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The effect of age on the FCSRT-IR and temporary visual memory binding

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ABSTRACT

Background: Cognitive markers of early Alzheimer's disease (AD) should be sensitive and specific to memory impairments that are not associated with healthy cognitive aging. In the present study, we investigated the effect of healthy cognitive aging on two proposed cognitive markers of AD: the Free and Cued Selective Reminding Task with Immediate Recall (FCSRT-IR) and a temporary visual memory binding (TMB) task.

Method: Free recall and the cost of holding bound information in visual memory were compared between 24 younger and 24 older participants in a mixed, fully counterbalanced experiment.

Results: A significant effect of age was observed on free recall in the FCSRT-IR only and not on the cost of binding in the TMB task.

Conclusions: Of these two cognitive markers, the TMB task is more likely to be specific to memory impairments that are independent of age.

Key words: Alzheimer's disease, cognitive assessment, clinical assessment, aging, memory

Introduction

The early detection of Alzheimer's disease (AD) requires neuropsychological tools that can reveal the subtle cognitive impairments present prior to clinical onset (Sperling *et al.*, 2011). Neuropsychological tasks should be sufficiently sensitive and specific to act as cognitive markers for AD pathology. Performance on cognitive tasks can often be affected by healthy aging (Balota *et al.*, 2000; Brockmole and Logie, 2013; Sperling *et al.*, 2013; Wakefield *et al.*, 2014) making them unsatisfactory as screening tools for detecting dementia (Dubois *et al.*, 2007; Parra *et al.*, 2010b). It is therefore important to investigate whether a neuropsychological task that could serve as a cognitive marker of AD is affected by age.

The current study investigated the effects of aging on two tasks devised to minimize the effects of age and that have been recently proposed as cognitive markers for AD: the Free and Cued Selective Reminding Task with Immediate Recall (FCSRT-IR) and a paradigm assessing temporary visual memory binding (TMB).

The FCSRT-IR was developed to distinguish memory impairments associated with amnesia from those associated with healthy aging (Grober and Buschke, 1987; Grober *et al.*, 1988). The task exploits the encoding specificity principle (Tulving and Thomson, 1973), wherein an individual's memory for items is enhanced by reference to the context in which they were learned. Specifically, in the FCSRT-IR, participants are asked to encode a list of items together with their semantic categories. At test, participants attempt to remember these items under free recall followed by selective reminding for unrecalled items using semantic categories as cues. Performance on this task is measured by free and cued recall scores, the sum of which produces a total recall score.

TMB is responsible for the integration of disparate visual information – such as shape and color – to produce a visual object which can be retained as a whole. Critically, the features of objects are retained along with the information of what features are attributed to which object. This

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information is necessary when detecting whether an object's features have changed. In the visual memory literature, this is typically assessed in a change detection paradigm whereby participants decide whether features between two visual objects have swapped between study and test arrays (Wheeler and Treisman, 2002). Performance on this task would represent a participants' memory for bindings (e.g. colored shapes), which would then be compared to their memory for single features (e.g. black shapes or blocks of color) to reveal a "cost" of binding.

Both tasks are reported to be sensitive to clinical and preclinical AD. For instance, poor free recall on the FCSRT-IR has been observed prior to a diagnosis of AD (Grober and Kawas, 1997; Grober *et al.*, 2008b, but see Papp *et al.*, 2015). Comparatively, poor TMB is associated with sporadic AD (Parra *et al.*, 2009) and preclinical familial AD (Parra *et al.*, 2010b). Furthermore, both tasks are reported to be sensitive and specific to AD, potentially aiding differential diagnosis from other patient groups that are also associated with memory impairment. In the case of the FCSRT-IR, total recall is argued to be an index of AD pathology in contrast to frontotemporal dementia (FTD) (Lemos *et al.*, 2014). Poor TMB is reported in AD but absent in FTD, vascular dementia (VaD), dementia associated with Parkinson's disease, and dementia with Lewy bodies (Della Sala *et al.*, 2012) as well as depression (Parra *et al.*, 2010a). Thus, both tasks are promising aids to the differential diagnosis, follow-up, and early screening of AD.

However, these tasks rely on different cognitive systems, suggesting that they are not revealing the same memory impairments in AD. Crucially, the FCSRT-IR is an assessment of associative (or relational) long-term memory, whereas binding is an assessment of conjunctive short-term memory (Parra *et al.*, 2013). Specifically, items in the FCSRT-IR are successfully retrieved if the association between the item, its category, and its encoding context are retained. Items in the TMB task are successfully remembered if their constituent parts are correctly bound and such bindings are accurately held in short-term memory. Recent studies have revealed that relational and conjunctive binding are two memory functions that dissociate not only across memory systems but within short-term (Piekema *et al.*, 2010; Parra *et al.*, 2013) and long-term memory (Bastin and Van der Linden, 2005). Moreover, the two tasks rely on different retrieval functions with the FCSRT-IR dependent on recall and the TMB task on recognition.

