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Working memory binding:
Insights from neuroimaging, behavioural and clinical studies

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ABSTRACT

Working memory binding (WMB) entails the integration of multiple sources of information to form and temporarily store coherent object representations (or conjunctions). To date, cognitive research on binding has mostly focused on visual WM and change detection paradigms (i.e., the WMB task), and documented that WMB is a function sensitive and specific to Alzheimer's Disease (AD).

Following a review of the most relevant studies on the topic in Chapter I, this PhD project aimed at addressing two main pending questions: 1) Whether deficits in WMB tasks reveal abnormalities in individuals at risk of developing dementia, such as those suffering from Mild Cognitive Impairment (MCI); 2) Whether visual WMB deficits observed in AD may generalise for material processed across different modalities (i.e., crossmodal WMB).

The first aim was addressed in Chapters II and III. Chapter II reports on the results from an fMRI study showing that MCI patients' conjunctive WMB abilities are impaired compared to healthy controls, and that such WMB deficits are coupled with lack of activation in key brain areas of the temporo-parietal-occipital network subtending WMB mechanisms for feature conjunctions. Results detailed in Chapter III reveal that MCI patients' performance on the WMB task is associated with reduced connectivity of structural networks formed by white matter tracts across the whole brain. Importantly, this held true especially for those MCI patients with more severe WMB deficits.

The second aim was addressed in Chapter IV, which reports on crossmodal WMB mechanisms found to be impaired in AD, but not in healthy ageing. This was true regardless of the modality though which features were integrated.

Chapter V brings together the relevant findings from Chapter II through IV to review current understanding of WMB as a diagnostic tool for AD. Relevant contributions from the above-mentioned studies are discussed and further research questions generated in the light of current findings.

This PhD thesis suggests that WMB functions are disrupted in the course of AD, thus, acknowledging that WMB deficits are a hallmark of the disease since the initial stages of its continuum. As such, WMB tasks are recommended as a valid neuropsychological tool to assess patients cross-sectionally or to screen for patients to be included in intervention trials aimed at investigating long-term effects on the disease progression.

LAY SUMMARY

This PhD project aimed at bringing together novel neuroimaging, behavioural and clinical evidence to advance understanding on working memory binding (WMB). WMB entails the integration of multiple sources of information, such as shapes and colours or sounds and objects, to form and temporarily store coherent object representations or feature conjunctions.

Chapter I provides a detailed review of the relevant research on the topic. I discuss key findings from studies conducted on both healthy individuals and populations suffering from brain diseases, in which WMB tasks have been used. A specific emphasis has been placed on studies investigating WMB functions in the Alzheimer's Disease (AD) continuum. WMB has proved differentially sensitive to the various stages of the continuum from normal ageing to AD dementia. I have outlined how WMB deficits in AD are the result of abnormal changes occurring in the brain, which are thought to commence in the early stages of the pathology and before the disease damages the hippocampus. This is relevant because the hippocampus has long been considered a memory region affected by AD in its earliest stages, a notion challenged by recent findings. I highlight the reliability of the WMB task in assisting the detection of AD, and have contrasted this test with other promising memory tasks known to assess the function of the hippocampus. One such a task, namely the Free and Cued Selective Reminding Test (FCSRT), assesses the temporary retention and processing of associations between items (e.g., words and categories). The FCSRT is known to be sensitive but not specific to AD.

Chapter II and III address the first research question of this PhD thesis: Whether deficits in performing the WMB task reflect AD-related brain abnormalities in individuals at risk of

developing dementia, such as those suffering from Mild Cognitive Impairment (MCI). MCI is a stage within the AD continuum, characterised by a cognitive decline that does not severely impair the patients' daily living functions and their ability to live independently. In Chapter II, I present behavioural and fMRI data documenting patterns of brain activation in 22 MCI patients and 22 healthy controls while they performed the WMB task within the MRI scanner. Behavioural results show that MCI patients are outperformed by healthy controls when instructed to retain colour-shape conjunctions. fMRI results show that binding-related areas, previously observed in healthy subjects during the encoding and maintenance of colour-shape conjunctions, supported peformance in healthy controls but not in the MCI patients. Importantly, no hippocampal activation was observed during the task.

Chapter III reports on behavioural and brain connectivity data. Results from the analysis of the integrity of white matter connections among brain areas (DT-MRI) in 18 MCI patients and 18 healthy controls were contrasted with behavioural responses during the WMB task and the FCSRT. Behavioural findings confirmed WMB deficits in MCI patients relative to healthy controls. The combined analysis (i.e., DT-MRI and WMB) revealed that impairments in both the WMB task and the FCSRT are associated to loss of white matter connectivity in MCI patients. Deficits to hold colour-shape conjunctions in WM were better accounted for by abnormal structural connectivity in individuals with MCI than deficits during the FCSRT.

The last question of this PhD project is addressed in Chapter IV. That is, whether WMB deficits observed in AD may be generalised to stimuli processed across different modalities (i.e., crossmodal WMB). This is relevant because previous studies had mainly focused on tasks assessing the visual domain (i.e., unimodal WMB). In Chapter IV, I discuss behavioural studies showing that bindings of colours and shapes perceived through the visual modality only were temporarily maintained as well as bindings of colours and shapes perceived through the auditory and visual modalities at the same time by both healthy older adults and

patients with full-blown AD. Due to the lower overall performance in the AD group, these findings add to the evidence that WMB mechanisms are impaired per se in the course of AD, despite the modality through which information is integrated in WM.

The conclusions of this thesis are presented in Chapter V. I acknowledge that deficits to bind colours and shapes and temporarily maintain them as unitary objects are sensitive and specific to AD from its very initial stages. Thus, WMB deficits can be considered a hallmark of AD. The WMB task is recommended as a valid neuropsychological tool to support the diagnosis of AD among at-risk individuals, and also to select suitable candidates for AD clinical trials. This will likely lead to more reliable and affordable selection procedures, which can improve drug and intervention studies.

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CHAPTER I

PART I - MEMORY BINDING IN THE HEALTHY BRAIN

1.1 The concept of binding

The physical world surrounding us consists of multiple and various objects, each one made of several attributes, such as colour, shape, texture, or sound, that are processed in parallel by our primary sensory cortices for a prompt identification (Treisman, 1996). For instance, thanks to its oblong shape, its red colour, the green tuft and the freckled seeds, we will surely recognise a strawberry among apples and oranges.

Later cognitive mechanisms should enable the recombination of an object's key properties to store coherent representations, which will be employed for further task goals and actions (Allen, 2015; Treisman, 1996; 2006; Zimmer, Mecklinger, & Lindenberger, 2006). *Binding* is the brain function underlying these integrative processes. It operates at many levels of cognition, ranging from perception, memory and action, to form stable and meaningful experiences. Binding can occur for different features, across diverse domains and modalities, by involving both bottom-up and top-down cognitive processes and relying upon distinctive neural structures (Allen, 2015; Luck & Vogel, 1997; Treisman & Gelade, 1980; Wheeler & Treisman, 2002; Zimmer et al., 2006).

1.2 Binding in perception: An overview

The idea of combining attributes into bigger units is not new. Miller (1956) originally proposed the term *chunking* to indicate an active, strategic method to group elements together on the

basis of prior semantic or phonological relatedness. Chunking was thought to enhance cognitive elaboration through verbal rehearsal and increase the capacity limit of immediate memory (Miller, 1956; 1962). Nevertheless, the primordial research that conceived, and consequently investigated, binding as a reconstructive cognitive mechanism should be dated to the work of Anne Treisman on the *Feature Integration Theory* (FIT) (Treisman, 1988; 1996; Treisman & Gelade, 1980).

According to the FIT, the mechanism of binding features in perception occurs across two functionally independent and sequential stages. During the first pre-attentive stage, the diverse features within the visual scene (e.g., colours, shapes, orientation, etc.) are perceived in an automatic fashion. They are all encoded at once, but processed through neural maps as independent entities. Subsequently, attention is required to recover the relations among features and bind them accordingly (Treisman, 1988; Treisman & Gelade, 1980). Within this scenario, location seems to play an important role. The identification of to-be-bound features across precise locations contributes to the "master map" of locations, a sort of coordinate system that frames all the independent maps associated with single features. It is through such system that each individual map corresponding to every feature of interest is activated, achieving their integration and suppressing other irrelevant information. Therefore, any features that receive attention at the same time and location, being in the so-called *spotlight of attention*, will be combined together to form an *object token* (Treisman, 1985; 1996).

The main empirical evidence in support of the FIT came from Treisman and Gelade' study on visual search (Treisman & Gelade, 1980). Participants were shown displays of either coloured letters (conjunction condition) or letters and colours separately (feature condition), and asked to search for the target item among lures. Feature-absent trials were also included, in which only lures were displayed. Results were analysed in terms of reaction time

(RT) and search function. Evidence that RT was unaffected by the increasing display size endorsed the notion that features are registered automatically and in parallel in the pre-attentive stage. Conversely, in trials wherein the target was not depicted, participants were observed to operate a more exhaustive visual search to rule out the presence of targets. Further supporting data in favour of the FIT derived from errors occurring in the binding process, when the focused attention required to process features and/or conjunctions (i.e., features bound to form one single object) is diverted or overloaded. These errors, the so-called *illusory conjunctions*, are generated when a feature related to one object is associated with one or more features characterising another object (Treisman, 1996).

The FIT was widely analysed and criticised over time (see Quinlan, 2003 for a review), so that Treisman came up with a final amended version in 1992 (Treisman, 1992). The main points of the *FIT Version 2* can be summarised as follows:

1. Features are distinctively registered, once detected, in specific points of the feature maps. That is, horizontal bars, for instance, are separated from those appearing at an angle, while these ones, in turn, are differentiated from vertical bars. Unmoving features are segregated from moving features, colours are coded in specific points of the feature maps, sheer contrasts in others, etc.

2. When conjunction search has begun, the attentional focus must be narrowed to sequentially check a small number of features (possibly one) at time. This should also happen when features are normally difficult to detect.

3. Accessing a location in the master map is possible through the immediate recovery of objects' attributes from the corresponding feature maps.

4. The spotlight of attention is replaced by the *attentional window*, which operates as a selective filter on the master map of locations. The size of the window is variable and modulated by top-down control. Typically, when participants perform a visual search task, their attention is divided among stimuli displayed on the whole screen. Therefore, the detection of one feature rather than another depends on the narrowing of attention to its location on the master map.

5. Rapid conjunctions search is possible whenever features irrelevant to the task are inhibited on the relative feature maps. In addition, since this process results in the suppression of feature locations on the master map, it contributes to increased speed of search processing. Nevertheless, in order to identify feature conjunctions properly, it is necessary to establish the presence of a particular combination of features even though it will not be further processed. This binding process is attention-demanding.

Notwithstanding, one of the major critiques to the FIT was that the theory did not provide a framework to assess how binding operates at neural level (Treisman, 1996; Vogel, Woodman, & Luck, 2001). The *Temporal Synchrony Hypothesis* (TSH) attempted to address this.

The TSH envisages that features belonging to the same object are coded by neurons that will fire with high synchronicity, on the time scale of fractions of a second, and at different frequencies compared to neurons coding other objects. Extended populations of brain cells are recruited to form neuronal circuits or assemblies whereby the binding process is achieved through a rapid sequence of 'micro states'. These correspond to single constituent features discriminated from other items, backgrounds, temporal concurrencies, and so forth (Gray, 1994; Shadlen & Movshon, 1999; Singer & Gray, 1995; von der Malsburg, 1995). Studies on the visual cortex of cats and on the frontal cortex in monkeys have showed that

there is a positive correlation between the strength of anatomical connections among brain regions and the percentage of synchronised activity between them (Fries, Roelfsema, Engel, Konig, & Singer, 1997; Roelfsema, Lamme, & Spekreijse, 1998; Treisman, 1996). This suggests that binding by synchrony is a flexible and dynamic mechanism, which facilitates both neural transmission throughout short and long connectivity pathways and learning of bound information.

Moreover, Fries and colleagues (1997) demonstrated that the degree of neuronal synchronicity mirrors perceptual discrimination at early stages of visual processing (Fries et al., 1997). The authors found that monocular stimuli evoked synchronised discharges in the visual cortex of cats affected by strabismus. However, with binocular vision, the stimulus that continued to be perceived evoked an increased neuronal synchronicity, whereas stimuli falling outside the visual field caused the opposite pattern. Similar findings have been lately endorsed by two fMRI studies, revealing that segregated features that are part of the same object and retained as bound, a phenomenon known as perceptual persistence, increased neuronal synchronicity in early visual areas (V2, V3, and V4) and in the lateral occipital cortex (Caplovitz, Barroso, Hsieh, & Tse, 2007; Wong, Aldcroft, Large, Culham, & Vilis, 2009). Importantly, available attentional resources limit the number of items to be processed, setting the amount of distinct firing rates at about four to six concurrent objects (Hummel & Holyoak, 1997; Treisman, 1999).

To conclude, the TSH offered a first account to explain how feature binding is achieved at neuronal level, laying the foundations for more recent neuroimaging evidence on the topic. The notion of neuronal assemblies underpinning cognition resembles white matter connectivity patterns linking neural structures within the brain, whose integrity appears to be fundamental in the processing of bound information. I will discuss current perspectives and novel findings on the relationship between binding mechanisms and efficient brain

connectivity in more details afterwards (see *Section 1.13* and Chapter III).

1.3 Binding in working memory

In memory, feature binding entails the formation and consolidation of meaningful units of information and warrants their retrieval during online and long-lasting memorial processing (Zimmer et al., 2006). The following sections will focus on feature binding in working memory (WM)[1] - *working memory binding* (WMB) - as this is the system at the core of my research thesis.

1.3.1 Encoding bindings

To store information in memory, our brain firstly needs to encode it at perceptual levels: perceived objects are dismantled into bits and pieces and encoded individually through the synchronous firing of specialised brain cells. Attention is what keeps mutual features together; however, our attentional resources are limited and can be spread across a certain amount of stimuli at time. It follows that the complexity of an object may affect the encoding of feature bindings, as the more complex an object is (e.g., face), the more attention it requires and the more susceptible to forgetting it will be (Eng, Chen, & Jiang, 2005; see also Yonelinas, 2013).

Bound representations will constitute object tokens (Treisman, 1985; 1996), which will be stored in visual WM for further recall and recognition, in episodic long-term memory (LTM) as

[1] The terms "visual working memory" and "visual short-term memory" are often used interchangeably in the literature. However, some theories stress the differences between tasks that require storage only (which some would claim to rely on short-term storage mechanisms) and those that require storage plus manipulation of information (in what most would refer to as working memory; for reviews see Cowan, 2017; Logie, 2011). This PhD thesis addresses the latter.

consciously retrievable traces of particular events, and in semantic memory to contribute to the consolidation of learned associations. Object tokens can be modified and implemented over time by adding novel features and characteristics, and new object files can be built to represent novel items for which we have no prior representations (von der Malsburg, 1995; Zimmer et al., 2006). Thus, such interactive connection between what we perceive and what we remember is fundamental to process bound information for future reference. In primates, the inferior temporal cortex has been identified as the neural site where this interaction takes place, acting like a bridge between the visual areas (V4, DP, VOT), the medial temporal lobes, and the frontal cortices (Bell, Summerfield, Morin, Malecek, & Ungerleider, 2016; Connor & Knierim, 2017; Miyashita, 1993).

1.3.2 Maintaining bindings

Once encoded, the doubt remains about whether single features are maintained in memory and then put together at occurrence or unified objects are bound in perception and retained as such. Luck and Vogel (1997) suggested that the capacity of visual WM is determined by the number of encoded objects rather than the number of encoded features to be bound within them. A seminal study was carried out in which participants were instructed to detect the colour change, if any, between the study and the test displays consisting of one to twelve coloured shapes. Performance was nearly perfect for arrays containing about four items, and then accuracy systematically declined as set size increased up to twelve stimuli. The same pattern of results was found when participants were assessed with combinations of four diverse features (i.e., colour, orientation, size, and presence/absence of a gap). Again, participants could effectively remember four objects displaying four features all together (sixteen features in total) as well as four single features. In the same paper, Luck and Vogel ruled out the possibility that a similar performance might have reflected the involvement of

different storage systems to maintain features according to feature type – such as holding a set of four colours together, another set of four shapes, a further set of four orientations, and so on. Indeed, it was shown that the maximum number of maintained bound objects was still set to four when features were varied within one dimension (e.g., colour – colour bindings) compared to individual colours (Luck & Vogel, 1997).

Although similar results were replicated by following experiments (Vogel, Woodman, & Luck, 2001), thus supporting the *strong-object hypothesis*, Wheeler and Treisman (2002) failed to corroborate these findings. The authors were unable to replicate the finding that feature capacity increases when objects comprise within-dimension features (Wheeler & Treisman, 2002; see also Olson & Jiang, 2002). They argued that Luck and Vogel (1997) had adopted a change detection paradigm wherein the change had involved just one single feature at time. This hinted at the possibility that performance could have been based on memory for a particular feature rather than for binding. Also, in Luck and Vogel's (1997) paradigm, the change implied the depiction of a new feature in the test phase compared to the study phase, suggesting that feature binding was not actually necessary for studied objects.

Wheeler and Treisman (2002) run a new experimental study thereafter, by including a binding condition in which a pair of features was swapped between two items in the test display. Participants found it less demanding to recall six unicoloured objects compared to three bicoloured objects, hence, showing a decline relative to the performance in the binding condition. It was concluded that visual WM capacity is based on individual features and that attention is what allows feature bindings to be retrieved as such (Treisman, 2006; Wheeler & Treisman, 2002). Therefore, an alternative hypothesis supporting the feature-based format of visual WM representations was posited (i.e., the *strong-feature hypothesis*).

Thus far, many research studies have brought evidence to either the former (Gajewski &

Brockmole, 2006; Luck & Vogel, 1997; Luria & Vogel, 2011) or the latter hypothesis (Delvenne & Bruyer, 2004; Olson & Jiang, 2002; Parra, Cubelli, & Della Sala, 2011; Wheeler & Treisman, 2002; Wilson, Adamo, Barense, & Ferber, 2012; Xu, 2002). Contrasting results may be likely due to different factors occurring in experimental paradigms, such as the type of features to bind (e.g., colours and shapes, colours and orientations, etc.), the memory domains wherein feature bindings are maintained (i.e., verbal or visual), the process through which bound information is retrieved (i.e., recall or recognition), and the retrieval cues to adopt (i.e., whole displays or single probes) (Olson & Jiang, 2002).

Nevertheless, it is worth mentioning that Olson and Jiang (2002) proposed another hypothesis to account for the maintenance of bound material in WM. The *weak-object hypothesis* posits that feature conjunctions are held as well as single features in WM, even though the level of performance is lower when participants are asked to maintain the former rather than the latter (Olson & Jiang, 2002, Experiment 3). This suggests that memory binding occurs at a cost, and that multiple pools of resources are needed to carry out the binding of sensory information (Olson & Jiang, 2002).

I may conclude that the weak-object hypothesis raised two important questions:

1. If processing bound material requires additional resources compared to single features, will this also result in increased neural resources (i.e., brain activity) associated with binding functions?

2. If such resources are curtailed, such as in the course of both healthy and pathological ageing, for instance, are binding functions preserved?

These questions will be matter of discussion in the following sections.

1.3.3 Retrieving bindings

The process through which information is retrieved from memory appears to be a fundamental variable to take into account when investigating binding functions. Recall and recognition mechanisms are demanding to a different extent, with recall involving more effortful processing than does recognition. Indeed, recognition paradigms involve the re-presentation of the study material, allowing participants to benefit from environmental cues to remember information; conversely, very few retrieval cues are provided in recall tasks, and participants must necessarily initiate appropriate mental operations to perform them (Craik, 1983; Craik & McDowd, 1987; Gajewski & Brockmole, 2006).

Most of the literature on memory binding has focused on the use of recognition tasks over recall tasks (Allen, Baddeley, & Hitch, 2006; Luck & Vogel, 1997; Moses & Ryan, 2006; Olson & Jiang, 2002; Opitz & Cornell, 2006; Wheeler & Treisman, 2002). Specifically, a *change detection paradigm* is typically used, whereby, in conditions assessing binding, experimental stimuli are presented in both study and test displays as either identical or rearranged to form new combinations (with 50% probability each). In the different trials, a feature from two items of the study array swaps at test, and participants have to recognise whether or not the test items are the same or different in respect to the studied items (yes/no response).

Importantly, the design of change detection paradigms may differ in the presentation of the test material as either one single feature combination (i.e., single-probe display) or the whole memory array (i.e., whole-test display). These discrepancies at the retrieval stage have been observed to lead to differences in performance accuracy (Wheeler & Treisman, 2002). Specifically, Wheeler and Treisman (2002) showed that participants were more accurate to judge whether or not tested feature conjunctions had been previously seen in single-probe

displays (Experiment 3B and 4B) rather than in whole-test displays (Experiment 3A and 4A). The authors claimed that the whole-test display binding decrement was due to perceptual interference: when multiple items are presented at test, the attentional resources engaged to hold feature bindings in memory are reallocated to assess the whole display. In contrast, when one item only is presented at test, attentional resources do not need to be parcelled out (Wheeler & Treisman, 2002).

This is an important point to address in the light of the present PhD project. Indeed, WMB literature on healthy populations has often adopted single-probe paradigms (Allen et al., 2006; Allen, Hitch, & Baddeley, 2009; Allen, Hitch, Mate, & Baddeley, 2012; Karlsen, Allen, Baddeley, & Hitch, 2010; Ueno, Allen, Baddeley, Hitch, & Saito, 2011), whereas studies on clinical samples have utilised whole-display designs (Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012; Parra, Abrahams, Fabi, Logie, Luzzi, & Della Sala, 2009a; Parra, Abrahams, Logie, & Della Sala, 2009b; Parra, Abrahams, Logie, & Della Sala, 2010a; Parra, Abrahams, Logie, Mendez, Lopera, & Della Sala, 2010b).

However, an important aspect that should be taken into account is the number of to-be-retrieved items (i.e., set size). In clinical studies, the set size is usually calibrated according to participants' cognitive capacities (see Della Sala, Kozlova, Stamate, & Parra, 2018), and this procedure mitigates the attentional burden that the whole-test display usually implies.

1.3.4 Binding and working memory models

From a theoretical point of view, several models have attempted to define how feature bindings are processed in WM. In the following sections, I will focus on those models that have shaped the concept of WMB. This will better frame my research questions and findings.

1.3.4.1 The multicomponent model of working memory

The *Multicomponent Model of WM* (Baddeley & Hitch, 1974) was proposed to account for the "working" nature of short-term memory. WM has been defined as a limited capacity memory system that allows the temporary manipulation and storage of information while attention is needed for other purposes (Baddeley & Hitch, 1974). The model posited that sensory (perceptual) information accesses WM, which in turn draws information from LTM. WM is hence a workspace wherein new and old information can interact during action and learning (Baddeley & Hitch, 1974; 2018; Logie, 2003). Originally, the model comprised an attentive control system (*central executive, CE*), needed to supply attention whenever WM tasks are undertaken. The CE aids two temporary systems (the *phonological loop* and the *visuospatial sketchpad*), which are recruited to store and process verbal and visuospatial information, respectively, over short periods of time.

At a primordial stage, the Multicomponent Model did not account for any interaction between the two subsystems, and this started to be a problem as soon as the first results from studies on verbal WM span tasks came out. Specifically, it was found that participants were highly capable of reading out an increasing number of sentences and then recalling the last word of each. This appeared to be surprising since verbal spans are typically of about three sentences (Daneman & Carpenter, 1980; Daneman & Merikle, 1996). Moreover, the phonological loop was formulated with a capacity of about two seconds, thus, it cannot provide enough time to rehearse a big amount of information (Barrouillet & Camos, 2015). It was also observed that, when articulatory suppression – that is, the repetition of an irrelevant sound, such as "the", throughout the whole cognitive performance in order to prevent verbal recoding – was used, participants' recall of visually presented digits was reduced but not eliminated (Baddeley, Lewis, & Vallar, 1984). Finally, the visual similarity effect was seen to disrupt the immediate recall of sequences of words (Logie, Della Sala, Wynn, & Baddeley,

2000). There is therefore accrued evidence suggesting that the phonological loop and the visuospatial sketchpad do communicate. Then, how and where are such bound representations stored?

The addition of a fourth component (*episodic buffer, EB*) to the model responded to the question (Baddeley, 2000). The EB was initially theorised as a multimodal storage system, acting as an interface between the WM subsystems and LTM and depending upon the CE. If the CE controls access to and from the EB, it follows that an attentionally demanding concurrent task should negatively affect participants' performance in binding WM information (dual-task methodology).

In order to assess the generality of this conclusion, WMB was studied across two diverse paradigms, namely, the binding of features in visual WM and the binding of words in the comprehension and retention of prose (Allen et al., 2006; Baddeley, Allen, & Hitch, 2011a; Jefferies, Lambon-Ralph, & Baddeley, 2004).

Jefferies, Lambon-Ralph and Baddeley (2004) instructed participants to recall auditorily presented stories, sentences and lists of unrelated words while carrying out a concurrent visuospatial task (i.e., detecting the location of a star visually presented across an array of boxes). The authors hypothesised that, if binding words into sentences and sentences into stories is attention-demanding, then a concurrent task might be expected to impair story recall to a greater extent than sentence recall. Results reported the opposite pattern, namely, that the recall of unrelated words was more disrupted by the secondary concurrent task compared to the recall of coherent senstences and stories (Jefferies et al., 2004).

Similarly, Allen and colleagues (2006) demonstrated that recognition memory for visually presented colour-shape conjunctions was impaired by backward counting in threes no more than individual colours and shapes (Allen et al., 2006).

Results from both research lines (Allen et al., 2006; Jefferies et al., 2004) revealed that encoding and maintaining bound information in WM do not require greater attention than single constituent features. This clearly indicated that the storage of bound material in the EB is not governed by the CE. Baddeley (2007) acknowledged that the EB receives to-be-bound information directly from the visuospatial sketchpad and the phonological loop, further revising the Multicomponent Model as illustrated in *Figure 1* (Baddeley, 2007; Baddeley et al., 2011a; Baddeley & Hitch, 2018).

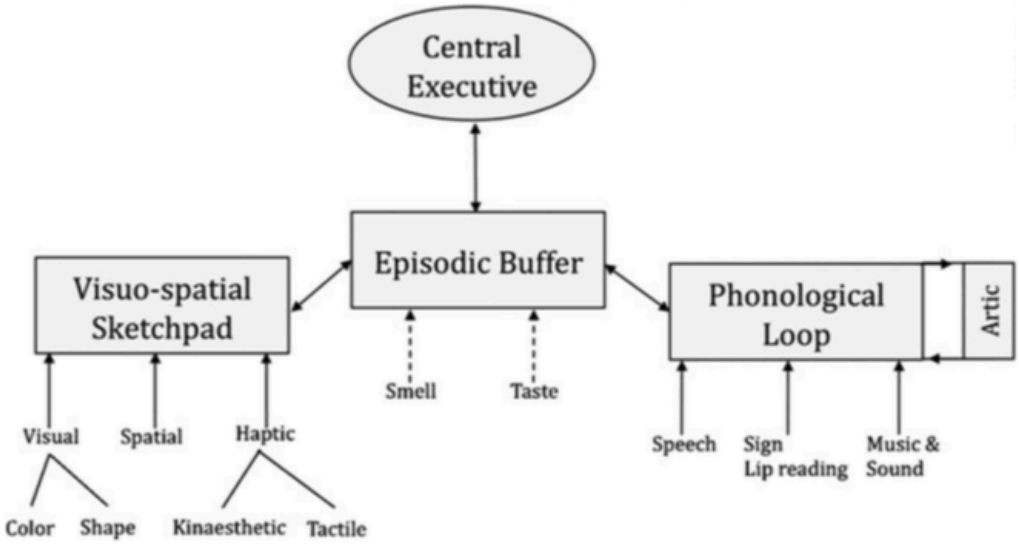


Figure 1 *– The current version of the Multicomponent Model of Working Memory (Baddeley & Hitch, 2018).*

1.3.4.2 The embedded-process model of working memory

The *Embedded-Process Model* (Cowan, 1999; 2008) proposes a definition of WM that is very similar to the one given by Baddeley and Hitch (1974), namely, a system that maintains

information accessible while carrying out any other task with a mental component (e.g., language production, problem solving, decision making, etc.). Nonetheless, the current model proposes a different WM structure and postulates the fundamental role of attention. The main attributes of the Embedded-Process Model are:

1. WM information is processed by hierarchically arranged faculties (as the word "embedded" indicates), comprising LTM, the sub-set of LTM that is activated, and the sub-set of activated memory that is in the focus of attention or conscious awareness.

