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Negative prospective memory in Alzheimer's Disease: "do not perform that action"

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Abstract

Relatively to "standard" prospective memory, i.e., remembering to perform a future action, little is known about negative prospective memory, i.e., remembering not to perform a future action. This study investigated the latter ability in Alzheimer's disease (AD). AD participants and healthy older adults were asked to click on the keyboard or not to click on it when a cue word was encountered. Results showed more omissions (i.e., forgetting to click the keyboard when the instruction was to do so) in AD participants than in healthy older adults, suggesting a prospective memory deficit. Interestingly, more commissions (i.e., clicking the keyboard when the instruction was not to do so) were also observed in AD participants than in healthy older adults. Similar levels of commissions and omissions were observed in AD participants and in healthy older adults. Also, commissions and omissions were correlated with performance on an inhibition assessment task. Our findings reveal that AD is characterized by not only difficulty in the retrieval of recent information, but also difficulty to inhibit no-longer appropriate stimulus-response associations previously learned, suggesting a specific deficit of negative prospective memory in AD.

Keywords

Alzheimer's disease; commission; inhibition; negative prospective memory; prospective memory

For goal-directed behavior, we often develop plans that cannot be carried out immediately and which must be executed in a particular context or at a particular time [1]. This ability to remember a plan of action and perform an intended action at an appropriate point in the future has been termed prospective memory [2–4]. Prospective memory is engaged in everyday life and is highly relevant for maintaining functional independence [5–8]. For instance, prospective memory allows us to remember to pay bills, keep appointments, acknowledge friends' and relatives' birthdays, turn off appliances and take medications. Because prospective memory has been widely regarded as the ability to remember

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performing an action in the future, Pink and Dodson [9] coined the term “negative prospective memory” to refer to the ability to remember not to perform an action. As the present paper will emphasize, assessing negative prospective memory is of interest because impairment of this ability, as may be observed in patients with Alzheimer’s disease (AD), may result in performing inappropriate future actions (e.g., failing to remember to not take medication that is no longer clinically indicated, to not eat after a particular medication, to not call a friend/relative).

Prospective memory impairment has been recognized as a general problem for older adults, especially those with dementia [10]. Prospective memory impairment has been also found to negatively impact instrumental activities of daily living in patients with AD and increase their caregivers’ burden [11]. Not surprisingly, there is a body of research suggesting impairment of prospective memory in AD. For instance, Kinsella, et al. [12] assessed a simple and naturalistic task on which AD patients read aloud a short story (ongoing task) within which a target word (prospective remembering cue) was embedded on multiple occasions. Patients had to make a word substitution (prospective remembering) whenever the target word was encountered. Kinsella, et al. [12] observed significant impairment of prospective memory in AD. Similar findings were reported by Thompson, et al. [13] who asked AD patients to turn an electronic device on once per day to tap a response box that automatically appeared on the screen. Compromise of prospective memory was also observed by Maylor, et al. [14], who asked AD patients to say “animal” when an animal appeared in the film (event-based prospective memory task) or to stop a clock every three min (time-based prospective memory task); the authors observed impaired prospective memory in both tasks. In a study by Duchek, et al. [15], patients with very mild AD and control participants performed an event-based prospective memory task wherein participants responded to a specific word embedded in a general knowledge test. Results indicated that prospective memory was clearly impaired in the very mild AD patients relative to the control participants. Prospective memory in AD was evaluated by Farina, et al. [16] who invited very mild AD patients and control participants to perform blocks of category decision in which participants had to respond to a focal prospective targets (e.g., the word “orange”) and a nonfocal prospective targets (e.g., words that begin with the letter “o”). Results indicated that both focal and nonfocal prospective memory performances were impaired in the very mild AD patients relative to the control participants.

Interestingly, AD has been found to compromise prospective memory even more than retrospective memory (i.e., memory for information encountered in the past) [17, 18]. The compromise of prospective memory in AD has been attributed to impairment in frontal functions, especially working memory and executive function [19–26]; this relationship will be further explored in the present study, which among other goals, aimed to specifically assess the relationship between negative prospective memory and inhibition in AD.

