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Title: Mediating Role of Inhibition Control on the Relationship Between Age and Memory Changes Throughout Adulthood: An Aging Developmental Study in Iran

Running title: Aging, Memory, Inhibition

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Abstract

Purpose: This study aims to investigate the age trends of various types of memory including priming, working memory (WM), episodic memory (EM), and semantic memory (SM) from adulthood to old age, as well as the mediating role of inhibition control (IC) in the relation between age and memory.

Methods: 796 healthy adults aged between 25 and 83 years participated in this cross-sectional study and were assessed using a comprehensive battery of memory, digit span, and the Stroop Color-Word tests

Results: The scatter plot with LOESS fitting line showed EM and WM declined steadily from age 25, SM increased mildly to 55 followed by a decrease, and priming did not change with age. The mediating analysis and bootstrap test showed that IC mediated the relation between age and EM and SM ($\beta = -0.097$, $P=0.002$), and SM ($\beta = -0.086$, $P=0.001$).

Conclusions: Our results showed that age and various types of memory had different trajectories and IC is a fundamental mediator in explaining age related decline in SM and EM.

Keywords: Episodic Memory, Semantic Memory, Age-Related Trends, Inhibition Control

Introduction

The continuous increase in life expectancy has led to profound changes in population structure, with an ongoing growth of the elderly population (Oeppen & Vaupel, 2002; Lutz, Sanderson & Scherbov, 2008). Globally, the number of individuals aged 65 years or over is estimated to grow to one billion by 2030 (Dobriansky, Suzman & Hodes, 2007). With this growth, Poor cognitive function probably is the most disabling condition in elderly people (Singh-manoux et al., 2012). While there is ample evidence that progressive memory decline is a normal component of the aging process (Salthouse, 1991; Boyle et al., 2013), there are considerable differences between individual trajectories and the onset of age-related memory decline (Finch, 2009; Finch, 2009; Salthouse, 2009).

According to the multiple memory systems theory proposed by Tulving (1985), human memory is divided into various subtypes, namely semantic memory (SM), episodic memory (EM), working memory (WM), as well as priming. The current literature suggests that the intensity of cognitive decline and the age of onset differ for each subtype. For instance, EM is highly age-sensitive and thus experiences the most significant age-related decline (Bäckman, Small, Wahlin, & Larsson, 2000; Nyberg et al., 2003; Rönnlund, Nyberg, Bäckman & Nilsson., 2005; Vieweg, Stangl, Howard & Wolbers, 2015). However, there is some discordance between studies about the age of onset for decline. While some studies suggest that it is likely for those who are 60 years of age or younger to begin experiencing EM decline (Schaie, 2005; Salthouse, 2009), another study found no evidence of such decline occurring before the age of 60 (Hedden & Gabrieli, 2004). Similar to EM, WM ~~also~~ declines with age (Hultsch, Hertzog, Small, McDonald-Miszczak & Dixon, 1992; Park et al., 2002, Klencklen, Lavenex, Brandne & Lavenex, 2017). However, this decline differs based on the type of information being processed and remembered, with visuospatial WM declining earlier than verbal WM (Chen, Hale & Myerson, 2003). Unlike EM and WM, SM exhibits stability and continued improvement until at least age 60, only slightly declining after age of 75 (Salthouse, 2009; Ofen & Shing, 2013). Despite this stability, aging still compromises the ability to access the information stored in SM (Craig & Bialystok, 2006). Studies that considered priming as a type of implicit memory did not support any remarkable age-related decline (Rybash, 1996; Fleischman, 2007). The results from the Betula project demonstrate a significant decline in EM beginning around the age of 35, as well as a decline in SM following an initial improvement up to ages 55-60, also a constant trend in WM was also observed (Nilsson, 2003). In the mentioned

project, age was the only variable that could significantly predict EM, but not SM performance, when the effects of education and intelligence were controlled (Nyberg, Bäckman, Erngrund, Olofsson & Nilsson, 1996).

There are various theories that explain how aging may cause a decline in cognitive functions (Birren, 1965; Salthouse, 1996; Craik & Lockhart, 1972). One of the most reliable theory is the inhibitory theory of memory deficits with age (Hasher & Zacks, 1988). This theory states that inhibitory control (IC), or the ability to filter out unnecessary stimuli, plays a critical role in human memory (Hasher & Zacks, 1988; Hasher, Lustig & Zacks, 2007). Age related decline in attention control is associated with more distractibility and lower focused attention, which in turn causes memory decline, especially in EM (Park & Festini, 2017). Therefore, it is important to investigate this mediating role of IC in the relationship between age and memory.

