Disturbances of behavioural control and associative memory as early markers of Alzheimer’s disease
Flores-Vazquez, Juan Francisco

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Chapter 2.

I Know your Face but Can’t Remember Your Name:

Age-Related Differences in the FNAME

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2.1 Abstract

Objective: The Face-Name Associative Memory test (FNAME) has recently received attention as a test for early diagnosis of Alzheimer’s disease. So far, however, there has been no systematic investigation of the effects of aging. Here, we aimed to assess the extent to which the FNAME performance is modulated by normal ageing.

Method: In a first step, we adapted the FNAME material to the Dutch population. In a second step, younger (n = 29) and older adults (n = 29) were compared on recall and recognition performance.

Results: Significant age effects on name recall were observed after the first exposure of new face-name pairs: younger adults remembered eight, whereas older adults remembered a mean of four out of twelve names. Although both age groups increased the number of recalled names with repeated face-name exposure, older adults did not catch up with the performance of the younger adults, and the age-effects remained stable. Despite of that, both age groups maintained their performance after a 30-min delay. Considering recognition, no age differences were demonstrated, and both age groups succeeded in the recognition of previously shown faces and names when presented along with distractors.

Conclusions: This study presents for the first time the results of different age groups regarding cross-modal associative memory performance on the FNAME. The recall age effects support the hypothesis of age-related differences in associative memory. To use the FNAME as an early cognitive biomarker, further subscales are suggested to increase sensitivity and specificity in the clinical context.
2.2 Introduction

Ageing is typically associated with memory loss. The first and most affected is probably episodic memory, the conscious recollection of personally experienced events (Harada et al., 2013; W. C. Wang & Cabeza, 2016). Serious changes, however, are observed in pathological ageing, such as Alzheimer’s disease (AD), a condition that noticeably affects everyday functionality (Toepper, 2017).

In AD, structural and functional brain changes occur years before the onset of clinically identifiable cognitive decline (Aisen et al., 2017). To anticipate this, new assessment tools need to be developed that are cognitively demanding, reduce the possibility of compensatory strategies, detect subtle cognitive deficits in the earliest preclinical phases, and meet the standard psychometric requirements, e.g., no ceiling or floor effects, validity, reliability, etc. In these preclinical stages, associative memory, binding attributes (e.g. visual, verbal or contextual) constitutes an essential process that seems particularly affected and has therefore been considered a priority (Loewenstein et al., 2018; Rentz et al., 2011).

An example of cross-modal associative memory is the ability to recall faces along with corresponding names, which has received special attention recently (Rubíño & Andrés, 2018). During a face-name task a rapid and stronger decrease in hippocampal brain activity was associated with longitudinal clinical decline in mild cognitive impairment (MCI) (O’Brien et al., 2010). This is consistent with the general observation of initial hippocampal changes in AD as opposed to the first prefrontal changes in healthy older adults (OA, Toepper, 2017). Rentz et al. (2011) developed a shorter behavioural version, the Face Name Associative Memory test (FNAME) with 16 face-name and 16 face-occupation pairs. To use the FNAME over the entire AD trajectory from healthy OA to MCI, Papp et al. (2014) developed a shorter version with 12 pairs, increased the learning trials, and included a delayed recall (FNAME-12). This is worth mentioning, since compared to measures of immediate memory, delayed recall has higher sensitivity and specificity for the detection of MCI and AD (Weissberger et al., 2017).
Psychometric analyses revealed high convergent validity of the FNAME with other episodic memory tests such as the Free and Cued Selective Reminding Test (FCSRT (Amariglio et al., 2012; Papp et al., 2014) and the Wechsler Memory Scale (Alegret, Valero, et al., 2015), and strong test-retest reliability (Amariglio et al., 2012). The FNAME-12 shows excellent convergent validity with the original FNAME-16, as well as with the FCSRT (Papp et al., 2014). The FNAME has high ecological validity, since remembering face-name pairs is important for everyday functioning, and a common complaint among OA. A highly perceived face validity can increase the test engagement of participants.

A special feature of the FNAME is its selective associations between face-name recall and amyloid-β. This is important, since it is the earliest detectable evidence of AD neuropathology is currently amyloid-β (Ottoy et al., 2019). Only face-name associations, but not the easier condition face-occupation or the Selective Reminding Test, were associated with amyloid-β load in brain regions of the memory network in healthy OA and individuals with subjective cognitive decline (Rentz et al., 2011; Sanabria et al., 2018). Since performance in the FNAME seems to be a promising early cognitive marker for amyloid-β associated memory impairment, the extent to which the FNAME performance is modulated by normal ageing remains to be investigated.

OA perform lower relative to YA in a number of associative memory measures, which is particularly pronounced in recall compared to recognition (Horn et al., 2018; Naveh-Benjamin & Mayr, 2018). Regarding the FNAME-16, Amariglio and colleagues (2012) referred graphically to an age-related performance decline using scatter plots. Alegret et al. (2015) revealed a significant age-effect on the Spanish FNAME-16 by studying healthy participants aged 48 years and older, with two groups and a cutoff of 65 years. Performance of the FNAME-12 showed a trend for a correlation with age (Papp et al., 2014), however a recent study, using the Colombian FNAME-12, demonstrated diminished age performance on stratified age groups (< 50, 50-65, > 65 years; Vila-Castelar et al., 2019).

