition lags of male and female participants in our sample. Of the 1571 perseverations described above, 615 were produced by male participants and 956 by female participants. Male and female participants produced perseverations at short lag of 0, 1 or 2 at comparable rates [Males: 15% of all perseverations, 92/615; Females: 13%, 128/956, $\chi^2(2) = .64$, $p > .4$]. Similarly, perseverations were equally likely to be produced at one of the three possible lags for male (44%, 270/615) and female participants [41%, 395/956, $\chi^2(2) = .92$, $p > .3$]. Gender appeared not to affect the number of produced words in semantic and letter fluency tasks combined [average, males = 45.52, females = 46.66; $F(1, 489) = .48$, $p = .48$] and repetition rates [average, males = 9.38, females = 9.82; $F(1, 489) = .37$, $p = .54$]. We therefore conclude that perseverations were at shorter lags less often and longer lags more often than would be expected by chance ($ps < .05$). Furthermore, while perseverations occurred less often then would be expected by chance for all three short lags, it appears that the likelihood that an item will be repeated in a fluency task is an increasing function of the distance from initial production of the word, with the lowest observed percentage at lag 0, a higher percentage at lag 1 and an even higher percentage at lag 2.

Several follow-up analyses confirmed this first result. First, to assure that the results extended to errors in which the source was fewer than six words from the end of the list, we carried out a similar analysis for the 344 errors in which the source word was between three and five words from the end of the response. For this analysis, we defined only two critical positions – a short and a long lag. In consideration of prior results showing that healthy participants (Campbell and Clark, 1989; Vitkovitch & Humphreys, 1991) and aphasic individuals (Hsiao et al., 2009) tend to avoid immediate (lag 0) repetitions, lag 0 repetitions were not included in the analysis. More conservatively, we contrasted lag 1 to the longest possible lag in which the perseveration was the final word in the response. Only 71 of 344 perseverations appeared at lag 1 (20.6%), while 119 were the final word in the response (34.6%). If perseverations were equally likely to appear in any position relative to the source, then, using a Monte Carlo simulation identical to the one described above, we estimated that 24.8% of the perseverations should be observed with a lag 1 and with the maximum lag. Only a single run of the 10,000 runs of the Monte Carlo simulation had a value either as high as or higher than the observed proportion of perseverations at the maximum lag, and fewer than 5% of the 10,000 runs had a value as low or lower than the observed proportion of perseverations at a lag of 1. Using this chance distribution, we conclude that there were significantly fewer perseverations at lag 1 ($p < .05$), and significantly more at the maximum lag than would be expected by chance ($p < .001$).

Next, we considered whether some individuals in the sample perseverated at short lags while others perseverated at long lags. We calculated a normalized lag for each perseveration error, with .0 being a perseveration at lag 0, 1.0 being a perseveration at the maximum lag, and intermediate values reflecting where the perseveration falls in the interval between the minimum and maximum lags. An average normalized lag was calculated for each administration of the fluency task, averaging across perseverations produced in both the semantic and letter fluency tasks. An average normalized lag of less then .5 would indicate that, during this administration of the task, perseveration lags tended to be shorter than average, while a normalized lag of greater than .5 would indicate that the perseveration lags tended to be longer than average. In total, there was at least one perseveration on 432/489 administrations of the fluency task (88%). Fig. 2 shows the histogram of average normalized lags for all 432 administrations with at least one perseveration. For 367/432 (85%) administrations, an average normalized lag of at least .5 was observed. For administrations with at least 5 perseverations, 91% had an average normalized lag of at least .5 and all 32 administrations with at least 10 perseverations had average normalized lags of at least .5. Less than 2% (8/432) of the administrations had extremely short normalized lags (<.25) while more than 30% of the administrations had extremely long normalized lags (>.75). These findings suggest that relatively long lags between source and perseveration is a common property of verbal fluency perseveration errors for most, if not all, individuals with AD.