Accordingly, these two forms of memory – as representing different cognitive systems – are also thought to depend on different structures and networks in the brain (Moses and Ryan, 2006; Mayes *et al.*, 2007). Variation in free recall in the FCSRT-IR has been shown to be associated with hippocampal volume and metabolic rate (Zimmerman *et al.*, 2008; Sarazin *et al.*, 2010). In AD patients, it has been posited that poor performance on the FCSRT-IR may be due to a disconnection between hippocampal and frontal areas necessary for checking the context in which items are learned (Lekeu *et al.*, 2003). Both findings are in line with the argument that the hippocampus is central to the formation of relational memories that link item and context information together (Davachi, 2006). In contrast, lesion and imaging data suggest that the hippocampus proper is not necessary for successful TMB (Baddeley *et al.*, 2010; Piekema *et al.*, 2010; Parra *et al.*, 2014). A dissociation between the binding paradigm and other hippocampal tasks has been observed, as performance on a shape-color binding paradigm is not correlated with performance on the Paired Associates Task (Parra *et al.*, 2011). Moreover, diffusion tensor imaging evidence suggests that, in familial AD patients, the impaired white matter structures associated with poor Paired Associates Task performance (hippocampal part of cingulum bundle) dissociate from the structures implicated in poor performance on the shape-color binding paradigm (Parra *et al.*, 2015). Instead, the maintenance of bindings is dependent on the ventral visual stream (Staresina and Davachi, 2010; Parra *et al.*, 2014) and may bear on the functioning of the perirhinal cortex (Staresina and Davachi, 2010; Tyler *et al.*, 2013; Watson and Lee, 2013; Clarke and Tyler, 2014).

The evidence above complements the hypothesis that parahippocampal functions are affected earlier in the progression of AD than hippocampal functions (Didic *et al.*, 2011), which suggests that the FCSRT-IR may be sensitive to memory impairments that occur relatively later than those detected by the TMB (see Papp *et al.*, 2015). Additionally, the hippocampus is also affected by healthy cognitive aging (Balota *et al.*, 2000; Mitchell *et al.*, 2000), which implies that tasks that assess its function are likely to reveal impairments in healthy elderly controls and AD patients (for example, performance on a relational (i.e. hippocampal) binding task declines with healthy aging and worsens with disease progression, van Geldorp *et al.*, 2015). Therefore, performance on the FCSRT-IR is likely to be affected by both disease and healthy aging.

Indeed, free recall as assessed by the FCSRT-IR is seen to decline over time in a healthy population (Grober *et al.*, 2008a). This effect is further

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confounded by an individual's level of education and their gender (Ivnik *et al.*, 1997; Grober *et al.*, 1998; Frasson *et al.*, 2011), necessitating the collection and use of norms across populations for the accurate identification of a genuine AD memory impairment (Ivnik *et al.*, 1997; Peña-Casanova *et al.*, 2009).

Previous research suggests that performance on the TMB is less likely to be affected by healthy cognitive aging. Brockmole and Logie (2013) showed that although overall visual short-term memory capacity declined with age, this did not necessarily affect the ability to bind; the percentage of correctly remembered bound objects in 75-year-olds (82%) was comparable to that seen in 20-year-olds (85%). Similarly, healthy older participants do not show a greater binding cost in comparison to healthy young participants (Brockmole *et al.*, 2008), and their performance is as affected by the presence of a dual task as it is in young participants (Brown and Brockmole, 2010). Thus, binding appears resistant to the effect of age, as confirmed with a recent replication (Isella *et al.*, 2015).

In sum, there is evidence to suggest that free recall and binding may be differentially affected by age, potentially due to their sensitivity to different cognitive systems supported by different neuronal networks. However, the two tasks have never been directly compared in the same study and as such it is not clear if this apparent differential sensitivity to aging is the result of different sampled populations between studies. Thus, the primary aim of the present study was to directly compare the effect of age on these two tasks in a sample drawn from one population. To this end, we observed performance on the FCSRT-IR and binding paradigm in healthy young and older participants, controlling for differences in gender distribution and years of education between these two groups.

Methods

Participants

Two groups, one of 24 healthy older participants (M = 70.6, SD = 6.41, range = 61–85) from the University of Edinburgh Volunteer Panel (14 females) and 24 healthy undergraduate and postgraduate students (M = 20.5, SD = 2.15, range = 18–25) from the University of Edinburgh (18 females) participated in this experiment. All reported good health and had normal or corrected to normal vision; none had premorbid neurological or psychiatric history. There was no significant difference between the years of education of the older (M = 15.8, SD = 3.23, range 11–20) and young (M = 16.0, SD = 2.31, range 12–20) participants ($t(46) = -0.36$, $p = 0.72$). All healthy older participants scored above the conservative cut-off of 88 points for the ACE-III (M = 97, SD = 2.75, range 90–100). All the participants signed a consent form prior to participation. The study was approved by the University of Edinburgh Psychology Research Ethics Committee (Ref. 36–1314/2).

Assessment

General assessment

English Version A of the ACE-III was used to screen for possible cognitive impairment associated with dementia in the healthy older group (Hsieh *et al.*, 2013).

FCSRT-IR

The word version of Form A of the FCSRT-IR was selected for this experiment based on the recommendation that the word version is sensitive to healthy participants at risk of AD (Auriacombe *et al.*, 2010), and that all forms of the FCSRT-IR are psychometrically equivalent (Grober *et al.*, 2009); our results are therefore unlikely to be driven by idiosyncrasies associated with this particular form.

The FCSRT-IR was administered according to the instructions provided by the Albert Einstein Medical College. The task is composed of an acquisition and test phase. In the acquisition phase, participants were presented with one of four A4 cards, on which were four printed words, one in each quadrant. Participants were asked to point to and give the name of an item that belonged to a category cue (e.g. "What is the furniture?"). Each item belonged to its own, unique category. Once participants had correctly pointed to and named all four items on the card, the card was taken away, and immediate cued recall was assessed for items (e.g. "What was the furniture?") in the same order they were encoded. Where participants failed to recall the item given a cue, the item and its cue were presented again ("The furniture was the desk.") and assessed again to ensure the association was learned. This procedure was repeated for the remaining three cards. Once the final set of four items was identified, the test phase began. This was composed of three trials. At the start of each trial, participants were instructed to count backwards from a number by decrements of 3 for 20 sec as a form of articulatory suppression. Participants were then given up to 2 min to recall as many of the words as they could in any order (free recall). After free recall was completed, participants were then presented with the categories of items that they did not remember (cued recall). The sum of a participant's free and cued recall represented their

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total recall. Participants completed two more trials of the test phase.