2. The focus of attention is like a pointer, which highlights long-term representations to be used for future reference (resembling the EB). The focus of attention is limited in capacity, and its activation is limited in time.

3. The focus of attention is controlled conjointly by voluntary processes (resembling the CE) and involuntary processes (an attentional orienting system). For instance, if an item is presented through an ignored channel while attention is oriented elsewhere (e.g., being called by own name by a background voice), it automatically activates some information stored in LTM. Then, if such information is sufficient, it recruits attention by resulting in a deeper encoding.

4. Stimuli that have remained unchanged over time, and that are not important for individual's plans and actions, can still activate some long-term representations but outside awareness (i.e., habituation of orienting).

5. Awareness allows new episodic representations to be available for explicit recall.

According to Cowan's view, feature binding is possible through the focus of attention (Cowan, 2008). However, if it is true that binding requires attention, the same applies to those interference tasks that are carried out concurrently to prevent verbal recoding or the employment of greater attentional resources. It is thus unclear how the Embedded-Process Model accounts for evidence that bound information can be retained in WM no differently than unbound features (Allen et al., 2006; 2009; 2012; Karlsen et al., 2010; Jefferies et al., 2004). Likewise, this theoretical framework does not provide any clear interpretations of the processing of novel information which is not available from LTM (Logie & Della Sala, 2003). Nevertheless, the Embedded-Process Model has framed Cowan's work on the capacity limit of visual WM (Chen & Cowan, 2013; Cowan, 2001; 2008; Cowan, Blume, & Saults, 2013), laying the foundations for new research on the topic.

1.3.4.3 The concentric model of working memory

The distinction between information that is accessed at any moment for further processing (i.e., WM) and information held available in the background for later use (i.e., LTM) accounts for the relation between "processing" and "storage", and it is mediated by the focus of attention (Cowan, 1999; 2008).

Major evidence on this issue has been brought by Oberauer, Demmrich, Mayr, and Kliegl (2001), who instructed younger and older adults to work on a mental arithmetic task while remembering a list of three or six digits at the same time. In one condition, the list appeared to be unrelated with the arithmetic task, whereas, in a further condition, participants were required to substitute algebraic variables (i.e., x, y and z) in the task with digits previously seen. As long as the two tasks were unrelated, there was no effect of memory load on arithmetic problem solving; however, the substitution condition caused decreasing speed and

accuracy in the main task. The authors concluded that the focus of attention is not needed when the two types of memory information are stored separately (i.e., the “processing” and the “storage” functions of WM are independent), hence, in such circumstances, its limited capacity cannot impair task performance (Oberauer et al., 2001).

This and following experiments led Oberauer to postulate a model of WM organised in concentric regions (Oberauer, 2002), wherein:

1. The activated part of LTM allows the memorisation of information over brief periods for later recall.

2. The region accessed through awareness holds a limited number of chunks to be used during ongoing processes.

3. The focus of attention holds the one chunk that has been selected for the next cognitive operation. When this item is selected again, the operation is executed several hundred milliseconds faster than when a new item must be drawn from the experienced set.

In conclusion, Oberauer emphasizes the role of attention in processing short-term memory information, as either single features or objects, and claimed that the conception of diverse regions of processing may be in line with different subsystems serving WM, such as the ones proposed by Baddeley and Hitch (1974). Indeed, Hitch, Allen and Baddeley (2020) have recently encouraged converging evidence in favour of a structure of WM which may be common to all the relevant models so far outlined.

Nonetheless, there is a point I would like to raise. In both Cowan and Oberauer’s models, attention plays a pivotal role in the temporary maintenance of bound representations.

Recently, Ortega, López, Carrasco, Escobar, García, Parra and Aboitiz (2020) have studied WMB mechanisms in people with deficits in attentional control (i.e., people affected by Attention-Deficit/Hyperactivity Disorder, ADHD). Researchers have found that these subjects could retain bound information (coloured shapes) in WM as well as single features (shapes only), hence, postulating that frontal areas, usually affected in ADHD, do not serve binding functions. A posterior network, including parietal, temporal and occipital regions, seems to be involved instead, and I will address more evidence in this regard later in the present dissertation.

Taken together, unitary models which consider attention as the helm of WM operations - including WMB - would not help in interpreting both existing and emerging findings, especially in clinical populations. A multicomponent model that allows for fractionation of such functions would be more appropriate, and it is the one from which my assumptions derive.

1.3.4.4 Slots models

In *Section 1.3.2*, I have outlined how diverse theories (i.e., strong-object hypothesis, strong-feature hypothesis, weak-object hypothesis) have been posited to account for how bound representations are maintained in visual WM by determining its capacity limit (Luck & Vogel, 1997; Olson & Jiang, 2002; Wheeler & Treisman, 2002). At present, existing theories regarding the capacity of visual WM can be divided in two opposite models: (i) *slots models*, and (ii) *resource models* (Donkin, Tran, & Le Pelley, 2015; see also Schneegans & Bays, 2019).

Slots models postulated that visual WM consists of a fixed number of discrete memory slots, usually between three and five, each capable of storing one whole visual object with high

precision (Cowan, 2001; Luck & Vogel, 1997; Rouder, Morey, Cowan, Zwilling, Morey, & Pratte, 2008; Zhang & Luck, 2008). By contrast, if one object is not stored in one of the slots, there is a complete loss of resolution for that object. It follows that slots models are all-or-none models and posit that precise cognitive states (memory vs no memory) govern performance in visual WM tasks. Conversely, resource models proposed that visual WM relies on a limited pool of resources distributed across a variable number of items (Bays, Catalao, & Husain, 2009; van den Berg, Shin, Chou, George, & Ma, 2012; Wilken & Ma, 2004). If the number of to-be-rememered items is small, thus high-resolution memory representations of all objects can be stored; on the contrary, if the number of objects increases, there is a decrease in the memory resolution associated with each item.

These two accounts have been widely investigated with change detection paradigms (Donkin, Nosofsky, Gold, & Shiffrin, 2013; Donkin, Tran, & Nosofsky, 2014), leading to the conclusion that slots models are the most reliable to predict correct and incorrect responses (i.e., the probability of 'change' judgement) in this type of tasks. That is, slots models are better than resource models to account for binding memories and binding errors (Donkin et al., 2015; 2014). On this purpose, it has been demonstrated that, in experimental paradigms in which participants were presented with an additional to-be-ignored coloured shape (i.e., stimulus suffix) in the retention interval between study and test phases, they had difficulties to remember the most recently displayed items. It was assumed that the suffix drew perceptual attention and gained access to visual WM, where it interfered with representations already stored (Hitch, Allen, & Baddeley, 2020; Hu, Hitch, Baddeley, Zang, & Allen, 2014; Ueno et al., 2011).

Importantly, Hu and collaborators (2014) classified error types during binding tasks as *within-series confusions* and *extra-series intrusions*. Confusions are evident whenever participants can remember the features presented in the to-be-studied array without recalling the exact

combinations between them. These errors can be considered as reflecting an error in WMB. On the contrary, intrusions are made whenever participants recall one or more combinations that were not displayed in the to-be-studied array.

In conclusion, slots models rely on the relation between to-be-remembered items (*N*) (i.e., set size), the capacity limit (*k*) of individuals, and the probability (*d*) that test item is one of the *k* items stored in memory (Donkin et al., 2015). The mathematical formulas to calculate the probability of the observer to correctly detect the change (hit, *h*) and the probability of the observer to 'guess' the change occurred (false alarm, *f*) rates are:

$$h = a(d + (1 - d)g) + (1 - a)g$$

$$f = a(1 - d)g + (1 - a)g$$

g expresses the probability that the subject guesses that a changed occurred; *a* expresses the probability that the subject has paid attention to the array.

Taken together, slots models seem to suggest that bound information is stored in visual WM as single objects (feature conjunctions), hence, hinting at the existence of a memory substrate that underpins binding functioning (Schneegans & Bays, 2019). Moreover, the all-or-none nature of binding mechanisms explains deficits observed in clinical populations.

1.4 Binding and the multicomponent model of working memory

The Multicomponent Model of WM (Baddeley, 2000; Baddeley & Hitch, 1974) is the theoretical framework by which this PhD research project is borne. As previously outlined, this model relies on distinctive domains, such as the verbal and the visuospatial ones, which have characterised research trends to the extent that specific types of WM have been defined (i.e., verbal and visuospatial WM). Over the past two decades, there has been a growing body of literature investigating feature binding within and across these two WM systems.

1.4.1 Visuospatial working memory binding

Following the wide investigation of feature binding in the area of visual perception (Treisman, 1996; 2006; Treisman & Gelade, 1980), Allen, Baddeley, and Hitch (2006) aimed at assessing the maintenance of surface features (i.e., colour and shape) combined together in WM. Participants were presented with visual arrays of either four colours only, or four shapes only, or four colour-shape bindings across three separate conditions, and, after a brief retention interval, they were shown a probe. The probe was a previously seen colour, shape or coloured shape on 50% of the trials, whereas it was a new item in the remaining 50% of the trials. Crucially, in the binding condition, the new probes were obtained from the recombination of target features. Participants' task was to recognise whether the probe had been previously displayed or not. Results showed that highly demanding interference tasks and presentation modes (i.e., backward counting, digit recall, sequential vs simultaneous presentation) did not disrupt the retention of visually presented colour-shape bindings more than single colours and shapes. The authors suggested that maintaining individual features and feature bindings relies on the same amount of attentional resources, and that visual WMB can be achieved relatively automatically (Allen et al., 2006).

Brown and Brockmole (2010) came to contrasting results: the maintenance of colour-shape combinations was undermined by a concurrent backward counting task to a greater extent than individual features (Brown & Brockmole, 2010). However, few important differences between the latter study and the one conducted by Allen and collaborators (2006) should be taken into account.

Firstly, in Brown and Brockmole' (2010) study, participants performed the concurrent task throughout presentation, delay, and test phases, whereas, in Allen et al.' (2006) study, the interference task was carried out throughout presentation and delay phases only. This has possibly elicited different patterns of results, since the recognition judgement for bindings requires a more complex decision process compared to single colours and shapes. As a result, carrying out the WM binding task (WMBT) and the interference task at the same time inevitably leads to disruption (Baddeley et al., 2011a). Secondly, Brown and Brockmole (2010) presented three coloured shapes for 900ms, providing considerably longer encoding time than 250ms used by Allen et al. (2006) to display four combinations. It is possible that WMB can be achieved automatically as it takes place at perceptual level, hence, when stimuli are encountered briefly; it follows that longer exposures to bound information may activate more consciously controlled binding mechanisms (Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000b). Thirdly, colours are usually easier to recognise than shapes and colour-shape bindings (Allen et al., 2006; Brown & Brockmole, 2010; Song & Jiang, 2006; Wheeler & Treisman, 2002), and, by using a set size three, Brown and Brockmole (2010) found that participants performed almost at ceiling in the colour condition. This means that accuracy comparisons were only reliable between shapes and colour-shape bindings. Lastly, a final difference between Allen et al. (2006) and Brown and Brockmole' (2010) studies concerns the measures used for data analysis: the former authors adopted *d'* as a measure of correct recognition, whereas the latter used *A'*.

For all these reasons, Allen, Hitch, Mate, and Baddeley (2012) conducted a new study wherein: (i) interference tasks (i.e., articulatory suppression and backward counting) were performed across presentation, delay, and recognition probe test phases in each experimental trial; (ii) the presentation duration was set at 1000ms; (iii) set sizes were varied across the task to compare both encoding and maintenance of three and four items; (iv) data were analysed in terms of *d'* and *A'*. Results showed that concurrent demanding tasks disrupted recognition memory to the same extent for both single and bound features. Nonetheless, a significant interaction between condition and concurrent attentional load was found for *A'*, as emerged in Brown and Brockmole (2010). The authors claimed that this was due to the ceiling effect in the condition assessing memory for colours under articulatory suppression, thus results from both studies actually appeared to be consistent (Allen et al., 2012; Brown & Brockmole, 2010). In conclusion, Allen and colleagues (2012) confirmed previous findings, namely, that processing feature bindings in visual WM does not require more attentional support than do individual features (Allen et al., 2012).

To recap, binding visual features in WM is automatic and this is likely because such process relies on principles of grouping and symmetry (i.e., Gestalt principles) that take place automatically at perceptual stage (Baddeley et al., 2011a). The further step was then to study what happens when such principles can no longer operate.

Karlsen, Allen, Baddeley, and Hitch (2010) investigated visual WMB by separating features across space and time. Participants were presented with colours and shapes depicted as separated either on the same screen (spatial separation) or across two diverse sequential screens (temporal separation), and then asked to retain features as bound in order to perform the probe recognition task previously explained (Allen et al., 2006). Also, participants underwent a condition in which colours and shapes were already displayed as unique objects in the study phase; concurrent interference tasks were performed in each task. The authors

not only concluded that binding features across space and time in WM is possible, but also that the concurrent executive load does not differentially impact on separated compared to unitised WM bindings (Karlsen et al., 2010).

It is important to note that, albeit spatially and temporally separated, colours and shapes were still close in space and time. Postulating spatial and temporal dependence between to-be-bound features is essential to guarantee that our perceptual system does not bind everything in a pure automatic fashion, resulting in perceptual chaos. Therefore, Baddeley et al. (2011a) concluded that visual WMB is automatic just under specific constrained experimental conditions. Although the compelling evidence in favour of the automaticity issue (Allen et al., 2006; 2012; Gajewski & Brockmole, 2006; Johnson, Hollingworth, & Luck, 2008; Karlsen et al., 2010; van Lamsweerde & Beck, 2012; Vergauwe, Langerock, & Barrouillet, 2014; but see also Vul & Rich, 2010), contrasting results have emerged (Gao, Wu, Qiu, He, Yang, & Shen, 2017; Olson & Jiang, 2002; Wheeler & Treisman, 2002) and the reason why may be ascribed to the fact that feature binding is a fragile mechanism indeed.

Slight variations in experimental paradigms - using single probes rather than whole displays, using concurrent interference tasks at various difficulty levels, processing between-dimension (colour-shape) bindings rather than within-dimension (colour-colour) bindings, presenting to-be-bound information visually and requiring to carry out a verbal secondary task, etc. - may yield different results (Gajewski & Brockmole, 2006; Luck & Vogel, 1997; Olson & Jiang, 2002; Treisman & Zhang, 2006; Wheeler & Treisman, 2002; Xu, 2002). Furthermore, Cowan, Blume and Saults (2013) have suggested that memory bindings can break down and lose features, leaving only partial representations available at retrieval (e.g., we remember that a yellow object was displayed in the study array, but not that it was a circle). The authors concluded that a fixed number of objects (around four items) can be

stored in memory, and the retention of these objects' attributes may be incomplete (Cowan et al., 2013).

Finally, Hitch, Allen, and Baddeley (2020) have recently argued that, although processing bindings in visual WM does not require more attentional resources than single features, attention does play a key role in prioritizing such information and slowing down its forgetting (Hitch et al., 2020). Indeed, a certain burden of attentional refreshing, which the authors have referred to as 'focus of attention' to abide by Treisman's theory (Treisman, 1985; 1996) and Cowan's and Oberauer's models (Cowan, 1999; 2008; Oberauer, 2002), is fundamental to maintain one bound object, usually the last in the series, in WM. The remaining items undergo progressive fragmentation over time instead.

The pending question promoted by Hitch and colleagues in their recent paper (Hitch et al., 2020) is whether the focus of attention may be equated with the EB. It has been concluded that further research is needed to examine (i) whether the focus of attention has the same multimodal properties of the episodic buffer, and (ii) how wide the capacity limit of the focus of attention is. This would entail the convergence towards a common structural model of WM. Of note, the arguments presented by Hitch et al. (2020) are based mainly on experiments using serial presentation of to-be-remembered stimuli. Thus, more work will be also needed to disentangle processes involved in processing items simultaneously encoded and recognised based on whole-display decisions, and items sequentially encoded and recognised based on single-probe decisions.

Lastly, discussion has focused so far on processing visual items that are 'unitised' or 'conjoint', that is, encoded and stored as unitary objects. It is also informative to examine how attributes are bound in memory when they are not parts of the same object. On this purpose, a distinction has been made between *intrinsic* and *extrinsic binding* (Ecker, Maybery, & Zimmer, 2013), with the former entailing feature conjunctions (e.g., coloured

shapes) and the latter referring to binding between a given item and the context (e.g., associating a book with the location it occupies on the shelf).

When required to recognise a shape as either an old or new item, while colour changing was task-irrelevant, participants' performance was disrupted when the colour was intrinsic (coloured shape) and not extrinsic (neutral shape on a coloured background). Ecker et al. (2013) claimed that intrinsic colours and shapes are bound at encoding in an automatic fashion, and the further presentation of each single feature activates the retrieval of the whole unified representation. On the contrary, extrinsic information is not bound at encoding, thus, the authors suggested that active and strategic processes should be employed in order to retrieve similar bindings from memory (Ecker et al., 2013). Indeed, the two mechanisms are subserved by diverse neural structures and further discussion on this will follow in *Section 1.5*.

1.4.2 Verbal working memory binding

WMB has been investigated in the verbal domain as well. Baddeley, Hitch, and Allen (2009) tested the recall of sentence over word lists under diverse concurrent verbal and visuospatial tasks of varying levels of difficulty. Results showed that the temporary retention of bound sentences and single words was equally impaired, and the authors came to the conclusion that verbal WMB is aided by LTM-based syntactic and semantic processes (Baddeley et al., 2009). It was postulated that verbal WMB operates in a hierarchical fashion, starting from the integration of syllables and phonemes to create words, proceeding with the combination of words together to form meaningful sentences and phrases, and finally terminating with the binding of sentences to build concepts and narratives of complex episodes (Allen, 2015).

While Baddeley and colleagues (2009) studied WMB within sentences, Jefferies, Lambon-Ralph, and Baddeley (2004) explored WMB across sentences boundaries. Participants had to recall short sentences that were either presented within a coherent narrative or in a random, meaningless order while carrying out a concurrent visuospatial task. Results reported that the secondary task had a significantly larger disruptive effect on the recall of unrelated sentences in respect to sentences framed in a story. It was concluded that verbal WMB requires additional attentional resources only when connections between elements need to be newly constructed and do not fit into a meaningful narrative (Allen, 2015; Jefferies et al., 2004).

In the light of the objectives of this research thesis, and on the grounds of parsimony, I will not get into more details here. However, the cognitive and neuropsychological literature on verbal WMB is very wide and thorough as it derives from studies on language processing and the phonological loop.

1.4.3 Crossdomain working memory binding

More than ten years after its introduction, the addition of the EB to the Multicomponent Model of WM (Baddeley, 2000; 2007; Baddeley & Hitch, 2018) has mainly led to the study of how information is bound together within the visuospatial and the verbal domains, individually. This is in contrast with one of the fundamental characteristics of the EB, that is, its function as a multimodal storage. Research has recently focused on how information streaming from the two components can be bound together across diverse domains and modalities.

Prabhakaran, Narayanan, Zhao, and Gabrieli (2000) investigated the temporary retention of verbal-spatial bindings. Six young adults were recruited to perform a letter-location binding

task while undergoing an fMRI scan. The task involved four experimental conditions, two assessing recognition memory of single features (letters and locations), and two measuring the ability to temporarily maintain stimuli presented either as bound (letters were shown in the locations to remember) or unbound (letters were shown in a string at the centre of the screen). In the binding condition, participants were required to study four letters appearing in four different locations, and, after a brief delay interval, judge whether the features making up the displayed letter-location probe were previously seen or not.

Of note, participants were instructed to respond positively if both the probed letter and the probed location had been presented in the study array, regardless of whether they had been bound together in one object. Two types of positive-probe were then conceived: (i) positive congruent probes, resulted from the presentation of the same letter in the same location as seen in the memory array, and (ii) positive incongruent probes, resulted from the presentation of a previously seen letter displayed in a location that had been occupied by another letter in the memory array (Prabhakaran et al., 2000). Prabhakaran et al. (2000) found out that participants were more accurate and faster during congruent than incongruent trials, and concluded that verbal and spatial information is stored in an integrated fashion in WM.

Campo et al. (2005) used magnetoencephalography (MEG) to investigate the maintenance of bound verbal-spatial information in WM. Participants were instructed to study arrays of four ellipses and four words, and remember them and their locations afterwards. In the bound condition, words were placed within the ellipses (creating a ‘pair’), whereas, in the separate condition, words were presented at the centre of the screen. Ellipses were located randomly on the display in both conditions. After an unfilled delay period, participants were probed with three word-ellipse pairs. The word was a semantic category this time. Participants had to judge whether the semantic category presented in the test phase

matched with the semantic category of any words seen in the study phase, and whether the ellipse was in the same location as one of the ellipses previously displayed. Results showed that participants were more accurate in the bound rather than separate condition, and the authors concluded that the allocation of cognitive resources across diverse items interfered with the maintenance of separate information, making the maintenance of bound material easier instead (Campo, Maestù, Ortiz, Capilla, Santiuste, Fernandez, & Amo, 2005).

Studies outlined so far have left few controversies behind. Although Campo and colleagues (2008) lately postulated that crossdomain stimuli are stored as unified objects (in superior parietal lobe), Campo et al. (2005) showed similarly activated neural patterns in both unbound and bound tasks. This indicates that individual features are stored in parallel instead (Campo, Maestù, Capilla, Morales, Fernandez, del Rio, & Ortiz, 2008; Campo et al., 2005). Moreover, Prabhakaran and collaborators (2000) did not analyse the explicit retention of verbal-spatial bindings in WM since participants recruited in their study were asked to recognise features independently of their earlier combination (Prabhakaran et al., 2000).

Morey (2009) thus attempted to investigate whether features perceived across domains are stored by means of domain-specific or domain-general WM resources. The same experimental procedure as in Prabhakaran et al.' (2000) study was adopted, but the intentional maintenance of letter-location bindings was analysed this time. No incongruent probes were considered, and participants were instructed to respond affirmatively on the recognition of the same bound probe as seen in the memory array. It was demonstrated that, while articulatory suppression disrupted the retention of letters but not of spatial locations in single feature conditions (Experiment 1), it impaired the temporary maintenance of letter-location bindings (Experiment 2). Therefore, both domain-specific and domain-general WM resources concur in processing verbal and spatial material, but their involvement depends on which information is necessary to complete the task (Morey, 2009). These results supported

the conclusion that features encoded across domains can be maintained separately as well as discrete objects in a designated domain-general WM system (i.e., the EB) (Baddeley, 2000; 2007; Luck and Vogel, 1997; Vogel et al., 2001).

The above-discussed studies raise the question of whether combining verbal and spatial information together relies on attentional resources. Elsley and Parmentier (2009) tested young adults' capacity to hold letter-location bindings in WM while maintaining the pitch order of three pure tones, presented at the start of each trial. As in Prabhakaran et al.' (2000) study, the positive response was given whenever the probe presented a letter and a location previously displayed in the study array, regardless of their initial pairing (intact and recombined probes). It was observed that participants were faster and more accurate to recognise intact than recombined probes (Elsley & Parmentier, 2009; Prabhakaran et al., 2000), and that the concurrent interference task disrupted their performance in the binding condition. This suggests that binding between letters and locations requires attention (Allen et al., 2006; 2012; Elsley & Parmentier, 2009).

Importantly, Elsley and Parmentier (2009) only assessed implicit binding (see also Morey, 2011) and did not account for any single feature conditions. Langerock, Vergauwe, and Barrouillet (2014) were interested in addressing the role of attentional resources when holding explicit crossdomain bindings compared to individual features. Participants were presented with series of an increasing (from two to seven) number of letters, spatial locations (squares), and letter-location pairs (letters within the squares), and asked to remember the correct order in which they had seen them. For instance, after the retention interval, they recalled the series of letters by pressing the corresponding keys on the keyboard, the locations by clicking on the right squares, and the letter-location bindings by typing the letter once clicked on the location. Throughout the whole maintenance phase, participants were

required to carry out a tone detection task (judging whether a tone was low or high in frequency) (Langerock et al., 2014).

Results showed that WM span for crossdomain bindings, which accounted for no more than three items, decreased when the cognitive load induced by concurrent response selections increased. However, there was no interaction between cognitive load and the type of stimuli (single vs bound), meaning that the maintenance of crossdomain information does not need greater attention over and above that required for constituent features (Allen et al., 2006; 2012; Baddeley et al., 2009; 2011a). Also, it was further clarified that domain-specific interference (secondary verbal and spatial tasks) did not disrupt the maintenance of crossdomain combinations (Langerock et al., 2014; Morey, 2009).

Finally, there is compelling evidence that visuospatial and verbal information are not only mutually interactive, but the former can also boost the retention of the latter. The term *visuospatial bootstrapping* was coined to explain such supporting effect.

When asked to retain a series of digits by either showing them (i) one by one at the centre of a screen, (ii) or in a horizontal string across a screen, (iii) or on a keypad resembling the mobile phones 'T9' keypad, participants were found to achieve a better performance in the last case (Darling & Havelka, 2010; see Darling, Allen, & Havelka, 2017 for a review). More recently, Calia, Darling, Havelka, and Allen (2019) assessed participants with the visuospatial bootstrapping paradigm while carrying out two concurrent demanding tasks: constantly repeating out loud the sequence of days of the week or months of the year (rote rehearsal) vs saying out loud day and month responses by alternating them, and keeping their temporal order (attentional shifting). Results showed that overall memory performance decreased under attentional manipulation, however, the effect was not more disruptive in keypad than single digit condition. Displaying digits on the keypad was beneficial for participants' digit recall indeed (Calia et al., 2019).

Taken together, the literature on crossdomain WMB informs us on the interaction between WM domains, namely, the visuospatial sketchpad and the phonological loop, and warrants the conception of a domain-general WM system (i.e., the EB) responsible for storing integrated representations.

However, the literature on crossdomain WMB does not take into account whether and to what extent the modality of presentation of to-be-bound material may impact on WMB functions. On this purpose, the scientific literature distinguishes crossdomain WMB from crossmodal WMB. I will address crossmodal WMB implications in the consecutive paragraph.

1.4.4 Crossmodal working memory binding

The scientific literature discussed so far has focused on the binding of verbal and visuospatial material that were still both visually presented. Engaging separate sensory channels at the same time and elaborating incoming information in an integrated fashion (e.g., recognising an object from the sound it makes) entails a process known as crossmodal WMB.

To my knowledge, the first study accounting for crossmodal binding mechanism in WM was led by Maybery et al. (2009), in which young adults' capacity to retain auditory-visual information was assessed. On every trial, four letters were delivered by different loudspeakers aligned in azimuth around each participant, and, after the retention interval, a probe consisting of one letter from one loudspeaker was presented. Participants had to judge whether the letter had been heard before as well as whether the location (loudspeaker) had been used in the study phase. Consistently with Prabhakaran et al.' (2000) study, there were congruent and incongruent probes: the response was positive whenever both letter and

location were recognised, regardless of their original association. It was found that participants' performance was higher when undergoing congruent rather than incongruent probe trials (Elsley & Parmentier, 2009; Prabhakaran et al., 2000), confirming that auditory-visual bindings were actually encoded and maintained in WM (Maybery, Clissa, Parmentier, Leung, Harsa, Fox, & Jones, 2009).