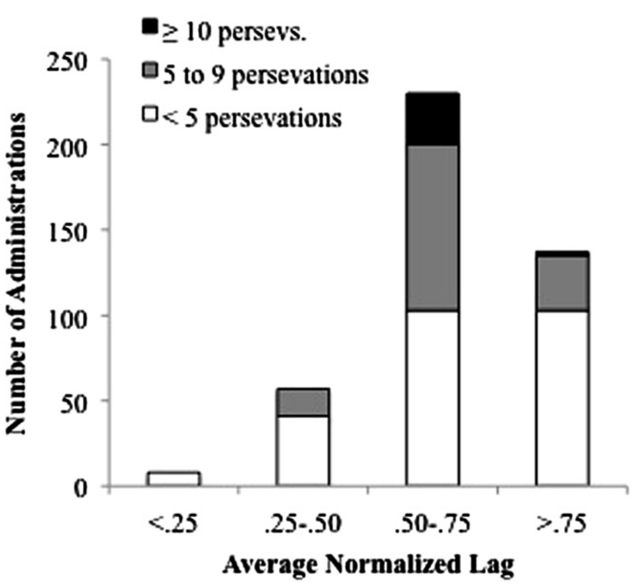

Fig. 2 – Histogram of the number of administrations with averaged normalized lags ranging from 0 to .25, .25 to .5, .5 to .75 and .75 to 1.0. The white portion of the bars correspond to the number of administrations with fewer than 5 perseveration errors, the gray portion to the number of administrations with 5–9 perseveration errors, and the black bars to the number of administrations with 10 or more perseveration errors. These results suggest relatively long lags between sources and perseverations.

Finally, we analyzed lag defined by the time elapsed between the source and perseveration. For a subset of administrations, timing information was recorded by binning words into 10 sec response bins. We analyzed the likelihood that the perseveration appeared in the same time bin as the source (the shortest time lag), the following time bin (the second shortest time lag) or the time bin as far from the source as possible (the maximum time lag). This analysis was limited to errors in which the source was not produced during either the 40–50 sec bin or the 50–60 sec bin, ensuring that the time bin as far as possible from the source is neither the same time bin as the source or the immediately following time bin. In all, 512 errors were identified that fit the criteria described above.

The results of this analysis are shown in Fig. 3. Of these errors, only 32 perseverations (6.3%) appeared in the same time bin as the source. For 105 errors (20.5%), the perseveration was in the time bin immediately following the time bin of the source. For 130 errors (25.4%), the perseveration was in the time bin farthest from the source. A chance analysis was carried out with similar logic to the analyses described above. All of the words following the source were randomly scrambled, maintaining the number of words that appeared in each time bin. The analysis of whether the perseveration appeared

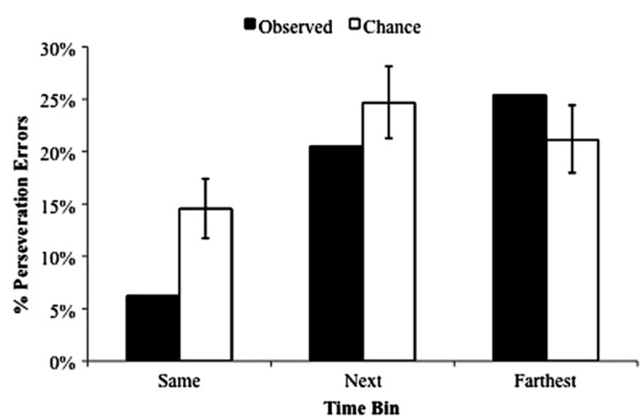

Fig. 3 – Proportion of perseverations that occurred at different lags defined by time bins. The black bars show the proportion observed in the same time bin as the source, the time bin immediately following the source, and the time bin maximally distant from the source. The white bars show the proportion expected in each of those time bins by chance, with the error bars reflecting a 95% confidence interval around those chance means. Compared to the frequencies expected by chance ($p < .05$), perseverations occurred less often in the same or immediately following time bins but more often in the farthest time bin.

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in the same, next or farthest time bin was carried out over these scrambled responses, and the process was repeated 10,000 times.