Negative prospective memory was assessed by Pink and Dodson [9] who asked young healthy participants to either routinely respond to prospective memory cues (i.e., typical prospective memory) or to respond to these cues one time only (i.e., negative prospective memory). Participants who were instructed to routinely respond to prospective memory cues were vulnerable to commissions, i.e., they occasionally mistakenly performed prospective

responses. According to Pink and Dodson [9], commissions occur under the combination of three conditions: when an action is associated with an intention, when the action has been performed many times, and when people are distracted. Interestingly, Pink and Dodson [9] suggested that inhibitory failures cause commissions and that inhibitory control is required to prevent making a previously habitual prospective memory response (for a similar view, see [27, 28]. The inhibitory account was also proposed by Scullin, et al. [29] who asked younger adults and older adults to perform a typical prospective memory task, in which participants had to press a given key when they saw a given word (i.e., prospective cues). Participants later performed a lexical decision task, in which participants were instructed that they no longer needed to press the key when the previous cues reappeared (i.e., negative prospective memory condition). Results showed that older adults were more prone than younger adults to commissions (i.e., to press the key on the lexical decision task when the previous prospective cues appeared). Interestingly, inhibitory performance was lower in older adults who made commissions than in those who did not. The implication of inhibitory performance in prospective memory, as observed by Scullin, et al. [29], is relevant to our study because AD has been widely associated with inhibitory deficits (for reviews see [30, 31]. These deficits have been observed in studies using the directed forgetting task in which participants are typically instructed to remember or forget certain types of information for a later memory test [32]. Research using the directed forgetting method suggests that AD patients experience difficulties when they are asked to suppress no longer relevant information in working memory [33], semantic memory [34], and episodic memory [35, 36].

To better understand the concept of negative prospective memory, we can refer to research on negative imperatives (e.g., “do not grasp”) [37, 38]. For instance, Tomasino, et al. [39] explored the interaction between action and language by assessing whether the linguistic context, in which an action word occurs, influences motor circuitry activity related to the processing of action words. More specifically, the authors examined whether the presentation of hand action-related verbs as positive or negative imperatives (e.g., “do grasp” vs. “do not grasp”) modulates neural activity in the hand area of primary motor cortex or premotor cortex. To this end, the authors invited young subjects to read silently imperative phrases, in which both meaningful action verbs and meaningless pseudo-verbs were presented, and to decide whether these phrases made sense. Results showed that decisions time was significantly longer for negative, compared to positive, imperatives. At the neural level, cerebral activity was differentially decreased by action verbs presented as negative imperatives for the premotor and the primary motor cortex of both hemispheres. The authors concluded that negative imperatives modulate the neural activity within key areas of the motor system. Interestingly, the authors suggested that negative imperatives may inhibit motor simulation or motor planning processes.

The aim of this study was to investigate 1) whether commissions occur in AD patients on negative prospective tasks, 2) whether AD patients demonstrate similar levels of commissions and omissions, and 3) whether commissions are correlated with inhibitory impairment in AD. To this aim, AD participants and healthy older adults performed a task assessing both standard and negative prospective memory. We expected that AD participants would show more commissions than healthy older adults, and also expected to uncover a significant correlation between commissions and inhibitory performance in AD patients.

Method

Participants

The study included 24 participants with a clinical diagnosis of probable AD at the mild stage (17 women and 7 men; *M* age = 71.63 years, *SD* = 4.98; *M* years of formal education = 8.79, *SD* = 2.23, see Table 1 for cognitive characteristics) and 27 control older adults (17 women and 10 men; *M* age = 68.89 years, *SD* = 6.98; *M* years of formal education = 9.22, *SD* = 2.39). The AD participants were recruited from local retirement homes. The patients were diagnosed with probable AD dementia of the amnestic form by an experienced neurologist or geriatrician based on the National Institute on Aging-Alzheimer's Association clinical criteria (McKhann et al., 2011). The fact that all patients had the amnesic form of AD is confirmed by their performance on the neuropsychological battery. The control participants, who were often spouses or companions of AD patients, were independent and living at their homes. These participants were matched with the AD patients according to age [$t(49) = 1.59$, $p > .10$], sex [X^2 (1, $N = 51$) = .35, $p > .10$], and educational level [$t(49) = .66$, $p > .10$].

Exclusion criteria for both AD patients and control participants were: significant psychiatric or neurological illness, history of clinical depression, habitual alcohol or illicit drug use. All participants presented no major visual or auditory acuity deficits that would have prevented completion of study tasks. They freely consented to participate and were able to withdraw whenever they wished.