We analyzed the *sum* of a participants' free recall, which was calculated as the sum of all words correctly recalled under free recall across all three trials (0–48 words). Similarly, we analyzed the sum of a participants' total recall across all three trials, which was calculated as the sum of all words correctly recalled under free recall *and* cued recall across all three trials (0–48 words). Additionally, a participants' sensitivity to cueing was calculated to demonstrate the degree to which they benefited from cueing (0–100%). This was calculated according to the formula presented by Tounsi *et al.* (1999):

$$\text{Sensitivity to cueing} = 100 * \frac{\text{Sum of total recall} - \text{Sum of free recall}}{48 - \text{Sum of free recall}}$$

TMB

The TMB paradigm used here was the three-item version of the paradigm reported by Parra *et al.* (2010a; 2010b) and Parra *et al.* (2010a). This paradigm has been used to identify preclinical AD and also differentiate AD from healthy cognitive aging. The use of a three-item paradigm was to better reveal the effect of age, as the two-item paradigm is associated with ceiling effects in single feature conditions in healthy older groups (Parra *et al.*, 2010a; Della Sala *et al.*, 2016)

Items consisted of eight 6-sided abstract shapes that were either black or colored with non-primary colors (see Parra *et al.* (2010a; 2010b)). The task was written and presented using E-Prime and E-Run 2.0, respectively (Psychology Software Tools, 2012). All visual information was presented through a 15.1″ LCD monitor, and viewing distance was not restrained. In all cases, participants responded with the mouse, using the left mouse button to indicate "different" and the right to indicate "same."

Participants first completed a perceptual screen to ensure that any subsequent difficulties on the task were not due to perceptual problems. In each trial, participants are presented with three colored shapes in the upper and lower half of a screen, as separated by a horizontal line. In half of the trials, the color and shape of the objects above the line was identical to those below the line. In the remaining half, two of the shapes had swapped colors. Participants completed ten trials, and had to respond to at least eight correctly before continuing to the TMB task.

The paradigm contained two conditions: shape only and shape-color binding. Each condition contained 32 trials. In the shape only condition, participants were presented with black, 6-sided shapes. In the binding condition, these shapes were colored with non-primary colors. The stimuli used in both conditions are described in more detail in the *Method* section of Experiment 2, Brockmole *et al.* (2008). In all condition trials, participants were presented with three objects in a study array at 2,000 ms. After this, they were removed for a 900 ms retention interval and the test array was presented indefinitely until participants make their response. The next trial would then be initiated by the participant by pressing any mouse key.

In the shape only condition, half of the trials displayed the same shapes at test that were present at study. In the remaining half of these trials, two new shapes were presented in the test array. These two types of trials (same shapes, new shapes) were presented randomly within the shape only condition. In the shape-color binding condition, half of the trials displayed the same combinations of shape and color in the study and test arrays. In the remaining half, two of the shapes from the study array swapped colors when shown in the test array. The presentation of these types of trials was also random. In all conditions, the position of the objects between study and test arrays was always random, making location an uninformative feature.

Participants' accuracy was calculated as a percentage of trials where they gave a correct response (hits and correct rejections). Furthermore, a participant's cost of binding was calculated as their accuracy in the binding condition subtracted from their accuracy in the shape condition.

Procedure and design

The order of the presentation of the FCSRT-IR and the TMB was counterbalanced, as was the presentation of the shape and binding condition within the binding paradigm. The experiment employed a mixed, fully counterbalanced design. Older participants completed the ACE-III at the end of the testing session. The assessment lasted 45 min.

Analysis

Variables from the FCSRT-IR and binding paradigm were analyzed separately.

Initially, the relationship between total recall and sensitivity to cueing was analyzed using paired correlations within each age group, as these variables have been seen to almost completely overlap (Grober *et al.*, 2010). Subsequently, differences between groups on the measures of free recall, total recall, and sensitivity to cueing were analyzed with unpaired *t*-tests.

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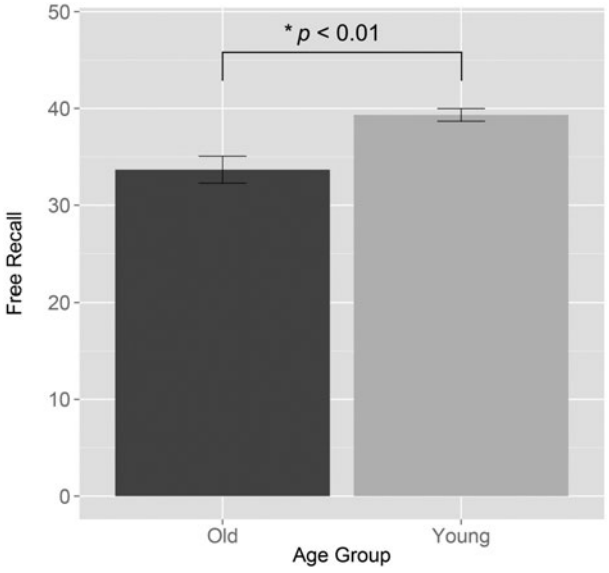


Figure 1. Mean number of words recalled by young and older participants under free recall. Error bars represent standard error.

