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Abstract

Remembering complex events requires binding features within unified objects (conjunctions) and holding associations between objects (relations). Recent studies suggest that the two functions dissociate in long-term memory (LTM). Less is known about their functional organization in short-term memory (STM). The present study investigated this issue in patient AE affected by a stroke which caused damage to brain regions known to be relevant for relational functions both in LTM and in STM (i.e., the hippocampus). The assessment involved a battery of standard neuropsychological tasks and STM binding tasks. One STM binding task (Exp. 1) presented common objects and common colours forming either pairs (relations) or integrated objects (conjunctions). Free recall of relations or conjunctions was assessed. A second STM binding task used random polygons and non-primary colours instead (Exp. 2). Memory was assessed by selecting the features that made up the relations or the conjunctions from a set of single polygons and a set of single colours. The neuropsychological assessment revealed impaired delayed memory in AE. AE's pronounced relational STM binding deficits contrasted with his completely preserved conjunctive binding functions in both Exp. 1 and 2. Only 2.35% and 1.14% of the population was expected to have a discrepancy more extreme than that presented by AE in Exp. 1 and 2 respectively. Processing relations and conjunctions of very elementary non-spatial features in STM led to dissociating performances in AE. These findings may inform current theories of memory decline such as those linked to cognitive ageing.

Keywords: Short-Term Memory Binding; Relational Binding; Conjunctive Binding; Hippocampus; Amnesia

Introduction

To keep track of complex stimuli experienced in the environment, multiple types and sources of information need to be bound. Two of types of memory binding functions appear to support these integrative processes (Mayes, Montaldi, & Migo, 2007; Moses & Ryan, 2006). One, named *relational binding,* supports the retention of the links between memory items (e.g., objects and locations, faces and names). Processing this kind of associations has been found to engage a network in which the hippocampus plays a fundamental role (Mayes, Montaldi, & Migo, 2007). This network appears to support both online relational representations (i.e., short-term memory - STM - Piekema, Kessels, Mars, Petersson, & Fernandez, 2006) and long-lasting associations (i.e., long-term memory – LTM - Mayes et al., 2004; 2007). The other one, named *conjunctive binding*, mediates the retention of integrated representations required to form new objects or events' identity (e.g., coloured items or natural scenes). Conjunctive binding functions in LTM and in STM have been less well investigated.

In LTM, conjunctive binding have different functions. It is thought to support the formation of blended structures (i.e., configural representations, Sutherland & Rudy, 1989, such as the arrangement of items within natural scenes, Moses & Ryan, 2006) which are building blocks of episodic memory. More important, it leads to new identity formation and supports LTM representations which require the integration of features within unified objects. Whereas the former forms of associations rely on a network which involves the hippocampus, the latter appear to rely on different network components (i.e., can be formed without an intact hippocampus, Mayes et al., 2004). Interestingly, recent evidence suggests that this also seems to be the case for STM (Baddeley, Allen, & Vargha-Khadem, 2010).

The present paper reports on the assessment of patient AE, who developed a post-stroke amnesia as the result of lesions to network components known to be relevant for relational binding functions. AE was assessed with a newly devised battery of STM tasks tapping relational (inter-item) and conjunctive (intra-item) binding functions. The aim was to investigate whether AE's relational and conjunctive STM binding functions were both affected due to his stroke or whether dissociating performances would emerge. In the present study we will refer to conjunctive binding within STM as the function supporting the integration of features within unified objects such as colours and shapes.

Evidence in support to a dissociation of these two functions comes from neuroimaging and behavioural studies. Neuroimaging studies in healthy young and older adults have shown greater activation of the hippocampus when participants were asked to process associations of items in STM than when they were asked to process single items (Mitchell, Johnson, Raye, & D'Esposito, 2000; Mitchell, Raye, Johnson, & Greene, 2006; Piekema et al., 2006; Piekema, Rijpkema, Fernandez, & Kessels, 2010). Converging evidence was provided by Olson, Page, Moore, Chatterjee and Verfaellie (2006) who showed that STM relational binding impairments in patients with medial temporal lobe amnesia were much greater than impairments in processing location information only. Furthermore, Piekema and collaborators (Piekema et al., 2006; 2010) showed activation of the hippocampus when inter-item but not intra-item bindings were processed in STM (see also Hannula & Ranganath, 2008; Ryan & Cohen, 2004). This evidence suggests that within STM the hippocampus supports the retention of relations but not of conjunction of features (see also case Jon for further supporting evidence, Baddeley, Allen, & Vargha-Khadem, 2010; Baddeley, Jarrold, & Vargha-Khadem, 2011). Conjunctive binding however, seems to be supported by a

network involving occipital-parietal regions (Shafritz, Gore, & Marois, 2002; Song & Jiang, 2006; Xu & Chun, 2006). Studies involving patients in the preclinical stages of familial Alzheimer's disease have shown affected conjunctive STM binding functions in the presence of completely preserved relational binding functions (Parra et al., 2010a; 2011), reinforcing the notion that these memory processes dissociate.

However, the studies reviewed above leave open the question of whether this relational/conjunctive dissociation in STM holds when the same type and amount of information forms either relations or conjunctions. The earlier studies used different stimuli in the tasks assessing the two functions. Moreover, the location of the items has consistently been an informative feature, forcing the involvement of the hippocampus. We need to learn if these two forms of binding are also dissociable in tasks presenting non-spatial features such as shapes and colours as relations (i.e., paired associates) or as conjunctions (i.e., integrated objects). This is relevant to current models of memory as, if proves valid, it would suggest that is not the nature of the to-be-remembered information but the format in which this information needs to be remembered that determines what memory processes are engaged. Moreover, this evidence would inform ongoing studies whose outcomes may lend further support to the relational/conjunctive binding dissociation across healthy and pathological ageing (Brockmole, Parra, Della Sala, & Logie, 2008; Cowan, Naveh-Benjamin, Kilb, & Saults, 2006; Mitchell, Raye, Johnson, & Greene, 2006; Parra, Abrahams, Logie, & Della Sala, 2009; Parra et al., 2010a; Parra, Abrahams, Logie, & Della Sala, 2010b). We first report on AE and his clinical assessment. We then present the outcomes from two experiments in which AE's and controls' relational and conjunctive STM binding functions were investigated.