Maybery et al.' (2009) study addressed the association between stimuli delivered across separate modalities. Specifically, these features were not merged together to form unified entities, but it was the temporary retention of their relationships what was tested.

Allen, Hitch, and Baddeley (2009) investigated how verbal and visual material is bound together to form unique, temporary mental representations (i.e., conjunctions). Younger adults were instructed to remember combinations of colours and shapes when: (i) presented as visual conjunctions; (ii) sequentially presented as visually separated entities; (iii) visual shapes were sequentially presented as blank outlines while colour names were delivered in synchrony through headphones; (iv) coloured blobs were sequentially depicted on the screen while shape names were delivered auditorily. Participants had to judge whether the test probe, consisting of a visually presented coloured shape, matched a previous combination in each of the four above-mentioned conditions. Three concurrent tasks (i.e., articulatory suppression, spatial tapping, and backward counting) were used across three different experiments to gauge both unimodal (visual) and crossmodal binding functions in recognition memory. Results showed that younger adults are able to bind features across modalities not requiring attentional resources above and beyond those needed to process feature conjunctions perceived through one single sensory channel (Allen et al., 2006; 2009; 2012).

In conclusion, research on WMB within and across domains, as well as across diverse modalities, is still expanding. There are still questions to be tackled, such as how these mechanisms may change across the lifespan or in the course of pathology, or whether or not

binding information coming from other modalities, such as vision and tact, may be achievable. I aim at responding to some of these queries, and potentially inducing new ones, in this research project.

1.5 Types of working memory binding

Despite the WM domains and the sensory modalities through which WMB is achieved, it seems clear now that feature binding can result in the formation of either single representations or paired associations. Summing up, this dichotomy accounts for the distinction between item memory and memory for the context in which the item is presented - including spatial and temporal information, associations with other relevant items, etc. - both widely investigated in WM. In this paragraph, I will address the difference between these two types of memory binding. To use the same terms found in the scientific literature (Moses & Ryan, 2006; Parra, Fabi, Luzzi, Cubelli, Hernandez Valdez, & Della Sala, 2015a), I will refer to them as *relational* and *conjunctive binding*.

Relational binding supports the retention of associations between memory items (e.g., objects and locations, names and faces, etc.) whereby elements are not bound into rigid inseparable representations, but rather maintained as individual entities. Consequently, each item can be retrieved independently or used as a memory cue to recall associative representations (e.g., a face cueing a voice). On the other hand, conjunctive binding mediates the maintenance of to-be-bound information to form new objects' identities (e.g., coloured shapes). It follows that each feature conjunction is more than the sum of its parts, and the later presentation of one feature either activates the whole combination or leads to no activation at all.

These two forms of memory binding dissociate in WM (Parra et al., 2015a) as well as in LTM (Mayes, Montaldi, & Migo, 2007; Moses & Ryan, 2006). Neuropsychological studies on amnesic patients have shed further light on the dichotomy between relational and conjunctive binding mechanisms by revealing that they are underpinned by diverse neural structures.

Olson, Sledge-Moore, Stark, and Chatterjee (2006b) assessed relational binding capacities in three patients with bilateral hippocampal damage. Patients, together with seven healthy older controls, were presented with visual arrays of *n* (with n= 3 or n= 6) green squares displayed at various locations on the screen. After the delay period (4000ms), a probe array with *n – 1* green squares re-appeared and participants had to indicate in which location the missing square was.

Results showed that amnesic patients performed worse than controls, at both memory loads (Ezzyat & Olson, 2008; Olson, Page, Sledge-Moore, Chatterjee, & Verfaellie, 2006a; Olson et al., 2006b; see also Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Mayes, Holdstock, Isaac, Montaldi, Grigor, Gummer, Cariga, Downes, Tsivilis, Gaffan, Gong, & Norman, 2004). In addition, Hannula, Tranel, and Cohen (2006) studied the capacity of amnesic patients to associate a single face with a complex visual scene, finding impairments at both long (e.g., 9000ms) and short (e.g., 1000ms) delays (see also Hannula, Ryan, Tranel, & Cohen, 2007).

It was argued that these studies more specifically reported hippocampal dysfunction in retaining relational and conjunctive binding in LTM, since too long retention intervals were adopted (Baddeley, Allen, & Vargha-Khadem, 2010; Baddeley, Jarrold, Vargha-Khadem, & 2011b; see also Nichols, Kao, Verfaellie, & Gabrieli, 2006; Shrager, Levy, Hopkins, & Squire, 2008). Moreover, item location was consistently used as an informative feature, and it is well-known that the hippocampus is engaged when spatial information is at play (Allen, Vargha-Khadem, & Baddeley, 2014; Burgess, Maguire, & O'Keefe, 2002; Hartley, Maguire, Spiers, &

Burgess, 2003; Holdstock, Mayes, Cezayirli, Isaac, Aggleton, & Roberts, 2000; O'Keefe & Nadel, 1978; Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001).

Two major points were left unsolved from the studies reported above:

1. Is the hippocampus needed to bind features within conjunctions in WM?

2. Posited that a neural dissociation between relational and conjunctive WMB exists and involves the hippocampus, does it still hold true when spatial information is not processed?

Baddeley, Allen, and Vargha-Khadem (2010) addressed the first question through an influential neuropsychological study. Patient Jon, who was diagnosed with a selective hippocampal malfunctioning (reduction of about 50% in both left and right hippocampi) due to a perinatal anoxia, was tested on his capacity to retain colours and shapes (i) presented as visually unitised bindings (Allen et al., 2006), (ii) presented in separate but adjacent spatial locations (Karlsen et al., 2010), (iii) or presented across different modalities (i.e., visual and auditory) (Allen et al., 2009). Results revealed that patient Jon's performance in each of these tasks equated that of six healthy controls, and the same emerged from a subsequent study in which patient Jon and healthy controls were tested with a range of complex visuospatial WM tasks (i.e., WM span task, speed of processing task, visual storage task) (Baddeley et al., 2011b). This proved that the maintenance of feature conjunctions in WM, as well as of other visuospatial WM information, does not rely upon the hippocampus (Baddeley et al., 2010; 2011b).

Regarding the second question, Parra and colleagues (2015a) analysed the relational vs conjunctive WMB dissociation by utilising non-spatial features (e.g., colours and shapes) as

relations (i.e., paired associations) or as conjunctions (i.e., integrated objects). The authors assessed patient AE - who suffered from ischemic lesions in the right medial temporal lobe (including the hippocampus), the right occipital lobe, and the right thalamus - and six older controls while performing the two binding tasks. In the conjunctive binding block, participants were told to remember the combinations of shape and colour within each object (e.g., a yellow car), while, in the relational binding block, they had to hold the shape and the colour forming each pair (e.g., the yellow patch next to the image of a car).

Patient AE had no difficulties in recalling conjunctions of features in WM, but he was unable to maintain associations with the same type and number of features (Experiment 1). The same pattern of results emerged from Experiment 2, whereby both patient AE and healthy normals were instructed to carry out two binding tasks entailing the visual reconstruction of either non-nameable colour-shape associations or conjunctions (Parra et al., 2015a). Although AE's vascular lesions were quite extended, the authors firmly stated that observed associative WMB deficits were specifically ascribed to disruptions in the medial temporal lobe, since LTM deficits were also found in the course of the neuropsychological assessment.

In a very recent single case study, Jonin, Calia, Muratot, Belliard, Duche, Barbeau and Parra (2019) examined the dissociation between relational and conjunctive WMB in patient KA, affected by severe and selective memory impairment due to the bilateral atrophy of the hippocampus, the fornix and the anterior thalamic nuclei following neonatal hypoxia (patient KA presented a disgnosis of developmental amnesia). To date, this is the first study to account for the relational vs conjunctive binding dissociation using assessment tools that are relevant to clinical settings.

After undergoing a neuropsychological assessment comprising reliable tests for both relational (retaining object-location associations, word-word associations, element-location associations, colour-shape associations) and conjunctive (retaining colour-shape conjunctions) binding capacities, results revealed that patient KA was not able to adequately perform relational binding tasks and hold three colour-shape associations in WM. Conversely, patients KA could retain three colour-shape conjunctions as well as normal controls. Finally, when tested after 15-sec (15000ms) delay filled with a verbal task, patient KA's performance dropped in both colour-shape associations and colour-shape conjunctions blocks (Jonin et al., 2019). The authors concluded that relational binding is responsible for associative learning impairments across test delays (i.e., LTM and WM), and it is highly dependent on the hippocampus contrary to conjunctive binding. Interestingly, colour-shape conjunctions were held by patient KA with no difficulties for 1-sec (1000ms) but not for 15-sec (15000ms), suggesting that low-level conjunctive binding mechanisms seem to operate only within WM (Jonin et al., 2019).

Taken together, the engagement of either one or the other binding mechanism is not due to the type of features to bind, rather to the format in which the information needs to be retained in memory and to the level of processing of that information, which may impact on either long- or short-term systems.

The hippocampus appears fundamental to process associations between features or items in WM, despite the presence of spatial information, but the question still remains about which neural structure serves the temporary maintenance of feature conjunctions. Recent neuroimaging studies have brought relevant evidence in favour of such dissociation; in addition, this dissociation seems particularly relevant to the literature on memory and ageing (both healthy and pathological).

1.6 Neural basis of working memory binding

Behavioural and neuropsychological evidence on the distinction between relational and conjunctive binding in WM has driven neuroimaging studies to investigate the neural correlates of such mechanisms. Prabhakaran and colleagues (2000) run an fMRI study to investigate the neural underpinnings of relational binding in WM. Participants were instructed to retain letter-location bindings or letters and locations separately (see *Section 1.4.3* for a description of the paradigm). Results showed that the maintenance of individual features activated posterior brain regions (i.e., middle temporal gyrus, premotor cortex, occipital gyrus, precuneus, cerebellum, inferior parietal cortex, cingulate cortex, middle/superior temporal gyrus, middle occipital/temporal gyrus), whereas the processing of letter-location associations caused a greater activation in the right prefrontal cortex (i.e., right middle/superior frontal gyrus). Baddeley (2000) acknowledged that this region would well be the neural correlate of the EB (Baddeley, 2000; Prabhakaran et al., 2000).

Besides prefrontal areas, other fMRI studies have confirmed the key role of the hippocampus to both temporarily encode and maintain relations between items. For instance, Piekema and collegaues (2006) tested healthy volunteers while performing a recognition task in the fMRI scanner in which they studied three different one-digit numbers, presented in three different colours at three different locations on the screen. After a variable delay (9000-20000ms), participants were instructed to judge whether the probed item, which could have been either a location, or a colour, or a number-location binding, or a number-colour binding, matched either a single feature or a combination seen before. Greater right hippocampal activation for the maintenance of number-location bindings was reported, while no hippocampal activation was registered for the retention of number-colour bindings or single features (Piekema, Kessels, Mars, Petterson, & Fernandez, 2006). The authors therefore concluded that the hippocampus is specifically involved in the online maintenance of associations with spatial

information (see also Hannula & Ranganath, 2008 for supporting results from an object-location binding task in complex scenes).

Nonetheless, similar findings were also confirmed without assessing memory for spatial information. Piekema, Kessels, Rijpkema, and Fernandez (2009) asked participants to study within-domain (i.e., house-house binding) and between-domain (i.e., house-face binding) associations while undergoing an fMRI scanning session. After the retention interval, they were presented with a probe which could either be a previously presented association or a recombined one (new combination of two previously seen items). It was shown that the temporary retention of both within- and between-domain associations activated the hippocampus and other medial temporal lobe (MTL) structures (including the bilateral parahippocampal gyri), but the degree of activation was inferior for information processed within the same domain. These findings confirmed that the MTL regulates the temporary processing of associations between items (Piekema et al., 2009).

In a further fMRI study, Piekema, Rijpkema, Fernandez, and Kessels (2010) accounted for the difference between intra-item and inter-item memory binding. Intra-item binding concerns the associations between an object and its features, so that, when bound together, they are perceived as a single entity (i.e., conjunctive memory binding); inter-item binding relates to relational configurations between separate items (i.e., relational memory binding). Participants were tested with a delayed-match-to-sample task wherein recognising face-colour bindings (intra-item binding with colour as the intrinsic feature), face-location bindings (intra-item binding with location as the extrinsic feature), and face-house bindings (inter-item binding) previously seen in the study display. Results revealed that retaining associations between faces and houses in WM activated the MTL, including the parahippocampal gyrus and the amygdala, in addition to the prefrontal cortex, the ventromedial prefrontal regions,

the superior parietal cortex, and the lateral temporal regions. The maintenance of spatial material (i.e., location) did not rely upon the MTL but on the superior parietal lobe instead.

The authors claimed that the discrepancy between this study and the one conducted in 2006 (Piekema et al., 2006), indicating the hippocampal recruitment for spatial processing, was due to differences in the duration of the delay period (9000-20000ms used in Piekema et al., 2006 against fixed 10000ms in Piekema et al., 2010). Finally, null results emerged for the retention of face-colour bindings, leading the researchers to postulate that face and colour are processed as a single item not requiring additional neural processing. Overall, it was concluded that the MTL is engaged in the binding of inter-item (relational) associations compared to intra-item (conjunctive) ones.

Parra, Della Sala, Logie, and Morcom (2014) measured the neural activation associated with encoding and maintenance of colour-shape conjunctions in WM compared to single features. Importantly, location was not used as an informative feature.
The presence of separate conditions accounting for the processing of bound and single features addressed whether conjunctive WMB has a neural cost, conversely to what argued by Piekema et al. (2010) for face-colour bindings. Furthermore, the authors used two binding conditions with different set sizes to assess that the requirement to bind features was not confounded with an increase in feature load.

Twenty-two healthy young adults were required to perform a change-detection task, consisting of four conditions, under the fMRI scanner. In the two single feature conditions (colour only and shape only), participants were presented with visual arrays of either four colours or four shapes and, after an unfilled delay, asked to judge whether a change had occurred in the test display. That is, they had to recognise whether two colours or two shapes from the study array had been replaced by new colours or shapes. In the two binding

conditions, either two or four colour-shape combinations were presented. Again, in the test phase, participants had to judge whether two shapes had swapped the colours in which they had been shown in the study display. Responses were given via buttonpress, pressing the button with the right hand to indicate that stimuli in the study and test displays were the same (50% of the trials) or with the left hand to state that the conjunctions in the study and test displays were different (50% of the trials).

Results yielded no binding-specific activity during the encoding phase, while the encoding of shapes activated regions within the ventral visual stream (i.e., right fusiform gyrus and left inferior temporal lobe). The authors stated that encoding shapes was a prerequisite to temporarily maintain both shapes only and colour-shape conjunctions (Parra et al., 2014). However, disctinct binding-specific and feature-specific activation was registered during the maintenance phase.

Regions engaged in the retention of bound features were located mainly in the left hemisphere, and included the fusiform gyrus, the postcentral gyrus, the superior and inferior parietal cortex, the dorsal premotor cortex, and the lateral occipital cortex. The role of parietal regions in the temporary maintenance of feature bindings has been identified in previous fMRI studies (Shafritz, Gore & Marois, 2002; Todd, Fougnie, & Marois, 2005; Todd & Marois, 2004; Xu, 2007; Xu & Chun, 2007), as well as the activation of lateral occipital regions (Song & Jiang, 2006; Xu & Chun, 2006).

Parra and collaborators (2014) claimed that the engagement of the fusiform gyrus and the lateral occipital cortex was specifically ascribed to the types of stimuli used as experimental material, and that parietal areas provided the ‘glue’ to keep features together during online processing (Birba, Hesse, Sedeño, Mikulan, Garcia, Avalos, Adolfi, Legaz, Bekinschtein, Zimerman, Parra, Garcia, & Ibañez, 2017; Parra et al., 2014; Tseng, Chang, Chang, Liang, & Juan, 2016). Crucially, the absent involvement of the hippocampus and other MTL structures

was consistent with prior behavioural and neuropsychological literature suggesting that these areas do not serve conjunctive memory binding (Baddeley et al., 2010; Piekema et al., 2006; 2010; Staresina & Davachi, 2010).

Colour-specific activity was observed in the left inferior frontal gyrus and the anterior cingulate, mirroring participants' tendency to rehearse colours throughout the task. Indeed, frontal regions have been seen to fire with the presentation of verbal material (Prabhakaran et al., 2000). This was not the case for shapes, as abstract polygons were possibly more difficult to verbalise. Finally, albeit no conclusion about the automaticity of encoding feature bindings can be drawn from this study, it was unequivocally demonstrated that maintaining bound information recruits different neural resources compared to individual constituent features. Moreover, processing either two or four conjunctions does not lead to any increase in brain activity (Parra et al., 2014; Xu, 2007).

The neural dissociation of relational and conjunctive memory binding mechanisms found support in research on cognitive ageing. The main objectives concerned the investigation of whether the two types of memory binding would highlight diverse neural and behavioural patterns in the older population as well as the estimation of the extent to which impairments in one type of memory binding or the other, or both, would be considered as a consequence of the age-related cognitive decline. This is an important field to explore in view of this PhD project.

1.7 Working memory binding in healthy ageing

As people get older, they start to experience ordinary lapses of memory - such as forgetting the location of common objects, the names of relatives or friends, etc. – which indicate that

some memory binding capacities change across the lifespan. Chalfonte and Johnson (1996) suggested that similar memory deficits stem from older adults' difficulty to bind features into complex episodes in LTM. Naveh-Benjamin extended findings from Chalfonte & Johnson (1996) beyond feature information and proposed the age-related Associative [2] Deficit Hypothesis (ADH) (Naveh-Benjamin, 2000). According to the ADH, age-related decrease in episodic memory is due to difficulties in binding features to form and retrieve new associations (Naveh-Benjamin, 2000; Nave-Benjamin, Guez, Kilb, & Reedy, 2004; Naveh-Benjamin, Guez, & Marom, 2003).

Chen and Naveh-Benjamin (2012) demonstrated that older adults also exhibit an associative deficit when undertaking WM tasks (Chen & Naveh-Benjamin, 2012; see also Mitchell et al., 2000b). As previously discussed, such associative deficits depend on hippocampal dysfunction (Baddeley et al., 2010; Parra et al., 2015a; Piekema et al., 2010) since hippocampal anatomical and functional integrity decline with healthy ageing (Geinisman, deToledo-Morrell, Morrell, & Heller, 1995; Raz, 2000). Supporting evidence derived from an fMRI study assessing both younger and older people's capacity to maintain object-location bindings in WM (Mitchell, Johnson, Raye, & D'Esposito 2000a). Results yielded a greater activation in the anterior hippocampus for younger adults only when bound information was processed compared to single features (age x condition interaction).

On the other hand, evidence showing an age-effect on the processing of feature conjunctions in WM has not been so clear-cut. Brockmole et al. (2008) tested both younger and older participants with the well-known WMBT (change detection). It was found that older participants' memory for colour-shape conjunctions was no more impaired than memory for single colours and shapes, compared to their younger counterparts (Brockmole, Parra, Della

[2] Studies on healthy and pathological ageing have initially aimed at addressing the processing of learned associations in LTM. Since then, the term "associative binding" has been usually preferred to "relational binding" when assessing these cohorts. This explains the change of therminology in this PhD thesis.

Sala, & Logie, 2008). Similar findings were further confirmed, demonstrating that healthy elderly are able to encode and retain bound as well as single features, despite short or long encoding periods, simultaneous vs sequential presentation of the stimuli, and the presence of irrelevant interference information to be ignored (Brown, Niven, Logie, Rhodes, & Allen, 2017; Rhodes, Parra, Cowan, & Logie, 2017; Rhodes, Parra, & Logie, 2015). Moreover, this holds true even for within-dimension (colour-colour) conjunctions (Parra et al., 2009b), and, more importantly, when the WMBT is adapted to a free recall paradigm (Yassuda, Carthery-Goulart, Cecchini, Cassimiro, Fernandes, Baradel, Garcia, Nitrini, Della Sala, & Parra, 2019).

Other studies reported that an age-related binding decline is indeed observable in WM. Brown and Brockmole (2010) found that a small age-related conjunctive binding deficit may accompany the normal ageing process, even when using the common change detection task. In their Experiment 2, older participants showed a reduced memory for colour-shape combinations compared to memory for single shapes (Brown & Brockmole, 2010). Also, Isella and colleagues (2015) reported a significant age x condition interaction using A' (but not proportion correct) with the older group achieving a lower level of accuracy in the conjunctive binding condition compared to younger controls (Isella, Molteni, Mapelli, & Ferrarese, 2015).

Of note, the study by Brown and Brockmole (2010) presented some important changes in the experimental design that made the task more demanding for older participants (see *Section 1.4.1* for a detailed description of such discrepancies). Specifically, the presentation time used by Brown and Brockmole (2010) might be argued to be too long for a WM paradigm (i.e., 900ms) (Allen et al., 2012). Someone may say that this possibly related the performance to long-term processing, on which age plays a disruptive effect (Naveh-Benjamin, 2000). Nevertheless, Rhodes, Parra and Logie (2015) have demonstrated that, by

presenting colour-shape bindings for both 900ms and 2500ms, presentation time does not account for age-related WMB performance.

Also, in Brown and Brockmole's (2010) experiment, the concurrent task was carried out throughout presentation, delay, and test phases of the WMBT, thus, interfering with the recognition judgement for bindings, which is more difficult than that for single colours and shapes. Therefore, such evidence, along with the lack of consistency between Isella et al.'s (2015) results, makes it hard to generalise the conjunctive WMB deficit in the ageing population.

To conclude, relational and conjunctive WMB is differentially impaired by normal ageing and it is established that the reason of this behavioural dissociation should be found at neural level. The recruitment of the hippocampus in the former mechanism, but not in the latter, clearly justifies these diverse lines of research.

1.8 Summary

There are some relevant theoretical implications that I would like to draw from this Part I of Chapter I before moving to the next section:

1. WMB has been largely investigated over the past two decades, since the Multicomponent Model has provided a useful account to drive its investigation. WMB within individual domains (i.e., verbal and visuospatial binding) has been examined more thoroughly than across domains and modalities (i.e., crossdomain and crossmodal binding), which have been addressed in young populations only. Thus, further research is still needed to address how the latter mechanisms, in particular, may operate in different cohorts.

2. The difference between recognition and recall memory is acknowledged, and recognition paradigms have been widely adopted to assess WMB capacities. The impact of recall procedures on the temporary retention of WMB is still quite unexplored, and it may be worth investigating whether, and to what extent, more retrieval-demanding tasks affect the processing of bindings in WM.

3. The hippocampus plays a fundamental role in the dissociation between relational and conjunctive WMB, independently of the spatial information processing (e.g., location) required in the task. Neuropsychological tests used in clinical settings should consider memory functions that are dependent and independent of the hippocampus very carefully, in order to not show sensitivity to signs of normal ageing and lead to more realistic diagnoses.

PART II - MEMORY BINDING IN THE PATHOLOGICAL BRAIN: THE ALZHEIMER'S DISEASE SPECTRUM

> *"[…] All my life I've accumulated memories - they've become, in a way, my most precious possessions. The night I met my husband, the first time I held my textbook in my hands. Having children, making friends, traveling the world. Everything I accumulated in life, everything I've worked so hard for - now all that is being ripped away. As you can imagine, or as you know, this is hell. But it gets worse. Who can take us seriously when we are so far from who we once were? Our strange behavior and fumbled sentences change other's perception of us and our perception of ourselves. We become ridiculous, incapable, comic. But this is not who we are, this is our disease. And like any disease it has a cause, it has a progression, and it could have a cure. […]"* (Still Alice - Lisa Genova, 2007)

In the first part of Chapter I, I have highlighted how the investigation of WMB capacities in amnesic patients and healthy elderly (Ezzyat & Olson, 2008; Hannula et al., 2006; Jonin et al., 2019; Mayes et al., 2002; 2004; Mitchell et al., 2000a; Olson et al., 2006a; 2006b; Parra et al., 2015a) has shed light on the role of the hippocampus in temporarily processing associations among features or items, but not feature conjunctions. The objective of this second part is to address current understanding of how WMB mechanisms operate in pathology, particularly in Alzheimer's Disease (AD).

AD is the most common type of dementia worldwide, counting 5.8 million of people in the USA and about 850,000 people in the UK in 2019 (Alzheimer's Association, 2019). No cure has been found yet but, since AD is a degenerative disease developing along a spectrum,

research is focusing on identifying the better stage in which interventions should be applied in order to halt AD progression. To do this, individuals at risk of AD should be correctly identified and included in clinical trials; however, at present, there is a lack of gold standards for reliable diagnosis.

I will then address why WMB functions in the course of AD seem to be a promising field to explore; however, I will first provide a brief clinical description of each stage of the AD spectrum.

1.9 The Alzheimer's disease spectrum: Historical overview and current perspectives

Alois Alzheimer, German psychiatrist and neuropathologist, discovered the syndrome called after him, the Alzheimer's disease, in 1906 (Hippius & Neundörfer, 2003). Patient Auguste D., who was admitted at the Frankfurt hospital where Dr Alzheimer was working in 1901, showed a complex set of symptoms never observed before and, importantly, too severe to be compared to typical age-related changes.

After Auguste D.'s death, Dr Alzheimer was able to dissect and study her brain. He noticed that her cerebral cortex was thinner than normal and deposits of proteins forming plaques and neurofibrillary tangles were spread all over it. Later in time, these formations were identified as beta-amyloid plaques and tau tangles and noticed to accumulate outside and inside neurons, respectively. Beta-amyloid plaques contribute to cell death by interfering with neuron-to-neuron communication (synapsis), while tau tangles prevent the transport of nutrients and other essential molecules within brain cells. As a result, the vain action of microglia (i.e., cells designated to activate the immune response to beta and tau proteins and clear the nervous system from the debris of dead and dying neurons) causes chronic inflammation and consequent deterioration (Bateman, Xiong, Benzinger, Fagan, Goate, Fox

et al., 2012; Xiong, Jasielec, Weng, Fagan, Benzinger, Head et al., 2016; Young, Oxtoby, Daga, Cash, Fox, Ourselin et al., 2014).

Alzheimer's discovery reached both scientific community and broad audience's interest, and soon another case, patient Josef F., drew the doctor attention. Josef F. was diagnosed with AD before death. The histological investigation confirmed the clinical diagnosis; however, Alzheimer noticed that there were no neurofibrillary tangles in the patient's brain but plaques only. Such a controversy was solved almost ninety years later, in 1995, when the Munich Institute of Neuropathology contrasted brain slide preparations from both cases (Auguste D. and Josef F.) through modern neurohistochemical techniques (Möller & Graeber, 1998). It was concluded that sings of plaques only and plaques and neurofibrillary tangles together characterise different stages of AD pathology (Hippius & Neundörfer, 2003; Lovestone, 2000; Möller & Graeber, 1998).

Current diagnostic perspectives (Albert, DeKosky, Dickson, Dubois, Feldman, Fox et al., 2011; Jack, Albert, Knopman, McKhann, Sperling, Carrillo et al., 2011; Jack, Bennett, Blennow, Carrillo, Dunn, Haeberlein et al., 2018; McKhann, Knopman, Chertkow, Hyman, Jack, Kawas et al., 2011; Sperling, Aisen, Beckett, Bennett, Craft, Fagan et al., 2011) have identified three stages within the AD spectrum:

1. Preclinical AD,
2. Prodromal AD,
3. Clinical AD.

It has been more recently proposed that each stage is characterised by a specific *biomarker* profile, resulting from the combination of diverse classes of biomarkers - factors that can be measured to indicate the presence or absence of a disease, the risk of developing a disease or disease progression – such as amyloid plaques, fibrillar tau, and neuronal injury, and by a cognitive profile, resulting from dementia-related clinical symptoms (Jack et al., 2018; Jack, Bennett, Blennow, Carrillo, Feldman, Frisoni et al., 2016).

At present, research is working on the combination of cognitive and biological markers to better understand how neuropathological signs affect cognition across the spectrum, that is, how the two profiles interact with each other. The ultimate goal is to aid earlier and more reliable diagnoses and more targeted therapeutic interventions (Jack et al., 2016; Jack, Wiste, Therneau, Weigand, Knopman, Mielke et al., 2019).