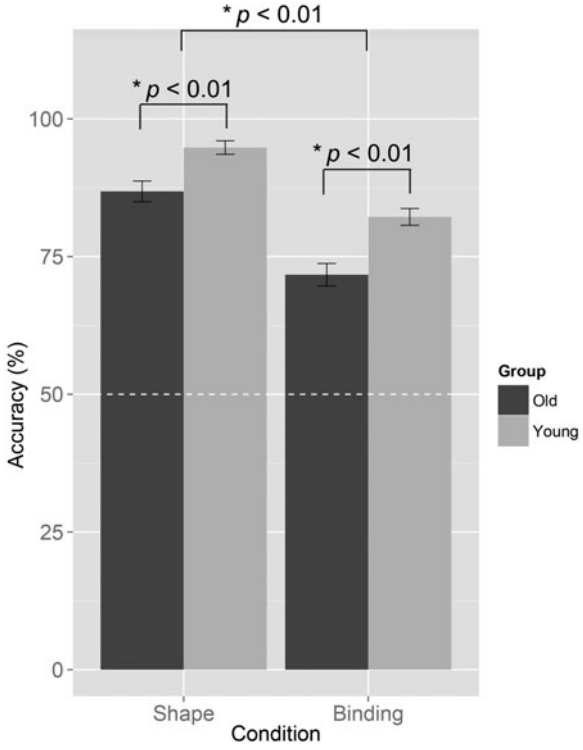


Figure 2. Accuracy for young and older participants in the TMB paradigm. Error bars represent standard error. Dotted white line represents chance performance (50%).

Binding variables were assessed using a mixed, 2-way ANOVA over the between-subjects variable of age group and the within-subjects variable of condition (shape only, shape-color binding). Binding cost was analyzed between the two age groups using an unpaired *t*-test.

The association between age and performance on the TMB and FCSRT-IR variables was also analyzed with paired Pearson's correlations (for the older group only).

Results

FCSRT-IR

Total recall was high in both the young ($M = 47.92$, SD = 0.3, range = 47–48) and older ($M = 47.63$, SD = 0.8, range = 45–48) participants (sensitivity to cueing was observed to be high in young ($M = 99.2$, SD = 2.7) and older ($M = 97.77$, SD = 4.76) participants). A Mann–Whitney–Wilcoxon test revealed no statistically significant difference in total recall performance between these groups ($W = 238$, p = 0.1). A one-sample *t*-test revealed that young participants' summed total recall was not significantly different from ceiling ($t(23) = -1.45$, p = 0.16). However, the same analyses revealed that older participants' performance was significantly different from ceiling ($t(23) = -2.39$, p = 0.02), although the absolute difference here was 0.37 words.

Free recall

Participants' free recall is represented in Figure 1. Younger participants recalled significantly more words in free recall than older participants ($M = 39.33$, SD = 3.22, range = 32–45; $M = 33.66$, SD = 6.84, range = 14–44, respectively, $t(32.67) = -3.67$, p = 0.001).

TMB task

Participants' performance on the TMB task is represented in Figure 2. Older participants were less accurate than the young participants overall, but both groups of participants were more accurate in the shape condition compared to the shape-color binding condition. A mixed, two-way ANOVA undertaken on accuracy revealed a significant effect of age ($F(1, 46) = 21.09$, p < 0.01, $\eta_G^2 = 0.24$ (this represents general η^2, which is a preferred estimate of effect size for repeated measures ANOVAs.)) and condition ($F(1, 46) = 112.28$, p < 0.01, $\eta_G^2 = 0.42$), but no significant interaction ($F(1, 46) = 0.94$, $\eta_G^2 = 0.006$). Similarly, although a cost of binding was seen for young ($M = 12.58$, SD = 8.11, range = −3 to 28) and older participants ($M = 15.13$, SD = 9.92, range = 0–35), this difference was not statistically significant ($t(44.29) = 0.972$, p = 0.34). Hence, both young and older participants were less accurate in the binding condition, but there was no evidence to suggest that this difficulty was exacerbated by age.

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The lack of a significant interaction between age and condition may be argued as representing limited power. Here, *post-hoc* analyses conducted using G*Power 3.1.9.2 revealed that the interaction effect of age and condition on accuracy would require at least 132 participants to become statistically significant with power at 90%. Similarly, at the same level of power, the difference in cost reported here would require 219 participants in *each* age group to become statistically significant. By contrast, the main effects of age and condition on accuracy were revealed with 99% and 100% power, respectively. Furthermore, the effect of age on free recall in the FCSRT-IR was revealed with 98% power. Thus, the lack of a statistically significant interaction effect suggests that any differential effect of age on binding memory is negligible in comparison to the effect of age on free recall, shape, and binding memory.

While the lack of an interaction effect suggests that there is no significant effect of age on binding cost, an effect was nonetheless observed ($d = 0.155$), but crucially smaller than what was observed for free recall ($d = 1.061$).

Correlational analysis

In the older group, a Pearson's correlation confirmed a significant relationship between age and free recall ability ($r = -0.45$, $p = 0.027$). There was a trend towards a significant negative correlation between age and shape memory ($r = -0.37$, $p = 0.079$) and age significantly correlated with binding memory ($r = -0.41$, $p = 0.047$), but no relationship was observed between cost and age ($r = 0.074$, $p = 0.73$).