Clinical assessment of AE

Medical History

AE (fictitious initials) is a right-handed man who was 72-year-old at the time of our assessment. He was admitted to hospital for severe memory loss and headache of abrupt onset. At admission he was alert and oriented, his neurological examination was normal. A CT scan showed regions of low density in the right mesial temporal lobe and right hippocampus encroaching upon the thalamus. On the following day, an MRI revealed multiple high signal abnormalities compatible with ischemic lesions (see MRI analysis below). His memory improved over the following days, but three and nine months post onset a mild forgetfulness persisted. We assessed AE and six matched healthy controls with a battery of STM binding tasks. AE also underwent standard neuropsychological assessment.

Brain MRI analysis

A complete description of the MRI techniques used to collect and process AE's neuroimaging data is presented in Supplementary Material. White matter hyperintensities, with total volume of 10.46 ml, were limited to a thin periventricular rim with medium-size caps in the anterior horns of the lateral ventricles and two punctual hyperintensities bilaterally in the centrum semiovale. These are compatible with healthy ageing changes. The ischaemic lesion, with total volume of 4.4 ml, was located in territories of the (right) posterior cerebral artery (PCA), being more intense in the hypothalamic region covered by the penetrating branches of the PCA, with small portions extended into the watershed regions of the posterior cortical border zone. Results of the computational assessment process are shown in Figure 1A. The exact anatomical regions it covers are labelled in

Figure 1B, parahippocampal gyrus, collateral sulcus, inferior lingual gyrus, hippocampus, cuneus, pulvinar, isthmus and ventral posterolateral thalamic nucleus, all in the right hemisphere. The coronal view is shown in Figure 1C.

Insert Figure 1 about here

Neuropsychological assessment

On standard neuropsychological tests nine months post stroke (Table 1), AE's performance was within the normal limits in all tests but those assessing LTM functions. AE's performance on verbal and visual LTM tasks was frankly impaired (Prose Memory, Delayed Recall Rey Auditory Learning Test and on the Recall phase of both versions of the Complex Figure).

Insert Table 1 about here

Experiment 1

Aim

Previous studies have investigated relational memory functions when the spatial location of the remembered stimuli was task relevant (e.g., Milner, Johnsrude, & Crane, 1997; Piekema et al., 2006; Smith & Milner, 1981). This requirement entails involvement of the hippocampus. In Experiment 1 we avoided this requirement by presenting AE and controls with stimuli with non-spatial properties which had to be recalled verbally, a procedure different from recognition or cued recall which tend to grant some meaning to the position of the items on the memory arrays. We wondered whether AE's relational and conjunctive binding functions would dissociate under these conditions.

Methods

AE and six controls matched for age (AE = 72; Controls: M = 66.1, SD = 3.4; t = 1.6, df = 5; p = 0.169) and years of formal education (AE = 8; Controls: M = 7.5, SD = 2.74; t = 0.17, df = 5; p = 0.872) entered Experiment 1. All participants gave their informed consent to take part in this study.

A recall task similar to that reported in Parra et al. (2009) was given to AE and the controls. This task was adapted so that the to-be-remembered stimuli were presented either forming conjunctions as in the earlier study or forming relations (see Figure 2). To construct the stimuli a set of eight objects (shoe, doll, shirt, bed, car, bell, cup and guitar) and a set of eight colours (red, blue, green, brown, orange, yellow, purple and turquoise) were used. Objects and colour were bound or paired randomly. Using a 15" personal computer (PC) screen participants were presented on each trial with a study array followed by a recall phase. Each visual array consisted of 3 conjunctions or 3 pairs which were presented for 1.5 sec per feature (4.5 seconds in total). Immediately after the array disappeared, the participants were asked to recall either the conjunctions or the relations of shapes

and colours verbally. The experimenter recorded the participants' responses using a scoring sheet. Participants were asked to "remember the combinations of shape and colour within each object" or "the shape and colour that form each pair" respectively for conjunctive and relational binding trials. Conjunctive and relational binding trials were randomised across participants but were presented in separate blocks. Each block consisted of six trials. As this was a free recall task, it was possible to assess memory for objects and colours separately as well as for conjunctions and relations of objects and colours. Therefore, the dependent variable was percentage of correct recall for Objects, Colours, Relations and Conjunctions of features.

Before the task, AE and controls were presented with two arrays, one of 20 objects and one of 20 colours. These arrays comprised the objects and the colours used during the task plus 12 additional objects and 12 additional colours. They were asked to name the objects and the colours. This test was used to rule out object or colour naming difficulties.

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Insert Figure 2 about here

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Statistical Analysis

We first investigated whether there were statistically significant differences between AE's memory scores and those of the controls for relations and conjunctions of features. We used the statistical analysis for single cases in neuropsychology devised by Crawford and Garthwaite (2002). This

methodology compares an individual patient's score with a control sample. This has proved useful to reduce Type I error rate regardless of the size of the control sample and proved very robust to departures from normality (e.g., severely skewed data). The method achieves two aims simultaneously: (1) testing whether a patient's score is significantly below controls (using a modified *t*-test), and (2) providing a point estimate (PE) of the abnormality of the score (p-value associated to the modified *t*); i.e. it estimates the percentage of the control population that would obtain a score lower than the patient.