There is inconsistency in the current literature on the role of IC as a mediator between age and memory. While some studies suggest that poor IC, especially in old age, is an indicative factor for the decline in WM performance (Head, Rodrigue, Kennedy & Raz, 2008; Fabiani, 2012), others fail to support this result (Salthouse, Atkinson & Berish, 2003; Borella, Carretti & De Beni, 2008). There is also an evidence that this role depends on the type of memory tasks; in more active and complex ones, the mediator role is more pronounced (Van Gerven, Van Boxtel, Meijer, Willems & Jolles, 2007). Spaan (2015) has also found that IC mediates the relationship between age and EM, but does not have an effect on SM. On the other hand, the results of Dias and colleagues' study (2018) show that the relationship between IC and memory depends on age, and IC may be a compensatory mechanism for impaired memory in older people.

To remain in line with previous studies, it is assumed that aging leads to the most significant decline in EM and WM, causes a more decline in SM, but does not impact priming. This study seeks to investigate the general age trends of various types of memory including priming, SM, EM, and WM, as well as the mediating role of IC in age-related memory decline. The data used in present study were obtained from the "Sepidar" project (Hatami et al., 2018).

Materials and Methods

Participants

This study was conducted on 796 healthy adults (without cognitive deficits including mild cognitive impairment, Alzheimer and dementia) between the ages of 25 and 83 years. Participants

included in this study were a subgroup from the project “Sepidar,” which is a long-term study at the University of Tehran.

All participants were assessed using the Mini-Mental State Examination (MMSE), SCWT, the Digit Span test (forward and backward), and a comprehensive computerized battery of memory tasks (based on Sepidar battery; Hatami et al., 2018). Assessments were done in person by a licensed clinical psychologist (Mottaghi Ghamsari, A) at the Cognitive Rehabilitation Laboratory at the University of Tehran. Data were collected annually over the course of 3 years, from September 2014 to September 2017.

The participants included in the study were able to speak and write Farsi. Those who had mild cognitive impairment according to the MMSE test (A score of 23 or lower, Ansari, Naghdi, Hasson, Valizadeh & Jalaie, 2010), reported auditory or visual impairments, or had a history of serious brain disorders (e.g., stroke, traumatic brain injury) were excluded from the study. All participants gave informed written consent prior to the completion of the assessments. In this consent, it was made clear that participation was voluntary and could be stopped at any time. It was also communicated that the demographic and cognitive testing would be conducted in two 1-to-1.5-hour sessions, and the data would be stored in an unidentifiable and confidential format. The participants were fully debriefed at the end of the study. This study has received the approval of the research ethics committee of the Iran University of Medical Science (IUMS).

Measures

Demographic Information

Age, gender, education (years of schooling), marital, and health status (including medical history and physical symptoms) of the participants were collected by self-reporting.

MMSE

A general cognitive screening was conducted using the MMSE. The MMSE consists of 11 questions that are commonly asked when screening for cognitive deficits in the domains of orientation, WM, attention, delayed recall, and language (Folstein, Folstein & McHugh 1975). The total score for the MMSE ranges from 0 to 30, with a higher score indicating greater cognitive performance. The Persian version of the MMSE, which has received validation from Ansari and colleagues (2010), was used in this study.

Betula Tests

In this study, the translated version of the Betula battery developed by Nilsson and colleagues (1997) was used (Hatami et al., 2018). This battery is composed of different tasks that assess various types of memory including priming, SM, and EM. The present analyses were based on six episodic tests, one priming test, and five semantic tests using this battery. The testing procedures are briefly described below.

Episodic tests. Face-name recognition: Participants were shown 16 images of children along with their full names, and were asked to remember the children's last names. Roughly 30 minutes into the session, participants were then presented with 24 faces (12 target and 12 distractor faces), and were asked to distinguish the familiar images from the distractors. In the recognition section of this test, the same 16 images of children were shown to the participants once again, and they were instructed to select the first and last names of each one from a list of four options.