1.9.1 Preclinical Alzheimer's disease

In preclinical AD, individuals show measurable changes in the brain, cerebrospinal fluid, and blood (biomarkers) that indicate the forthcoming onset of AD. Nevertheless, these individuals have not developed AD-related symptoms yet, as deduced from routine neuropsychological assessments. The brain compensates for these early changes by enabling preclinical AD patients to function normally (Parra, Mikulan, Trujillo, Della Sala, Lopera, Manes, Starr, & Ibáñez, 2017; Parra, Pattan, Wong, Beaglehole, Lonie, Wan, Honey, Hall, Whalley, & Lawrie, 2013), a condition that is also typical of healthy ageing (i.e., *Scaffolding Theory of Cognitive Ageing* - Grady, 2002; 2008; Grady, McIntosh, Beig, Keightley, Burian, & Black, 2003; Park & Router-Lorenz, 2009).

So far, the preclinical stage of AD has been the least explored, however, two conclusions may be inferred about it: (i) albeit presenting biomarkers, it is possible that not all individuals are going to meet a full-blown AD diagnosis in future (Bennett, Schneider, Arvanitakis, Kelly, Aggarwal, Shah, & Wilson, 2006; Knopman, Parisi, Salviati, Floriach-Robert, Boeve, Ivnik, Smith, Dickson, Johnson, Petersen, McDonald, Braak, & Petersen, 2003); (ii) people, who will develop clinical AD indeed, are likely to be subject to genetic risk factors, such as carrying mutations in apolipoprotein E (APOE) gene, amyloid precursor protein (APP) gene, presenilin 1 (PSEN 1) and presenilin 2 (PSEN 2) genes (Bagyinszky, Youn, An, & Kim, 2014; Bertram & Tanzi, 2005; Sorbi, Forleo, Tedde, Cellini, Ciantelli, Bagnoli, Nacmias, 2001).

The APOE gene is responsible for the production of a protein that transports cholesterol in the bloodstream. Everyone inherits one of three forms (alleles) of the APOE gene (i.e., e2, e3, e4) from each parent, resulting in six possible genetic combinations (i.e., e2/2, e2/3, e2/4, e3/3, e3/4, e4/4) in the DNA. It has been found that having the e4 form of the APOE gene increases one's risk of developing AD, especially in younger age (Holtzman, Herz & Bu, 2012; Loy, Schofield, Turner, & Kwok, 2014; Mayeux, Saunders, Shea, Mirra, Evans, Roses, Hyman, Crain, Tang, & Phelps, 1998; Michaelson, 2014; Spinney, 2014; Ward, Crean, Mercaldi, Collins, Boyd, Cook, & Arrighi, 2012).

The APP gene is located on chromosome 21. Triplication of chromosome 21, leading to Down syndrome, results in the inevitable triplication of APP gene. Thus, individuals with Down syndrome are more likely to encounter early-onset AD pathology (Prasher, Farrer, Kessling, Fisher, West, Barber, & Butler, 1998).

Finally, PSEN 1 and PSEN 2 are two similar transmembrane proteins, designated to facilitate substances transport across the neuronal membrane. If misfolded, such proteins cause an overproduction of amyloid plaques resulting in the highest percentage of conversions to AD (approximately 30 – 70%), with people starting to develop symptoms in their 30s (Campion,

Dumanchin, Hannequin, Dubois, Belliard, Puel et al., 1999; Cruts, Hendriks, & van Broeckhoven, 1996; Lemere, Lopera, Kosik, Lendon, Ossa, Saido et al., 1996; Wolfe, Xia, Ostaszewski, Diehl, Kimberly, & Selkoe, 1999).

Having a family history of AD and sharing unhealthy environmental and lifestyle factors (e.g., diet, physical activity, etc.) may also increase the likelihood of developing the pathology (Green, Cupples, Go, Benke, Edeki, Griffith, Williams, Hipps, Graff-Radford, Bachman, & Farrer, 2002; Lautenschlager, Cupples, Rao, Auerbach, Becker, Burke et al., 1996; Loy et al., 2014).

1.9.2 Prodromal Alzheimer's disease: Mild cognitive impairment

People in the prodromal stage of AD exhibit a well-defined diagnostic profile, typically referred to as Mild Cognitive Impairment (MCI). MCI patients show evident AD-related neuropathological changes (e.g., high levels of beta-amyloid plaques) accompanied by memory (i.e., amnestic MCI) and/or other cognitive problems (i.e., multi-domain MCI) beyond what is expected for their age and level of education. Importantly, these symptoms do not interfere with their independence in daily living (Petersen, Doody, Kurz, Mohs, Morris, Rabins, Ritchie, Rossor, Thal, & Winblad, 2001).

Amenstic MCI patients have a higher predisposition to develop clinical AD compared to multi-domain MCI patients (Kantarci, Weigand, Przybelski, Shiung, Whitwell, Negash, Knopman, Boeve, O'Brien, Petersen, & Jack, 2009; Mitchell & Shiri-Feshki, 2009), and age is a risk factor in such case (Petersen, Lopez, Armstrong, Getchius, Ganguli, Gloss, Gronseth, Marson, Pringsheim, Day, Sager, Stevens, & Rae-Grant, 2018). Crucially, MCI may not warrant a definite risk of a future diagnosis of dementia, as only approximately 32% of MCI

patients convert to clinical AD within 5 years' follow-up (Ward, Tardiff, Dye & Arrighi, 2013; see also Mitchell & Shiri-Feshki, 2009). In the remaining cases, MCI may revert to normal cognition or remain stable. This variability may occur for several reasons, such as (i) the natural heterogeneity of recent and progressive impairments in memory within the examined group, (ii) the diverse selection criteria used to recruit patients across clinical studies, and (iii) the different ways through which criteria for conversion to AD may be applied (Daly, Zaitchik, Copeland, Schmahmann, Gunther, & Albert, 2000; Livingston, Sommerlad, Orgeta, Costafreda, Huntley, Ames et al., 2017). It is therefore important to carefully select MCI patients for clinical studies, by screening individuals for neurological and/or psychiatric diseases that may contribute to cognitive decline (see Chapter II and III). Also, it is crucial that large populations of MCI patients embark on longitudinal studies to better design intervention trials.

Researchers and clinicians are interested in raising awareness on AD-related early symptoms to make people approach health services earlier. Indeed, self-reported memory and thinking problems in older adults (i.e., subjective cognitive decline) may be a valid index of early AD dementia, which necessitates further examination (Buckley, Maruff, Ames, Bourgeat, Martins, Masters et al., 2016; Fernandez-Blazquez, Avila-Villanueva, Maestu, & Medina, 2016; Gifford, Liu, Lu, Tripodis, Cantwell, Palmisano et al., 2014; Jessen, Amariglio, van Boxtel, Breteler, Ceccaldi, Chételat et al., 2014; Jessen, Wolfsgruber, Wiese, Bickel, Mosh, Kaduszkiewicz et al., 2014; Reisberg & Gauthier, 2008; Reisberg, Schulman, Torossian, Leng, & Zhu, 2010).

1.9.3 Clinical Alzheimer's disease

As AD progresses along the spectrum, neuropathological signs and cognitive symptoms become more and more severe, affecting a wide range of brain functions, besides memory, as a consequence of the degree of damage to diverse neural areas. *Table 1* illustrates clinical symptoms due to AD dementia as opposed to cognitive flaws typical of healthy ageing. As a result, AD patients' independence in daily life is utterly impaired.

Table 1 *– Clinical signs of AD dementia compared to age-related cognitive decline*.

AD dementia symptoms	Typical age-related flaws
Memory loss: forgetting of recently learned information, important dates and events; asking for the same information over and over again; constant need to rely on memory aids (e.g., reminder notes, diaries, etc.) or family members to carry out easy tasks.	Tendency to forget some names and appointments, but remembering them later.
Planning and problem-solving deficits: difficulties to execute tasks according to a planned schedule (e.g., cooking by following a recipe, keeping track of monthly bills, payments, etc.); lack of concentration.	Making occasional errors.
Difficulties to complete familiar tasks: incapability to carry out daily tasks which used to be familiar (e.g., driving to a well-known destination, remembering rules of a card game, reading, etc.).	Occasionally needing help, especially when dealing with new technologies.
Time and space orientation loss: deficits to keep track of days, months, seasons, and years; mixing up the temporal occurrence of personal life events; AD patients tend to forget where they are or why they got there.	Being confused about the day of the week, but figuring it out later.
Deficit to understand visual images and spatial relationships: difficulties with reading and writing, judging distance, determining colours and contrasts; agnosia.	Vision changes due to age-related diseases, such as glaucoma, cataracts, macular degeneration, etc.
Language impairments: difficulties to find words (anomia); confabulations; tendency to repeat what already said; deficit to follow and take part in a conversation; aphasia.	Sometimes having troubles with finding the appropriate word (e.g., tip-of-the-tongue phenomenon).
Misplacing things and not retracing steps: tendency to put objects in unusual places and to not being able to retrace steps in order to find them. Sometimes, AD patients may accuse others to steal from them.	Misplacing things but being able to focus on retracing previous steps to find them.
Poor judgement: troubles with judgment and decision-making (e.g., poor judgement when dealing with money, neglecting personal cure and hygiene, etc.).	Making a bad decision once in a while.
Withdrawal from work or social activities: tendency to avoid social interactions or undergo leisure activities once loved.	Sometimes feeling weary of work and social events.
Changes in mood and personality: becoming suspicious, fearful, anxious and even aggressive.	Becoming irritable when a personal routine is interrupted.

As previously reported, age and genetics are substantial risk factors for AD pathology. Two forms of clinical AD have been proposed to account for the presence/absence of genetic factors. *Sporadic AD* is often used to indicate cases due to the co-occurrence of age and environmental and lifestyle variables as risk factors. It is also referred to as “late-onset AD” to strengthen its correlation with ageing. *Familial AD* (FAD), instead, refers to the burden of genetic factors on the early onset of the disease.

In conclusion, AD is a degenerative pathology developing along a spectrum and exhibiting aetiology and symptomatology at different magnitudes at separate stages. The definition of reliable tools to detect AD-related signs since stage I is essential for accurate diagnosis and rapid and targeted interventions.

On this purpose, research is working on the identification of good cognitive markers for AD which, based on Logie, Parra and Della Sala (2015), should meet the following criteria:

1. be sensitive and specific to AD since very early stages;
2. not show sensitivity to healthy ageing or other diseases;
3. not show improvements due to repeated testing;
4. avoid very low performance when the symptomatology becomes severe;
5. be able to identify impairments in daily living;
6. be not invasive;
7. be not sensitive to level of education or cultural background of tested individuals;
8. be easy to access, administer and interpret;
9. be low-cost.

A recent hypothesis paper has suggested which cognitive mechanism should be considered as a promising marker candidate.

1.10 Neuropathology in Alzheimer's disease: Explaining binding deficits

It is clear that AD is a degenerative disease characterised by amyloid and tau depositions causing neuronal and synaptic loss. These neuropathological signs commence in very early stages of the spectrum, leading to irreversible cognitive dysfunctions that reflect damages to precise neural structures. It is also clear that the development of tools and procedures able to detect cognitive deficits and identify their neural correlates on time is a fundamental step to hasten the diagnostic process and enrol at-risk patients in clinical trials.

It has been hypothesised that the diverse magnitude of AD-related cognitive impairments across the spectrum is ascribed to the pattern of diffusion of amyloid plaques and neurofibrillary tangles in the brain (Didic, Barbeau, Felician, Tramoni, Guedj, Poncet, & Ceccaldi, 2011). Specifically, neurofibrillary tangles first develop in the mesial temporal lobe and spread in a sequential fashion, starting from the medial portion of the perirhinal cortex, moving forward to the transentorhinal cortex, the entorhinal cortex, the hippocampus and finally reaching the temporal neocortex (Braak & Braak, 1991; Delacourte, David, Sergeant, Buee, Wattez, Vermersch, Ghozali, Fallet-Bianco, Pasquier, Lebert, Petit, & Di Menza, 1999; Van Hoesen, Hyman, & Damasio, 1991).

Therefore, atrophy of perirhinal and entorhinal cortices (i.e., anterior MTL network), occurring in the so-called "sub-hippocampal stage of AD" (i.e., Braak and Braak' stages I and II), has been posited as a hallmark of preclinical AD. It is also considered as a better predictor for the

conversion from MCI to clinical AD compared to reduced hippocampal volume, which is typical of the "limbic stage of AD" (i.e., Braak and Braak' stages IIII and IV) instead (deToledo-Morrell, Stoub, Bulgakova, Wilson, Bennett, Leurgans, Wuu, & Turner, 2004; Dickerson, Goncharova, Sullivan, Forchetti, Wilson, Bennett, Beckett, & deToledo-Morrell, 2001; Du, Schuff, Amend, Laakso, Hsu, Jagust, Yaffe, Kramer, Reed, Norman, Chui, & Weiner, 2001; Killiany, Gomez-Isla, Moss, Kikinis, Sandor, Jolesz, Tanzi, Jones, Hyman, & Albert, 2000; Stoub, Bulgakova, Leurgans, Bennett, Fleischman, Tumer, & deToledo-Morrell, 2005).

As outlined in the literature review on the dissociation between relational and conjunctive memory binding in Part I of the current chapter (see *Section 1.5*), damages to the anterior MTL network underpin context-free memory deficits, that is, the incapacity to remember item-related information (e.g., conjunctive binding) despite contextual material (Gour, Ranjeva, Ceccaldi, Confort-Gouny, Barbeau, Soulier, Guye, Didic, & Felician, 2011). By contrast, subsequent disruptions in the medial entorhinal cortex, the parahippocampal cortex, the posterior hippocampus, and the posterior cingulate cortex (i.e., posterior MTL network) lead to deficits in context-rich memory processing, namely, impairments to process associations among items and/or features (e.g., relational binding) (Didic et al., 2011).

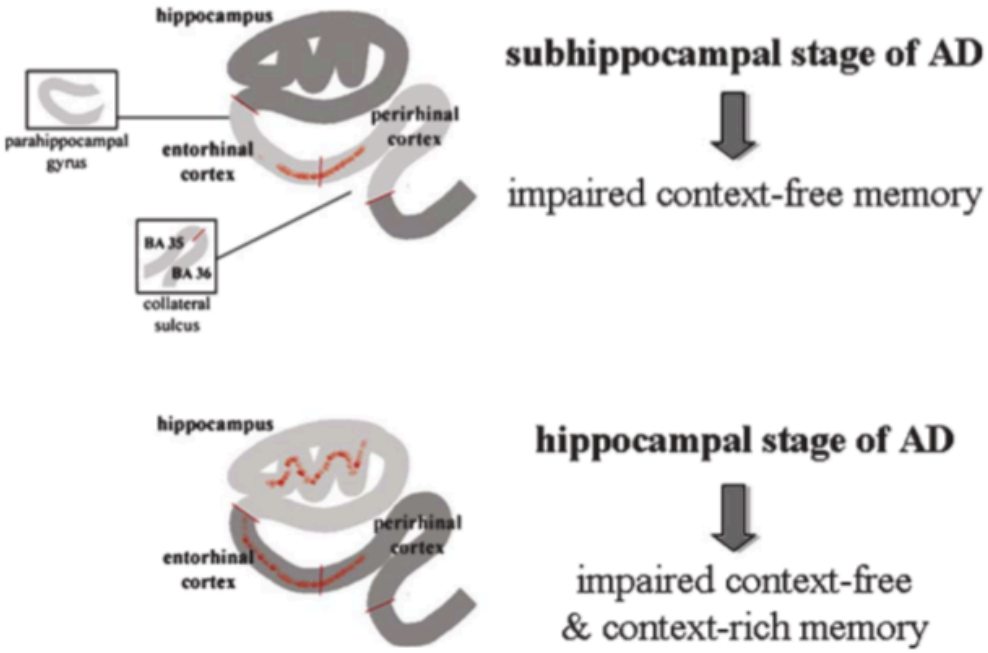


Figure 2 *– Neurodegeneration of MTL along the AD spectrum according to the hypothesis article by Didic, M., Barbeau, E.J., Felician, O., Tramoni, E., Guedj, E., Poncet, M., & Ceccaldi, M. (2011). Which memory system is impaired first in Alzheimer's disease?. Journal of Alzheimer's Disease, 27(1), 11-22. doi:10.3233/JAD-2011-110557*

To conclude, the hypothesis posited by Didic and colleagues (2011) provides a valid account to explain memory binding deficits in the course of neurodegeneration across the diverse stages of the AD spectrum. The model here proposed highlights that hippocampal dysfunction is a key feature of AD dementia, but not the earliest one to occur. Thus, relational memory binding tasks, which rely on the hippocampus, should not be recommended by consensus papers as markers for the early detection of AD. Nonetheless, scientific evidence supporting the reliability of these tests has been given credit for years, as I will discuss in the next paragraph.

1.11 Associative binding deficits in Alzheimer's disease

Swainson and colleagues (2001) attempted to identify which neuropsychological test was the most efficient in differentiating AD patients from healthy matched controls and from people suffering from depression or MCI. The Paired Associates Learning (PAL) task, taken from the Cambridge Automatic Neuropsychological Battery (CANTAB), showed this property (Cambridge Cognition, 2007). It was found that, when instructed to remember item-location pairs displayed in patterns of increasing length, AD patients performed worse than control groups (i.e., healthy controls, major depression patients, and MCI patients). Moreover, by splitting the MCI group in two clusters, Swainson et al. (2001) noticed that one subgroup yielded a performance similar to that of AD patients while the other equated healthy controls' level of accuracy. The authors labelled the former group "converter MCI" and the latter "non-converter MCI", and hypothesised that the PAL task could predict the conversion from MCI to clinical AD (Swainson, Hodges, Galton, Semple, Michael, Dunn, Iddon, Robbins, & Sahakian, 2001).

Fowler et al. (2002) corroborated the prior finding by assessing MCI patients and healthy controls longitudinally with the PAL task. Their results revealed that the subgroup of MCI patients who had presented impairments in recalling item-location associations, compared to the healthy normals, converted to clinical AD after 2 years (Fowler, Saling, Conway, Semple, & Louis, 2002). Other neuropsychological studies revealed associative binding deficits in AD and at-risk MCI patients, not only when testing their memory for object-location bindings (Blackwell, Sahakian, Vesey, Semple, Robbins, & Hodges, 2004; de Jager, Milwain, & Budge, 2002; Hanaki, Abe, Fujii, Ueno, Nishio, Hiraoka, Shimomura, Iizuka, Shinohara, Hirayama, & Mori, 2011; Huijbers, Bergmann, Olde Rikkert, & Kessels, 2011; Kessels, Feijen, & Postma, 2005; O'Connell, Coen, Kidd, Warsi, Chin, & Lawlor, 2004), but also for word-picture bindings (Algarabel, Fuentes, Escudero, Pitarque, Peset, Mazon, & Melendez,

2012; Lowndes, Saling, Ames, Chiu, Gonzalez, & Savage, 2008; Wolk, Dunfee, Dickerson, Aizenstein, & DeKosky, 2011), face-name bindings (Pariente, Cole, Henson, Clare, Kennedy, Rossor, Cipoloti, Puel, Demonet, Collet, & Frackowiak, 2005; Sperling, Bates, Chua, Cocchiarella, Rentz, Rosen, Schacter, & Albert, 2003), and word-colour bindings (Bastin, Bahri, Miévis, Lemaire, Collette, Genon, Simon, Guillame, Diana, Yonelinas, & Salmon, 2014).

Overall, these studies suggested that tasks measuring relational binding are sensitive to AD and useful for its early detection.

The PAL task from the CANTAB has been widely used until the 1990s, although substantial limitations, such as the high sensitivity to normal ageing and pathologies with robust hippocampal dysfunction, the long assessment duration, the extensive training to be administered and scored, and the high cost relative to other cognitive tests, were soon acknowledged (Logie et al., 2015).

The Free and Cued Selective Reminding Test (FCSRT) (Buschke, 1984; Grober & Buschke, 1987) has been more recently adopted. It requires participants to encode a list of items together with their semantic categories, and then remember as many of them as possible under free recall. Unrecalled items are then specifically tested with the provision of corresponding semantic categories as cues. Performance on this task is therefore measured by free and cued recall scores, the sum of which gives the total recall score. Lower free recall scores have been observed in at-risk individuals prior to a diagnosis of AD (Grober, Hall, Lipton, Zonderman, Resnick, & Kawas, 2008; Grober & Kawas, 1997; Grober, Lipton, Hall, & Crystal, 2000; Grober, Veroff, & Lipton, 2018; Lemos, Afonso, Martins, Waters, Blanco, Simoes, & Santana, 2016; see also Papp, Amariglio, Mormino, Hedden, Dekhytar, Johnson, Sperling, & Rentz, 2015), while the total recall index has been argued to distinguish AD from frontotemporal dementia patients (Lemos, Duro, Simões, & Santana, 2014).

Nonetheless, the FCSRT appears to be age-sensitive (Killin, Abrahams, Parra, & Della Sala, 2018), and patients with dysexecutive symptoms (e.g., vascular dementia patients, Roman, 2003) also perform poorer than controls on the test (Traykov, Baudic, Raoux, Latour, Rieu, Smagghe, & Rigaud, 2005). This indicates that the FCSRT is not specific to AD, thus, it cannot be considered as a cognitive marker for the pathology.

More recently, Buschke has proposed a modified version of the FCSRT, the Memory Binding Test (MBT), thought to be more sensitive to subtle cognitive changes in early stages of the AD spectrum, and hence more reliable to screen for patients who will likely develop AD dementia in future (Buschke, 2014; Buschke, Mowrey, Ramratan, Zimmerman, Loewenstein, Katz, & Lipton, 2017; Gagliardi, Epelbaum, Houot, Bakardjian, Boukadida, Revillon, Dubois, Dalla Barba, & La Corte, 2019; Mowrey, Lipton, Katz, Ramratan, Loewenstein, Zimmerman, & Buschke, 2016). The MBT notably measures participants' ability to recall two individually learned items in response to a single category cue (e.g., "tulip" and "carnation" to the clue "flower").

Finally, a new paradigm has been developed to test associative learning in AD. The Face-Name Associative Memory Exam (FNAME) is based on 16 face-name pairs and 16 face-occupation pairs that participants have to remember. The test appears to have a good reliability and concurrent validity (Amariglio, Frishe, Olson, Wadsworth, Lorius, Sperling, & Rentz, 2012), especially since it taps ecologically relevant associative skills. Moreover, test scores have been observed to correlate with amyloid load in people in the preclinical stage of AD (Lu, Nicholas, Collins, James, Parker, Lane, Keshavan, Keuss, Buchanan, Murray-Smith, Cash, Sudre, Malone, Coath, Wong, Henley, Crutch, Fox, Richards, & Schott, 2019; Papp, Amariglio, Dekhtyar, Roy, Wigman, Bamfo, Sherman, Sperling, & Rentz, 2014; Rentz, Amariglio, Becker, Frey, Olson, Frishe, Carmasin, Maye, & Sperling, 2011; see also Loewenstein, Curiel, Duara, & Buschke, 2018).

Although the MBT and the FNAME are quite novel and require further examination, the fact that all the tests reported thus far measure hippocampus-dependent relational binding capacities questions their reliability as cognitive markers for AD (Carlesimo, Perri, & Caltagirone, 2011; Foley, Cocchini, Logie, & Della Sala, 2015; Gainotti, Quaranta, Vita, & Marra, 2014; Logie et al., 2015). It may seem therefore plausible to deter their unique use in the diagnostic process.

1.12 Conjunctive binding deficits in Alzheimer's disease

Conversely from relational binding tasks, the WMBT (change detection paradigm) seems to comply with the definition of cognitive marker (see *Section 1.9.3*) (Rentz, Parra Rodriguez, Amariglio, Stern, Sperling, & Ferris, 2013).

To recap, the WMBT entails the maintenance of visually presented colours, shapes, and colour-shape combinations in WM, and, after a delay interval, participants are asked to judge if a change had occurred by indicating whether the study and test arrays were the same or different (Brockmole et al., 2008; Luck & Vogel, 1997).

To the best of my knowledge, the first study investigating conjunctive WMB in sporadic AD patients was conducted by Parra, Abrahams, Logie, and Della Sala (2009a). The authors tested both AD and healthy control groups' capacities to verbally recall arrays of either colours, or common objects, or colours and objects presented on the same screen but as separate entities, or, finally, coloured objects. Results showed that AD patients performed worse than healthy elderly overall. In addition, their memory was lower for colour-object conjunctions than for single features (i.e., colours and objects) and colour-object associations (i.e., unbound). These results were also confirmed when healthy controls were assessed with

an increased memory load compared to AD patients, suggesting that conjunctive binding deficits cannot be accounted for by a general memory impairment (Parra et al., 2009a).

The specificity and sensitivity of conjunctive WMB deficits in AD were investigated further by accounting for diverse domains (e.g., visual and verbal) and retrieval processes (e.g., recall and recognition). Parra and colleagues (2010a) were interested in determining that impairments in recalling feature conjunctions were not due to major depression (MD), a clinical age-related condition that can precede AD and characterise its early stages (Buerger, Zinkowski, Teipel, Arai, DeBernardis, Kerkman et al., 2003; Hill & Spengler, 1997; Jankowiak, 2002). The authors found that the AD group had great difficulties to perform the task, whereas the performance from MD patients equated that of healthy controls (Parra et al., 2010a). It was again concluded that conjunctive WMB deficits seem to be specific to AD.

Evidence that deficits to retain feature bindings in WM can discriminate between AD patients and healthy elderly (Parra et al., 2009a), and AD and MD patients (Parra et al., 2010a), raised the question of whether such impairments are typical of AD dementia or can be found in other types of dementia whose cognitive profiles overlap with AD. Della Sala, Parra, Fabi, Luzzi, and Abrahams (2012) tested patients affected by AD dementia, frontotemporal dementia, vascular dementia, dementia associated with Parkinson's disease, and dementia with Lewy bodies with the same verbal recall task used in Parra et al. (2009a). Participants were instructed to observe visual arrays of colours, objects, colours and objects unbound but presented simultaneously, and coloured objects (conjunctions), before being asked to verbally recall as many items as possible (Della Sala et al., 2012). Results yielded the specificity of binding deficits for AD patients and not for non-AD dementias.

Della Sala and collaborators (2012) adopted diverse set sizes for the experimental (patients) and control groups, hence, titrating the difficulty of the task to keep performance level on

baseline conditions (i.e., single features) similar across groups. Cecchini et al. (2017) conducted a similar free recall study on AD and frontotemporal dementia patients and older controls by utilising the same memory load. It was reported that people with frontotemporal dementia and healthy controls outperformed AD patients in the binding condition. This study supported the notion that WMB deficits are typical of AD dementia only, and confirmed the validity of the WMBT in clinical settings (Cecchini, Yassuda, Bahia, de Souza, Guimarães, Caramelli, Carthery-Goulart, Patrocinio, Foss, Tumas, Lima-Silva, Brucki, Nitrini, Della Sala, & Parra, 2017).

Summing up, conjunctive binding deficits in WM can differentiate AD patients from healthy elderly (Parra et al., 2009a), depression patients (Parra et al., 2010a), and non-AD dementia patients (Cecchini et al., 2017; Della Sala et al., 2012). All these studies have focused on the investigation of binding impairments in clinical AD, namely, in those patients who have already developed the pathology. Importantly, the WMBT has been also shown to be a valid tool to screen for people at risk of developing the pathology.