We then assessed whether AE's performance during relational and conjunctive binding conditions met the criteria for classical single dissociation using the method devised by Crawford and Garthwaite (2005). According to their method, a classical dissociation is established only when the patient has a deficit on Task X, is within normal limits on Task Y, and the difference between performance on Task X and Y is significant. This reduces the probability of finding classical dissociations when differences in performance are just trivial. Using a modified paired-sample *t*-test the methods assesses whether the difference between scores on two tasks for an individual is sufficiently large such that it is unlikely to have come from the distribution of differences in the population of controls. The scores on the two tasks are standardized (i.e., z scores based on the mean and standard deviations of the control sample). The probability value for *t* provides a point estimate of the abnormality of the patient's difference score (i.e., it quantifies the proportion of the control population that would exhibit a difference more extreme than the patient's). For all statistics we report the PE of abnormality, the one-tailed t-value, and the probability that his scores were outside the normal range.

Results

Relative to controls, AE showed no impairment in processing single features in STM (objects or single colours) [PE = 7.22%; $t(5)$ = 1.81; n.s.] or conjunctions of features [PE = 41.62%; $t(5)$ = 0.23; n.s.]. However, AE showed a dramatic deficit in STM performance with relations between features [PE = 1.88%; $t(5)$ =3.10; p = 0.019] (Figure 3). The analysis showed that 41.62% of the population is expected to perform the conjunctive task more poorly than AE whereas only 1.88% is expected to perform the relational task more poorly than AE. This suggests a dissociation which points to compromised relational and preserved conjunctive binding functions in AE. To assess this hypothesis we contrasted AE's and controls' STM performance for relation and conjunction of features. Only 2.35% of the population was expected to have a discrepancy more extreme than that presented by the patient [$t(5)$ = 2.62; p = 0.047]. Hence, AE's pattern of performance fulfils the criteria for a classical single dissociation.

Insert Figure 3 about here

Comment

AE had no problems in processing conjunctions of features in STM but he was unable to process relations comprising the same type and amount of features. This finding suggests that the dissociation previously reported in the literature holds when the remembered relations or conjunctions of feature do not comprise spatial information. However, the task used in Experiment 1 assessed free recall of complex stimuli. There is some evidence suggesting that free recall may rely contextual information, a process which may recruit episodic representations (Eichenbaum, Yonelinas, & Ranganath, 2007; Isarida & Isarin, 2007; Siekmeier, Hasselmo, Howard, & Coyle,

2007; Uncapher, Otten, & Rugg, 2006). Moreover, the stimuli used in Experiment 1 were highly familiar items (i.e., common objects and colours), making the contribution from LTM likely (see for example Bergmann, Rijpkema, Fernandez, & Kessels, 2012). Therefore, it is possible that AE's deficit reflects an impairment of those processes responsible for retrieving context-based information which may have imposed additional relational memory load or impairments to access LTM during online processing. It is important to investigate whether AE's deficit is linked to a specific retrieval process (i.e., recall) or whether this reflects a general impairment of relational binding functions of STM which is independent of the retrieval mechanism engaged during the task and of the memory system supporting task performance. This was the aim of Experiment 2.

Experiment 2

Aim

To investigate whether AE's relational memory deficits observed in Experiment 1 are retrieval specific.

Methods

AE and six controls, three took part in Experiment 1 and three were new, entered Experiment 2. They were matched with AE for age (AE = 72; Controls: M = 64.0, SD = 3.8; t = 1.69, df = 5; p = 0.06) and education (AE = 8; Controls: M = 7.6, SD = 2.24; t = 0.16, df = 5; p = 0.44). All participants gave their informed consent to take part in this study.

A memory binding reconstruction task similar to that reported by Parra and collaborators (Parra et al., 2009) in their Experiment 4 was given to AE and controls. Performance on this task is thought to rely both on recognition (i.e., the single features are all presented along with distracters) and on recall (i.e., the binding between features is missing). In terms of contextual demands this task is less challenging than a pure recall task as it provides cues to retrieve the correct items. This task was adapted for the present study in two ways. Firstly, random polygons were used instead of common objects. Secondly, polygons and colours were presented forming conjunctions as the stimuli used in the earlier study or forming relations (see Figure 4).

To construct the stimuli for this study a set of eight polygons (see Parra et al., 2010a & b) and a set of eight non-primary colours were used. Objects and colours were bound or paired randomly. The other task parameters including set size, presentation time, number of trials and relational and conjunctive blocks were as in Experiment 1. The participants studied visual arrays of three items each and then they were presented with a new array which showed two sets of items. One consisted of four line drawings of polygons and the other one consisted of four colour patches. Three polygons and three colours corresponded to the studied items while one polygon and one colour were new. The participants were asked to select using the mouse or pointing with their fingers the polygons they saw earlier and their corresponding colours. They were instructed to "choose a polygon and then its colour until the three studied items had been selected". We calculated the percentage of correct reconstruction when memory for relation and conjunction of features was assessed. If AE's impairment is not due to context-based retrieval processes, his impairment should be replicated with this task. Alternatively, he would perform the task well.

Insert Figure 4 about here

Statistical Analysis

The same analytical approach described in Experiment 1 was used in Experiment 2.

Results

Relative to controls, AE showed no impairment in processing in STM conjunctions of features [PE = 64.67%; $t(5)$ = 0.40; n.s.]. In fact, AE outperformed controls in these trials (see Figure 5). However, AE showed a dramatic decline in STM performance with relations between features [PE = 1.65%; $t(5)$ =2.91; p = 0.016]. The analysis showed that 64.67% of the population is expected to perform the conjunctive task more poorly than AE whereas only 1.65% is expected to perform the relational task more poorly than AE When these data were submitted to the dissociation analysis, the results showed that 1.14% of the population was expected to have a discrepancy more extreme than AE [$t(5)$ = 3.24; p = 0.011]. Hence, AE's pattern of performance in this task fulfils the criteria for a classical single dissociation.

Insert Figure 5 about here

Comment

When complex stimuli with no previous representation in LTM were held in visual STM and had to be reconstructed using memory cues provided, AE's impairment to process feature relations was again observed. His conjunctive binding functions were found to be preserved thus suggesting that the relational/conjunctive binding dissociation in STM holds regardless of whether features are common or abstract in nature or whether they are retrieved from memory with (i.e., reconstruction) or without (i.e., free recall) memory cues.