Discussion

This study investigated the effect of age on the FCSRT-IR and the TMB. To our knowledge, this is the first study to directly compare performance of these two cognitive markers for AD in a single older cohort. In contrast to young participants, older participants demonstrated significantly poorer free recall on the FCSRT-IR, but did not significantly differ in their relative memory for binding. The comparable levels of education and gender distributions between the experimental groups suggest that this represents a differential effect of age on one task but not the other, which in turn may reflect their sensitivity to different memory systems. Specifically, the TMB paradigm appears less affected by memory systems that are also affected by healthy cognitive aging (i.e. hippocampal functions).

Both the FCSRT-IR and TMB paradigm have been used to distinguish patients with AD from healthy older controls and other patient groups, and have therefore been proposed as sensitive and specific cognitive markers. However, the literature associated with these tasks and the results from the current experiment suggest that these tasks may be sensitive to different memory systems.

Specifically, our findings comply with the idea of two separate forms of memory – recall and recognition – that in turn are differentially affected by age (Danckert and Craik, 2013) and distinctly associated with separate parts of the MTL, with recognition bearing on the entorhinal cortex, and recall the hippocampus (Yonelinas *et al.*, 2007). The clinical relevance of this dissociation is outlined in Didic *et al.*'s (2011) model of progressive memory impairments in AD pathology, wherein pathology occurs in sub-hippocampal areas prior to the hippocampus proper. Crucially, the authors review evidence to argue that sub-hippocampal areas (e.g. perirhinal and entorhinal cortices) are associated with context-free object memory, and thus impairments of this type of memory are observed before the context-dependent episodic memory impairment classically associated with AD. Of note, regions proposed to be part of the sub-hippocampal network declines in AD earlier than the hippocampus (Juottonen *et al.*, 1998) and seem to remain unaffected across the life span (Insausti *et al.*, 1998). Overall, our results – in concert with previous findings regarding the TMB – conform to a framework that proposes two forms of memory (context free recognition vs. context dependent recall) that are dependent on different parts of the MTL and, as such, are differentially affected by healthy aging and impaired at different stages of AD pathology.

We have outlined fundamental differences between these tasks that may be responsible for this differential effect of age, with the key distinction being that one task assesses relational long-term memory and the other conjunctive short-term memory.

However, there is an additional difference in the use of recognition and recall, in that the former (as assessed in the binding paradigm) is less affected than the latter in healthy aging (Perlmutter, 1979; Danckert and Craik, 2013). This discrepancy has been interpreted as a need for more cognitive resources in recall tasks compared to recognition tasks (Craik and McDowd, 1987; Danckert and Craik, 2013). Indeed, it has been posited that free recall in the FCSRT-IR necessitates retrieval strategies (Lekeu *et al.*, 2003) that are affected by age-associated changes in anterior brain regions (Buckner, 2004). By contrast, the formation and memory for bindings has been argued to be

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automatic but fragile (Allen *et al.*, 2006), and thus not as resource-demanding or as dependent on effective strategies. This position is supported by evidence that patients with dysexecutive symptoms (e.g. VaD patients, Román, 2003) are poorer than controls on the FCSRT-IR (Traykov *et al.*, 2005) yet comparable in TMB (Della Sala *et al.*, 2012). This in turn highlights the utility of the TMB impairment in differential diagnosis, as its high specificity and sensitivity to AD reflects that it is not driven by impairments associated with other dementias (Della Sala *et al.*, 2012), aging, or depression (Parra *et al.*, 2010a).

It may be argued that the difference reported here is an experimental artifact given the use of words on the FCSRT-IR and visual information in the binding paradigm and the picture superiority effect in older individuals (Winograd *et al.*, 1982). Specifically, older participants may rely only on verbal codes in the former task, but *both* verbal and visual codes in the latter. Although possible, this is unlikely, as the materials used in the binding paradigm were abstract shapes and low frequency colors that discourage verbal encoding. Furthermore, an effect of age on immediate and delayed free recall has also been demonstrated in a picture version of the FCSRT-IR (Frasson *et al.*, 2011). Ultimately, it is more likely that the differential effect of age on free recall reflects the nature of the FCSRT-IR rather than its chosen presentation format.

Age effects shown by our results are usually addressed in clinical neuropsychology with the use of age-adjusted normative data. Although this is a necessary practice in some neuropsychological assessments, there are particular problems when this is done with free recall for the purposes of identifying AD (as opposed to comparison to peers for the purposes of ranking). Critically, Sliwinski *et al.* (1997) demonstrated with the Selective Reminding Task that a variable's sensitivity to dementia was reduced when confounding yet predictive factors (i.e. age) were controlled for. Moreover, adjusted, standardized scores can lead to a loss of discrimination between health and AD in very old populations (Bondi *et al.*, 2003), and these forms of control are also seen to weaken the association between test performance and brain integrity (Mungas *et al.*, 2009). Thus, although robust normative data are necessary for interpreting neuropsychological performance (see Mitrushina *et al.*, 2005; Slick, 2006), this practice when using free recall as an indicator of AD must be approached with caution (Carlesimo *et al.* 2011; Gainotti *et al.*, 2014).

Although we assessed a healthy elderly and young population's free recall, it should be noted that the FCSRT-IR was initially intended to be an assessment of episodic memory in older adults with reference to total recall (Grober *et al.*, 1988). However, we revealed that total recall is also a limited variable, as we replicated the finding that healthy elderly participants were virtually at ceiling on measures of cue efficiency – total recall and sensitivity to cueing (Frasson *et al.*, 2011). The ceiling effect seen in total recall introduces an increased risk of diagnostic false alarms; one isolated error would be misconstrued as abnormal. The high prevalence of this effect in the 40–94-year-old Frasson *et al.* (2011) cohort suggests that this issue is evident throughout the lifespan. Other tasks following the same general principles, such as the RI48 (Ivanoiu *et al.*, 2005) capture a participants' use of semantic cues without the ceiling effects associated with the FCSRT-IR, and thus may be more appropriate for assessing impairments in sensitivity to cueing in a healthy population.