The results of chance analysis are shown in the white bars of Fig. 3. By chance, an average of 14.6% of perseverations were expected to appear in the same time bin as the source, 24.7% in the next time bin and 21.1% in the farthest time bin. The error bars indicate the range of the middle 9500 runs of the chance analysis program, or the 95% confidence interval. In none of the 10,000 runs of the chance analysis program were as few or fewer perseverations found in the same time bin as the number of perseverations actually observed, meaning that at a $p < .0001$, fewer perseverations appeared in the same time bin than would be expected by chance. Furthermore, the observed number of perseverations found in the immediately following time bins fell below the 95% confidence interval, meaning that, at a $p < .05$ fewer perseverations appeared in the next time bin than would be expected by chance. Finally, the observed number of perseverations in the final time bin fell above the 95% confidence interval for that time bin, meaning that, at a $p < .05$, significantly more perseverations were observed in the farthest time bin from the source than would be expected by chance. These results once again indicate that perseveration errors in this task tend to occur at long, as opposed to short, lags from their sources, here with lag defined by time elapsed rather than number of intervening items.

3.2. *Word frequency analyses*

An additional analysis tested the prediction that words that are easier to generate are more likely to be repeated. For each correct response on a fluency task, we took the number of administrations in which the response was produced as a measure of how easy that word was to generate. Different exemplars are produced at very different frequencies. For example, the word *dog* was produced at least once in 423/489 (87%) administrations of the animal fluency task, while the word *stork* was produced at least once in only 1/489 administration (<1%). Note that this approach to ease of generation has a clear advantage over simply looking at frequency of occurrence in the language as a whole. The prediction depends on how easily a word comes to mind given the context of the animal fluency task; examining at actual responses on this task is a suitable way to measure this construct. Of the fluency tasks administered, the animal fluency task included the broadest range of values for this ease of generation measure, ranging from words that were produced in nearly all administrations (*dog*, *cat*) to words that were produced in approximately half of the administrations (*elephant*, *lion*) to words that were produced on only a handful of occasions (*emu*, *tortoise*). We, therefore, limited the analysis to words produced in the animal fluency task.

Our measure of perseveration rate calculated the likelihood that a word is produced multiple times, given that it is produced at least once. For example, the word *dog* is produced at least once in 423 administrations, and more than once in 66 administrations, for a perseveration rate of 66/423 (.156). The word *pig* is produced at least once in only 84 administrations and more than once in 13 administrations, for a similar perseveration rate of 13/84 (.155). A reasonable estimate of perseveration rate requires a relatively large number of administrations in which the word is produced; if the word is only produced in one administration, then the perseveration rate is limited to be either .00, when the word is not repeated in that administration, or 1.00, when the word is repeated. We therefore calculated the perseveration rate only for the 51 most frequently used animal names, which were operatively defined as the words that appeared in at least 20 administrations.

Fig. 4 plots the correlation between how frequently a word is produced (horizontal axis) and the likelihood that if it is produced, it will be repeated (vertical axis). A significant positive correlation was observed [$r = .64$, $t(49) = 5.82$, $p < .0001$]; the easier a word is to generate, the more likely it is that the word will perseverate if it is produced at least once.

3.3. *Result summary*

The principal results that emerged from our investigation of the verbal fluency task in AD can be summarized as follows. (1) We replicated the finding that individuals with AD have abnormally high perseveration rates on verbal fluency tasks; furthermore, we observed that perseverations increase in parallel to cognitive deterioration as measured by MMSE. (2) Measures of attention, verbal short-term memory, episodic memory, and naming were found to be differently related to number of perseverations and number of correct responses on verbal fluency tasks, a result suggesting that the mechanisms causing a rise in perseverations are at least partially distinct from those involved in word elicitation. Similar findings were reported by Bayles et al. (2004). (3) Relatively long lags were observed between a word and its repetition. (4) Finally, we observed a frequency effect wherein words that are commonly produced in a verbal fluency task tend to be likely candidates for perseveration.