General Discussion

In two experiments we have tested the hypothesis that binding in visual STM relations and conjunctions of non-spatial features are dissociable functions. This is the first study in which these two functions (Moses & Ryan, 2006) have been assessed in the same patient using the same stimuli with non-spatial properties which were remembered either as pairs of features or as features integrated within objects. AE, a patient with a recent vascular lesion which affected regions within the territory of the right PCA, including the hippocampus, was assessed with a battery of relational and conjunctive binding tasks as well as with standard neuropsychological tasks. On standard neuropsychological tasks AE showed clear impairments in delayed visual and verbal memory, suggesting the presence of a dense amnesia likely due to his right hippocampal lesion. In the STM task used in Exp. 1 we found that recalling relations of features, but not conjunctions, was severely impaired in AE. This dissociation could not be explained by the retrieval process as it was also observed with a visual reconstruction task (Exp. 2). AE's stroke impacted on several brain regions making it more challenging to interpret his functional impairments based on neuroanatomical evidence. Nevertheless, the patterns of dissociations observed in AE have important implications for our understanding of the functional organization of binding functions in STM. In the section that

follows we address potential links between his behavioural impairments and the lesions found in his brain. We discuss the dissociations observed in AE in the light of recent studies on memory binding.

The three brain areas affected by the stroke were the right medial temporal lobe (hippocampus and parahippocampal gyrus), the right occipital lobe (inferior lingual gyrus including the collateral sulcus and cuneus), and the right thalamus. The results from the different assessments suggest that these lesions might have contributed differently to AE's pattern of spared and impaired performance. For example, the regions within the occipital lobe have been previously found to play a role in STM and working memory tasks such as object recognition, categorization and spatial matching (Schendan & Stern, 2008) as well as in visual encoding and object and space perception functions (Ventre-Dominey et al., 2005). All these functions were found to be spared in AE. The thalamus also has a role in STM and working memory tasks supporting connectivity among cortical and subcortical components of the network (e.g., with prefrontal cortex) (Piras, Caltagirone, & Spalletta, 2010; Watanabe & Funahashi, 2012). We did not find a general STM deficit in AE but his specific relational STM binding deficit could somehow reflect impaired connectivity between elements of the STM network such as hippocampus and frontal regions. There is evidence that holding associations in working memory engages such a network (Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000). AE's medial temporal lobe lesions appear to explain most of the outcomes from his assessment. First, LTM was the only function found to be affected during the neuropsychological assessment. Second, his relational binding functions were severely impaired even when he could integrate the same amount and type of features within object representations perfectly well. This pattern resembles that previously described in patients with hippocampal damage (e.g., preserved conjunctive binding e.g., Baddeley et al., 2010 but impaired relational

binding e.g., Olson, Moore, Stark, & Chatterjee, 2006). We now further discuss why AE's medial temporal lobe lesions could provide a main account for his pattern of dissociation.

The relational and conjunctive accounts of hippocampal functions were proposed to explain how the hippocampus contributes to LTM formation (Mayes et al., 2007; Moses & Ryan, 2006). It is less well understood whether the same account applies to the role of the hippocampus in STM processing (Moses & Ryan, 2006; Olsen, Moses, Riggs, & Ryan, 2012). Moses and Ryan (2006) reviewed the animal and human literature on LTM and concluded that the hippocampus is necessary to process relational representations. The authors also stated that forming conjunctions in LTM via blending items within configural representations, a process which seems to occur via repetition and learning (Cer & O'Reilly, 2006), requires the functional integrity of the hippocampus. However, other studies have demonstrated that when conjunctive binding functions carried out in LTM support the integration of features within unified objects, damage to the hippocampus does not impair this function (Mayes et al., 2004). Here, we are reporting a dissociation of relational and conjunctive binding functions in STM in a patient whose right hippocampus was damaged. This dissociation was observed when very basic forms of representations which involve conjunctions or relations of features such as shape and colour were processed in STM.

The relational and conjunctive binding tasks used in Experiments 1 and 2 require the participants to process features which could be combined either to form new objects (i.e., conjunctions) or pairs of independent items (i.e., relations). The only difference between these two tasks is the type of binding function required to keep the link between features. The results presented here indicate that representing features as pairs or as integrated units requires support from different network components. Baddeley and collaborators (Baddeley et al., 2010; 2011) asked Jon, a patient with a

bilateral hippocampal damage, to remember features with Gestalt properties such as shapes and colours presented in different locations. Jon could perform these tasks perfectly well. As in our relational task, in Baddeley et al.'s task features were presented separately during the study phase. However, during their test phase, Jon had to make conjunctive decisions as the test items were always presented as feature conjunctions. It might be possible that, after a few trials, he adopted a conjunctive strategy whereby he merged the separated features into object representations and held them in STM as such until the test phase. Our data appear to support this suggestion as in our conjunctive binding conditions memory was tested by presenting two sets of single features (similarly to Baddeley et al., 2010's study arrays) which were used to reconstruct the conjunctions. AE could perfectly recombine the features into conjunctive but not into relational representations. Taken together the results presented here and those from the earlier studies suggest that hippocampal damage does not preclude the formation of feature conjunctions in STM.

A case which may be relevant to this discussion is YR (Mayes et al., 2004; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002). YR's relational (labelled inter-item association by the authors) and conjunctive (i.e., intra-item association) LTM functions were extensively investigated. She suffered from an acquired bilateral damage to the hippocampus due to an opiate treatment. YR's ability to process inter-item relations in LTM was dramatically impaired whereas she could process intra-item associations (e.g., features of faces) without difficulties. Our current results with AE and those from earlier studies with YR suggest that LTM and STM may be supported by similar processes when it comes to process relations of features. This evidence also supports the suggestion that AE's relational impairment could be accounted for primarily by his hippocampal damage. Processing stimuli relations may follow a continuum from the very early stages of information processing (i.e., perception) to the stable representation in memory (i.e., LTM) as suggested by

Olsen et al. (2012; see also Baddeley et al., 2011; Eichenbaum, 2004). The relational binding functions addressed in Olsen et al.'s (2012) review involve the association of disparate elements which have high perceptual complexity. These elements (e.g., faces, houses, natural scenes, etc.) need first to undergo intra-item binding process through which the individual identities are formed and then they are associated with other elements in the visual scene as to form relational representations. We have demonstrated that these relational binding processes encompass very elemental features such as shapes and colours, which are the basis for identity formation.