Our results may be somewhat limited in that we have only observed the effect of age in a population with a high average level of education. However, previous research suggests that our findings may hold across a wider population. Specifically, TMB performance is not affected by differences in education between experimental groups (Parra *et al.*, 2011) or study cohorts (Parra *et al.*, 2010a; 2010b), but free recall is negatively affected by education (Grober *et al.*, 1998). Thus, it may be that the differential age effect observed here is relatively conservative, and may be more striking in a low-education population.

In sum, we revealed that two tests that are promising tools in assisting the early detection of AD have differential sensitivity to the effect of age in a healthy older population. This suggests that the tasks may be sensitive to different memory systems that are differentially affected by age. The resilience of the binding task to aging combined with its sensitivity to AD indicates this may provide a more suitable baseline from which to detect cognitive deterioration due to pathological neurodegeneration of AD. Future research may confirm this possibility by directly comparing the tasks' diagnostic utility in a clinical population.

Conflict of interest declaration

None.

Description of authors' roles

LK designed the study, conducted data collection, data analysis, and wrote the manuscript. SA and

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SDS gave supervision on the design of the study and writing. MAP gave supervision on analysis and writing.

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References

Allen, R. J., Baddeley, A. D. and Hitch, G. J. (2006). Is the binding of visual features in working memory resource-demanding? *Journal of Experimental Psychology: General*, 135, 298–313.

Auriacombe, S., Helmer, C., Amieva, H., Berr, C., Dubois, B. and Dartigues, J. F. (2010). Validity of the free and cued selective reminding test in predicting dementia: the 3C study. *Neurology*, 74, 1760–1767. doi: 10.1212/WNL.0b013e3181df0959.

Baddeley, A., Allen, R. and Vargha-Khadem, F. (2010). Is the hippocampus necessary for visual and verbal binding in working memory? *Neuropsychologia*, 48, 1089–1095.

Balota, D. A., Dolan, P. O. and Duchek, J. M. (2000). Memory changes in healthy older adults. In E. Tulving and F. I. M. Craik (eds.), *The Oxford Handbook of Memory* (pp. 395–409). Oxford: Oxford University Press.

Bastin, C. and Van der Linden, M. (2005). The effects of aging on the recognition of different types of associations. *Experimental Aging Research*, 32, 61–77.

Bondi, M. W. *et al.* (2003). Neuropsychological deficits associated with Alzheimer's disease in the very-old: discrepancies in raw vs. standardized scores. *Journal of the International Neuropsychological Society*, 9, 783–795.

Brockmole, J. R. and Logie, R. H. (2013). Age-related change in visual working memory: a study of 55,753 participants aged 8–75. *Frontiers in Psychology*, 4, 10–3389.

Brockmole, J. R., Parra, M. A., Della Sala, S. and Logie, R. (2008). Do binding deficits account for age-related decline in visual working memory? *Psychonomic Bulletin & Review*, 15, 543–547. doi: 10.3758/PBR.15.3.543.

Brown, L. A. and Brockmole, J. R. (2010). The role of attention in binding visual features in working memory: evidence from cognitive ageing. *Quarterly Journal of Experimental Psychology*, 63, 2067–2079.

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron*, 44, 195–208. doi: http://dx.doi.org/10.1016/j.neuron.2004.09.006.

Carlesimo, G. A., Perri, R. and Caltagirone, C. (2011). Category cued recall following controlled encoding as a neuropsychological tool in the diagnosis of Alzheimer's disease: a review of the evidence. *Neuropsychology Review*, 21, 54–65.

Clarke, A. and Tyler, L. K. (2014). Object-specific semantic coding in human perirhinal cortex. *The Journal of Neuroscience*, 34, 4766–4775.

Craik, F. I. and McDowd, J. M. (1987). Age differences in recall and recognition. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 13, 474–479.

Danckert, S. L. and Craik, F. I. M. (2013). Does aging affect recall more than recognition memory? *Psychology and Aging*, 28, 902–909. doi: 10.1037/a0033263.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Current Opinion in Neurobiology*, 16, 693–700.

Della Sala, S., Kozlova, I., Stamate, A. and Parra, M. A. (2016). A transcultural cognitive marker of Alzheimer's Disease. *International Journal of Geriatric Psychiatry*. doi: 10.1002/gps.4610. Retrieved from PMID: 27805729.

Della Sala, S., Parra, M. A., Fabi, K., Luzzi, S. and Abrahams, S. (2012). Short-term memory binding is impaired in AD but not in non-AD dementias. *Neuropsychologia*, 50, 833—840. doi: 10.1016/j.neuropsychologia.2012.01.018.

Didic, M. *et al.* (2011). Which memory system is impaired first in Alzheimer's disease?. *Journal of Alzheimer's Disease*, 27, 11–22.

Dubois, B. *et al.* (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology*, 6, 734–746. doi: 10.1016/S1474-4422(07)70178-3.

Frasson, P. *et al.* (2011). Free and cued selective reminding test: an Italian normative study. *Neurological Sciences*, 32, 1057–1062. doi: 10.1007/s10072-011-0607-3.