Parra, Abrahams, Logie, Mendez, Lopera, and Della Sala (2010b) assessed binding deficits in FAD patients. Also, they investigated whether similar deficits could distinguish between carriers, who had not yet developed AD as emerged from the neuropsychological assessment (preclinical AD), and non-carriers (controls) of the mutation E280A in the presenilin-1 gene (Lemere et al., 1996). Asymptomatic carriers, FAD patients and healthy controls were asked to perform the WMBT. Results revealed a clear impairment to maintain colour-shape bindings in WM in both preclinical FAD patients and asymptomatic carriers of the mutation. The authors also carried out an under the curve analysis to explicitly examine sensitivity and specificity of the WMBT to classify patients correctly. The task proved to be sensitive for detecting both FAD patients (sensitivity = 77%) and asymptomatic carriers (sensitivity = 73%), and for separating them from healthy controls (specificity = 83%). It

would be worth noting that such a classification power was achieved when none of the classical neuropsychological tests (i.e., Paired Associates Learning task, Recall of Rey-Osterrieth Complex Figure, Verbal Fluency Tests, Wisconsin Card Sorting Test, Trail Making Test) detected differences between groups (Parra et al., 2010b). 77% may not be great in other contexts, but in such a context it is appealing.

Taken together, results from Parra et al.' (2010b) study suggested that conjunctive binding deficits are not only sensitive and specific to AD but can also predict the onset of the pathology since very early stages, conversely to other neuropsychological tests (Parra et al., 2010b).

Koppara and colleagues (2015) tested WMB capacities in people likely to convert to sporadic AD, that is MCI patients, in people with a subjective cognitive decline and in healthy controls. Participants were instructed to study visual arrays of single shapes or colour-shape combinations, and then recognise whether the test display presented identical or different items. It was shown that people with subjective cognitive decline performed the WMBT worse than controls, however MCI patients exhibited the lowest level of accuracy when retaining both single shapes and feature bindings (Koppara, Frommann, Polcher, Parra, Maier, Jessen, Klockgether, & Wagner, 2015; see also Gatchel, Lopera, Norton, Baena, Guzman-Velez, Sanchez et al., 2020 for new diagnostic trajectories involving people with subjective cognitive decline).

The drop in accuracy in the single shape condition reported by MCI patients may have indicated a non-specific decline in WMB functions, however, the authors hypothesised that the same memory load (i.e., three stimuli) in both conditions might have precluded the specificity of binding deficits.

Parra, Calia, Garcìa, Olazaràn-Rodriguez, Hernandez-Tamames, Alvarez-Linera, Della Sala, and Fernandez Guinea (2019) verified that, with a lower memory load (i.e., two items), such

specificity is restored and MCI patients' performance mirrors that of AD patients (Della Sala et al., 2018). Strikingly, Parra et al. (2019) observed that a subgroup of healthy controls showed performance below a recently reported cut-off (Della Sala et al., 2018) despite an intact neuropsychological profile. A potential explanation may be that, under higher WM load, participants' capacities rely more on the hippocampus (Doherty & Logie, 2016; Unsworth, Brewers, & Spillers, 2013). Thus, with the three-item load, the paradigm is less specific to AD cohorts and a cognitive load of two stimuli has been proposed for diagnosis accuracy (Parra et al., 2019). Indeed, requiring participants to hold two items instead of three or four does not undermine the need of binding (Parra et al., 2014).

Taken together, WMB deficits are sensitive and specific to AD since preclinical and prodromal stages, and the WMBT has been proposed as a good cognitive marker to detect early signs of the pathology. One of the current aims of neuroscientific research is to combine a similar neuropsychological test with biological evidence to yield a more reliable procedure to predict the onset of the disease and actualise more rapid interventions. In the next section, I will better discuss to what extent current research on the topic has progressed.

1.13 Neuroimaging evidence of the reliability of conjunctive binding deficits to diagnose Alzheimer's disease

Although current diagnostic perspectives endorse the importance of biomarkers as 'gold standard' for early AD diagnosis (Jack et al., 2018; 2016), biomarkers alone appear to not wholly discriminate between dementia patients; they are invasive and painful (e.g., some techniques require a needle in the spine), very expensive (e.g., brain imaging), finally, they are just available in specialist centres with a highly trained staff (Logie et al., 2015). New

research is indeed aiming at unveiling a structural-functional coupling between behavioural impairments and neuropathological signs to endorse the reliability of the WMBT.

In a diffusion tensor MRI (DT-MRI; Basser, 1995) study, Parra and collaborators (2015b) measured white matter integrity in healthy older controls and in mutation E208A-PSEN1 carriers, who did and did not meet criteria for FAD, while performing the conjunctive (WMBT) and relational (PAL task) binding tasks. Results revealed that reduced white matter connectivity in frontal areas and in the anterior part of the corpus callosum coupled conjunctive binding impairments, whereas relational memory binding deficits reflected lower white matter integrity values in the frontal regions and the hippocampus (Parra, Saarimäki, Bastin, Londoño, Pettit, Lopera, Della Sala, & Abrahams, 2015b). Critically, this occurred in clinical patients only, while asymptomatic carriers did not show differences in brain connectivity compared to older controls. The authors concluded that the WMBT is able to disclose cognitive decline before neurodegeneration changes arise.

A more recent electrophysiological (EEG) study was carried out to investigate whether the well-documented binding deficits could be accounted for by altered brain information sharing mechanisms, as revealed by the EEG analysis of connectivity, in the prodromal stages of FAD (i.e., in FAD patients who showed a clinical profile compatible with that of amnestic MCI patients) (Parra et al., 2017). Researchers found the predicted structural-functional coupling in the sample of interest, suggesting that patients who have already embarked on the neurodegenerative course of FAD exhibit conjunctive binding impairments as patients in clinical AD. Brain connectivity analysis revealed that, during the WMBT, connectivity was reduced over frontal and posterior regions in FAD patients compared to controls, but, puzzlingly, correct trials were associated with increased connectivity over central regions. The authors concluded that MCI-FAD patients recruited a larger functional network to compensate for initial structural defects (e.g., loss of axons), and this elicited a major

connectivity to cope with the demanding cognitive task (Parra et al., 2017). Consistently, reduced modulations over both parieto-occipital and fronto-central regions have been also observed in MCI patients compared to healthy controls when performing the WMBT (Pietto, Parra, Trujillo, Flores, García, Bustin, Richly, Manes, Lopera, Ibáñez & Baez, 2016).

Interestingly, novel perspectives have suggested that a major focus should be dedicated to structures outside the MTL and parietal networks, such as the striatum and the basal ganglia, to explain conjunctive WMB deficits (Jonin et al., 2019). On this purpose, Valdes Hernandez et al. (2020) investigated the extent to which diruptions to temporarily store colour-shape conjunctions in MCI patients were due to volumetric changes in the above-mentioned structures. It was shown that regions within the striatum (i.e., globus pallidus) accounted for such impairments specifically, while changes in the hippocampal grey matter volume did not significantly correlate with impaired abilities to temporarily hold colour-shape conjunctions (Valdes Hernandez, Clark, Wang, Guazzo, Calia, Pattan, Starr, Della Sala, & Parra, 2020).

Taken together, the reviewed literature opens a new avenue in the investigation of neuropathological signs causing degeneration in the course of AD, and, more importantly, strengthens the reliability of the WMBT to detect them. Nevertheless, more research is needed on the links between memory binding – neurodegeneration across the AD spectrum as predictive evidence of conversion.

1.14 Summary

Research on conjunctive WMB in the AD continuum has highlighted some important points to meditate on:

1. AD is the most common form of dementia worldwide, and the lack of a reliable diagnosis, as well as of a cure, makes it hard to change these facts. The diagnostic process is usually hampered by the complexity of the disease itself, which appears to develop along a spectrum characterised by diverse stages displaying different cognitive and physiological symptoms. Therefore, there is currently a race towards the development of cognitive and biological markers to detect such impairments and carry out targeted pharmacological and rehabilitative interventions. Also, similar tools and procedures may be useful to sensitise both clinicians and health service users and guarantee a better prevention.

2. The WMBT is a powerful tool in this regard. Neuroimaging research has shown how deficits to maintain and retrieve feature conjunctions are associated with loss of white matter integrity and neural information sharing in patients at risk of developing AD due to genetic factors. However, at present, there is a lack of similar evidence in people who will develop the pathology in the course of ageing but who already present memory dysfunctions (i.e., MCI patients).

3. It has been hypothesised that conjunctive WMB deficits are ascribed to a sub-hippocampal phase of AD, corresponding to preclinical and prodromal stages; however, no fMRI studies have been conducted yet to localise such impairments and verify such hypothesis. In addition, an fMRI study may address whether AD-related

deficits are more greatly due to the encoding rather than the maintenance of feature bindings in WM.

4. Finally, research has focused on a visual WMBT to build a transcultural tool to assess dementia. However, very little is known about the generalizability of binding deficits in AD when using diverse types of material and/or presentation modalities.

These premises constitute the main hypotheses of my experimental studies, of which more will follow in the next chapters.

CHAPTER II

ASSESSING WORKING MEMORY BINDING DEFICITS IN OLDER PEOPLE AT RISK OF SPORADIC ALZHEIMER'S DISEASE: INSIGHTS FROM AN fMRI STUDY

2.1 Introduction

In Chapter I, I have reviewed the available literature on WMB functions by addressing significant research trends in both healthy and pathological individuals, with a specific focus on the AD spectrum.

WMB deficits seem to characterise AD since the very early stages of the dementia continuum, when first neuropathological signs (i.e., amyloids and tau tangles) also commence to appear (Didic et al., 2011; Parra et al., 2010b; Parra et al., 2019). Current research perspectives are devoting a great focus on combining cognitive and biological markers to investigate their co-occurrence in the AD aetiology.

To date, the neuroimaging literature on WMB deficits in the AD spectrum presents two important gaps:

1. Available MRI studies on WMB in AD have focused on familial AD (FAD). It is well-known that carriers of autosomal dominant mutations that lead to FAD (e.g., E280A-PSEN1) will inevitably develop dementia. The WMBT detects impairments from the asymptomatic phase of E280A-PSEN1 FAD (Parra et al., 2010b). An MRI study investigating white matter integrity in this variant of FAD showed poorer connectivity in frontal areas and in the anterior part of the corpus callosum when performing the conjunctive WMBT, by contrast, deficits to retain word-location associations (PAL task) reflected lower white matter integrity in the frontal regions

and the hippocampus (Parra et al., 2015b). Notwithstanding, the MRI correlates of WMB in patients with or at risk of non-genetic variants of AD dementia are unknown. Contrary to FAD patients, sporadic AD patients have typically developed the pathology in the course of ageing, undergoing a stage of transition between healthy and pathological ageing known as MCI. Neuroimaging research investigating the biological underpinnings of WMB deficits in MCI would contribute with novel evidence on the links between neural drivers of such cognitive impairments and current understanding of AD pathology in the prodromal stages.

2. There is currently a lack of fMRI evidence on WMB deficits in pathological populations. A temporo-parieto-occipital circuit has been previously identified in relation to conjunctive WMB functions, suggesting that healthy younger volunteers do recruit precise neural structures to process feature conjunctions instead of single features (Parra et al., 2014; see *Section 1.6* for a full description of the study). Accrued evidence suggests that the hippocampus, known to be severely impaired in AD dementia, is not involved in conjunctive WMB functions. It remains to be investigated if the regions suggested by Didic et al. (2011), specially those emerged from Parra et al.' (2014) study (i.e., the fusiform gyrus, the inferior temporal lobe, the postcentral gyrus, the parietal cortex, the dorsal premotor cortex, and the lateral occipital cortex), are engaged indeed in performing the WMBT once neurodegeneration has commenced. This would shed light on those brain regions whose functioning has been damaged by neuropathological changes since early stages of AD. Moreover, an fMRI paradigm might assess the diverse neural whereabouts of binding-specific activity during encoding and maintenance phases.

The fMRI study discussed in this chapter attempted to account for these objectives.

However, before discussing its methods and implications, it may be useful to provide a brief explanation of the relevant mechanisms and basic principles concerning fMRI design and methodology. This would hopefully guarantee a familiarisation with the fMRI environment.

2.2 Principles of fMRI

fMRI allows the identification of the neurobiological substrates associated with specific functions of the brain to understand how behaviour is determined. It provides maps detecting the locations of critical areas underpinning such fundamental functions, such as memory or language, which are crucial to make diagnoses and plan interventions during clinical assessments. The popularity of fMRI should be also ascribed to the fact that it is a safe (i.e., does not involve radiations), non-invasive technique applicable to both adults and children (Gore, 2003).

fMRI accounts for both functional and structural imaging of the brain across a temporal sequence, relying on a low spatial resolution but on a very high temporal one, on the order of seconds. Images are acquired in volumes (i.e., clusters of slices covering the whole brain) in 2-3 seconds under the fMRI scanner, a machine in which the individual must lay supine and face a monitor. The process through which images are produced is the result of a physical-chemical mechanism. The radiofrequency (RF) pulses, such as the echo-planar imaging (EPI) pulses, delivered by a superconductive magnet in the scanner, produce a magnetic field of between 1.5-7 Tesla (T), which alters the spinning of hydrogen protons in the water molecules of any body tissue of individuals. The alternation between induced spinning (transverse relaxation) and equilibrium phases or regular spinning (longitudinal relaxation) of water protons constitutes the MRI signal and forms images of the underlying tissue (Amaro & Barker, 2006).

Intensities in MR images may vary because hydrogen protons exhibit diverse magnetic field strengths (i.e., inhomogeneities) due to their surroundings. For instance, hydrogen protons in fat and hydrogen protons in free water molecules will have different relaxation times and, hence, will produce diverse contrasts (signals) in the MR image. Contrasts allow the differentiation between tissues within the brain, such as grey matter, white matter and cerebrospinal fluid (CSF), and are expressed by three constants: T_1, T_2 and T_2*. Specifically, T_1 refers to the realignment of the water proton spins to the magnetic field applied by the RF pulse; T_2 refers to the attenuation rate of the magnetic field after the application of the RF pulse; T_2* relates to T_2 but depends on local inhomogeneities caused by changes in blood flow and oxygenation (Amaro & Barker, 2006; Lindquist & Wager, 2015).

Such changes, better known as *blood oxygen level-dependent* (BOLD) changes, are the contrasts detected by fMRI (Ogawa, Lee, Nayak, & Glynn, 1990). More precisely, the BOLD signal represents changes in neuronal activity following a variation in the brain state, such as the one induced by a stimulus or a cognitive task (Gore, 2003). It is well established that an increase in neural activity in a particular brain region induces an increase in blood flow, which carries oxygen (arterial blood). Oxygen molecules are bound to haemoglobin through a chemical link (covalent link), and the balance between their electric charges creates a neutral molecule (diamagnetic molecule). However, once oxygen has been supplied to the cortical area of interest, such link is broken: oxygen is consumed, while deoxygenated blood (paramagnetic molecule) must be drained from the brain through the veins. The electric charge displayed by the deoxy-haemoglobin at this point causes distortions in the magnetic field: areas with higher concentration of oxy-haemoglobin give a higher signal (a brighter image) than areas with low concentration. This is the BOLD contrast imaging (Amaro & Barker, 2006; Gore, 2003).

The BOLD signal is mathematically expressed by the *hemodynamic response function* (HRF) over time (Friston, Fletcher, Josephs, Holmes, Rugg & Turner, 1998). The HRF presents an initial dip, resulting from the initial consumption of oxygen that has already flown across the area of interest before cognitive stimulation. Consequently, the BOLD response reaches peak amplitude in 4-6 seconds once increasing levels of oxy-haemoglobin have been supplied. Finally, the BOLD response returns to baseline in 10-12 seconds after stimulation (i.e., post-stimulus undershoot) (Buxton, Wong & Frank, 1998; Logothetis & Pfeuffer, 2004; Shah, Anderson, Lee, & Wiggins, 2010; Yacoub, Shmuel, Pfeuffer, van der Moortele, Adriany, Ugurbil, Hu, Haacke, Lin, Hu, & Thulborn, 2001). *Figure 3* shows an example of the canonical HRF.

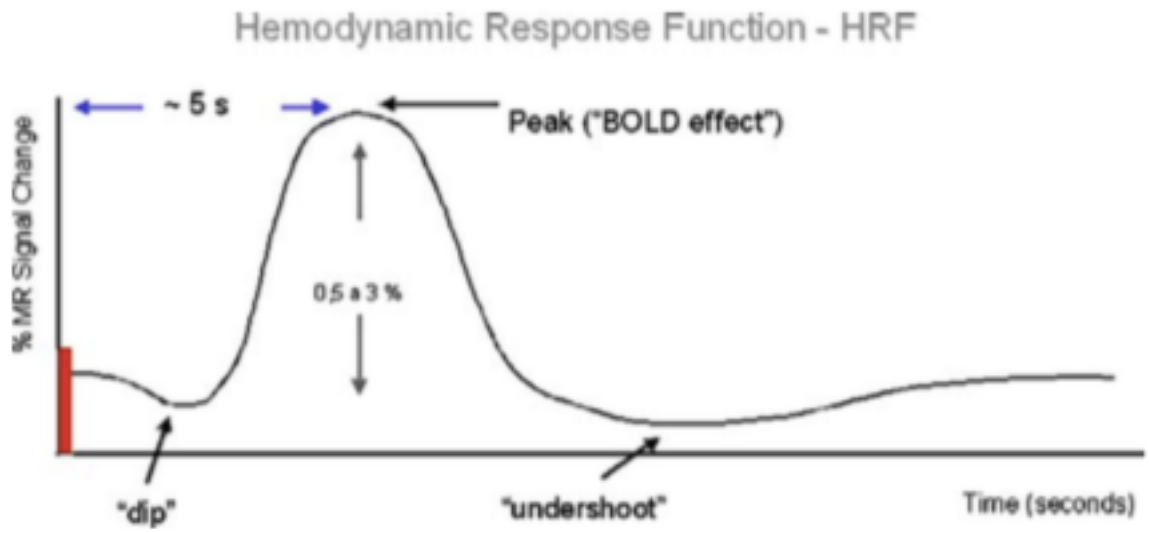


Figure 3 *– HRF from a hypothetical short duration stimulus, as depicted in Amaro Jr., E., & Barker, G.J. (2006). Study design in fMRI: Basic principles. Brain and Cognition, 60(3), 220-232. doi:https://doi.org/10.1016/j.bandc.2005.11.009*

The HRF can be detected in specific points of the brain/MR image, called *voxels*. The voxel is a 3D analogue of a pixel, whose size, typically measuring 3mm x 3mm x 3mm, is determined by slice thickness and field of view (i.e., slice dimension). Activated voxels allow the construction of maps of localised signal to be compared to a model of expected BOLD response to the paradigm in order to check for statistical significance. The common method to analyse these maps, and to test hypotheses on functional imaging data across diverse conditions or individuals, is to use *statistical parametric mapping* (SPM) (Ashburner & Friston, 1999; Friston et al., 1998; Friston, Holmes, Worsley, Poline, Frith, & Frackowiak, 1995; or see http://www.fil.ion.ucl.ac.uk/spm).

On this purpose, a software, called SPM, has been implemented over recent years. It is very popular worldwide, and it has been used in the fMRI study described in this chapter too.

2.2.1 Event-related fMRI

In order to better detect transient variations in the HRF and allow a greater temporal characterisation of BOLD signal changes, event-related fMRI designs have emerged in the mid '90s (Amaro & Barker, 2006; D'Esposito, Zarahn, & Aguirre, 1999; Friston et al., 1998). Event-related designs have the advantage to analyse individual responses to trials, such as errors throughout the cognitive paradigm (Braver, Barch, Gray, Molfese, & Snyder, 2001; Kiehl, Liddle, & Hopfinger, 2000; Schacter, Buckner, Koutstaal, Dale, & Rosen, 1997), as well as signal changes associated with different events within each trial, such as the presentation of stimuli, the delay interval and the motor response in a recognition task (D'Esposito et al., 1999).

Therefore, event-related fMRI designs have been widely used to analyse neural substrates of temporally dissociable components within WM paradigms. Specifically, they can easily discriminate between WM encoding, maintenance and retrieval by modelling each event with an HRF shifted to the appropriate time period when that event is thought to occur (D'Esposito et al., 1999). Finally, event-related fMRI designs can also allow for randomisation of the order of experimental conditions and variation of the time between trial presentation (i.e., inter-trial intervals) (Amaro & Barker, 2006; Rosen, Buckner, & Dale, 1998).

2.3 fMRI study

2.3.1 Aims

The present fMRI study was aimed at investigating brain activity during both encoding and maintenance of single shapes and colour-shape conjunctions in MCI patients and healthy controls.

2.3.2 Ethics statement

The study was approved by the West Midlands - Edgbaston Research Ethics Committee (REC reference: 06/MRE07/40. Lothian NHS REC R&D Reference: 2006/P/PSY/22. Forth Valley NHS REC R&D Reference: FV682). Prior to involvement, all participants read the information sheet about the study and the experimenter provided a thorough explanation on each aspect of the testing session, any potential risks and benefits of taking part, how research and personal data would be handled after collection, confidentiality issue, who organised and funded the research, and who reviewed and accepted it. Once the participant

agreed on involvement, he/she was presented with the consent form, to be dated and signed by both the person giving and taking consent.

2.3.3 Methods

2.3.3.1 Participants

Table 2 *– Demographic variables of MCI patients and healthy controls.*

	MCI patients (N = 22)			**Healthy controls** (N = 22)			**Statistics**
	M	**±**	**SD**	**M**	**±**	**SD**	**T(42), p-value**
Age	76.45	±	4.05	78.68	±	4.51	1.72, .09
Years of Education	14.45	±	2.70	14.82	±	3.33	.397, .69
Sex	13 men; 9 women			8 men; 14 women			$X^2(1)$= 2.27, .13

Note: N= Numerosity; M= Mean; SD= Standard deviation.

Current knowledge about statistical power in fMRI suggests that around twenty participants for a repeated measure design are required for power ~ = .80 (Mumford & Nichols, 2008). Although this cannot be calculated directly when both the design and the effect being studied are novel (Desmond & Glover, 2002; Mumford & Nichols, 2008), results from Parra et al.' (2014) study showed that, with twenty participants, over 80% power was achieved for most of the relevant regions of interest (ROIs). For the current task, the actual sample consisted of twenty-four MCI patients and twenty-six healthy older controls, all matched for age and years of education. Eleven healthy controls and ten MCI patients had been already assessed before the starting of my PhD, and were already part of the study cohort; the remaining fifteen normal controls and fourteen patients were recruited by me.

Patients received a diagnosis of MCI, according to criteria proposed by Petersen (2004), by consultants specialised in Gerontology and Old Age Psychiatry and were invited to

participate in the study if they met the inclusion criteria (see below). MCI patients were recruited from the NHS Scotland from two Boards, Lothian and Forth Valley, whereas healthy controls were recruited through the volunteer panel of the University of Edinburgh. Healthy controls could also be relatives of patients with MCI. Among the patients, one individual abandoned the scanning session because of claustrophobia, whereas images collected from another individual were too noisy to be analysed because of movement under the scanner. Among normal controls, behavioural data for three participants were not registered due to a technical issue with the machine and poor quality images were collected from one further individual who wore fixed braces. The final pool of participants consisted of twenty-two MCI patients and twenty-two healthy controls, whose demographic variables are shown in *Table 2*.

Inclusion criteria for MCI patients were: 1) patients with amnestic MCI according to standardly accepted criteria (Petersen, 2004); 2) vision and physical abilities adequate to perform assessments (corrective aids allowed); 3) Modified Hachinski Ischemia Scale score of 4 or less. There were some other exclusion criteria which applied to both MCI and controls: 1) past or present significant underlying medical and/or neurological conditions; 2) addiction to alcohol and/or drugs; 3) assumption of medication which may interfere with cognition; 4) not comply with the Health and Safety requirements for MRI assessment (i.e., having a cardiac pacemaker; having had intracranial surgery/aneurysm clip; having had abdominal surgery/stents; having any ferrous metal in the body/orbits; having history of renal impairment).

2.3.3.2 Neuropsychological assessment

In order to support the diagnosis and better characterise the sample, MCI patients underwent a neuropsychological assessment. The same was done for healthy controls for a full comparison with the experimental group. The neuropsychological battery included tests of global cognitive functioning (*Addenbrooke's Cognitive Examination-Revised, ACE-R* – Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006; Rey-Osterrieth Complex Figure Test – Osterrieth, 1944; Rey, 1941), pre-morbid intelligence (*Test of Premorbid Functioning, TOPF* – Wechsler, 2011; *Digit Symbol Substitution Test* – Wechsler, 2010), memory (*Hopkins Verbal Learning Test-Revised, HVLT-R* – Benedict, Schretlen, Groninger, & Brandt, 1998; *Free and Cued Selective Reminding Test, FCSRT* - Buschke, 1984; Grober & Buschke, 1987), attention and executive functions (*Digit Span* - Wechsler, 2010; *Trail Making Test, TMT Version A & B* – Reitan, 1958), verbal fluency (*FAS* – Borkowski, Benton, & Spreen, 1967), language (*Graded Naming Test, GNT* – Mckenna & Warrington, 1983), depressive symptoms (*Geriatric Depression Scale, GDS short form* – Sheikh & Yesavage, 1986). Patients' carers were also asked to respond to the *Instrumental Activities of Daily Living* (*IADL*) questionnaire (Lawton & Brody, 1969). The assessment took place at the University of Edinburgh, Department of Psychology, on a different day in respect to the scanning session. MCI patients recruited at NHS Forth Valley were assessed at the Stirling Community Hospital (Stirling, UK). The time between neuropsychological and fMRI assessment was kept below one month.

2.3.3.3 The Working Memory Binding Task

The WMBT was the well-known change detection paradigm described in *Section 1.3.3*, and widely utilised in the prior relevant literature on the topic (Brockmole et al., 2008; Parra et al.,

2010b; 2014; 2015b). Visual stimuli were selected from a pool of eight non-nameable shapes (*Figure 4A*) and eight non-nameable colours (*Figure 4B*) derived from Parra et al. (2010b).

(A)

(B)

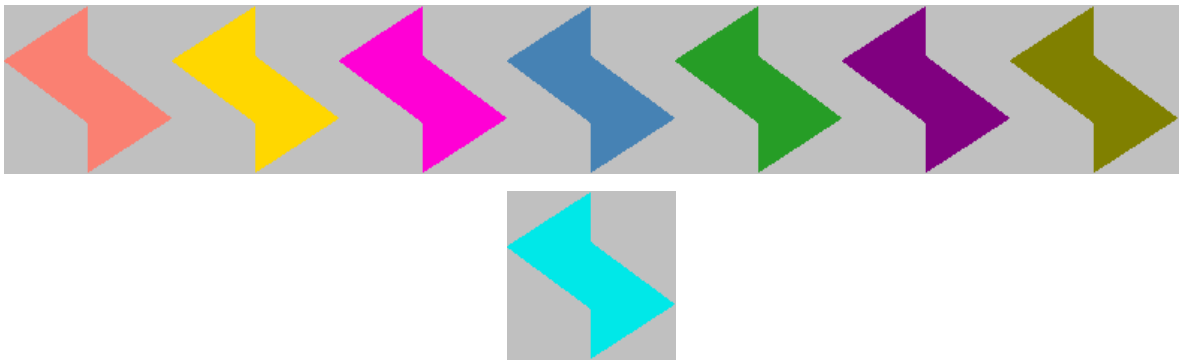


Figure 4 *– (**A**) Eight shapes and (**B**) eight colours used as stimuli in the WMBT.*

Participants were presented with two items per array (i.e., set size 2) consistently with previous studies suggesting that such memory load elicits the typical drop in accuracy in AD

patients (Della Sala et al., 2018; Parra et al., 2019). Healthy controls were tested with the same cognitive load.

At the beginning of each trial, participants were shown a warning screen for 2500ms informing them as to which condition was to be tested. A fixation period of 3000ms followed, wherein a white fixation cross turned from white to black to indicate that the study array was about to be displayed. A 250ms blank screen delay with a grey background[3] and a 2000ms display with a reminder of the instructions preceded the study display, which was then presented for 2000ms. Another blank display followed for an unfilled delay period of a variable duration. The delays were randomly and evenly selected from a set of four (i.e., 2000ms, 4000ms, 6000ms, 8000ms) due to the fMRI design optimisation (Parra et al., 2014). Finally, the test display was showed for 4000ms, and the inter-trial interval (ITI) lasted for 2000ms. *Figure 5* illustrates an example of an experimental trial.