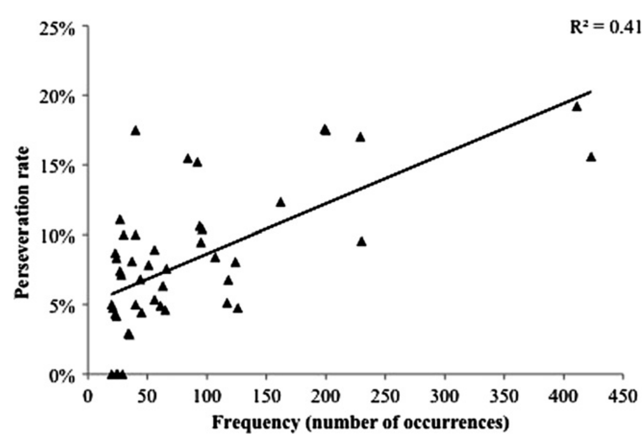

Fig. 4 – A plot of the frequency with which a given animal name was produced in the 489 administrations of the animal fluency test compared with the observed perseveration rate for the animal name. Only animal names that were generated in at least 20 administrations are plotted. There is a significant positive correlation between frequencies and perseveration rates. See text for details.

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4. General discussion

The key novel finding of our investigation of verbal fluency in AD is that a word is typically repeated after a (relatively) long lag from its first occurrence. Importantly, results demonstrating this temporal characteristic of AD perseverations converged from analyses that used distinct methods – one based on lag defined by the number of intervening items and the other based on lag defined by the time elapsed between the source and the perseveration. The *long* lags we found with perseverations in AD contrast sharply with findings from aphasia that repeatedly showed that, in word production tasks, perseverative responses are associated with a *short* lag. As illustrated in the Introduction, the perseverations observed in aphasia have been explained as resulting from a deficit that limits the ability to activate the target lexical item. Assuming that recently produced words retain relatively high activation levels only for a short time interval, these recently produced words are likely to be produced again when the current target item is not properly activated. As a result, it is more likely that items would be repeated after short intervals rather than long intervals in conditions of lexical deficits. However, the result that perseverations occur at long lags from sources makes it unlikely that the high perseveration rates observed on verbal fluency tasks in AD patients stem primarily from lexical deficits. A variety of sources provide further evidence similarly inconsistent with a lexical deficit account of AD perseverations on verbal fluency tasks. First, Bayles et al. (2004) found that AD and normal elders perseverated at similar rates (3–4% on average) in picture naming and picture description tasks, unlike in verbal fluency tasks where perseverations were exceedingly more common in AD. This finding was fully replicated in our study. In picture naming, we found an average perseveration rate of 5%, very similar to the normal elders' rate reported by Bayles et al. (2004). The lack of abnormal perseveration rates across word production tasks is a finding at odds with a lexical deficit account, which instead anticipates frequent perseverations in any of the production tasks in which lexical access is critical. Second, when Arroyo-Anlló et al. (2012) compared the performance of aphasic and AD individuals on a category fluency task, it was found that despite similar overall performance, AD individuals were nearly twice as likely to perseverate. Individuals with aphasia tend to perseverate in picture naming but not fluency tasks, while the opposite pattern is true for AD individuals, suggesting that different deficits give rise to perseverations in the two populations.

A crucial question for understanding perseverations concerns characterizing the mechanisms that give rise to response repetition. One possible mechanism of perseveration is the failure to inhibit responses after they are produced. Response inhibition could efficiently prevent response repetition, and deficits affecting the mechanisms responsible for response inhibition would result in perseverations. Crucially, an explanation of perseverations based on inhibition would not predict the observation of long lags between a word and its repetition; the failure-to-inhibit hypothesis predicts short lags. In fact, because the activation of recently produced words declines with time, inhibition failures should be especially frequent at short intervals. It should be emphasized that this conclusion is not restricted to inhibitory mechanisms at the lexical level; it holds for other types of inhibitory mechanisms as well [e.g., the mechanism of suppression of previously retrieved responses that Rosen and Engle (1997) attribute to working memory]. Naturally, further research is needed to reach more definitive conclusions on the role of inhibition in word retrieval and word production more generally. We should note, however, that accounts of verbal fluency that incorporate the notion of inhibition (Azuma, 2004; Chiappe and Chiappe, 2007; Rosen and Engle, 1997) are confronted with the challenging task of demonstrating that inhibitory mechanisms are at play. The crux of the problem is that results suggesting inhibition can typically be accounted for by assuming a fast post-response decay of activation.