Recall of actions: In this test, participants were asked to memorize and recall two lists of 16 imperative sentences. One list was enacted by the participant during encoding, while the other list was only encoded by the participant auditorily. The number of sentences recalled from each list was used as the quantitative measure in data analyses.

Cued recall of nouns: Participants were provided with eight different noun categories (e.g., stationery, furniture, kitchenware, clothing, edibles, toy, tool, and sewing accessory), each consisting of four nouns. Using this semantic cue, they were asked to recall the nouns of the imperative sentences provided to them in the previous test. The number of nouns recalled correctly was used in data analyses.

Recognition and cued recall of nouns: Participants were provided with a series of nouns and asked to identify the ones that were used in the sentences provided in the previous test. They were then given a series of verbs and asked to recall the noun that the verb accompanied in the provided sentences. They were then asked to determine whether or not the verb was part of the sentences in the enactment category in the previous test.

Word recall under divided and focused attention: In this test, participants were given a list of 12 words and were asked to recall the words immediately after listening. Participants had to complete this word recall under four different conditions: with the concurrent task of sorting cards during encoding only, during retrieval only, during both encoding and retrieval, and during neither encoding nor retrieval. While conducting the concurrent task of sorting cards, the participants had

to use divided attention, without conducting this task they were able to use focused attention. The number of words recalled under each condition was used in data analyses.

Recollection of completed activities: Following the evaluations described above, participants were asked to describe all the tests they had completed during the session. The number of tests that they were able to recall accurately served as the quantitative measure used in analyses.

Priming test. Word stem completion: In this test, 32 two-letter word stems were presented to participants, who were asked to identify the first family name beginning with those word stems that came to their mind. Sixteen of these stems were from the last names presented in the face-name recognition test, while the remaining were distractors. The number of mentioned priming targets (presented family names in the face-name recognition test) were entered as a measure in analyses.

Semantic tests. Word fluency (WF): In this assessment, participants were presented with five WF tests. In each of the tests, they were given one minute to list as many words as they could in a specific category. The five different categories includes; words beginning with the letter “a”, five-letter words starting with the letter “t”, four-letter words beginning with the letter “b”, professions beginning with the letter “m”, four-letter bird names.

The number of words generated correctly in each test was the index of WF and entered in analyses. To reduce the number of variables of various types of memory, an exploratory factor analysis was used by Hatami and colleagues (2018). This analysis yielded six factors labelled in line with Betula (Nilsson et al., 1997) including Sentences Memory (SM), Recall Attention (RA), Action Memory (AM), Name Recognition (NR), WF, and priming. Cronbach's alphas for SM, RA, AM, and NR were 0.91, 0.84, 0.76, 0.51, 0.62 respectively. Because priming is measured by an item, Cronbach's alpha is not calculated for it. Also, a factor-based composite score for the EM score using SM, RA, AM, and NR was created (Hatami et al., 2018).

The Psychology Experimental Language Building (PEBL) Tests

In the present study, the translated version of the forward and backward digit span tests (for measuring WM) and SCWT (for measuring IC) from PEBL test battery (Muller & Piper, 2014) was used (Hatami et al., 2018). PEBL is a free and open-source battery with approximately 70 behavioral tests that is used in psychological and neuropsychological research.

Forward and backward digit span tests: In the forward digit span test, a series of numbers from 0 to 9 were presented randomly to participants both auditory and visually. The length of first two

chain was three digits. The participant was asked to remember the numbers that he/she had heard and seen, in the same order. The chain length would be increased by one number if one of two attempts was correct. This process continued until participants could not recall or incorrectly recalled both attempts of a chain or until he/she recalled 10-digit chains (0 to 9) correctly. The backward digit span test is similar to the forward test; except, that the chain of digits must be recalled in a reverse order. In each test, the final span of digit served as a measure in analyses.

SCWT: In this test some words, including 4 color names (blue, yellow, green, red) and neutral words, sequentially appeared on the screen in one of the four colors mentioned. In each attempt, participants were asked to press the key corresponding to the text color as quickly as possible regardless of the content of it (key 1 for red, key 2 for blue, key 3 for green, and key 4 for yellow). There were three conditions: neutral condition with neutral words, congruent condition where the text color and meaning of the color name were compatible, and incongruent condition where the text color and meaning of color name was incompatible. The first two conditions did not need IC, whereas in incongruent condition the participants had to do a less automatic test (naming the font color) while inhibiting interference coming out from a more automatic test (reading the word). An index for IC was the score of incongruent reaction time and entered in analyses.