[3] The grey background was set as layout and was necessary for visual stimuli to hold psychophysics properties (e.g., luminance) (see also Parra et al., 2010a).

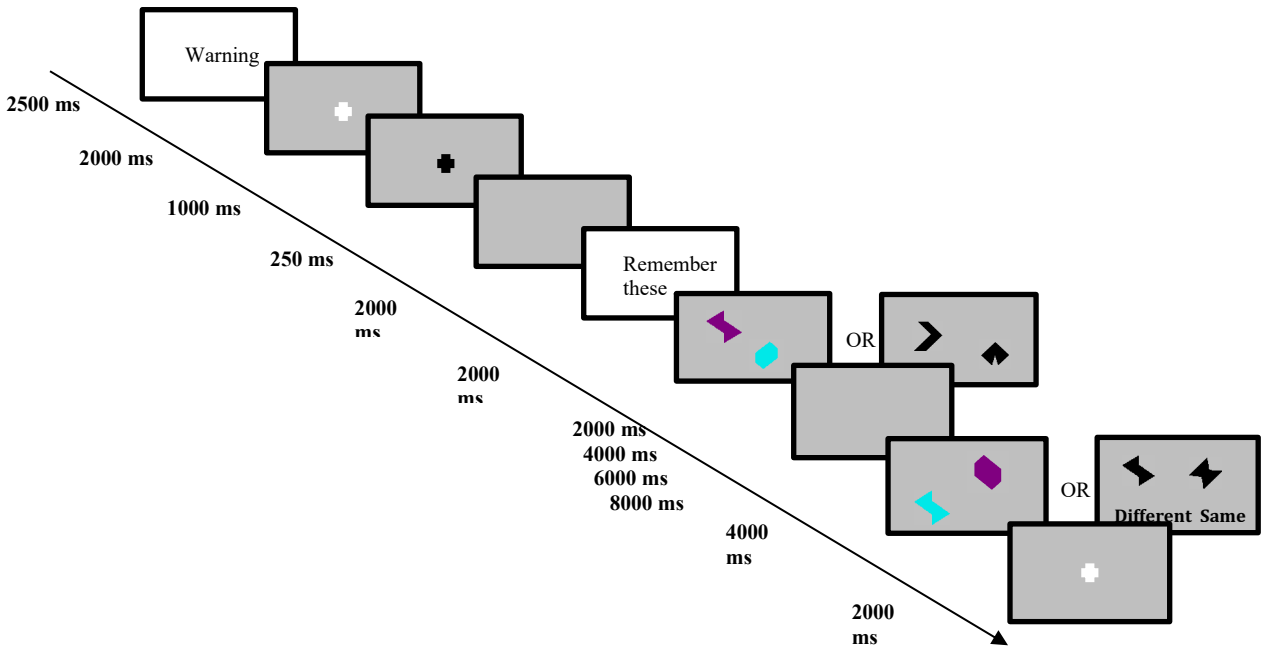


Figure 5 *–Example run of an experimental trial in both Shape Only and Binding conditions.*

Differently from prior studies whereby the experimental task comprised two conditions measuring single features (i.e., shapes and colours) and one testing binding (i.e., colour-shape conjunctions) (Parra et al., 2010a; 2010b; 2014; 2015b), the current paradigm included two conditions only. The colour only condition was discarded on the basis of previous results showing that processing colours has never constrained memory for binding as shapes did (Parra et al., 2019; Pietto et al., 2016). Also, discarding one condition made the task shorter and more suitable for older people who had to lay down still under the scanner. In the *Shape Only Condition*, participants had to detect whether or not the shapes presented in the study display had been replaced by new ones in the test phase. In the *Binding Condition*, they were asked to process coloured shapes and detect whether features swapped between items in the test display (see *Figure 5*). In both conditions, on 50% of the

trials the study and test displays showed the same items, whereas, on the remaining 50%, items of the test display were different from those shown in the study display.

Responses were given via button press: participants were instructed to press the button in their right hand to indicate that stimuli were the same, or the button in their left hand whenever the visual arrays were different. Visual stimuli were projected from the computer screen onto a display in the scanner and adjusted via googles to match participants' visual acuity. No features were repeated within a given array. Items randomly changed locations from study to test phases, so that location could not be used as a cue for retrieval. There were 32 experimental trials for each condition; trials were fully randomised across participants and conditions were blocked and delivered in a counterbalanced order. Testing was controlled from a computer synchronised with the MRI scanner and E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) was used to run the experiment.

2.3.3.4 Experimental procedure

Pre-scanning session: Participants were required to be at the Clinical Neuroscience Department, Brain Imaging Centre, Western General Hospital (Edinburgh) at least 30 minutes prior to the scanning time in order to be debriefed on the procedure by the radiographers and familiarise with the experimental task. They underwent a short practice session outside the scanner, consisting of a perceptual binding task. Both patients and controls were presented with 10 trials displaying two sets of three coloured shapes depicted on the screen at the same time. They were asked to detect if the set presented above a horizontal black line consisted of the same or different coloured shapes to those presented in the set below the line. In 5 trials, two shapes of one set swapped their colours. In the other 5 trials, the two sets showed the same coloured shapes. This procedure was also useful to

screen participants for potential perceptual deficiency. In fact, those who did not reach 80% of correct responses were not tested further. Testing outside the scanner was controlled on a Dell laptop with a 10-inch screen, placed at approximately 35 cm from the subject and subtending a visual angle of approximately 17°.

Scanning session: Once the localising scans were collected, participants were reminded of the instructions via the intercom. The scanning session lasted about 60 minutes overall. The first 20 minutes were used to perform the WMBT; the remaining 40 minutes were used to collect structural MRI and DTI data.

2.3.4 fMRI design

2.3.4.1 fMRI design optimisation

To ensure an efficient design for the key fMRI contrasts, the temporal characteristics of the task were determined. Custom scripts were created in MATLAB 9.4 (The MathWorks, Natick, MA, USA, http://www.mathworks.com) to estimate the efficiency of encoding and maintenance phase between-condition contrasts in order to select the best trial parameters. Delay periods of 2000ms, 4000ms, 6000ms and 8000ms and ITI of 4000ms, 8000ms, 12000ms, 16000ms were equally distributed across 32 trials in both Binding and Shape Only conditions. Also, they were presented in random order. Collinearity between regressors pertaining encoding and maintenance phases was approximately 0.5. Specifically, the fMRI analysis measured activity attributable to the encoding and maintenance phases (Curtis & D'Esposito, 2003; Sakai, Rowe, & Passingham, 2002; Zarahn, Aguirre, & D'Esposito, 2000).

2.3.4.2 fMRI data acquisition

fMRI data acquisition was carried out at the University of Edinburgh Brain Research Imaging Centre (BRIC; http://www.sbirc.ed.ac.uk/) through a GE Signa Horizon HDxt 1.5 T clinical scanner (General Electric, Milwaukee, WI, USA). Once localisation scanning was completed, a structural T_1 weighted sequence was acquired (5 contiguous 5 mm sagittal slices; matrix 1⁄4 256 x 160; fov 1⁄4 24 cm). During the WMBT, contiguous interleaved axial gradient EPI were collected alongside the intercommissural plane throughout two continuous runs (TR/TE 1⁄4 2000/40 ms; matrix 1⁄4 64 x 64; field of view 1⁄4 24 cm; 27 slices per volume, thickness 1⁄4 5 mm, 0 mm gap). Data for each participant consisted of 598 volumes, of which the first 3 scans were discarded to allow for T_1 equilibration effects. T_2-weighted fast spin-echo sequence was acquired afterwards.

2.3.5 Statistical analyses

2.3.5.1 Behavioural analysis

Statistical analyses on behavioural data were conducted in R Studio (version 1.1.456; R Core Team, 2013) and JASP (version 0.9.2; JASP Team, 2019). Group differences in demographic (i.e., age and years of education, see *Table 2*) and neuropsychological (see *Table 4*) variables were examined with both parametrically (i.e., Tukey's test) and non-parametrically (i.e., Mann-Whitney test) t-tests. For the WMBT, proportion of correct responses was calculated. Group differences in performing the task were analysed by means of non-parametric mixed ANOVA (i.e., ART ANOVA; Leys & Schumann, 2010), with group membership (MCI patients vs Healthy controls) as the between factor and task condition (Shape Only vs Binding) as the within factor.

Different dependent variables (i.e., A', Beta, and percentage/proportion of correct recognition) have been compared across studies on AD patients to assess the performance in the WMBT (Parra et al., 2010b; Parra et al., 2011). Interestingly, all these measures have provided complementary results on the ability to extract the signal (changing items) from the noise (distractors). Hence, for the sake of comparability with (Parra et al., 2014), I decided to opt for the percentage of correct responses (i.e., accuracy rate) as the index to examine patients' ability to remember colour-shape bindings compared to healthy older controls.

2.3.5.2 fMRI analysis

Detecting significant neural activation may be problematic sometimes since MR images may display high-frequency spikes, artefacts and distorsions, low-frequency drifts, and periodic fluctuations. The main causes of this 'noise' are usually thermal motion of free electrons in the system, gradient and magnetic field instability, head movement and its interactions with the magnetic field, physiological effects, such as heartbeat and respiration. Therefore, it is necessary that fMRI data undergo a pre-processing stage prior to statistical analysis.

2.3.5.2.1 Pre-processing

fMRI pre-processing aims at (i) minimising the influence of data acquisition and physiological artefacts, (ii) checking statistical assumptions and transforming data to meet the same assumptions, (iii) standardising the locations of brain regions across subjects to achieve validity and sensitivity in group analysis (Lindquist & Wager, 2015).

In the current study, pre-processing was conducted in SPM 12 (Statistical Parametric Mapping: The Wellcome Department of Cognitive Neurology and collaborators, Institute of

Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) running in MATLAB 9.4 (The MathWorks, Natick, MA, USA, http://www.mathworks.com/). Numerous steps were achieved at this stage.

2.3.5.2.1.1 Outliers detection

To ensure a good quality of data, customed scripts were created in MATLAB 9.4 (The MathWorks, Natick, MA, USA, http://www.mathworks.com/) to detect outlier slices (variance of > 5 standard deviations) (see Morcom, Bullmore, Huppert, Lennox, Praseedom, Linnington & Fletcher, 2010). These were then replaced by a new image resulted from the average of their previous and consecutive scans. Problematic scans accounted for the 0.75% of the total number of collected scans for the two groups.

2.3.5.2.1.2 Realignment

It is assumed that a time series associated with a specific voxel depicts the same brain region at every time point. However, if the participant moves between acquisitions, voxel's signal intensity will not correspond from slice to slice. To correct for this, each fMRI image in the time series should be rotated and translated to match a reference image. In the present study, all images have been spatially realigned to the mean volume of each data sequence by using B-spline interpolation.

2.3.5.2.1.3 Slice-timing correction

fMRI data analysis assumes that voxels are acquired simultaneously. In reality, this is not

possible since there is always a difference in time, even if minumum, between slices acquisition. Slice-timing correction was thus undertaken to correct for differences in slice acquisition, and match every images of the time series with the middle slice in time (reference image) by estimating the signal intensity in all voxels at the same moment in the acquisition period (i.e., temporal sinc interpolation).

2.3.5.2.1.4 Coregistration

Both structural (T_1) and functional images, acquired for each subject during the scanning session, were coregistered to allow the visualisation of individual's task activation overlaid on the individual's anatomical information.

2.3.5.2.1.5 Segmentation

Each participant's T_1 structural scan was segmented using extended prior probability maps (i.e., probabilistic atlases) (SPM 12; Ashburner & Friston, 2005) to obtain diverse tissue class images (i.e., grey matter, white matter, CSF).

2.3.5.2.1.6 Normalisation

Normalisation is needed to adapt all participants' brains, presenting differences in shape and size, for instance, to a template brain. In the present study, the Montreal Neurological Institute (MNI) atlas has been used. Segmented T_1 images were normalised to the MNI atlas by using segmentation parameters and DARTEL diffeomorphic mapping functions (Ashburner, 2007; Ashburner & Friston, 2009). Lastly, the same procedure was carried out

for functional images.

2.3.5.2.2 Statistical modelling

fMRI statistical analysis was also conducted in SPM 12 (Statistical Parametric Mapping: The Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm) through MATLAB 9.4 (The MathWorks, Natick, MA, USA, http://www.mathworks.com). A two-level General Linear Model (GLM) was employed to run statistical analysis (Penny & Friston, 2005).

2.3.5.2.2.1 First-level analysis

Analysis of Shape Only and Binding conditions were performed in two separate sessions, which, at the individual level, were incorporated in the GLM with a constant term for each. Separate covariates for the encoding, maintenance and probe trial phases were used to model the two experimental conditions, and correct and incorrect trials were modelled per phase (e.g., Shape-ENCODING, Shape-MAINTENANCE, Shape-PROBE). Missing responses, which accounted for the 2.6% of the total amount of responses from both MCI patients and healthy controls, were modelled as errors. Whenever incorrect responses were not given, errors were not included in the model. Also, outlier scans were not entered in the model (see *Section 2.3.5.2.1.1*). The covariates in the GLM comprised sequences of delta functions at the event onset times for each condition and trial phase, convolved with a canonical HRF and downsampled at the midpoint of each scan.

For the encoding phase (i.e., the duration of stimulus presentation), modelled event durations

were 2000ms. Variable maintenance phase delay durations (i.e., 2000ms, 4000ms, 6000ms and 8000ms) were modelled by including randomly varying timings. The duration of probe presentation was set at 4000ms within the task design. This represented a serious caveat in terms of modelling, since the overlap between maintenance and probe durations induced regressors pertaining maintenance and probe phases to be highly correlated (i.e., violation of collinearity assumption). For this reason, and since I was not interested in analysing brain activity associated with the WMBT during the probe presentation phase, probe durations were modelled as 0ms for both correct and incorrect trials in both Shape Only and Binding conditions.

Residual movement-related artifacts were modelled for each session as 6 covariates, representing the 3 rigid body translations and rotations estimated during the realignment stage. Bad scans were also modelled as confounds with "1" in a column of zeros. Voxel-wise parameter estimates for each covariate were obtained using Restricted Maximum Likelihood (-ReML), modelling autocorrelation across scans with an AR(1) plus white noise model (Friston, Glaser, Henson, Kiebel, Phillips & Ashburner, 2002). Data for each session were highpass filtered to 1/128 Hz and scaled to a grand mean of 100 across all voxels and scans within a session.

2.3.5.2.2.2 ROIs definition

Regions of Interest (ROIs) have been defined to explore data and reduce the severity of correction for multiple testing (Poldrack, 2007). Also, one of the main goals of the current study was to investigate whether brain regions showing binding-specific activity in our participants would overlap with regions found by Parra and colleagues (2014) in younger volunteers (Parra et al., 2014). Moreover, current ROIs definition has been also led by Didic

et al.'s (2011) hypothesis suggesting that memory binding deficits are the result of neuropathological changes occurring at diverse stages and magnitudes across the AD spectrum (Didic et al., 2011).

Therefore, in the present study, coordinates of ROIs were defined *a priori* according to previous literature (Parra et al., 2014; Piekema et al., 2006; 2009; Staresina & Davachi, 2010). They are reported in *Table 3* below:

Table 3 *– ROIs adopted in the a priori analysis of the current fMRI study.*

Brain Region	Brodmann Area	Talaraich Coordinates	Comments
Left middle frontal gyrus	11	x= -26, y= 44, z= -4	Feature-related activity during encoding
Left inferior temporal gyrus	20	x= -50, y= -58, z= -14	
Thalamus	10	x= 14, y= -22, z= 4	
Left precentral gyrus	6	x= -52, y= -4, z= 48	
Right fusiform gyrus	37	x= 44, y= -60, z= -14	
Left postcentral gyrus	1	x= -56, y= -24, z= 38	
Left inferior frontal gyrus	47	x= -38, y= 18, z= -4	Feature-related activity during maintenance
Anterior cingulate gyrus	32	x= 4, y= 12, z= 40	
Right fusiform gyrus (close to LOC)	37	x= 45, y= -63, z= -15	Binding-related activity during encoding
Left fusiform gyrus	37	x= -44, y= -64, z= -14	Binding-related activity during maintenance
Left postcentral gyrus	2	x= -40, y= -34, z= 62	
Left superior parietal lobule	7	x= -26, y= -50, z= 64	
Left dorsal premotor cortex/middle frontal gyrus	6	x= -30, y= -10, z= 44	
Left inferior parietal lobule	40/2	x= -30, y= -10, z= 44	
	40	x= -40, y= -48, z= 30	
Right Hippocampus		x= 30, y= -20, z= -10	From Piekema et al., 2006 – used in Parra et al., 2014
		x= 26, y= -16, z= -16	From Piekema et al., 2009
Perirhinal cortex		x= 28, y= -14, z= -28	From Staresina & Davachi, 2010 – used in Parra et al., 2014
		x= -24, y= -15, z= -30	
Entorhinal cortex		x= 20, y= -8, z= -24	From Staresina & Davachi, 2010 – used in Parra et al., 2014
		x= -20, y= -6, z= -24	
Parahippocampal gyrus	37	x= 34, y= -32, z= -16	From Piekema et al., 2009
	37	x= -26, y= -20, z= -16	

2.3.5.2.2.3 Second-level analysis

Linear contrasts on parameter estimates obtained during first-level analysis were further examined at second-level. Statistical parametric maps were initially thresholded at $p < .001$, uncorrected. The *a priori* ROI analysis was conducted by employing a small volume correction based on Gaussian Random Field theory and selecting spheres of radius 5 mm around coordinates of interest (Worsley, Marrett, Neelin, Vandal, Friston & Evans, 1996). The family-wise error (FWE) rate was then corrected for each analysis at both ROIs and whole-brain levels ($p < .05$).

Where exclusive masking was utilised to discount voxels showing any hint of additional effects (e.g., condition effect), masks were applied at an uncorrected threshold of $p < .05$. Peaks of suprathreshold clusters were localised with reference to participants' mean EPI and structural images, and the MNI reference brain (Cocosco, Kollokian, Kwan, & Evans, 1997). They were then labelled consistently with Talairach and Tournoux (1988) and Brodmann (1909) nomenclatures through http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html website and Talairach Client software (Version 2.4.3) available at http://www.talairach.org/client.html and running in Java 8 (Java™ Platform, Standard Edition 8 API Specification, 2020. Available at: https://www.java.com/en/download). Importantly, all results reported afterwards are just exploratory.

2.3.5.2.3 fMRI analysis strategy

The main, whole-brain fMRI data analysis focused on regions showing binding-specific activity, that is, greater activity for Binding than Shape Only condition during encoding and maintenance phases. A one-sample T-contrast comparing the two conditions was run during

first-level analysis, accounting for neural activation for each participant and phase (i.e., binding > shape). At second-level analysis, two-sample T-tests examined the neural activation elicited by each condition in both healthy controls and MCI patients. An additional exploratory analysis tested for neural activity during the Binding condition compared to the fixation inter-trial baseline (i.e., binding > baseline). To discount those regions showing binding-specific or binding-related activation independently of groups, I exclusively masked the results with the bidirectional contrast Healthy controls vs MCI patients.

2.3.6 Results

2.3.6.1 Behavioural results

Table 4 *– Neuropsychological variables of all participants entering the study.*

	MCI patients (N = 22)			Healthy Controls (N = 22)			T-tests
	M	**Mdn (range)**	**SD**	**M**	**Mdn (range)**	**SD**	**T(42), U (p-value)**
ACE	79.91	81.5 (65 – 97)	10.79	94.86	96.5 (84 – 100)	4.64	**442.5 (<.001)**
MMSE	25.32	26 (17- 28)	3.24	29	29 (25 – 30)	1.27	**428 (<.001)**
TMT-A	66.27	55 (30 – 317)	57.37	44.45	43 (26 – 63)	11.24	**131 (.009)**
TMT-B	180.4	154.5 (56 – 492)	129.9	103.3	101.5 (46 – 164)	34.2	**118 (.004)**
HVLT-REC	9.31	9 (4 – 12)	1.96	10.86	11 (5 – 12)	1.75	**371 (.002)**
HVLT-DELAY	2.68	1 (0 – 10)	3.25	6.77	7 (4 – 12)	3.4	**387.5 (<.001)**
HVLT-TOT	14.36	15 (4 – 29)	5.75	21.45	21.5 (14 – 32)	5.37	**4.22 (<.001)**
FAS	32.82	32 (9 – 65)	14.36	51.14	50 (31 – 75)	11.35	**4.69 (<.001)**
ANIMAL FLUENCY	7.36	6 (1 – 21)	5.14	10.91	7 (5 – 28)	7.44	**327 (.044)**
DIGIT SYMBOL	38.55	38.5 (10 – 60)	12.19	56.86	58.5 (35 – 85)	12.12	**5 (<.001)**
DIGIT SPAN	5.13	5 (4 – 7)	.99	5.9	6 (4 – 9)	1.01	**347 (.009)**
REY-COPY	33.11	34 (24 – 36)	2.6	34.39	34 (31 – 36)	1.57	319.5 (.057)
REY-IMMEDIATE	13.02	13 (0 – 23.5)	7.48	22.5	22.75 (7 – 34)	7.36	**4.23 (<.001)**
REY-DELAY	12.41	15.25 (0 – 21.5)	9.16	21.34	21 (8 – 34)	6.56	**370 (.003)**
GNT	18.09	19 (7 – 25)	4.26	24.55	25.5 (14 – 30)	4.22	**5.04 (<.001)**
CLOCK	4.9	4 (3 – 5)	3.22	4.72	5 (3 – 5)	.55	**322.5 (.034)**
FCSRT-IFR	12.5	11.5 (0 – 33)	9.67	27.73	27 (12 – 38)	6.57	**6.1 (<.001)**
FCSRT-ICR	21.32	22 (2 – 36)	8.6	19.14	19.5 (10 – 28)	5.53	-1 (.323)

FCSRT-ITR	34.45	42.5 (3 – 48)	15.16	46.86	48 (31 – 48)	3.66	**397.5 (<.001)**
TOPF	55.23	57.5 (33 – 70)	13.39	65.95	68 (48 – 70)	4.91	**366 (.004)**
GDS	2.13	1.5 (0 – 10)	2.39	1.31	1 (0 – 5)	1.42	198 (.289)
IADL	5.84	6 (3 – 8)	1.85	7.77	8 (7 – 8)	1.85	**384.5 (<.001)**

Significant ($p < 0.05$) tests highlighted in bold.

Note: N= Numerosity; M= Mean; Mdn= Median; SD= Standard deviation.
ACE= Addenbrooke's Cognitive Examination; MMSE= Mini Mental State Examination; TMT = Trail Making Test (Version A and B); HVLT= Hopkins Verbal Learning Test-Revised (Recognition, Delayed Recall, Total Recall); REY= Rey-Osterrieth Complex Figure Test (Copy, Immediate Reproduction, Delayed Reproduction); GNT= Graded Naming Test; FCSRT= Free and Cued Selective Reminding Test (IFR= Immediate Free Recall; ICR= Immediate Cued Recall; ITR= Immediate Total Recall); TOPF= Test of Premorbid Functioning; GDS= Geriatric Depression Scale; IADL= Instrumental Activities of Daily Living.

Table 4 shows the neuropsychological profile of both MCI patients and healthy older controls entering the study. The parametric and non-parametric t-tests revealed that MCI patients performed poorer than healthy normals on all the tests comprised in the neuropsychological battery, except on the copy of the Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1941) and the immediate cued recall of the FCSRT (Buschke, 1984; Grober & Buschke, 1987). Also, both groups reported, on average, similar levels of depressive traits (Sheikh & Yesavage, 1986).

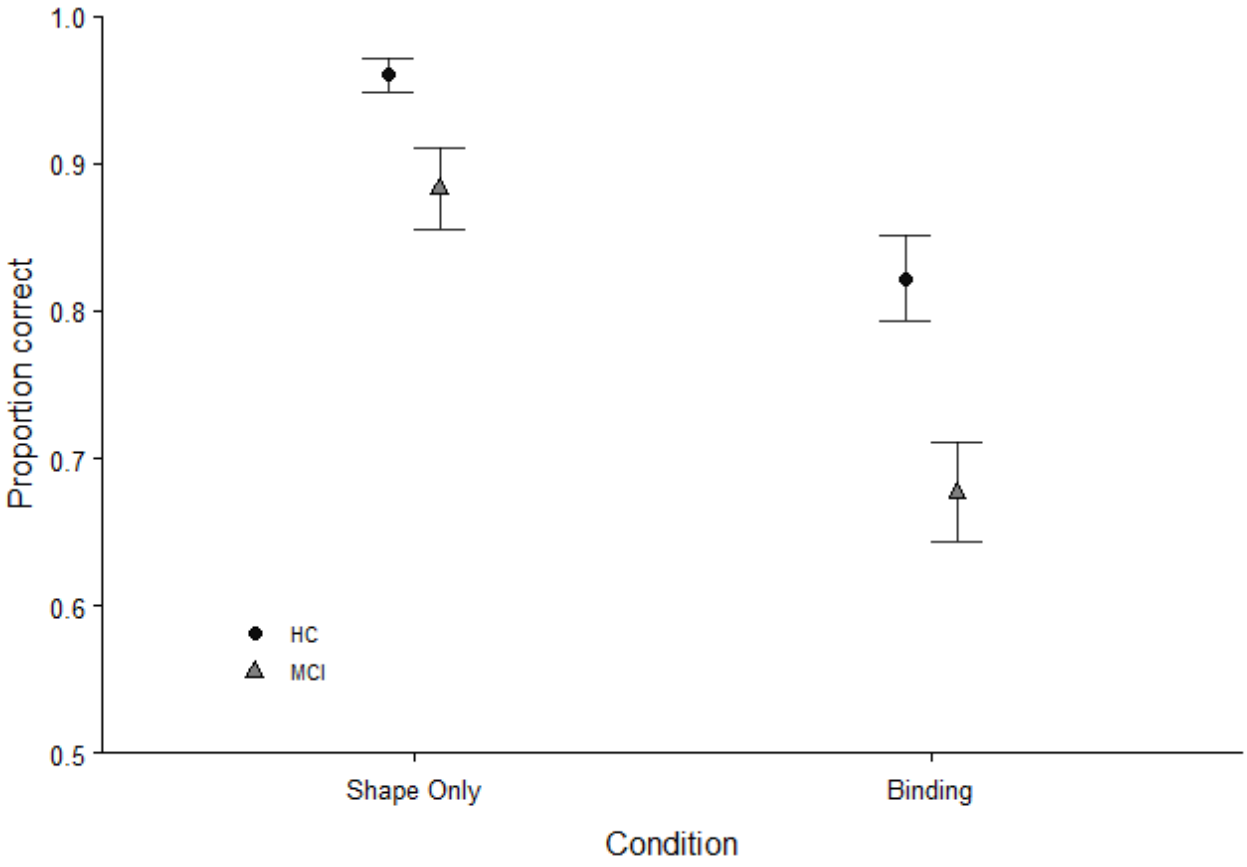


Figure 6 *- Proportion correct in Shape Only and Binding conditions for both MCI patients and healthy controls.*

A 2 x 2 non-parametric mixed ANOVA yielded a significant main effect of condition ($F(1,42)= 67.88$, $p< .001$, $\eta^2p= .61$) and a significant main effect of group ($F(1,42)= 16.69$, $p< .001$, $\eta^2p= .28$), with healthy controls being more accurate than MCI patients in Shape Only (HC: M= .96, SD= .05; MCI: M= .88, SD= .13) and Binding conditions (HC: M= .82, SD= .13; MCI: M= .67, SD= .16). A group*condition interaction was also found ($F(1,42)= 5.82$, $p= .02$, $\eta^2p= .12$). Mann-Whitney t-tests revealed that healthy controls outperformed MCI patients in both Shape Only ($U=125.5$, $p= .005$, $r= -.42$) and Binding ($U=118.5$, $p= .004$, $r= -.43$) conditions (see *Figure 6*). However, it is possible to conclude that the larger effect size associated with the comparison between MCI patients and healthy controls in performing the Binding

condition reflected the stronger association between group and condition factors, hence, driving the interaction.