Gainotti, G., Quaranta, D., Vita, M. G. and Marra, C. (2014). Neuropsychological predictors of conversion from mild cognitive impairment to Alzheimer's disease. *Journal of Alzheimer's Disease*, 38, 481–495.

Grober, E. and Buschke, H. (1987). Genuine memory deficits in dementia. *Developmental Neuropsychology*, 3, 13–36.

Grober, E. and Kawas, C. (1997). Learning and retention in preclinical and early Alzheimer's disease. *Psychology and Aging*, 12, 183–188. doi: 10.1037/0882-7974.12.1.183.

Grober, E., Buschke, H., Crystal, H., Bang, S. and Dresner, R. (1988). Screening for dementia by memory testing. *Neurology*, 38, 900–903.

Grober, E. *et al.* (2008a). Neuropsychological strategies for detecting early dementia. *Journal of the International Neuropsychological Society*, 14, 130–142. doi: 10.1017/S1355617708080156.

Grober, E., Hall, C. B., Lipton, R. B., Zonderman, A. B., Resnick, S. M. and Kawas, C. (2008b). Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society*, 14, 266–278. doi: 10.1017/S1355617708080302.

Grober, E., Lipton, R. B., Katz, M. and Sliwinski, M. (1998). Demographic influences on free and cued selective

https://doi.org/10.1017/S104161021700165X Published online by Cambridge University Press

reminding performance in older persons. *Journal of Clinical and Experimental Neuropsychology*, 20, 221–226.

Grober, E., Ocepek-Welikson, K. and Teresi, J. A. (2009). The free and cued selective reminding test: evidence of psychometric adequacy. *Psychology Science Quaterly*, 51, 266–282.

Grober, E., Sanders, A. E., Hall, C. and Lipton, R. B. (2010). Free and cued selective reminding identifies very mild dementia in primary care. *Alzheimer Disease & Associated Disorders*, 24, 284–290. doi: 10.1097/Wad.0b013e3181cfc78b.

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E. and Hodges, J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 36, 242–250. doi: 10.1159/000351671.

Insausti, R. *et al.* (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *AJNR*, 19, 659–671. Retrieved from PMID: 9576651.

Isella, V., Molteni, F., Mapelli, C. and Ferrarese, C. (2015). Short term memory for single surface features and bindings in ageing: a replication study. *Brain and Cognition*, 96, 38–42.

Ivanoiu, A. *et al.* (2005). Memory evaluation with a new cued recall test in patients with mild cognitive impairment and Alzheimer's disease. *Journal of Neurology*, 252, 47–55. doi: 10.1007/s00415-005-0597-2.

Ivnik, R. J., Smith, G. E., Lucas, J. A., Tangalos, E. G., Kokmen, E. and Petersen, R. C. (1997). Free and cued selective reminding test: MOANS norms. *Journal of Clinical and Experimental Neuropsychology*, 19, 676–691. doi: 10.1080/01688639708403753.

Juottonen, K. *et al.* (1998). Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease. *Neurobiology of Aging*, 19, 15–22. Retrieved from PMID: 9562498.

Lekeu, F. *et al.* (2003). Brain correlates of performance in a free/cued recall task with semantic encoding in Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 17, 35–45.

Lemos, R., Duro, D., Simões, M. R. and Santana, I. (2014). The free and cued selective reminding test distinguishes frontotemporal dementia from Alzheimer's disease. *Archives of Clinical Neuropsychology*, 29, 670–679.

Mayes, A., Montaldi, D. and Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends in Cognitive Sciences*, 11, 126–135.

Mitchell, K. J., Johnson, M. K., Raye, C. L. and D'Esposito, M. (2000). fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. Cognitive Brain Research, 10, 197–206.

Mitrushina, M., Boone, K. B., Razani, J. and D'Elia, L. F. (2005). *Handbook of Normative Mata for Neuropsychological Assessment*. Oxford: Oxford University Press.

Moses, S. N. and Ryan, J. D. (2006). A comparison and evaluation of the predictions of relational and conjunctive accounts of hippocampal function. *Hippocampus*, 16, 43–65.

Mungas, D., Reed, B. R., Farias, S. T. and DeCarli, C. (2009). Age and education effects on relationships of cognitive test scores with brain structure in demographically diverse older persons. *Psychology and Aging*, 24, 116–128.

Papp, K. V. *et al.* (2015). Free and cued memory in relation to biomarker-defined abnormalities in clinically normal older adults and those at risk for Alzheimer's disease. *Neuropsychologia*. doi: S0028-3932(15)30011-7 [pii];10.1016/j.neuropsychologia.2015.04.034. Retrieved from PMID: 26002757.

Parra, M. A., Abrahams, S., Fabi, K., Logie, R., Luzzi, S. and Della Sala, S. (2009). Short-term memory binding deficits in Alzheimer's disease. *Brain*, 132, 1057–1057.

Parra, M. A., Abrahams, S., Logie, R. H. and Della Sala, S. (2010a). Visual short-term memory binding in Alzheimer's disease and depression. *Journal of Neurology*, 257, 1160–1169. doi: 10.1007/s00415-010-5484-9.

Parra, M. A., Abrahams, S., Logie, R. H., Méndez, L. G., Lopera, F. and Della Sala, S. (2010b). Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain*, 133, 2702–2702.

Parra, M. A., Della Sala, S., Abrahams, S., Logie, R. H., Méndez, L. G. and Lopera, F. (2011). Specific deficit of colour–colour short-term memory binding in sporadic and familial Alzheimer's disease. *Neuropsychologia*, 49, 1943–1952.