We proposed to view the long lags between repeated words as markers of memory deficits that impair word generation in verbal fluency tasks. The verbal fluency task requires both generating exemplars of a category as well as monitoring those generated words for repetitions. We propose that subsequent to a memory impairment, memory traces indicating that the word has already been produced become increasingly less available with time or as more intervening words have been generated. As a result, as lag increases, the likelihood of recognizing that a word has already been produced decreases, and perseveration errors become more probable. While our analyses looked at lag defined both by time elapsed and number of intervening item, it is critical to note that we are not making any claims about whether memory traces become less available as a function of time or as a function of intervening items. Whether forgetting is due to time or interference from intervening items remains an open question in memory research (Oberauer and Lewandowsky, 2008). Our analyses have not pitted these two competing hypotheses against each other; future research with more fine-grained temporal information about when responses are produced would be required for such an analysis.

An additional prediction of our proposal is that easy to generate words, i.e., words that are frequently listed as category members because they are categorically prototypical or commonly used in the language, should be more likely to be perseverated. We reasoned that it is more difficult to keep track of the generation of frequent words that persistently pop-out in retrieval. Confirming our expectation, analyses of AD patients' responses on the animal fluency task revealed a propensity to repeat frequent words. Although frequency likely exacerbates the effects of memory deficits, it is also very plausibly linked to the lexical deficits commonly observed in AD, which are typically characterized by word finding difficulties more severely affecting low frequency than high frequency words. The propensity of perseverating high frequency words in the fluency task would thus stem jointly from a lexical access restricted to high frequency words and failures to recognize that high frequency words repeatedly (and prepotently) present themselves as candidate responses in the task. If we are correct in positing a relationship between lexical and memory deficits, it is not surprising that naming-accuracy scores, a plausible index of lexical deficits, correlated with repetition rates in the fluency tasks.

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While the results converge in suggesting a memory deficit as the cause of the AD patients' perseverations, working memory, particularly its central executive component, appears to be the likely locus of this deficit. Response monitoring, one of the functions attributed to the central executive (Rosen and Engle, 1997; Baddeley, 2002, 2003), is crucial in discriminating between old and new words in fluency tasks, and a deficit affecting this function would result in abnormally high rates of repetitions that, critically, would characteristically occur at long intervals and involve frequently generated words. Impaired verbal fluency adds to a series of other deficits demonstrated by AD individuals on tasks that are assumed to tap the central executive (e.g., dual tasks) rather than other components of working memory (e.g., the phonological loop) and that are considered to be independent of storage deficits or processing speed (Belleville et al., 2007; Colette et al., 1988; Peters et al., 2007; Stopford et al., 2012; for a review, see Huntley and Howard, 2010). Interestingly, deficits associated with central executive impairment were observed in the mild and moderate AD population that also participated in our study.

The monitoring mechanism we propose to be at the basis of AD perseverations in fluency tasks is one of the components of working memory identified by Rosen and Engle (1997). Another component is the generation of cues for accessing new names, which is associated to switching, an aspect of the fluency performance that – as we have seen – directly determines the efficiency of fluency performance. Anomalies in switching have been observed in AD (Troyer et al., 1998). An interesting question is whether such anomalies co-occur in AD along with the long gaps we found with perseverations. Addressing this question is of potential interest for understanding the extent to which the working memory mechanisms for response monitoring and cue generation/switching are dissociable and reliant on (partially) distinct neural substrate. On the other hand, there is widespread agreement that working memory fractionates into a central executive and modality-specific subsidiary slave systems (i.e., the phonological store, the verbal phonological loop and the visual visuospatial sketchpad; Baddeley, 2003; Baddeley and Hitch, 1974). In line with this hypothesis, we found a non-significant correlation ($r = .04$, $p > .05$) between perseverations rates and verbal digit-span, a measure of the intactness of the phonological loop. Our analyses of perseverations converge with those from the AD study conducted by Peters et al. (2007) in which noticeable deficits were observed in working memory tasks but not in phonological loop tasks, at least in the initial stages of the disease. Confirmatory evidence that long-lag repetitions are subsequent to damage to the central executive rather than modality-specific systems of working memory would emerge from acquired deficits of the phonological store that are observed in conduction aphasia (Baldo and Dronkers, 2006; Caramazza et al., 1981) or in lesions to the inferior parietal regions (Buchsbaum et al., 2011). Specifically, long-lag repetitions should not appear in these conditions.