Data Analysis

Descriptive analysis was used to describe the demographic characteristics of the test subjects. ANOVAs and post hoc tests were used to compare memory performance between age groups. To investigate the age trends of various types of memory, the scatter plot with a LOESS fitting line (a method for fitting a smooth curve between two variables) was used. Finally, to measure the mediating role of IC in age-related memory changes, mediating analysis and the bootstrap test were used. The data were analyzed using SPSS (version 26; IBM, Armonk, NY, USA). The data for this project have been published and is accessible on the Open Science Framework under the title “Age Trends of Memory with Mediating Role of Inhibition.”

Results

Descriptive Data

The initial sample consisted of 819 participants, 796 (527 females, 266 males, and three missing gender information) of whom completed the memory assessment. The average age of the participants was 48.39 ± 14.24 years. The participants' demographic information is shown in Table 1. Assessment of cognitive functions in this study was performed in two sessions. In the first

session, EM and SM items were measured. In the second session, digit span tests and the Stroop Color-Word Test (SCWT) were administered. A remarkable number of participants did not attend the second session; thus, data from 587 participants for digit span tests and from 563 participants for SCWT were analyzed. The participants were then divided into five age groups: 25 to 34 years, 35 to 44 years, 45 to 54 years, 55 to 64 years, and 65 years and older.

Age Trends of Various Types of Memory

We performed one-way ANOVA for each memory test, using memory score as the outcome variable and the age group as the factor. Following ANOVA, significant pairwise comparisons were further analyzed with Tukey post hoc tests. In order to simplify the comparison between age groups, participants were divided into three groups: younger adults (aged 18–39), middle-aged adults (aged 40–64), and older adults (aged 65–88). The results of the ANOVA are summarized in Table 2.

One-way ANOVA revealed a significant age effect on all types of memory, and scores differed across the three groups. Pairwise comparisons confirmed that the memory scores were significantly higher for the younger adults than the middle-aged adults and older adults. Also, middle-aged adults significantly performed better than the older participants. The effect size for EM ($\eta^2 = .348$) is larger than that of WF ($\eta^2 = .074$), indicating that EM is influenced more by age.

The age trends in the decline of various types of memory from adulthood (25 years) to old age (83 years) have been represented by a scatter plot with a LOESS fitting line. Due to differences in years of schooling, scores of each type were corrected by regressing them on education and using residuals. As seen in Figure 1, there was a gradual decline in SM and RA from 25 to 80 years, with a steeper slope after 50 years. In AM, a mild and monotonous decline was seen in adulthood. In these types of memories, the decrease in the slope accelerated after 60 years. Moreover, NR experienced a steady decline. According to the composite score of EM, it declined steadily with a mild slope up to 50 years, and memory decline occurred more rapidly thereafter. Similar to EM, WM also decreased from 25 to 80 years. The declining slope of this type of memory was relatively mild and steady. The age trend of WF was different from EM. This memory had a mild improvement up to 55 years, then experienced a much more rapid decline. Priming scores did not significantly change with increasing age. As seen, the plots did not change significantly after taking the effect of varying education levels into account.

The Mediating Role of IC in Memory Changes

In order to determine the direct effects of aging on memory, a partial mediation model was created for each memory type. The strength of each relationship is shown in Figure 2. On the basis of the literature, this model hypothesized that aging would have a negative effect on IC, which in turn would have a negative effect on memory. Excluding NR, all tested indirect effects were significant. In this model age negatively influenced IC ($\beta = -0.561$, $P < 0.01$), and impairment in IC affected SM ($\beta = -0.087$, $P = 0.001$), AM ($\beta = -0.075$, $P = 0.003$), RA ($\beta = -0.097$, $P = 0.002$), EM ($\beta = -0.097$, $P = 0.002$) and WF ($\beta = -0.086$, $P = 0.001$). The regression weights of each structural path are presented in Table 3.