Cognitive characteristics—Cognitive characteristics of all participants were evaluated with a battery tapping general cognitive functioning, working memory, verbal fluency, inhibition, and depression. General cognitive functioning was assessed with the Mini Mental State Exam (MMSE) [40]. For working memory assessment, participants had to repeat a string of single digits in the same order (i.e., forward span) or in the inverse order (i.e., backward span). Verbal fluency was assessed with a task on which participants had two minutes to generate as many words as they could beginning with the letter P. Proper nouns and variations on words (e.g., “psychology” and “psychologist”) were not allowed. Score was the number of correctly generated words. Inhibition was assessed with the Stroop task [41]. This task consisted of three subtests: word reading, color naming, and color-word interference. In the word reading subtest, participants had to read 100 words printed in black ink, all words naming colors. In the color naming subtest, they had to name the color of 100 colored ink squares. In the color-word interference subtest, participants had to name the color of 100 color-words printed in incongruously colored ink (for instance, the word “red” was written in blue). Inhibition score referred to the completion time for the interference condition minus the average completion time for word reading and color naming. For assessment of depression, the Hospital Anxiety and Depression Scale [42] was administered. This self-report scale consists of seven items on a four-point scale from 0 (not present) to 3 (considerable). As recommended by Herrmann [43], the cut-off for definite depression was set at > 10/21 points. Neuropsychological and clinical scores for study participants are summarized in Table 1.

Procedures

The prospective memory task was designed to be simple enough to be achievable by AD participants so that to avoid a floor effect. The task was based on the procedures by Kinsella, et al. [12] as our participants were required to read aloud a short text (ongoing task) within which a target word was associated with performing an action (prospective memory) or not performing that action (negative prospective memory).

In order to mimic everyday life situations of negative prospective memory (e.g., when a physician asks a patient to no longer take a medication), participants were briefed in advance that the task assessed their ability to remember not to perform a given future action. Participants were also instructed that they had to read aloud a text about characteristics of cats, and that the text would be presented on a laptop screen. To ensure that the participants fully understood the instructions, a training session was conducted. First, the experimenter instructed participants that they had to read aloud a phrase and click the spacebar if that word “cat” was encountered. After this task was completed, the experimenter instructed participants that they had to read aloud another phrase, but they should not click the spacebar (or any other key) if the word “cat” was encountered.

After the training session was completed, the testing session took place. The participants read a longer text (336 words) that was divided into six similar-length paragraphs, each paragraph contained four times the word “cat”. At the beginning of the first paragraph, the experimenter asked participants to click the spacebar each time word “cat” was encountered. After the first paragraph was read, he asked them not to click the spacebar if that word was encountered. The switch between “click” and “do not click” was repeated three times so participants alternated between three prospective paragraphs and three negative prospective ones. Two dependent variables were recorded: commissions and omissions. The commissions, an index of negative prospective memory, referred to the number of times that participants mistakenly clicked the spacebar (while they were instructed not to do so); the maximum score was 12 as the target word was encountered 12 times on the three negative prospective paragraphs. The omissions, an index of prospective memory, referred to the number of times that participants omitted to click the spacebar (while they were instructed to do so); the maximum score was 12 as the target word was encountered 12 times on the three positive prospective paragraphs.

Results

We compared differences on commissions and omissions between the two populations (i.e., AD patients vs. healthy older adults). We then assessed correlations between commissions, omissions, and inhibition (based on Stroop test) in the two populations. Owing to the skewed distribution of data, non-parametric tests were conducted. Between-group comparisons were performed using the Mann-Whitney U test and within-group comparisons were performed using the Wilcoxon signed rank test. Besides statistical significance, we also calculate the effect size for non-parametric tests following recommendations by Rosenthal and DiMatteo [44], and Ellis [45]. An effect size $d = .2$ can be considered small, $d = .5$ represents a medium effect size and $d = .8$ refers to a large effect size [46]. Non-parametric correlations

were calculated with Spearman correlations. For all tests, the level of significance was set as $p \leq 0.05$, and p values between 0.051 and 0.10 were considered as trends.

More commissions and omissions in AD participants than in healthy older adults

Scores are depicted in Figure 1. Relative to healthy older adults, AD participants showed more commissions ($Z = -2.85$, $p < .01$, Cohen's $d = .87$) and omissions ($Z = -2.76$, $p < .01$, Cohen's $d = .81$). Similar commissions and omissions were observed in AD participants ($Z = -1.17$, $p > .1$, Cohen's $d = .33$) and healthy older adults ($Z = -.59$, Cohen's $d = .17$).