Our goals were the following. I) We aimed to adapt and validate a 12 pair version for the Netherlands (FNAME-12NL) with only face-name pairs. We included a second learning exposure to assess the repetition benefits, and a delayed memory phase due to the higher sensitivity and specificity for the detection of MCI and AD as opposed to immediate memory. II) To disentangle
the exact age-related effects, we compared YA and OA for the first time across all subscales. We predicted better performance in YA compared to OA in face-name recall and assessed recognition in an exploratory way.

2.3 Methods

General aspects

The current study included two experiments: in Experiment 1, stimuli were developed, and pictures and names selected; in Experiment 2, age-effects were assessed in the FNAME-12NL. All participants were informed about the study and gave written consent. Both experiments were approved by the ethics committee of the University of Groningen, and were conducted in accordance with the Declaration of Helsinki.

Experiment 1

Stimuli development

Social identities can have a strong effect on cognitive abilities, as is the case with common ethnic features in faces when used as stimuli for experimental tasks. For example, individuals are 1.4 times more likely to correctly identify a previously viewed face of their own ethnicity than faces of other ethnicities (Meissner & Brigham, 2001). Thus, an adapted version of the FNAME is required.

To create a set of photographic stimuli, 73 volunteers were recruited at the University of Groningen, in the Netherlands. Stratified and convenient sampling methods ensured that ages were evenly distributed amongst all ranges (20 to 80 years of age). Volunteers included a minority of non-stereotypically Dutch-looking individuals to account for the current make-up of Dutch society. Pictures were taken by a professional photographer. Volunteers were asked to stand upright against a white background, face the camera and show a neutral expression.
Another 49 participants were recruited for picture selection and validation (female = 24, male = 25, mean age = 47 years, age range 20-82 years). Participants were instructed to estimate the age of the 73 randomly presented pictures in Qualtrics in decades, and to rate on a five-point Likert scale how typically Dutch (from least to most) the faces looked. No definition nor a picture of a typically Dutch looking face was provided.

Pictures that were scored on the highest (most Dutch looking) as well as on the lowest (least Dutch looking/minority) quartile on typicality were selected as targets. To balance the test for age, gender and multiculturality, six target pictures per gender were selected, balanced across the different age categories (20s-30s, 40s-50s, 60s-70s), out of which four were rated as ‘least Dutch looking’ and eight as ‘most Dutch looking’. Two additional pictures per age category and gender, not previously presented nor associated with a name (so-called distractors), were selected from the remaining high-concordance pictures and grouped with the targets that matched the classification variables. These were used as foils in the recognition task.

Name selection

Names were selected from a databank of most common first names in the Netherlands (Meertens Instituut, 2020). Composite or gender-neutral names were excluded. From the names that were listed both in male and female variations, only the most frequent was selected.

Experiment 2

Test overview

The FNAME-12NL was presented using Microsoft Office Power Point with instructions in black letters over a white background. The test included 10 steps (see Figure 1).
Figure 1: Outline of the ten different phases of the adapted FNAME version

Familiarisation: To ease identification for the next phase and to habituate participants to faces, the 12 target faces were initially displayed individually for two seconds each without names. Participants were instructed to look at the picture. Learning Phase I: The 12 face-name pairs were presented one-by-one for six seconds each in a different, randomized sequence. Participants were instructed to read the names out loud and to memorize them. Immediate Recall. Next, only the faces were presented in a different random order (for eight seconds each) and participants were asked to recall the corresponding names out loud. Learning Phase II: Face-name pairs were presented again, six seconds each. Immediate Recall II: For the second time, faces were presented without names and participants were again asked to recall the names. Re-learning phase: Picture-name pairs that were not remembered during Immediate Recall II were shown to the participant again. After the 30-minute delay, Face Recognition followed: each of the learned faces was presented for five seconds together with two previously not shown distractor faces. Participants had to recognise the familiar face in each trial by pointing at the respective picture. Delayed Recall: The 12 faces were presented each for eight seconds without names and participants were asked to recall the name out loud. Name Recognition: The 12 pictures were presented each for six
seconds with the correct and two distractor names. Participants were instructed to indicate the familiar name.

**Participants and procedure**

In total, 62 participants were recruited and included based on general cognitive performance using the Dutch version of the Montreal Cognitive Assessment (Nasreddine et al., 2005). During the 30-minute delay, general demographic data were collected and the MoCA was performed. Participants with a score below the cut-off of 26 were excluded (one YA and four OA were excluded). Our final sample consisted of 58 participants, 29 YA, and 29 OA. YA were in average 19.7 (SD = 2.1) years old (74.1% female) and OA in average 63.5 (SD = 7.6; 57.1% female). YA and OA did not differ statistically regarding years of education (YA: M = 16.5, SD = 2.9, OA: M = 15.3, SD = 3.6, t (56) = 1.403, p = .166).