In the visual domain, relational binding (both in LTM and STM) has been mainly assessed using tasks which require remembering the relation of items and their locations (i.e., visuo-spatial processing; Chalfonte & Johnson, 1996; Chalfonte, Verfaellie, Johnson, & Reiss, 1996; Cowan, Naveh-Benjamin, Kilb, & Saults, 2006; O'Connell et al., 2004). Less is known about the relational binding functions which do not involve spatial information. We observed deficits in AE when he had to recall features relations in a complete absence of memory cues (i.e., free recall in Exp.1) and when he was asked to reconstruct feature relations but the individual features were provided as non-spatial memory cues (Exp. 2). The first task poses greater contextual memory load than the second task. Nevertheless, AE was severely impaired in both tasks thus suggesting a context-independent impairment. Furthermore, the STM relational impairment of AE was observed with tasks requesting verbal recall of arbitrarily bound familiar items (Exp. 1) or visual recognition of novel unfamiliar items (Exp. 2), thus suggesting a domain-independent (i.e., verbal or visual) impairment.

In line with recent behavioural (e.g., Baddeley et al., 2010) and neuroimaging studies (Piekema et al., 2010), we found no involvement of the hippocampus in conjunctive binding. This dissociation is relevant to the literature on memory and ageing. Recent studies suggest that age also dissociates

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conjunctive and relational binding processes carried out in STM (Brockmole et al., 2008; Cowan et al., 2006; Mitchell et al., 2006; Parra et al., 2009). Conjunctive binding in STM has consistently proved to be insensitive to healthy ageing (Brockmole et al., 2008; Brown & Brockmole, 2010; Parra et al., 2009). When older adults are asked to process in STM conjunctions of features or individual features similar to those used in Experiment 2, they show a general decline of STM but no discrepancy across the two conditions. However, when they are asked to process relations of features either in STM or in LTM, the overall age-related decline is accompanied by a dramatic discrepancy whereby memory for feature relations is significantly more affected than memory for single features (Chalfonte & Johnson, 1996; Mitchell et al., 2000a; Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000b). Hence, age seems to impact on relational memory process but not on conjunctive memory functions. This is in line with the age-related associative memory decline hypothesis (Naveh-Benjamin, Brav, & Levy, 2007; Old & Naveh-Benjamin, 2008) which seems to be accounted for, at least in part, by the hippocampal decline observed in healthy ageing (Grady, 2008; Grady, McIntosh, & Craik, 2003; Mitchell et al., 2000a). This poses limitations to the selection of tasks for the cognitive assessment of older adults who may be at risk of developing abnormal variants of ageing (e.g., dementias) (de Jager, Milwain, & Budge, 2002; Didic et al., 2011).

Acknowledgments

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Table 1. AE' performance on a range of neuropsychological tests compared to norms..

Neuropsychological test	Cut-off value	AE's Raw Score
MMSE	24	28
VIQ	68-108	101
Raven Progressive Matrices	14.75[a]	26
Short-Term Memory		
Verbal Span (Digit Recall)	3.33[a]	4
Visual-Span Span (Corsi Block)	3.45[a]	4
Long Term Memory		
Prose memory	9.06[a]	8
Rey Auditory Learning Test		
Immediate	28.53[a]	30
Delayed	4.69 [a]	5
Complex Figure of Rey (ROCF)		
Recall	12.99 [a]	7
Rey-Osterrieth Complex Figure B recall (ROCF-B)		
Immediate	22.13[a]	14
Delayed	21.24 [a]	13
Visual Perceptual and Praxis		
VOSP Shape Detection	15	20

VOSP Object decision	14	16
Incomplete letters	14	16
Silhouette	9	15
VOSP Position discrimination	18	20
VOSP Cube analysis	6	8
VOSP Dot Counting	8	10
ROCF (Copy)	31.22 [a]	32
ROCF-B (Copy)	28.85 [a]	30
Executive Functions		
TMT (B-A)	185 [a]	81
Verbal Fluency – Categories	11.78 [a]	39
Verbal Fluency – Phonological (FAS)	17.25 [a]	26

[a] Cut-off = mean–1SD taken from published normative studies. **MMSE** = Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975; Magni et al. ,1996); **Prose memory** (Total Recall) (Spinnler & Tognoni, 1987); **Raven Progressive Matrices** (Basso, Capitani & Laiacona, 1987); **Rey Auditory Learning Test** (Carlesimo et al., 1996); **ROCF** = Complex Figure of Rey (Caffarra et al., 2002); **ROCF-B** = Rey-Osterrieth Complex Figure B (Luzzi et al., 2011); **TMT =** Trail Making test parts A and B (B-A) (Giovagnoli et al., 1996); **Verbal Span (Digit Recall)** (Orsini et al., 1987); **Verbal Fluency- Categories** (Novelli et al., 1986); **Verbal Fluency – Phonological** (Carlesimo et al., 1996); **Visual-Span Span (Corsi Block)** (Orsini et al., 1987); **VIQ** (Colombo, Sartori & Brivio, 2002); **VOSP** = Visual Object and Space Perception Battery (Object decision) (Warrington & James, 1991).