Discussion

The aim of this study was to investigate the age trends of various types of memory in a sample of Iranian adults. The results showed that all types of memory changed significantly with age, with priming being the only exception. These differences were more pronounced in EM and WM, and less significant in WF. EM declined in all age groups, with the most significant decrease occurring after 55-60 years. Similar to EM, WM also declined in all age groups. Performance in WF (SM index) improved up to 55 years and then began to decline. Priming remained nearly constant and did not decline from adulthood to old age. These findings are in line with and validate the current literature (Nyberg et al., 2003, 2012; Bäckman et al., 2000; Rönnlund et al., 2005; Schaie, 2005; Park et al., 2005; and Hultsch et al., 1992).

The variance in the effects of aging on SM compared to EM and WM may be explained by their infrastructural components. EM and WM are based on fluid intelligence (Nyberg et al., 1996) whereas SM is a type of crystallized intelligence scale (Small, Dixon, & McArdle, 2011). Various studies have shown that fluid intelligence declines from young age to old age, while crystallized intelligence remains steady and may even grow with age (Horn & Cattell, 1967; Willis & Baltes, 1980; Zaval, Li, Johnson & Weber, 2015). The unique nature of priming may also help explain its characteristic stability over the lifespan. SM, EM, and WM are forms of declarative memory (Moscovitch, Nadel, Winocur, Gilboa & Rosenbaum, 2006). Declarative memory consists of memory for events and facts that can be explicitly stored and retrieved (Tulving, 1985). While different types of declarative memory are related to each another, as well as to other cognitive functions such as verbal processing speed and verbal comprehension, which are age-related, priming has no relation to declarative memory nor to other cognitive functions (Hultsch, Masson

& Small, 1991). Since priming differs from other types of memory, it can be implied that its underlying mechanisms and related process are also different.

In addition to investigating the changes in human memory with increasing age, this study also sought to investigate the mediating role of IC in the relationship between age and memory. The results showed that IC mediates the effect of aging on both EM and WF. This finding is in line with some previous studies, which illustrated that the intermediate role of IC in memory and aging was significant to varying extents (Head et al., 2008; Bäuml, Pastötter & Hanslmayr, 2010; Fabiani, 2012; Spaan, 2015). However, other studies found this role to be either negligible or does not exist (Salthouse et al., 2003; Borella et al., 2007).

EM relies on the processes of WM, in which the ability of suppressing unrelated thoughts is important (Plancher, Gyselinck & Piolino, 2018). The inhibitory theory of age-related memory deficit, proposed by Hasher and Zacks (1988), suggested that IC reduces the activation of off-goal-path thinking levels in WM and facilitates sufficient memory processing. The significant relationship between IC and memory is in line with the perspective that successful memory retrieval depends on the ability to ignore irrelevant information and to focus on the target information (Park & Festini, 2017). IC is largely related to WM, controls the flow of information within WM, acts to prevent unrelated information from entering WM, and suppresses information that is no longer relevant (Hasher & Zacks, 1988; Zacks & Hasher, 1994).

Elderly people who are impaired in IC are easily distracted, and more likely to be focused on background information instead of the target information that they are presented with (Rabbitt, 1965; Diamond, 2013). Poor IC leads to poor selective attention and confusion of WM, which in turn limits the capacity of absorbing new information. In addition, this mental disorganization leads to competition during memory retrieval, leading to increased processing time, data entry rates, and memory interference in elderly people (Park & Festini, 2017).

However, it seems that the mediating role of IC in explaining age-related memory decline depends on the features of the task. While the role of IC is evident in tasks that require WM processing capacity, it is not apparent in tasks that depend on WM storage capacity (Van Gerven et al., 2007; De Bruin & Sala, 2018). Aging may be associated with selective rather than general reduction in IC, and there are multiple inhibitory mechanisms. For example, inhibitory mechanisms subserved by the dorsal-ventral visual pathways that are equivalent in young and old adults, and the

mechanisms subserved by the frontal lobe that show age-related deficits (Kramer et al.,1994; Reymermet & Gade, 2017).

When analyzing the collected data, it is crucial to consider the limitations that may have compromised the accuracy of this study. Firstly, since this study was cross-sectional, did not assess the changes in memory function of the participants over time. Given that a longitudinal study is more sensitive to these changes, conducting such a study may provide a more reliable and accurate picture of the age trends of memory over time. Additionally, due to the voluntary nature of sampling, most of the participants were women and had post-secondary education. Thus, the present results must be interpreted and generalized with caution.