Parra, M. A., Della Sala, S., Logie, R. and Morcom, A. M. (2014). Neural correlates of shape–colour binding in visual working memory. *Neuropsychologia*, 52, 27–36.

Parra, M. A., Fabi, K., Luzzi, S., Cubelli, R., Hernandez Valdez, M. and Della Sala, S. (2013). Relational and conjunctive binding functions dissociate in short-term memory. *Neurocase*, 21, 56–66. doi: 10.1080/13554794.2013.860177.

Parra, M. A. *et al.* (2015). Memory binding and white matter integrity in familial Alzheimer's disease. *Brain*, 138, 1355–1369.

Peña-Casanova, J. *et al.* (2009). Spanish multicenter normative studies (NEURONORMA Project): norms for the Rey-Osterrieth complex figure (copy and memory), and free and cued selective reminding test. *Archives of Clinical Neuropsychology*, 24, 371–393. doi: 10.1093/arclin/acp041.

Perlmutter, M. (1979). Age differences in adults' free recall, cued recall, and recognition. *Journal of Gerontology*, 34, 533–539. doi: 10.1093/geronj/34.4.533.

Piekema, C., Rijpkema, M., Fernandez, G. and Kessels, R. P. (2010). Dissociating the neural correlates of intra-item and inter-item working-memory binding. *PLoS ONE*, 5, e10214. doi: 10.1371/journal.pone.0010214.

Psychology Software Tools, Inc. [E-Prime 2.0]. (2012). Retrieved from: http://www.pstnet.com.

Román, G. C. (2003). Vascular dementia: distinguishing characteristics, treatment, and prevention. *Journal of the American Geriatrics Society*, 51, S296–S304. doi: 10.1046/j.1532-5415.5155.x.

Sarazin, M. *et al.* (2010). The amnestic syndrome of hippocampal type in Alzheimer's disease: an MRI study. *Journal of Alzheimer's Disease*, 22, 285–294. doi: 10.3233/JAD-2010-091150.

Slick, D. J. (2006). Psychometrics in neuropsychological assessment. In E. Strauss, E. M. S. Sherman and

https://doi.org/10.1017/S104161021700165X Published online by Cambridge University Press

O. Spreen (eds.), *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary* (3rd ed., pp. 3–43). Oxford: Oxford University Press.

Sliwinski, M., Buschke, H., Stewart, W. F., Masur, D. and Lipton, R. B. (1997). The effect of dementia risk factors on comparative and diagnostic selective reminding norms. *Journal of the International Neuropsychological Society*, 3, 317–326.

Sperling, R. A. *et al.* (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the national institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia: The Journal of the Alzheimer's Association*, 7, 280–292.

Sperling, R. A., Karlawish, J. and Johnson, K. A. (2013). Preclinical Alzheimer disease-the challenges ahead. *Nature Reviews Neurology*, 9, 54–58. doi: 10.1038/nrneurol.2012.241.

Staresina, B. P. and Davachi, L. (2010). Object unitization and associative memory formation are supported by distinct brain regions. *The Journal of Neuroscience*, 30, 9890–9897.

Tounsi, H. *et al.* (1999). Sensitivity to semantic cuing: an index of episodic memory dysfunction in early Alzheimer disease. *Alzheimer Disease & Associated Disorders*, 13, 38–46.

Traykov, L. *et al.* (2005). Patterns of memory impairment and perseverative behavior discriminate early Alzheimer's disease from subcortical vascular dementia. *Journal of the Neurological Sciences*, 229, 75–79. doi: 10.1016/j.jns.2004.11.006.

Tulving, E. and Thomson, D. M. (1973). Encoding specificity and retrieval processes in episodic memory. *Psychological Review*, 80, 352–373. doi: 10.1037/H0020071.

Tyler, L. K. *et al.* (2013). Objects and categories: feature statistics and object processing in the ventral stream. *Journal of Cognitive Neuroscience*, 25, 1723–1735.

van Geldorp, B., Heringa, S. M., van den Berg, E., Olde Rikkert, M. G., Biessels, G. J. and Kessels, R. P. (2015). Working memory binding and episodic memory formation in aging, mild cognitive impairment, and Alzheimer's dementia. *Journal of Clinical and Experimental Neuropsychology*, 37, 538–548.

Wakefield, S. J., McGeown, W. J., Shanks, M. F. and Venneri, A. (2014). Differentiating normal from pathological brain ageing using standard neuropsychological tests. *Current Alzheimer Research*, 11, 765–772.

Watson, H. C. and Lee, A. C. (2013). The perirhinal cortex and recognition memory interference. *The Journal of Neuroscience*, 33, 4192–4200.

Wheeler, M. E. and Treisman, A. M. (2002). Binding in short-term visual memory. *Journal of Experimental Psychology: General*, 131, 48–64.

Winograd, E., Smith, A. D. and Simon, E. W. (1982). Aging and the picture superiority effect in recall. *Journal of Gerontology*, 37, 70–75.

Yonelinas, A. P., Widaman, K., Mungas, D., Reed, B., Weiner, M. W. and Chui, H. C. (2007). Memory in the aging brain: doubly dissociating the contribution of the hippocampus and entorhinal cortex. *Hippocampus*, 17, 1134–1140.

Zimmerman, M. E. *et al.* (2008). Hippocampal neurochemistry, neuromorphometry, and verbal memory in nondemented older adults. *Neurology*, 70, 1594–1600. doi: 10.1212/01.wnl.0000306314.77311.be.

https://doi.org/10.1017/S104161021700165X Published online by Cambridge University Press