**Statistical design**

We used a 2 age (YA, OA) x 3 recall-type (Immediate Recall I, Immediate Recall II and Delayed Recall) mixed-model ANOVA using FNAME scores (number of recalled items, ranging from 0-12) as dependent variable. Cohen's $d$ was calculated for effect sizes. A second mixed-model ANOVA with a 2 age (YA, OA) by 2 recognition-type (Face versus Name Recognition) was carried out on the FNAME scores (number of recognised items, ranging from 0-12) as dependent variable. In case of violations of sphericity, we report Greenhouse-Geisser corrected $p$ and $\eta^2$ values. Statistical analyses were performed with SPSS software version 26 (IBM Corp., 2020)

**2.4 Results**

As shown in Fig. 2, the number of correctly recalled face-name associations was consistently higher in YA than in OA for: i) Immediate Recall I YA = 8.3 (SD = 2.2), OA = 4.3 (SD = 2.4); ii) Immediate Recall II, YA = 11.2 (SD = 1.3), OA = 7.1 (SD = 3.0); and iii) Delayed Recall, YA = 11.1 (SD = 1.9), OA = 7.3 (SD = 3.0). In contrast, the between group differences in the recognition subtests were much smaller: i) Face Recognition, YA = 11.9 (SD = 0.4), OA = 11.8 (0.5); ii) Name Recognition, YA = 11.8 (SD = 0.8), OA = 11.9 (SD = 0.3).
Chapter 2: I Know your Face but Can't Remember Your Name: 
Age-Related Differences in the FNAME

As expected, the recall results showed a significant main effect of age ($F_{(1, 55)} = 79.826, p < .0001$, $\eta^2 = 0.592$) with an outstanding effect size ($d = -2.409$; following Salkowski’s expansion of Cohen’s $d$ as small: 0.2, medium, large: 0.8; very large: 1.2, huge 2.0). Type of recall was also significant, ($F_{(1.449, 459.571)} = 37.41, p < .001, \eta^2 = 0.405$), demonstrating that differences in recall performance depends on the recall stage (Immediate Recall I, Immediate Recall II, Delayed Recall). The age x recall type interaction was not significant ($F_{(1.449, 459.571)} = 0.51, p = .95, \eta^2 = 0.001$).

Concerning recognition, no statistically significant effects were found for age ($F_{(1, 53)} = .23, p = .875, d = 0$), recognition type ($F_{(1, 53)} = .192, p = .66$), nor for the interaction between them ($F_{(1, 53)} = 1.324, p = .255$).

**Discussion**

In this study, we developed and adapted the FNAME-12NL, and assessed, for the first time, age-related effects by comparing YA and OA in all subscales of recall and recognition. The results show significant age differences in recalling names when viewing faces from previously learned face-name pairs. In contrast, YA and OA performed equally well in recognizing names or faces from learned face-name pairs. These results show that FNAME-12NL can detect age-related changes in episodic recall.
The recall results show a three-fold pattern. First, YA and OA increase the number of remembered items as the face-name pairs are repeated, thereby improving their immediate recall performance. Second, both age groups maintain their performance after the 30 min delay: once recalled then retained. Third, YA and OA, start from different performance levels, this is where the age effect occurs. After the first learning period, YA recall about eight items, whereas OA remember only four. Although OA benefit from the second learning phase, they do not catch up with YA and the age difference remains. This difference translates into a large effect size.

There were no age effects on recognition. The observation of a stronger age-difference in recall compared to recognition is a known phenomenon in the literature (Rhodes et al., 2019), but the comparison of both memory abilities in OA is of interest. Although OA could only recall 2/3 after the 30-minute delay, they could recognize almost all faces and names, even if flanked by unknown faces or names. This pattern of results provides indications of possible processes underlying these age-differences. OA and YA might differ regarding their ability to successfully bind different features during memory encoding, or to access these bound components as consequence of differences in memory strength or noise in retrieval computations. These effects can be specific to recall or affect recall stronger than recognition (Rhodes et al., 2019). Eventually, these results underscore the importance of focusing on encoding in OA in memory trainings, for instance by taking memory strategies and extended training into account.

This study has some limitations. First it is worth mentioning the existence of some ceiling effects of YA suggesting that this test version is relatively easy for them. OA also showed ceiling effects, but only in recognition. Another caveat concerns the inclusion of only two age groups, excluding middle-aged adults. It is therefore not possible to assess when performance differences begin.

For future work, we first of all encourage replication of this study for instance in in different laboratories and countries. Regarding the clinical use of the FNAME as an early cognitive biomarker of AD, we suggest the following to improve sensitivity and specificity. Based on the recall performance pattern, we recommend keeping the 12 face-name pairs, but propose to increase the difficulty of the recognition by rising the number of distractor names and faces. We furthermore suggest including free-recall as the most effortful recall test. We also recommend reporting standard reporting diagnostic validity statistics such as specificity and sensitivity
measures (see STARDdem Initiative) to advance the clinical utility of the FNAME. Last but not least, a pending longitudinal validation of the test would be crucial for a better characterisation of neuropsychological evolutions in different neurodegenerative diseases.