Figure Captions

Figure 1. (A) Results of the lesion extraction and quantification. Binary masks of the white matter hyperintensities (blue) and ischaemic lesion (red) are superimposed on consecutive axial views of the FLAIR-MR image. **(B)** Consecutive axial views of the ischaemic lesion in the mean diffusion coefficient image with the labels of the anatomical regions covered by the lesion. Abbrev. pg:parahippocampal gyrus, cs: collateral sulcus, ilg: inferior lingual gyrus, vptn: ventral posterolateral thalamic nucleus. **(C)** Consecutive coronal views of the ischaemic lesion in the mean diffusion coefficient image.

Figure 2. Examples of the conjunctive and relational trials used in the STM binding task in Experiment 1.

Figure 3. Mean performance of AE and Controls on the task used in Experiment 1 (the error bars represent standard deviations).

Figure 4. Examples of the conjunctive and relational trials used in the STM binding task of Experiment 2.

Figure 5. Mean performance of AE and Controls on the task used in Experiment 2 (the error bars represent standard deviations).Chance performance is 16%.
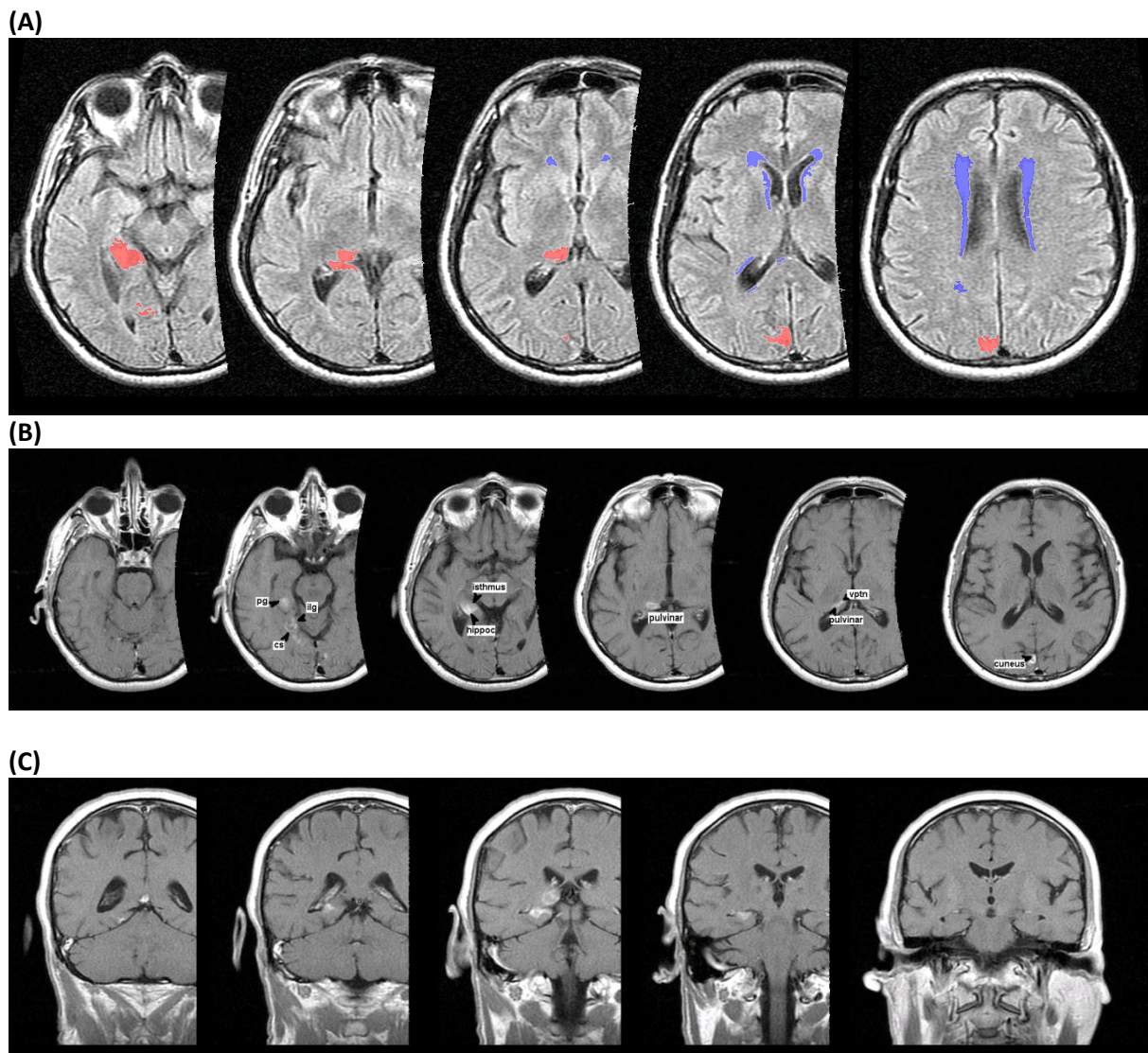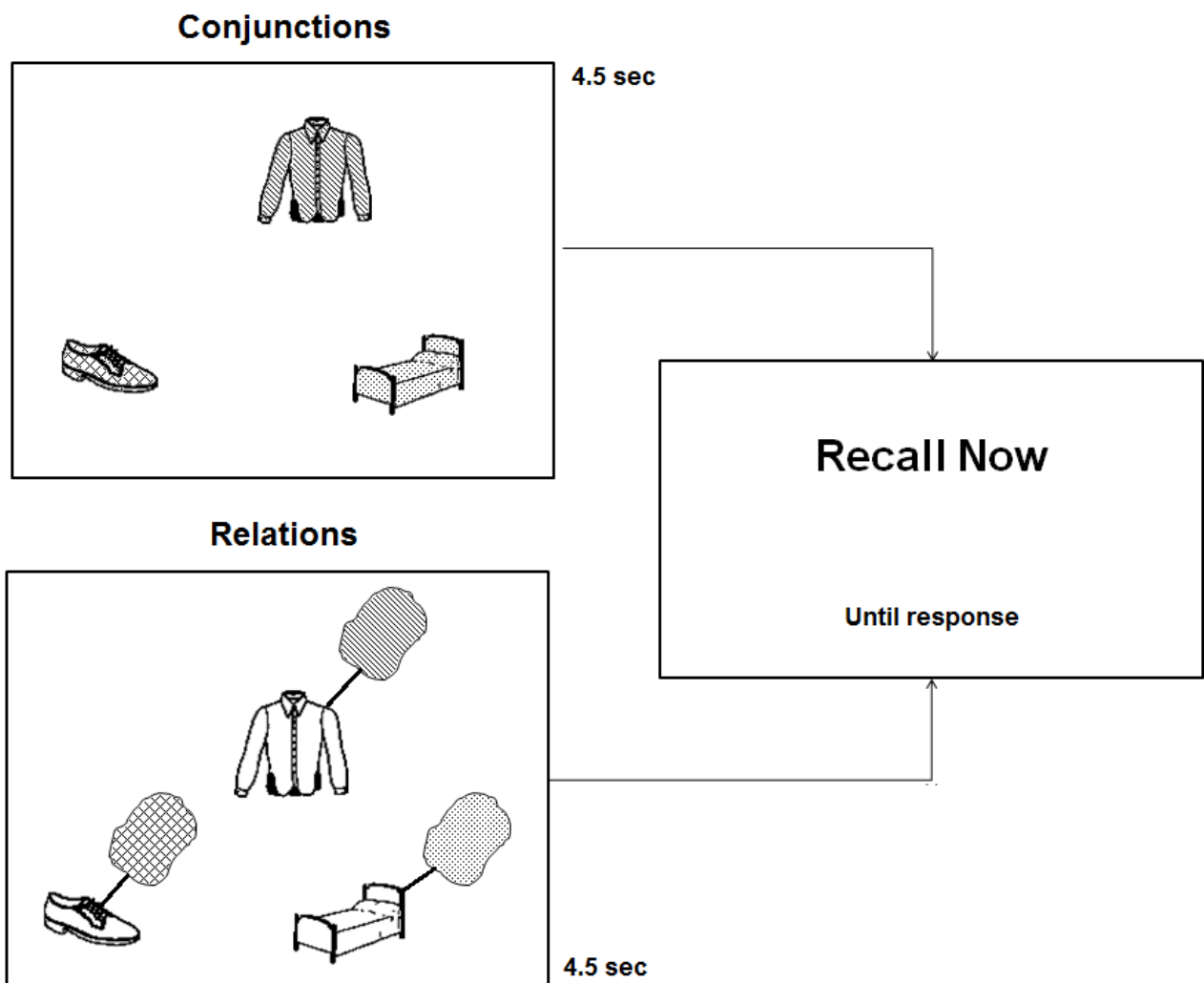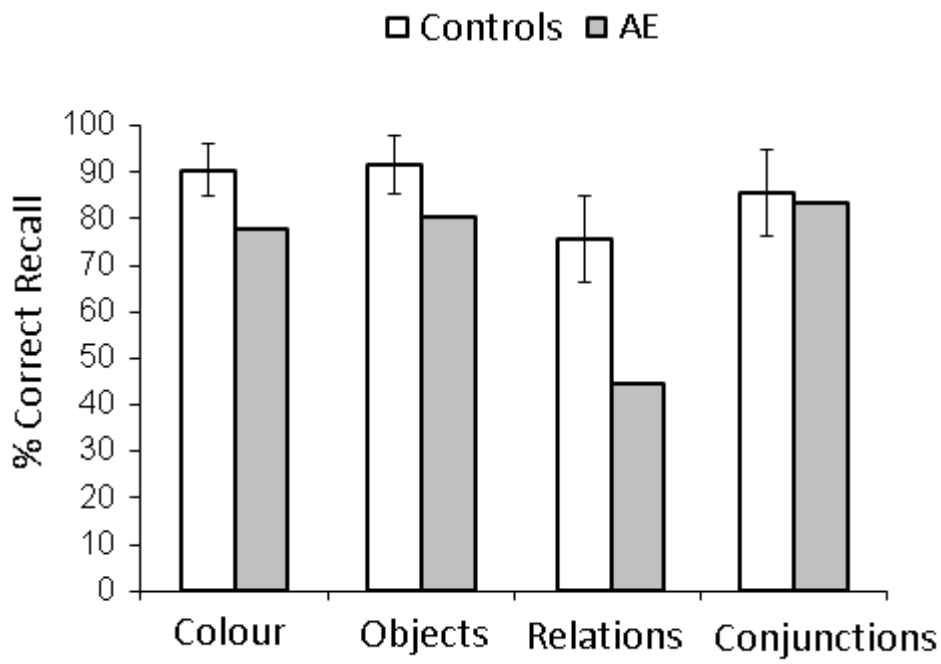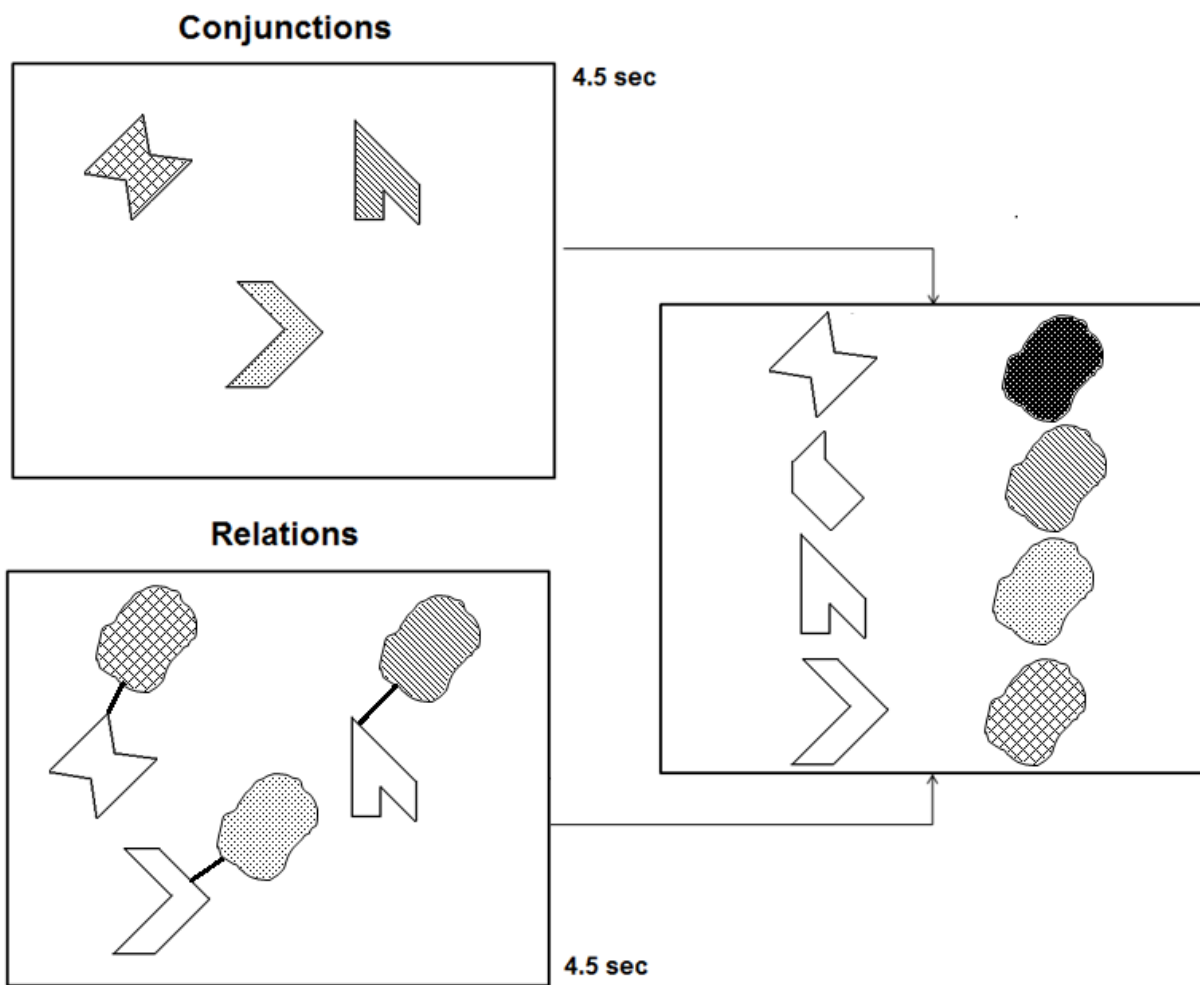
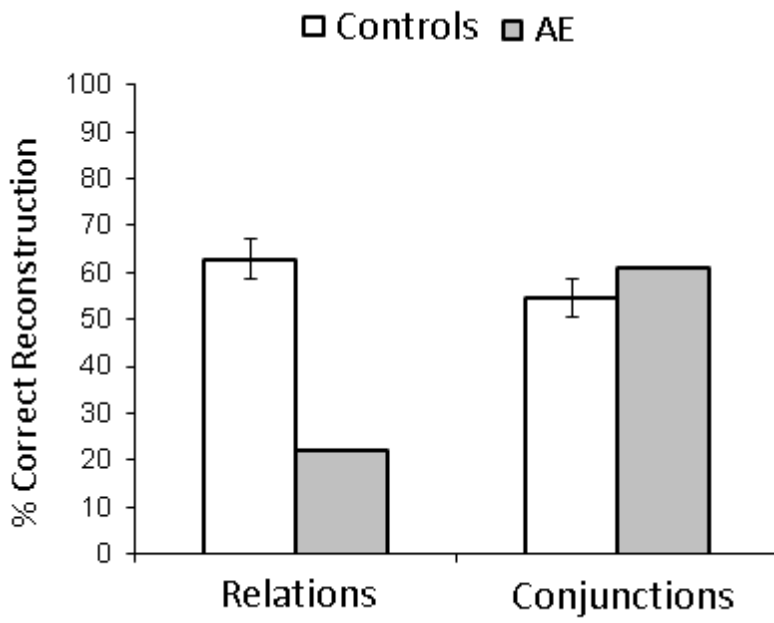**Figure 1.**