Correlations between commissions, omissions, and inhibition

As depicted in Table 2, significant correlations were observed between commissions, omissions, and inhibition in both populations.

For convenience, we assessed correlations between 1) commissions and working memory (forward and backward spans) and 2) omissions and working memory, no significant correlation was found in any population ($p > .1$). We also assessed correlations between 1) commissions and verbal fluency and 2) omissions and verbal fluency, no significant correlation was found in any population ($p > .1$).

Discussion

This study investigated negative prospective memory, i.e., the ability to remember not to perform a future action, in AD. As expected, our findings demonstrated more commissions in AD participants than in healthy older adults, i.e., AD participants mistakenly clicked the spacebar more often than control participants, when the instruction was not to do so. Interestingly, commissions and omissions were significantly correlated with inhibitory performance in both groups. We also found that AD participants made more omissions than healthy older adults, i.e., AD participants forgot to click the spacebar more often than control participants, when the instruction was to do so. In both populations, similar levels of commissions and omissions were observed.

A large body of literature has suggested compromise of future thinking in AD [47–50], and more specifically, compromise of prospective memory in the disease [11–18, 51]. Our findings are in agreement and further extend this literature by demonstrating one additional element of impaired future thinking in AD. Impaired negative prospective memory means that AD patients may not only perform an inappropriate future action (e.g., take a medication at the wrong time), but may also perform no-longer appropriate future actions (e.g., take a medication that is no longer indicated). In the experimental paradigm we employed in this study, participants were required to first develop a habitual association (i.e., click the spacebar once the target word appeared) then to inhibit this habitual association (i.e., not click the spacebar). The paradigm was tailored to assess the difficulty to inhibit no-longer appropriate future actions, which may explain the significant correlations between commissions and inhibitory performance we observed.

The relationship between commissions and inhibitory performance, as observed in the present study, can be viewed under the broader attribution of memory compromise to the

inhibitory decline in aging. According to May and Hasher [52], older adults experience difficulties in suppressing the activation of irrelevant thoughts and stimuli, and consequently, their memory becomes overloaded with task-irrelevant information. This account has been supported by studies showing that older adults are prone to interference in verbal working memory, visuospatial working memory, and even implicit memory [52, 53]. Regarding AD, studies have shown difficulties in suppressing no longer relevant information in working memory [33], semantic memory [34], and episodic memory [35, 36]. Therefore, AD patients tend to maintain information from past task performance, even when this information is no longer relevant for the current situation [31]. This may explain why our AD participants demonstrated difficulties in inhibiting clicking on the spacebar when this action was no-longer required.

Unlike inhibition, no significant correlations were observed between prospective/negative prospective memory and working memory. These findings reflect a study by Schnitzspahn, et al. [54] who used a structural equation model to find that prospective memory compromise in normal aging was not significantly related with working memory. In a similar vein, Zeintl, et al. [55] found that, in normal aging, prospective memory compromise is independent of decline in working memory or speed of processing. In our study, the absence of relationship between prospective/negative prospective memory and working memory can be interpreted as an index of independence between the ability to remember to perform or not to perform an action and the ability to retain a limited amount of verbal information for a brief period of time (i.e., verbal working memory). Similarly to working memory, no significant correlations were observed between prospective memory/negative prospective memory and verbal fluency. Verbal fluency has been considered as an ability reflecting shifting (the ability to switch between clusters) [56–59]. Thus, prospective and negative prospective memory, at least as assessed in our study, seem to be independent of shifting between our instructions to click (i.e., prospective memory) and not to click the keyboard (i.e., negative prospective memory). Together, prospective and negative prospective memory seem to be more related to inhibition than to working memory or shifting.

Another finding in our study was that omissions and commissions were similarly correlated in AD participants as well as in healthy older adults. Besides illustrating at the clinical level how AD patients can be similarly prone to omissions and commissions, this finding has important theoretical implications, suggesting a functional association, but also dissociation, between prospective memory and negative prospective memory. In our view, both abilities require remembering to respond to cues at some point in the future. However, one main dissociation is that prospective memory requires remembering to perform an action whereas negative prospective memory requires remembering not to perform any action. The association and dissociation between prospective memory and negative prospective memory can also be framed using the inhibition account. Prospective memory requires inhibition of appropriate action after inappropriate cues (e.g., remembering to take the medication after lunch and not after breakfast), whereas negative prospective memory requires inhibition of inappropriate actions (e.g., remembering not to take the medication after the lunch). This view represents a cohesive theoretical framework that includes both prospective memory and negative prospective memory.