2.3.6.2 fMRI results

Results from fMRI data analysis, reported in this section, are merely exploratory since differences in brain activation (within-groups and between-groups) were found at uncorrected level only.

2.3.6.2.1 Encoding phase

Table 5 *- Binding-specific activity, at uncorrected level (p< .001), during encoding phase in healthy controls and MCI patients.*

Contrast	MNI coordinates (*x, y, z*)	Talaraich coordinates (*x, y, z*)	Peak Z	N in cluster	Region	Brodmann Area
One-sample t-test binding > shape (Healthy controls)	30 -54 15	30 -52 17	3.85	38	Right subgyral temporal lobe	Undef.
	-42 -39 -12	-39 -40 -6	3.56	9	Left parahippocampal gyrus	BA19
	-21 -51 27	-20 -49 27	3.32	4	Left cingulate gyrus	BA31
	-21 -51 18	-20 -49 19	3.16	3	Left cingulate gyrus	Undef.
	15 15 -6	14 12 -2	3.12	1	Right putamen	
One-sample t-test binding > shape (MCI patients)	0 39 12	0 36 11	3.64	39	Left anterior cingulate cortex	BA32
	Sub-peak 9 45 9	8 41 8	3.41		Right anterior cingulate cortex	BA32
	Sub-peak 6 60 9	5 55 6	3.35		Right medial frontal gyrus	BA10
	0 57 0	0 51 -1	3.55	29	Right medial frontal gyrus	Undef.
	Sub-peak -21 45 -3*	-21 40 -2	3.37	2	Left medial frontal gyrus	BA10
	Sub-peak -15 51 0	-15 46 0	3.33		Left anterior cingulate cortex	BA10
	33 39 -18	31 34 -14	3.23	2	Right middle frontal gyrus	BA11
Two-sample t-test (binding > shape) – (Healthy controls > MCI patients)	-18 -72 60	-18 -67 54	3.17	1	Left Superior parietal lobule	BA7

*Significant voxels after *a priori* ROI analysis. *Note:* N= Numerosity.

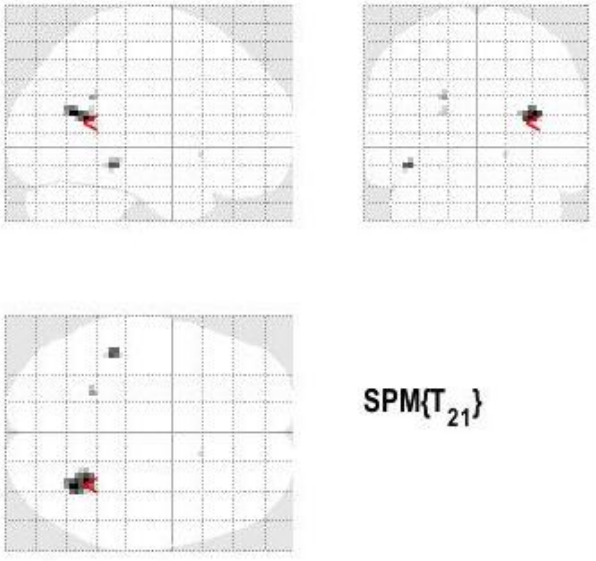


Figure 7 *– Binding-specific activation in healthy controls during encoding phase.*

In healthy older controls, *a priori* ROI and FWE corrected whole-brain analyses did not show any suprathreshold clusters during the encoding phase. However, at uncorrected level ($p < .001$), results revealed significant binding-specific activity in the right subgyral temporal lobe, in the left parahippocampal gyrus, in the left cingulate gyrus, and in the right putamen (see *Table 5*), as displayed in *Figure 7* (see also *Figure 9A*).

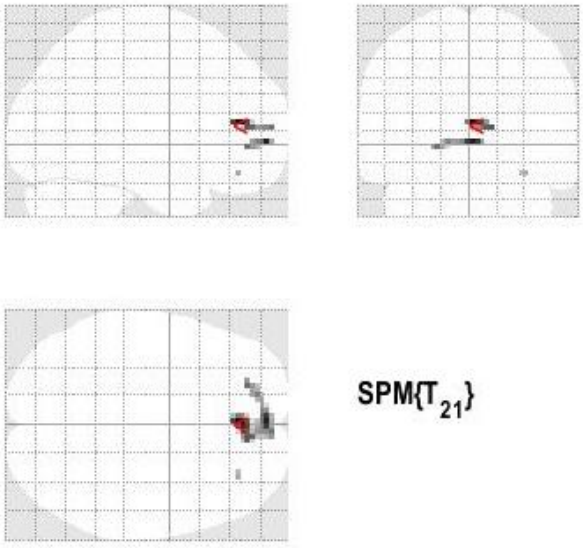
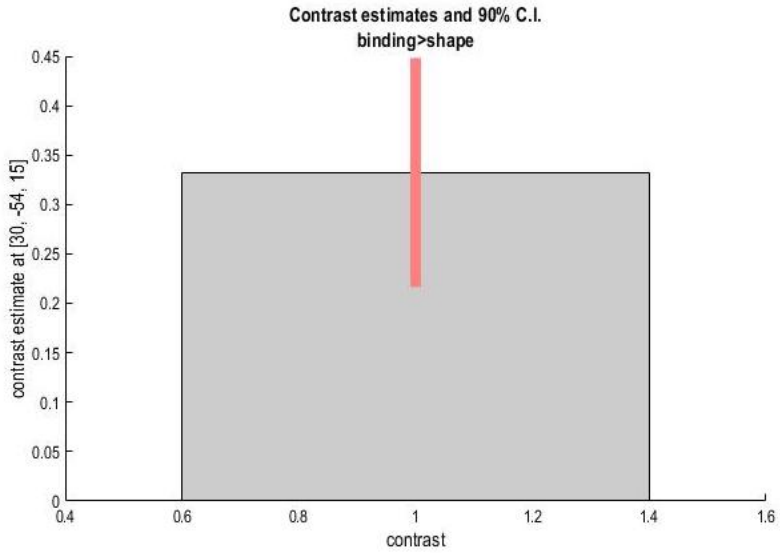


Figure 8 *– Binding-specific activation in MCI patients during encoding phase.*

In MCI patients, the whole-brain analysis did not show any suprathreshold clusters during the encoding phase. However, the *a priori* ROI analyses showed suprathreshold activation in the left medial frontal gyrus. Moreover, at uncorrected threshold, other significant activation appeared in the anterior cingulate cortex, in the right medial frontal gyrus, and in the right middle frontal gyrus (see *Table 5*). *Figure 8* illustrates such binding-specific activity pattern (see also *Figure 9B*).

(A)



(B)

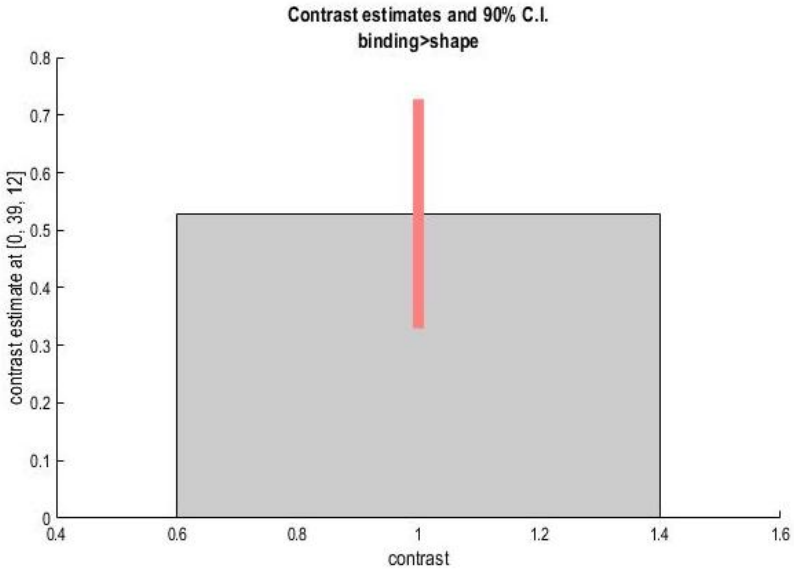


Figure 9 *– Contrast estimates comparison between healthy controls (A) and MCI patients (B) during encoding phase.*

Table 5 also reports results from the two-samples t-tests accounting for the condition x group interaction. No activated clusters were revealed after the *a priori* ROI analysis and FWE correction, but an activation was found at uncorrected threshold for the Binding condition rather than the Shape Only condition in the left superior parietal lobule.

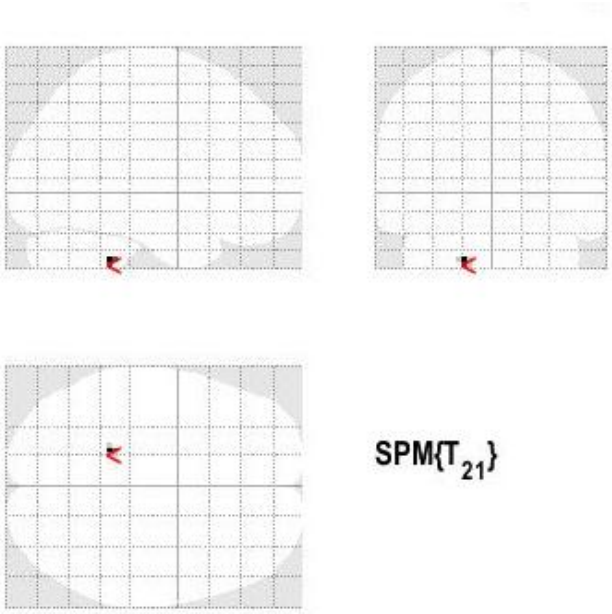
Finally, testing for binding-related activity in Healthy controls and MCI patients by exclusively masking out any voxels that were found in the one group or the other did not yield any significant results.

2.3.6.2.2 Maintenance phase

Table 6 *- Binding-specific activity, at uncorrected level (p< .001), during maintenance phase in healthy controls.*

Contrast	MNI coordinates (x, y, z)	Talaraich coordinates (x, y, z)	Peak Z	N in cluster	Region	Brodmann Area
One-sample t-test (Healthy controls)	-18 -42 -39	-17 -43 -30	4.04	7	Left cerebellum	Undef.

Note: N= Numerosity.



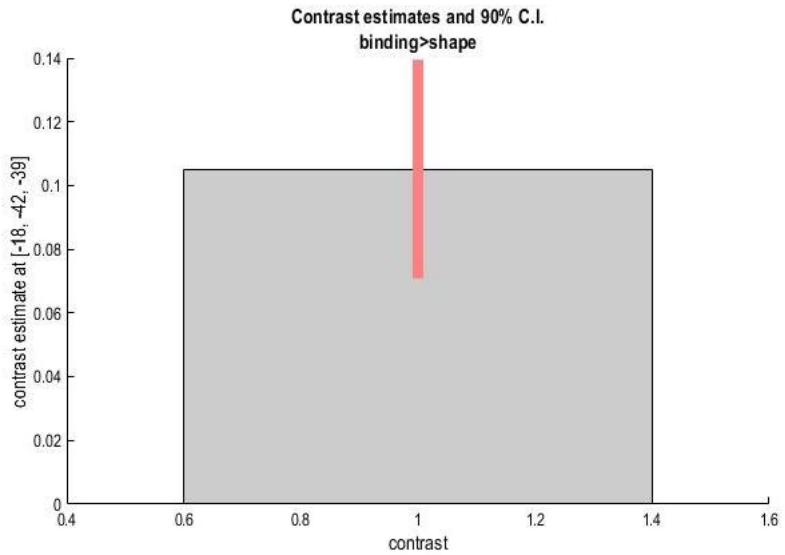


Figure 10 *– Binding-specific activation and contrast estimate in healthy controls during maintenance phase.*

As shown in *Table 6* and *Figure 10*, during maintenance, significant binding-specific activity was observed in healthy older controls only, at uncorrected threshold level, in the left cerebellum.

Any other contrasts, both masked and unmasked, did not show any suprathreshold clusters to report.

2.3.7 Discussion

The present study investigated differential neural activation associated with the encoding and maintenance of single shapes and colour-shape conjunctions in both MCI patients and healthy older controls. MCI has been identified as the transitional stage between healthy ageing and dementia, characterised by neuropathological signs that will convert to clinical symptoms lately (Albert et al., 2011; Didic et al., 2011; Jack et al., 2018). Deficits to retain colour-shape bound representations in WM hint at the neurodegeneration occurring at this stage (Didic et al., 2011; Koppara et al., 2015; Parra et al., 2019), and, according to new diagnostic criteria, results from cognitive testing should be coupled with neuroimaging findings for earlier and more reliable diagnoses (Jack et al., 2018). To our knowledge, this is the first study in which fMRI methodology is employed in association with the WMBT to assess binding deficits in prodromal AD.

2.3.7.1 Behavioural findings

Neuropsychological findings supported the diagnosis of MCI, since patients reached lower performance levels in the majority of the cognitive tests included in the neuropsychological battery. MCI and control groups performed equally on the copy of the Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1941) and, more importantly, on the immediate cued

recall (ICR) of the FCSRT (Buschke, 1984; Grober & Buschke, 1987). Evidence of no substantial difference found for the ICR score between MCI patients and healthy controls seems to suggest that this index may not be a reliable criterion to predict the onset of clinical AD as previously suggested (Gagliardi et al., 2019; Sarazin, Berr, De Rotrou, Fabrigoule, Pasquier, Legrain, Michel, Puel, Volteau, Touchon, Verny, & Dubois, 2007).

Regarding the WMBT, behavioural results showed that MCI patients displayed major difficulties to process colour-shape conjunctions compared to healthy older controls, as indicated by the larger effect size associated with the different performance of the two groups in the Binding condition.

It may be argued, however, that MCI patients performed worse than healthy controls in the Shape Only condition too, making WMB deficits losing their selectivity in our cohort of interest. Conversely to prior studies (Parra et al., 2019; 2010a; 2015b), the number of displayed stimuli within visual arrays was not titrated to avoid floor and ceiling effects in the pathological and control groups, respectively. Indeed, assessing participants with a set size calibrated to each group's memory capacity would have been challenging, since the task needed to be adjusted to the fMRI design (see also Della Sala et al., 2018). Therefore, both MCI patients and controls were presented with two items in both conditions. This may have elicited the significant difference between the two groups in the Shape Only condition, with healthy controls performing at ceiling.

Nonetheless, effect sizes clearly inform on the nature of the group x condition interaction emerged from behavioural analyses. Therefore, we can state that current results endorse the specificity of WMB deficits in prodromal AD.

2.3.7.2 fMRI findings

Although at uncorrected level, fMRI results yielded significant binding-specific over shape-specific activity during encoding and maintenance phases in healthy controls and MCI patients, separately, and in relation to the group membership.

2.3.7.2.1 Encoding bindings in working memory

When required to encode colour-shape conjunctions compared to single shapes, healthy older controls exhibited a greater activation in the right subgyral temporal lobe, in the left parahippocampal gyrus, in the left cingulate gyrus, and in the right putamen.

The subgyral areas around the bilateral temporo-parietal junction and the ventral stream are typically associated with visual attention and visual processing. Specifically, the right temporo-parietal junction has been proposed as the key neural locus of the stimulus-driven attentional network (Corbetta & Shulman, 2002; Todd et al., 2005; Tseng, Hsu, Muggleton, Tzeng, Hung, & Juan, 2010) involved in the identification and evaluation of salient visual stimuli (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Marois, Leung, & Gore, 2000). Moreover, in a recent transcranical alternate current stimulation (tACS) study, Tseng and collaborators (2016) revealed that the temporo-parietal network plays a causal role in both encoding and maintenance of colour-shape bindings, especially when there is gamma coherence between temporal and parietal cortices (Tseng et al., 2016).

Interestingly, healthy controls involved in the current study showed a meaningful activation in the left parahippocampal gyrus (BA19). According to the hypothesis proposed by Didic and colleagues (2011), impairments to process feature conjunctions commence in a sub-hippocampal phase of AD, which coincides with disruptions in the parahippocampal cortex of

preclinical AD patients and MCI patients (Aminoff, Kveraga, & Bar, 2013; Della Sala et al., 2012; Didic et al., 2011; Valdes Hernandez et al., 2020). Thus, the results emerging in the healthy group, along with the lack of parahippocampal activation in our MCI patients, seem to support this evidence.

The role of the parahippocampal cortices in memory binding mechanisms have been addressed in various fMRI paradigms. Mitchell et al. (2000a) reported that both younger and older participants, engaged in an object-location memory binding task, showed a greater activation in BA19 when processing objects compared to locations. Consistently, the recruitment of BA19 has been also observed when temporarily retaining letters and locations as unbound items (Meier, Nair, Meyerand, Birn, & Prabhakaran, 2014; Prabhakaran et al., 2000), as well as between-domain associations (i.e., face-house pairs) (Piekema et al., 2009).

BA19 has been thus observed to subtend relational binding mechanisms; however, it has been posited that this region actually supports the unitisation of items or features to store conceptual representations (Staresina & Davachi, 2010). This is also consistent with studies on crossmodal integration (Taylor, Moss, Stamatakis, & Tyler, 2006), which I will better address in Chapter IV. Future research should be then carried out to explore a more general role of the parahippocampal cortex in the binding mechanism per se, despite the format (relational vs conjunctive) and the modality in which information is presented.

Other two relevant areas showing some binding-specific activation in older controls were the left cingulate gyrus (BA31) and the right putamen.

BA31 has been posited to underpin retrieval mechanisms (Fuji, Okuda, Tsukiura, Ohtake, Miura, Fukatsu, Suzuki, Kawashima, Itoh, Fukuda, & Yamadori, 2002; Mitchell, Raye, Johnson, & Greene, 2006). Particularly, Mitchell et al. (2006) observed greater BA31 activation in younger adults, rather than in older subjects, when required to recognise a

probe as new or previously seen (old). The authors concluded that the larger recruitment of BA31 mirrored younger adults' tendency to use much memorial information to make old/new judgements (Mitchell et al., 2006). In the light of the present study, it seems plausible to reach an analogous conclusion for healthy controls in respect to MCI patients.

Finally, evidence of binding-specific activity in the right putamen may be accounted for by recent findings from a volumetric analysis paper. Loss of grey matter volume of structures within the basal ganglia has been seen to be associated with WMB deficits in MCI patients (Valdes Hernandez et al., 2020). Thus, evidence of neural activation in this region in healthy controls, and not in MCI patients, adds to the evidence that the search for conjunctive WMB biomarkers should shift away from the hippocampus and include the basal ganglia (Valdes Hernandez et al., 2020).

Indeed, in accord to previous research (Jonin et al., 2019; Parra et al., 2014; 2015b; Valdes Hernandez et al., 2020), no hippocampal activation has been found in association with the Binding condition of the WMBT. Deriving conclusions on null effects is a very sensitive topic, however, the conducted *a priori* power analysis, in which the desirable level of power (80%) was set, as well as consistent evidence brought to light by prior studies may lead to strengthen the notion that the hippocampus does not underpin conjunctive WMB functions.

Contrary to healthy controls, MCI patients exhibited a major binding-specific activity in the bilateral anterior cingulate (BA32), in the bilateral medial frontal gyrus (BA10), and in the right middle frontal gyrus (BA11). In Parra et al.' s (2014) fMRI study, BA32 and BA10 resulted to support a greater colour-related activity, leading Parra and colleagues to hypothesise that such frontal areas mirror the rehearsal processing of colours (Parra et al., 2014). Although we were not interested in colour processing in the current study, it seems likely to postulate the occurrence of a similar rehearsal mechanism in our case as well. It is plausible to

hypothesise indeed that such strategy was adopted by patients to compensate for the demanding task.

Finally, BA11 has been seen to be involved in encoding shapes mainly in healthy younger adults (Parra et al., 2014). I might speculate that the recruitment of such brain area in MCI patients to encode colour-shape conjunctions may represent that patients' memory for binding is still defined by memory for shapes (Parra et al., 2014; Pietto et al., 2016). This seems to suggest that the relationship between memory for binding and memory for shape is not lost yet in prodromal AD.

The condition x group interaction yielded greater binding-specific activity in the left superior parietal lobule (BA7): healthy controls more greatly recruited such area compared to MCI patients during the encoding of colour-shape bindings rather than single shapes. The role of the superior parietal lobule is well-known in the WM literature (Meier et al., 2014; Mitchell et al., 2000a; Parra et al., 2014; Piekema et al., 2010; Shafritz et al., 2002; Song & Jiang, 2006; Todd & Marois, 2004). Specifically, its engagement highly correlates with increasing WM load and object complexity (Song & Jiang, 2006; Todd & Marois, 2004).

It has been shown that major activation in this area underpins the processing of colour-shape conjunctions compared to single colours and single shapes (Parra et al., 2014; Shafritz et al., 2002; Song & Jiang, 2006). Moreover, Shafritz et al. (2002) demonstrated that this held particularly true when stimuli were presented simultaneously and not sequentially, as in the current paradigm.

Lastly, Grot et al. (2018) tested healthy volunteers' WM capacities to associate verbal-spatial material, presented as separated on the study display, and to maintain it as bound afterwards. Results revealed that the superior parietal lobule is crucial to actively bind features and temporarily retain new bound representations (Grot, Leclerc, & Luck, 2018).

2.3.7.2.2 Maintaining bindings in working memory

Regions showing suprathreshold activity during the maintenance of bound features in WM were located in the left cerebellum, specifically in healthy controls.

These findings are consistent with prior neuroimaging studies showing a task x age interaction: Meier et al. (2014) reported that older adults displayed greater activation in this region when processing bound compared to unbound information. In addition, greater cerebellum activation has been more recently reported when participants had to actively bind features before retaining them as bound in WM (Grot et al., 2018). It is well-established indeed that the cerebellum contributes to high-level cognitive processes (Buckner, 2013; Stoodley, 2012; Stoodley & Schmahmann, 2009), therefore, further neuroimaging reseach is needed to account for such specific hypothesis.

2.3.7.3 Limitations and conclusions

The present fMRI study presents two critical caveats in terms of experimental design. Firstly, Binding and Shape Only conditions were entered in two separate blocks instead of being presented within the same session. This caveat in the experimental design did not allow a direct comparison between the BOLD signal elicited from one or the other condition. Indeed, brain regions showing some neural activation common to both conditions, albeit at diverse magnitudes, may have been equally active across the two sessions, making the difference not so clear-cut in the SPMs, and, hence, not suitable for direct comparison.

The second caveat concerns the duration of probe presentation within the task design. BOLD signal registered during probe-duration and maintenance-duration intervals overlapped in the present fMRI design, meaning that regressors modelling the two phases were highly correlated. Modelling-wise, the right expedients were adopted to diminish the effects of such

glitch and analyse binding-specific activity during encoding and maintenance phases, which was the core aim of this study (see *Section 2.3.5.2.2.1*). Nonetheless, we cannot rule out the possibility that maintenance-related activation has been contaminated by activity evoked by the retrieval phase, such as for the cerebellar involvement.

These limitations may have caused also some discrepancies in brain activation between the present study and Parra et al.'s (2014) study, leading to a failure of replication of the previous results. Another cause of lack of replication may be attributed to the selection of ROIs too small (5 mm-radius spheres; Worsley et al., 1996), which may have not have revealed relevant activated voxels.

Nonetheless, this study firstly adds to the evidence that conjunctive WMB deficits commence before a diagnosis of full-blown AD can be made. Secondly, it provides some insights on the neural substrates underpinning conjunctive WMB deficits in prodromal AD. Interestingly, such deficits seem to be mirrored by changes in neural activation patterns compared to the ones recruited by healthy elderly. Also, the engagement of various brain regions, especially during encoding of feature conjunctions in both groups, hints at the importance of efficient brain connections to transfer information in such mechanism.

Further research is needed in larger samples to confirm the reliability of the WMBT as a neurocognitive marker for AD. This will entail a better understanding of the mechanisms underlying dementia and ultimately hasten the diagnostic process.

CHAPTER III

ABNORMAL WHITE MATTER CONNECTIVITY PATTERNS UNDERPIN WORKING MEMORY BINDING DEFICITS IN OLDER PEOPLE AT RISK OF SPORADIC ALZHEIMER'S DISEASE

3.1 Introduction

Chapter II has provided an exploratory account to investigate neural correlates of conjunctive WMB deficits in people at risk of sporadic AD, that is, MCI patients.

Although the results that emerged from the fMRI study reported in Chapter II are not robust, three main leading ideas should be promoted at this stage:

1. The WMBT has been confirmed to be a reliable neuropsychological test to early detect subtle cognitive changes in MCI patients compared to people of the same age and level of education.

2. Various brain areas have been identified in association with performance in the WMBT in both MCI and control groups. Some identified regions seem to overlap with areas located in the temporo-parieto-occipital network found in Parra et al.' s (2014) fMRI study conducted on healthy young volunteers instructed to hold colour-shape conjunctions in WM. Importantly, hippocampal activation has been registered in neither of the two studies (see also Valdes Hernandez et al., 2020).

3. The involvement of a wide neural circuit supports the notion that WMB functions rely upon effective connectivity between brain areas (Parra et al., 2017; Smith, Ricaud, Shahid, Rhodes, Starr, Ibañez, Parra, Escudero, & Vandergheynst, 2017).

Focusing more specifically on point 3, I have previously addressed how neuropathological changes characterising AD, such as neurofibrillary tangles and amyloid plaques, spread in a hierarchical fashion within the brain (Braak & Braak, 1991; Didic et al., 2011; see *Section 1.10*). Early protein misfolding deposits disrupt afferent and efferent connections among cortical and sub-cortical structures, hence, producing a disconnection of the different systems (Babiloni, Blinowska, Bonanni, Cichocki, De Haan, Del Percio et al., 2020; Parra et al., 2017; Sheline, Morris, Snyder, Price, Yan, D'Angelo, Liu, Dixit, Benzinger, Fagan, Goate, & Mintun, 2010; Van Hooren, Riphagen, & Jacobs, 2018).

AD has been therefore conceived as a disconnection syndrome (Bozzali & Cherubini, 2011; Chua, Wen, Slavin, & Sachdev, 2008; Delbeuck, Van der Linden, & Collette, 2003; Gili, Cercignani, Serra, Perri, Giove, Maraviglia, Caltagirone, & Bozzali, 2011; Stahl, Dietrich, Teipel, Hampel, Reiser, & Schoenberg, 2007), and WMB deficits may be accounted for by such disease mechanisms.

In a diffusion tensor MRI (DT-MRI; Basser, 1995) study, Parra and collaborators (2015b) tested both conjunctive (WMBT) and associative memory binding (PAL task) capacities in healthy older controls and in mutation E208A-PSEN1 carriers, who did and did not meet criteria for familial AD (FAD). Results revealed that, in FAD patients, reduced white matter integrity in frontal areas and in the anterior part of the corpus callosum coupled WMB impairments, whereas associative memory binding deficits were associated with lower white matter integrity values in the frontal regions and the hippocampus (Parra et al., 2015b). It was concluded that abnormalities in white matter integrity subtend memory binding deficits, and may be a hallmark of AD.

To my knowledge, this is the only study that have combined memory binding tasks and such biological markers in people at risk of sporadic late-onset AD. However, open questions remain on whether:

1. An abnormal structural-functional coupling may be registered in individuals at risk of developing AD in the absence of a predisposition due to genetic factors (i.e., MCI patients). I have already highlighted the importance of targeted interventions at the MCI stage in order to slow down the progression of sporadic AD, known to be the most common form of dementia.