In conclusion, it was found that the aging process has a unique impact on each type of memory. While EM and WM were found to be highly age-sensitive, SM was found to experience a less significant impact from the aging process. Priming, on the other hand, did not exhibit age sensitivity. The differences in the infrastructural components of memory types can support and explain the results of this study. Moreover, the results confirm the mediating role of IC in the relationship between increasing age and the decline in EM and WF. This study provides valuable insights regarding the changes of memory types in adulthood as well as the influence of IC in age-related memory changes.

Disclosure Statement

There is no conflict of interest reported by the authors.

Authors' contribution

Mottaghi Ghamsari wrote the paper, Hatami designed the procedure, Karsazi contributed to the analysis, Kormi-Nouri edited the paper, and Mottaghi Ghamsari ran the experiment.

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Tables

Table 1. Characteristics of the study participants

Variables	(N= 796)
Age range (n (%))	
years $\leq$ 34	188 (23.6)
35-44	87 (10.9)
45-54	191 (24.0)
55-64	220 (27.6)
years $\geq$ 65	102 (12.8)
Missing	8 (1)
Gender (n (%))	
Female	527 (66.2)
Male	266 (33.4)
Missing	3 (0.4)
Education level (n (%)) (years of schooling)	
High school diploma and below: (years $\leq$ 12)	166 (20.9)
Bachelor's degree: (13-16 years)	215 (27.0)
Master's/Doctoral degree: (years $\geq$ 17)	202 (25.4)
Missing	213 (26.8)
Marital status (n (%))	
Married	513 (64.4)
Single	158 (19.8)
Divorced	29 (3.6)
Widowed	29 (3.6)
Missing	67 (8.4)

Table 2

Descriptive information and analysis of age group differences in memory performance tasks.

SM: sentences memory, AM: action memory, RA: recall-attention, NR: name recognition, EM: episodic memory, WF:

	Young (n = 227)		Middle (n = 459)		Old (n = 102)		ANOVA on group difference			Significant pairwise comparisons
	M	SD	M	SD	M	SD	F	p	η^2	
SM	.519	.790	-.090	.841	-.774	.805	93.25	.001	.192	Y > M > O
AM	.414	.689	-.050	.752	-.740	.832	86.30	.001	.180	Y > M > O
RA	.593	.614	-.119	.573	-.810	.563	224.61	.001	.364	Y > M > O
NR	.418	.762	-.089	.639	-.529	.505	82.12	.001	.173	Y > M > O
EM	.507	.533	-.093	.529	-.733	.515	209.95	.001	.348	Y > M > O
WF	.190	.586	.018	.729	-.445	.591	31.41	.001	.074	Y > M > O

word fluency, Y: Young, M: Middle, O: Old

Table 3. Mediation effects of inhibition decline on the relationship between age and memory types (indirect effects)

		Age	Age	Age	Age	Age	Age
		↓	↓	↓	↓	↓	↓
Path		Inhibition	Inhibition	Inhibition	Inhibition	Inhibition	Inhibition
		impairment	impairment	impairment	impairment	impairment	impairment
		↓	↓	↓	↓	↓	↓
		SM	AM	RA	NR	EM	WF
Unstandardized coefficient		-0.006	-0.004	-0.005	-0.002	-0.004	-0.004
Standardized coefficient(β)		-0.087***	-0.075**	-0.097**	-0.046	-0.097**	-0.086***
Standard error		0.025	0.025	0.027	0.024	0.022	0.028
Significance level		0.001	0.003	0.002	0.063	0.002	0.001
Bootstrap boundaries (%95CI)	Lower	-0.135	-0.130	-0.138	-0.094	-0.140	-0.145
	Upper	-0.039	-0.031	-0.054	-0.002	-0.054	-0.034
	bound						

** $p < 0.01$, *** $p < 0.001$

Figures

Figure 1. Scatter plots of corrected vs. non-corrected memory factor scores against age with LOESS fitting line (shadows indicate 95% confidence intervals)

Figure 2. Partial mediation models (direct effects). Arrows reflect relationships between variables. Standardized coefficients are shown next to each path. ** $P < 0.01$, *** $P < 0.001$. ID: inhibition decline, SM: sentences memory, AM: action memory, RA: recall attention, NR: name recognition, EM: episodic memory, WF: word fluency