To understand the neural basis of negative prospective memory, researchers can build on studies on negations. Negations have been found to both increase and decrease sensorimotor areas [60], and sentential negations have been found to transiently reduce the access to mental representations of the negated information [38]. Indeed, it has been demonstrated that activation in left fronto-parietal regions and the effective connectivity in concept-specific embodied systems are reduced in the case of action-related negative sentences [38]. Also, activations in the hand region of the primary motor and premotor cortices have been found to decrease for negative hand-action-related imperatives [39]. The premotor cortex has been also found to be activated, rather than reduced, by negations in research involving a sentence-picture verification task [61]. According to the two-step simulation hypothesis of negation processing [62], when people process negations, they generate a simulation of the negated state of affairs, and a simulation of the actual state of affairs. Together, this research suggests that negations activate the sensorimotor cortex depending on whether the simulation the corresponding content of an event has or not been blocked. In our view, research on negations can constitute a basis for the understanding of neural basis of negative prospective memory.

Our procedures were primarily based on event-based design, according to which participants had to execute, or not, an action following a previously specified cue-word occurrence. Future research can further develop this paradigm by implementing a time-based design according to which participants would be asked execute an action at a specific point in time. Such a paradigm would be interest, as age effects are particularly marked on time-based prospective tasks, which posit greater demands for self-initiated processing involved in time-based tasks, which lack any external reminders [63, 64]. Another issue to be considered by future research is potential strategies for rehabilitation of negative prospective memory in AD. In a study in patients with severe chronic traumatic brain injury, participants were asked to create a mental image representing the association between a prospective cue and an intended action; the study showed a positive effect of this strategy on prospective memory [65]. Similar findings were observed in patients with mild cognitive impairment [66]. Future research can assess these rehabilitation strategies on negative prospective memory.

To summarize, relatively to the substantive body of research on “standard” prospective memory, little research has focused on negative prospective memory [9, 67, 68]. Our paper extends the latter field of research by demonstrating that deficits in inhibitory processes and negative prospective memory are an important component of AD, which needs to be taken into account in neurospsychological interventions.

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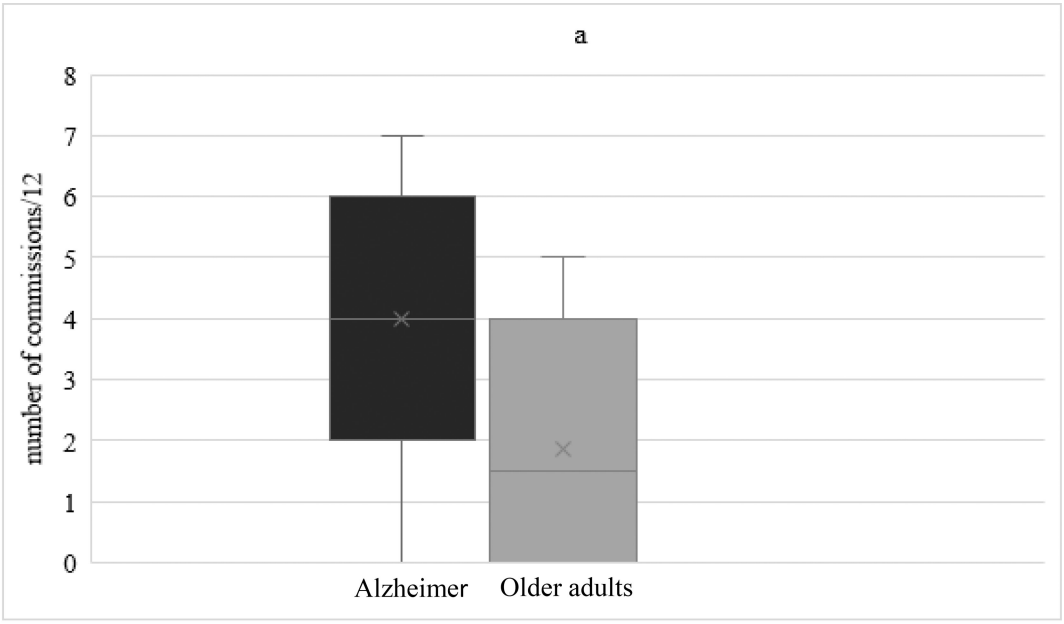