Deficits affecting working memory and the central executive more specifically are typically attributed to frontal impairments (Baddeley, 2002; Curtis and D'Esposito, 2003; Fuster, 1997; Miyake et al., 2000; Moscovitch and Winocour, 1992; Roberts et al., 1998; Smith and Jonides, 1999). Evidence that damage to frontal regions results in impaired performance in fluency tasks (e.g., Capitani et al., 2009; Pachana et al., 1996; Stopford et al., 2012; Troyer et al., 1998) support this hypothesis. In line with this evidence, it seems plausible to consider that the perseverations in verbal fluency, that our results relate to a deficit in working memory processes, reflect frontal damage. This conclusion is supported by results showing frontal pathology in AD (Klunk et al., 2004; Morris and Price, 2001). However, the presence in AD of conspicuous changes on functional neuroimaging in posterior regions paired with the apparent lack of a frontal quality to the clinical profile of AD (Stopford et al., 2012) are findings that call for cautionary conclusions about the neural underpinnings of perseverations in AD. Results highlighting differences between the working memory impairments observed in AD and in neuropsychological deficits that result from frontal damage (Capitani et al., 2009; Stopford et al., 2012) are particularly promising in this context, as they may offer informative cues for understanding the specificities of these two types of working memory impairments. A contribution of this sort may derive from the comparison of the temporal aspects of perseveration in individuals affected by AD and selective frontal lesions.

Other than a rise in perseveration rates, the generation of fewer words represents a pathological feature of verbal fluency in AD (e.g., Capitani et al., 2009; Shindler et al., 1984; Troyer et al., 1998). Replicating the findings of Bayles et al. (2004), we also observed that measures of attention, language, long and short-term memory are far more strongly correlated with the number of generated words than the number of perseverations. Although it is not clear how each of these functions contribute to word generation, a potentially relevant aspect of our correlational results concerns whether these functions are differently related to word generation and word perseveration, respectively. The implication of our correlational findings is twofold. Insofar as the temporal characteristics of perseverations suggest a working memory impairment, the differences in correlational findings further indicate that the effects of the working memory impairment are primarily circumscribed to perseverations rather than extending to word generation. That is, other types of impairments appear to be the primary cause of the word generation difficulties observed in AD. Very plausible candidates are the lexical deficits that in AD affect the retrieval of the semantic and phonological features of words (Croot et al., 2000; Cummings et al., 1985; Huff et al., 1986) and that manifest themselves as word retrieval deficits. As recently reviewed by Indefrey (2011), there is mounting evidence that the posterior regions of middle and superior left temporal gyri play a pivotal role in lexical access for word production. This evidence strongly suggests that the word generation problems observed in AD stem from brain deficits affecting temporal regions. A corollary of this hypothesis is that perseverations are likely to be caused by brain deficits localized in partially distinct regions (possibly in frontal components). In essence, careful comparisons between the brain correlates of perseverations and word generation impairments may provide relevant cues for localizing the brain deficits associated with AD as well as the cognitive manifestations of such brain deficits.

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Although our investigation focused primarily on the perseverations in verbal fluency tasks, our results have ramifications for characterizing perseverations more broadly. Explanations of perseverations that are based on activation levels proved to be successful in a wide range of conditions – from spoken word production, to spelling, to action – in part because activation provides a powerful framework for describing cognitive processes and their impairments. Our results suggest that the perseverations that punctuate verbal fluency performance in individuals with AD cannot be explained in terms of activation; instead, they seem traceable to working memory deficits. While our results reveal a new form of perseverations, they contribute to underscore the fact that perseverations can have multiple causes, each of which reflects the functioning of specific cognitive mechanisms that, for some reasons, are malfunctioning in normal or pathological conditions.

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