(A)

(B)

(C)

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Supplementary Material

MRI acquisition

Images were acquired with a GE Signa Excite MR scanner at 0.35T. The protocol included Fluid Attenuated Inversion Recovery (FLAIR) (TE/TR/TI = 107.492/8000/2000 ms, % FOV =75, pixel bandwidth = 40.7 KHz), fast spin-echo T2-weighted (TR/TE = 3820/102.6 ms, pixel bandwidth = 81.367 KHz) and T1-weighted (TR/TE = 420/25 ms, pixel bandwidth = 30.5078 KHz) all in axial orientation with slice thickness = 6, inter-slice gap of 6.6 mm and voxel size of 0.47x0.47x6.6 mm3. The in-plane acquisition matrix was 512x512 pixels. Coronal FLAIR and sagittal T2-weighted were also acquired, and the mean diffusion coefficient was generated.

Image analysis

The hyperintensities in white matter and subcortical grey matter were extracted semi-automatically by thresholding in the FLAIR image using the region growing algorithm of the Image Edit Tool in Analyze 11.0TM. The boundaries were obtained from seeds placed manually on the hyperintense regions and set at the intensity range: min – intensity threshold equal to six standard deviations above the mean intensity of the normal appearing white matter, max – maximum intensity. These white matter hyperintensities were visually identified as diffuse patchy areas larger than 3 mm in diameter and hyperintense with respect to the intensity of the normal tissues (grey and white matter) in T2-weighted and FLAIR, hypointense in T1-weighted and isointense in the mean diffusion coefficient image.

Separately, following the same procedure, the ischaemic lesion, hyperintense in the diffusion weighted image, was also extracted.