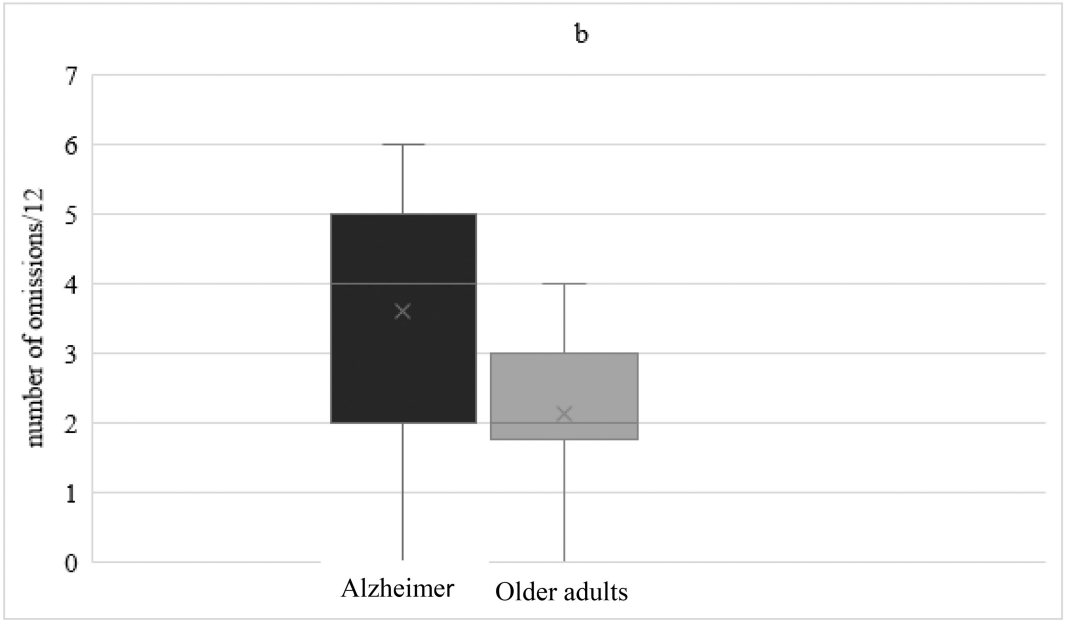

Figure 1.

Boxplots of rate of commissions (negative prospective memory errors, Figure 1a) and omissions (prospective memory errors, Figure 1b) in Alzheimer's disease and control participants.

Table1

Cognitive characteristics of Alzheimer's disease (AD) patients and control participants

	Task	AD *n* = 24	Older adults *n* = 27	Effect size
General Cognitive functioning	Mini-Mental State Examination (MMSE)	21.38 (1.81) ***	27.74 (1.48)	3.93
Working memory	Forward span	5.13 (1.03) ***	6.70 (1.54)	1.21
	Backward span	3.75 (1.15)*	4.74 (1.72)	.68
Verbal fluency	Letter "P"	16.75 (5.88) ***	23.22 (4.50)	1.26
Inhibition	Stroop	58.13 (9.59) ***	35.78 (9.65)	2.36
Depression	HADS	8.21 (1.28)*	6.74 (2.44)	.75

Note. Standard deviations are given between brackets; the maximum score on MMSE was 30 points; performances on the forward and backward spans referred to number of correctly repeated digits; the fluency score was the number of correctly generated words; scores on the Stroop referred to reaction time; the cut-off on the HADS (Hospital Anxiety and Depression Scale) was > 10/21 points;

differences between groups were significant at: ** $p < .01$,

*** $p < .001$.

Table 2

Correlations between commissions, omissions, and inhibition in Alzheimer's disease (AD) patients and control participants

		1. Commissions	2. Omissions	3. Inhibition
Alzheimer	1. Commissions	-		
	2. Omissions	.58, $p < .01$ CI [.23, .80]	-	
	3. Inhibition	.49, $p < .01$ CI [.11, .74]	.47, $p < .05$ CI [.09, .73]	-
Older adults	1. Commissions	-		
	2. Omissions	.54, $p < .01$ CI [.20, .76]	-	
	3. Inhibition	.51, $p < .05$ CI [.16, .74]	.51, $p < .05$ CI [.16, .74]	-

We assessed correlations between 1) commissions and working memory (forward and backward spans) and 2) omissions and working memory, no significant correlation was found in any population ($p > .1$). We also assessed correlations between 1) commissions and verbal fluency and 2) omissions and verbal fluency, no significant correlation was found in any population ($p > .1$).