2. Conjunctive and associative memory binding are supported by different white matter connectivity patterns. In their DT-MRI study, Parra and colleagues (2015b) administered the PAL task to assess learning of associations between words. Today, new associative memory tests, which are more sensitive to early stages of AD, have been proposed (Rentz et al., 2013), and the Free and Cued Selective Reminding Test (FCSRT, Buschke, 1984; Grober & Buschke, 1987) is among those (see also *Section 1.11*). Therefore, following Parra et al.'s (2015b) experiment, one of the aims of the present study was to investigate the conjunctive – associative binding dissociation by utilising novel diagnostic tools to detect connectivity disruptions.

3. Finally, such conjunctive – associative binding dissociation should be explored at large-scale brain level to unveil how abnormal changes in connectivity affect cognition, and memory binding particularly. The disconnecting nature of AD is indeed reflected in the loss of relevant properties of the network linking all the regions and structures of the human brain, the so-called *human connectome* (Sporns, Tononi, & Kötter, 2005).

Below I will discuss these three objectives in greater depth. However, first I will provide a brief overview of some basic knowledge on DT-MRI methodology and applications.

3.2 Principles of diffusion MRI

As described in Chapter II, diffusion MRI uses the random movement of water protons in biological tissues, including the brain, to generate image contrast. In a pure sample of warm water, and in the absence of gravity, water molecule diffusion would be equal in all directions (i.e., isotropic diffusion). In the brain, however, water molecules tend to diffuse along white matter tracts rather than across them due to the presence of macroscopic structures consisting of microscopic axons and microtubules. Water diffusion is then constrained by these barriers as well as by the collision with other molecules during random motion generating anisotropic diffusion (Emsell, Van Hecke, & Tournier, 2016).

DT-MRI models this anisotropic water molecule diffusion in each voxel of the brain from a number of diffusion-weighted images acquired with strong magnetic field gradients applied along different directions of interest. A 3 × 3 diffusion tensor is then calculated from the diffusion-weighted signals in each voxel from which biomarkers of white matter structure, such as *mean diffusivity* (MD) and *fractional anisotropy* (FA), can be calculated. The former gives a measure of the mean displacement of water molecule diffusion, while the latter gives a measure of directional coherence. FA takes values between 0, which indicates purely isotropic diffusion, and 1 which indicates complete anisotropic water molecule diffusion. Low (high) values of MD (FA) indicate structurally coherent white matter. The diffusion signal can also be analysed to give the principle direction of diffusion in each voxel, which can be followed from voxel to voxel to generate 3D maps of white matter trajectories through a technique called *tractography*. These maps of white matter fibre pathways can be used to

map connections between different cortical regions to study the human structural connectome (Curran, Emsell, & Leemans, 2016).

3.3 The human connectome

A connectome is a network that maps both structural and functional connections of the brain (Sporns, 2011; Sporns et al., 2005). The first structural connectome DT-MRI studies run in healthy volunteers, demonstrating that brain networks show a remarkable degree of similarity from person to person but are not identical (Hagmann, Cammoun, Gigandet, Meuli, Honey, Wedeen, & Sporns, 2008; Hagmann, Kurant, Gigandet, Thiran, Weeden, Meuli, & Thiran, 2007). Importantly, they all have various non-trivial properties in their organisation. For instance, the human brain, and the brain of other mammals, is characterised by *hubs* or *nodes*, such as cortical regions highly connected to each other through *edges* (Hagmann et al., 2008; Honey, Sporns, Hagmann, Cammoun, Gigandet, & Meuli, 2008; Sporns, 2011; Van Den Heuvel & Sporns, 2011; Yan, Gong, Wang, Wang, Liu, Zhu, Chen, Evans, Zang & He, 2011).

Further metrics derived from *Graph Theory*, which is the mathematical study of networks, can be used to describe properties of the connectome and measure its connectivity. The most common graph metrics are reported in *Table 7* (Latora & Marchioni, 2001; Rubinov & Sporns, 2010; Watts & Strogatz, 1998; Xie & He, 2012).

Table 7 *– Most commonly used network properties to study the human connectome.*

Metrics	Discussion
Mean edge weight	Average connection weight
Density	Measure of global connectivity or total 'wiring cost'
Degree	Number of links connected to a node
Strength	Number of connecting links incorporating connection weights
Mean shortest path	Average shortest path length (distance) between all pairs of nodes
Global efficiency	Global measure of integration, inversely related to mean shortest path
Clustering coefficient	Measure of local clusters around a node in terms of its direct neighbours

In a seminal study, Watts and Strogatz (1998) determined that the way these properties combine informs about the structure of brain networks. For example, a *small-world network* is characterised by both (i) a higher clustering coefficient compared to random graphs and (ii) a mean shortest path comparable to that of a random network with the same number of nodes and edges.

A small-world network underpins good cognition (Hagmann et al., 2008; Honey et al., 2008; Sporns, 2011; Van Den Heuvel & Sporns, 2011; Yan et al., 2011). Therefore, numerous DT-MRI studies have focused on pathological cohorts, including AD populations, to investigate how changes in the intrinsic attributes of brain connectivity patterns may have diagnostic and prognostic utility.

3.4 DT-MRI study

3.4.1 Aims

The DT-MRI study conducted for this research project aimed at investigating associations between structural connectivity, as measured by connectome metrics, and performance on both WMBT and FCSRT in order to further investigate the white matter correlates of conjunctive and associative memory functions in people at risk of dementia using (i) more promising assessment tools (WMBT and FCSRT) and (ii) network connectivity approaches rather than measures of white matter integrity, as it was done previously (Parra et al., 2015b).

3.4.2 Ethics statement

The study was approved by the West Midlands - Edgbaston Research Ethics Committee (REC reference: 06/MRE07/40. Lothian NHS REC R&D Reference: 2006/P/PSY/22. Forth Valley NHS REC R&D Reference: FV682). Informed consent was taken from all participants prior to experimental participation, as explained in *Section 2.3.2*.

3.4.3 Methods

3.4.3.1 Participants

Table 8 *– Demographic variables of MCI patients and healthy elderly.*

	MCI patients (N = 18)			**Healthy Controls** (N = 18)			**Statistics**
	M	**±**	**SD**	**M**	**±**	**SD**	**T(34), p-value**
Age	75.06	±	5.82	78.11	±	5.25	1.65, .10
Years of Education	14.06	±	2.79	15.44	±	3.50	1.31, .19
Sex	10 men; 8 women			6 men; 12 women			$X^2(1)$= 1.80, .18

Note: N= Numerosity; M= Mean; SD= Standard deviation.

The initial sample consisted of forty participants, twenty MCI patients and twenty healthy controls. Participants were selected from the sample that underwent the fMRI study (twenty-two MCI patients vs twenty-two healthy controls, see *Section 2.3.3.1*), however two MCI patients and two healthy controls could not stand final scanning sessions (i.e., DTI, GRE, FLAIR), hence, there were not available data to analyse.

Moreover, behavioural data for two healthy controls and one MCI patient were not collected due to technical problems with the computer program, while one further MCI patient displayed poor quality of the DT-MRI data. These four participants were also discarded from analysis, with the final pool consisting of eighteen MCI patients and eighteen healthy older controls. Demographic variables of the two samples are showed in *Table 8*.

Inclusion criteria for both patients and controls, as well as recruitment strategies, were the same as for the fMRI study described in Chapter II (see *Section 2.3.3.1*).

3.4.3.2 Neuropsychological assessment

Both MCI patients and healthy older controls underwent the same neuropsychological assessment described in *Section 2.3.3.2*. This was needed to confirm the diagnosis of MCI and characterise the patients' sample. Controls underwent the same cognitive assessment to confirm the healthy status and provide data for a full comparison with patients. Thirty-two participants were tested at the University of Edinburgh, Department of Psychology, whereas four MCI patients were tested at the Stirling Community Hospital (Stirling, UK). Cognitive testing took place on a different date in respect to the DT-MRI assessment. The time between neuropsychological and DT-MRI assessment never exceeded one month.

3.4.3.3 Experimental tasks and procedure

3.4.3.3.1 The Working Memory Binding Task

All participants performed the WMBT outlined in Chapter II (*Section 2.3.3.3*) and underwent the same experimental procedure as for the fMRI study, described in *Section 2.3.3.4*.

3.4.3.3.2 The Free and Cued Selective Reminding Test

The experimental material for the FCSRT consisted of four cards displaying four different printed words associated with objects corresponding to diverse category cues (e.g., fruit – grapes, bird – owl, furniture – desk, etc.; Grober & Buschke, 1987; Grober, Buschke, Crystal, Bang, & Dresner, 1988).

The experimenter showed the participant one card at a time, and for each one asked to point at and name each item on the card (e.g., grapes) in response to the right category cue (e.g., fruit). Category cues were read from the response sheet in the same order as they appeared.

Once the participant identified all the items, the card was removed. Immediate Cued Recall (ICR) was then assessed by giving the category cues in the same order as for identification and naming. The participant recalled the corresponding item each time.

After the encoding phase and before the Immediate Free Recall (IFR) phase, participants were required to carry out an interference task (e.g., counting backwards by threes). They were then instructed to recall as many words as possible from the four cards. Words not recalled freely were tested afterwards by aiding memory retrieval with the category cue. These procedures were repeated three times. The sum of free recalled and cued recalled items is the Immediate Total Recall (ITR). To score the test, ICR, IFR and ITR scores are calculated.

IFR and ITR measures have been taken into account in the current study because of their sensitivity to early stages of AD (Grober & Kawas, 1997; Grober et al., 2008; 2000; Lemos et al., 2014; Papp et al., 2015).

3.4.4 DT-MRI assessment

3.4.4.1 Data acquisition

All MRI data were acquired using a GE Signa Horizon HDxt 1.5 T clinical scanner (General Electric, Milwaukee, WI, USA) using a self-shielding gradient set with maximum gradient strength of 33 mT/m and an 8-channel phased-array head coil. The diffusion MRI examination consisted of 3 T_2-weighted (b = 0 s mm^{-2}) and sets of diffusion-weighted (b = 1000 s mm^{-2}) single-shot spin-echo echo-planar (EP) volumes acquired with diffusion gradients applied in 32 non-collinear directions. Volumes were acquired in the axial plane with a field-of-view of 240 × 240 mm, imaging matrix of 128 × 128, and 58 contiguous 2.5

mm thick slice locations, giving voxel dimensions of 1.875 × 1.875 × 2.5 mm. The repetition and echo times for each echo-planar volume were 13.75 s and 78.4 ms, respectively. A 3D T_1-weighted inversion recovery-prepared fast spoiled gradient-echo (FSPGR) volume was also acquired in the coronal plane with 160 contiguous slices and 1.3 mm^3 voxel dimensions.

3.4.4.2 Image processing

Each 3D T_1-weighted FSPGR volume was parcellated into 85 cortical (34 per hemisphere) and sub-cortical (8 per hemisphere) regions of interest (ROIs), plus the brain stem, using the Desikan-Killiany atlas and default settings in FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu). The results of the segmentation procedure were visually checked for gross errors and then used to construct grey and white matter masks for use in network construction and to constrain the tractography output. Using tools provided by the FDT package in FSL (http://fsl.fmrib.ox.ac.uk/fsl), the diffusion MRI data were pre-processed to reduce systematic imaging distortions and bulk subject motion artefacts by affine registration of all subsequent EP volumes to the first T_2-weighted EP volume (EDDY_CORRECT). Skull stripping and brain extraction were performed on the registered T_2-weighted EP volumes (BET) and applied to the FA volume calculated in each subject (DTIFIT).

The neuroanatomical ROIs determined by FreeSurfer were then aligned from 3D T_1-weighted volume to diffusion space using a crossmodal nonlinear registration method. As a first step, linear registration (FLIRT) was used to initialise the alignment of each brain-extracted FA volume to the corresponding FreeSurfer extracted 3D T_1-weighted brain volume using a mutual information cost function and an affine transform with 12 degrees of freedom. Following this initialisation, a non-linear deformation field based method (FNIRT) was used to

refine local alignment. FreeSurfer segmentations and anatomical labels were then aligned to diffusion space using nearest neighbour interpolation.

3.4.4.3 Tractography

Whole-brain probabilistic tractography was performed using FSL's BedpostX/ProbTrackX algorithm. Probability density functions, which describe the uncertainty in the principal directions of diffusion, were computed with a two-fibre model per voxel. Streamlines were then constructed by sampling from these distributions during tracking using 100 Markov Chain Monte Carlo iterations with a fixed step size of 0.5 mm between successive points.

Tracking was initiated from all white matter voxels and streamlines were constructed in two collinear directions until terminated by the following stopping criteria designed to minimise the amount of anatomically implausible streamlines: 1) exceeding a curvature threshold of 70 degrees; 2) entering a voxel with FA below 0.1; 3) entering an extra-cerebral voxel; 4) exceeding 200 mm in length; and 5) exceeding a distance ratio metric of 10. The distance ratio metric (Bullitt, Gerig, Pizer, Lin, & Aylward, 2008) excludes implausibly tortuous streamlines. For instance, a streamline with a total path length 10 times longer than the distance between end points was considered to be invalid. The values of the curvature, anisotropy and distance ratio metric constraints were set empirically and informed by visual assessment of the resulting streamlines.

3.4.4.4 Network construction

FA-weighted networks were constructed by recording the mean FA value along streamlines connecting all ROI (network node) pairs. The endpoint of a streamline was considered to be

the first grey matter ROI encountered when tracking from the seed location. Self-connections were removed, and if no streamlines were found between a pair of nodes, the corresponding matrix entry was set to 0. Across the cohort, only connections which occurred in at least two-thirds of subjects were retained (De Reus & Van Den Heuvel, 2013). Finally, for each FA-weighted connectivity matrix, a range of global network measures (see *Table 7*), plus mean edge weight (i.e., mean FA for the network), were computed using the brain connectivity toolbox (https://sites.google.com/site/bctnet).

3.4.5 Statistical analyses

Statistical analyses were conducted in R Studio (version 1.1.456; R Core Team, 2013). Group differences in demographic (i.e., age and years of education, see *Table 8*) and neuropsychological (see *Table 9*) variables were examined with both parametric (i.e., Tukey's test) and non-parametric (i.e., Mann-Whitney test) tests. Group differences on performance in the WMBT and FCSRT were analysed by means of non-parametric mixed ANOVA (i.e., ART ANOVA; Leys & Schumann, 2010) and t-tests, respectively. Specifically, we were interested in the Immediate Free Recall (FCSRT-IFR) and Immediate Total Recall (FCSRT-ITR) scores.

The relationship between WMBT performance and connectome metrics, depending on task conditions and group membership, was examined with generalised linear mixed-effects models as implemented by the lme4 package (Bates, Mächler, Bolker, & Walker, 2015) in R Studio (version 1.1.456; R Core Team, 2013). The fixed effects taken into consideration were: Connectome metrics (i.e., mean edge weight, density, degree, strength, mean shortest path, global efficiency, and clustering coefficient), Group (Healthy controls, MCI patients), and Condition (Shape Only, Binding). Connectome metrics were entered one by one in the

model and centred to reduce co-linearity. The random variable included in the models, both as intercept and slope, was Subject (36). Performance on the FCSRT was analysed through linear regression models, and predicted by the interaction between each connectome metric and the group membership.

3.4.6 Results

3.4.6.1 Behavioural results

Table 9 *– Neuropsychological tests administered to all participants entering the study.*

	MCI patients (N = 18)			Healthy Controls (N = 18)			T-tests
	M	**Mdn (range)**	**SD**	**M**	**Mdn (range)**	**SD**	**T(34), U (p-value)**
ACE	79.06	80 (53 – 96)	11.51	95.5	97 (85 – 100)	4.14	**301 (<.001)**
MMSE	24.94	25.5 (17 – 30)	3.43	29.39	30 (28 – 30)	.77	**301 (<.001)**
TMT-A	69.06	55 (30 – 317)	63.27	42.61	43 (30 – 59)	10.02	**76.5 (.007)**
TMT-B	190.6	145.5 (56 – 585)	140.3	105.4	110.5 (46 – 164)	35.5	**78 (.008)**
HVLT-REC	9.5	9.5 (4 – 12)	2.06	11.11	11 (9 – 12)	.9	**243.5 (.008)**
HVLT-DELAY	2.66	1 (0 – 10)	3.32	7.22	7.5 (0 – 12)	3.26	**267.5 (<.001)**
HVLT-TOT	14.33	14.5 (4 – 29)	6.12	21.89	21.5 (13 – 32)	5.10	**4.01 (<.001)**
FAS	32.83	33 (9 – 65)	15.77	52.17	50 (31 – 75)	11.91	**4.15 (<.001)**
ANIMAL FLUENCY	7.22	6 (1 – 21)	5.33	10.5	7 (5 – 28)	7.51	219.5 (.06)
DIGIT SYMBOL	36.83	34.5 (10 – 60)	12.85	58.11	60 (35 – 85)	12.57	**5.02 (<.001)**
DIGIT SPAN	5.11	5 (3 – 7)	.96	6	6 (5 – 9)	1.02	**240 (.009)**
REY-COPY	32.86	34 (30 – 36)	2.82	34.36	34 (31 – 36)	1.55	221 (.05)
REY-IMMEDIATE	12.44	13 (0 – 23)	7.52	23.61	23.25 (7 – 32)	7.15	**4.56 (<.001)**
REY-DELAY	11.69	15.25 (0 – 24)	9.11	22.17	21.25 (10 – 34)	6.15	**265 (<.001)**
GNT	17.83	19 (7 – 25)	4.59	25.56	26 (19 – 30)	3.18	**5.86 (<.001)**
CLOCK	5.05	4 (3 – 5)	3.55	4.66	5 (3 – 5)	.59	203 (.15)
FCSRT-ICR	20.44	21 (2 – 36)	9.26	19.22	19.5 (13 – 28)	5.48	-.48 (.63)
TOPF	53.78	56.5 (33 – 70)	14.31	65.83	68 (48 – 70)	5.18	**242.5 (.01)**

GDS	1.88	1 (0 – 10)	2.56	1.5	1 (0 - 5)	1.5	163 (.98)
IADL	5.77	6 (3 – 8)	1.86	7.77	8 (7 - 8)	.42	**265 (<.001)**

Significant ($p < 0.05$) tests highlighted in bold.

Note: N= Numerosity; M= Mean; Mdn= Median; SD= Standard deviation.
ACE= Addenbrooke's Cognitive Examination; MMSE= Mini Mental State Examination; TMT = Trail Making Test (Version A and B); HVLT= Hopkins Verbal Learning Test-Revised (Recognition, Delayed Recall, Total Recall); REY= Rey-Osterrieth Complex Figure Test (Copy, Immediate Reproduction, Delayed Reproduction); GNT= Graded Naming Test; FCSRT= Free and Cued Selective Reminding Test (ICR= Immediate Cued Recall); TOPF= Test of Premorbid Functioning; GDS= Geriatric Depression Scale; IADL= Instrumental Activities of Daily Living.

Both parametric and non-parametric t-tests revealed that MCI patients were worse than healthy normals in all the tests comprised in the neuropsychological battery, except in the animal fluency test (Mioshi et al., 2006), the copy of the Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1941), the clock test (Mioshi et al., 2006), and in the immediate cued recall of the FCSRT (Buschke, 1984; Grober & Buschke, 1987). Also, both groups reported, on average, similar scores on the GDS (Sheikh & Yesavage, 1986). *Table 9* illustrates the differential attainment of MCI and control groups in each neuropsychological test.

Table 10 *– Differences in performance in the WMBT and the FCSRT for both experimental groups.*

	MCI patients (N = 18)			**Healthy Controls** (N = 18)		
	M	**Mdn**	**SD**	**M**	**Mdn**	**SD**
Shape Only	.87	.90	.14	.95	.96	.05
Binding	.66	.61	.16	.82	.83	.13
FCSRT-IFR	12.17	9.5	9.72	27.89	25.5	5.65
FCSRT-ITR	33.22	38.5	14.94	47.67	48	1.02

Note: N= Numerosity; M= Mean; Mdn= Median; SD= Standard deviation.

A non – parametric 2 (Shape Only condition vs Binding condition, within factor) x 2 (MCI patients vs Healthy controls, between factor) mixed ANOVA yielded a significant main effect of condition ($F(1,34)= 53.37$, $p< .001$, $\eta^2p = .61$) as well as of group ($F(1,34)= 17.10$, $p< .001$, $\eta^2p = .33$). A significant condition*group interaction ($F(1,34)= 7.29$, $p= .01$, $\eta^2p= .17$) was also found, and post-hoc comparisons revealed a significant difference between the two groups in both conditions (Shape Only: $U= 236.5$, $p= .01$, $r= .46$; Binding: $t(34)= 3.31$, $p= .002$, $d= 1.10$)[4] with a larger discrepancy shown in the binding condition, as expressed by the effect size, which likely accounted for the interaction.

Mann-Whitney t-tests analysed differences in performing FCSRT-IFR and FCSRT-ITR between the two groups. Healthy controls showed both higher FCSRT-IFR ($U= 288$, $p< .001$, $r= .77$) and FCSRT-ITR ($U= 286$, $p< .001$, $r= .76$) rates compared to MCI patients. Group average scores, medians, and SDs in both tasks are displayed in *Table 10*.

[4] Whenever participants' scores were not normally distributed, non-parametric t-tests are reported.

3.4.6.2 Relationship between connectome metrics and behavioural tasks

3.4.6.2.1 Performance in the WMBT as predicted by connectome metrics

Table 11 *– Generalised linear mixed-effects model output for accuracy in the WMBT with mean edge weight as a predictor.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.51	.30	11.54	**<.001**
Proportion correct	Mean Edge Weight	.40	.28	1.45	.14
	Group (MCI)	-1.25	.38	-3.25	**.001**
	Condition (Binding)	-1.75	.25	-6.87	**<.001**
	Mean Edge Weight x Group	-.76	.36	-2.08	**.03**
	Mean Edge Weight x Condition	-.29	.22	-1.29	.19
	Group x Condition	.27	.30	.90	.36
	Mean Edge Weight x Group x Condition	.47	.27	1.71	.08

Significant (p< 0.05) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (Healthy controls, MCI patients), Condition (Shape Only, Binding). Planned comparisons were: Healthy controls vs MCI patients, and Shape Only vs Binding in relation to the variable 'Mean Edge Weight'.

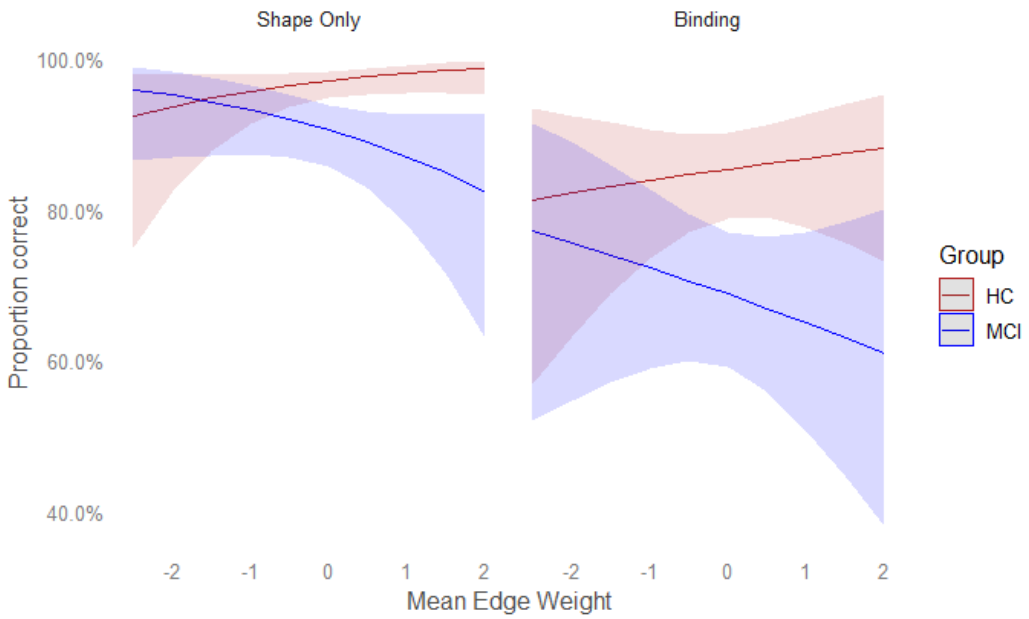


Figure 11 *- Trends in performance for healthy controls and MCI patients in both experimental conditions as predicted by mean edge weight.*

Mean edge weight. The model including mean edge weight as a predictor (*Table 11*) showed a main effect of condition, suggesting that performance in the Binding condition relied on edges of decreasing weight compared to the Shape Only condition. Also, a significant main effect of group was found, hinting at the evidence that the MCI group exhibited lower weighted edges compared to healthy elderly. This was also confirmed by the mean edge weight*group interaction. *Figure 11* shows the trends in performance for both groups in both experimental conditions.

Table 12 *– Generalised linear mixed-effects model output for accuracy in the WMBT with density as a predictor.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.43	.29	11.70	**<.001**
Proportion correct	Density	-.16	.29	-.56	.56
	Group (MCI)	-1.18	.37	-3.14	**.001**
	Condition (Binding)	-1.66	.24	-6.80	**<.001**
	Density x Group	-.01	.39	-.04	.96
	Density x Condition	-.10	.24	-.41	.67
	Group x Condition	.22	.29	.77	.44
	Density x Group x Condition	.61	.32	1.86	.06

Significant (p< 0.05) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (Healthy controls, MCI patients), Condition (Shape Only, Binding). Planned comparisons were: Healthy controls vs MCI patients, and Shape Only vs Binding in relation to the variable 'Density'.

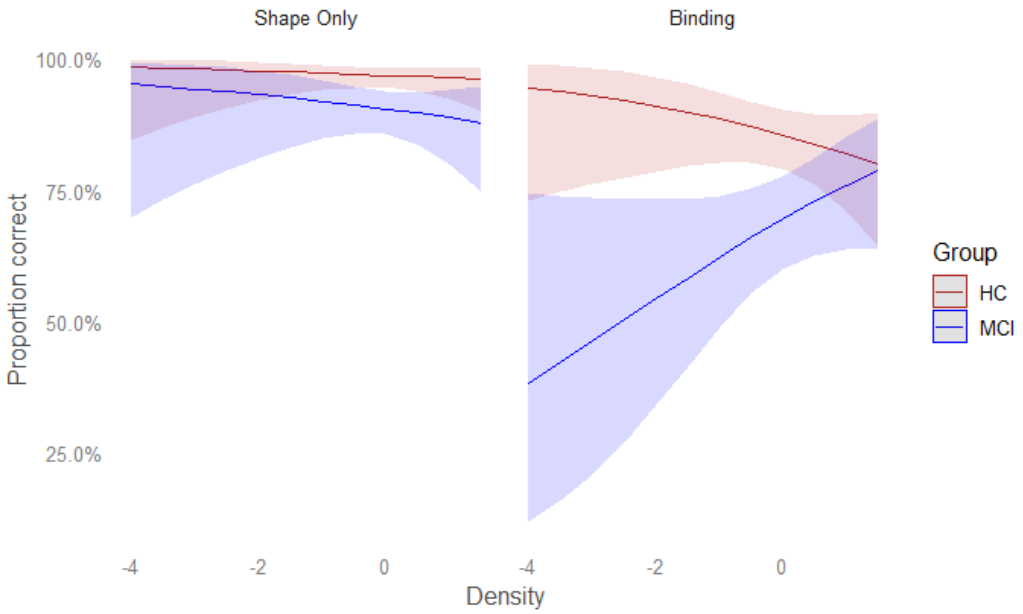


Figure 12 *- Trends in performance for healthy controls and MCI patients in both experimental conditions as predicted by density.*

Density. Overall performance was more dependent on lower global connectivity in MCI patients than in healthy controls, as demonstrated by the generalised linear mixed-effects model involving node density as a predictor, displayed in *Table 12*. This also held true for the Binding condition rather than the Shape Only condition in both groups, as suggested by the significant main effect of condition. Performance trends are shown in *Figure 12*.

Table 13 *– Generalised linear mixed-effects model output for accuracy in the WMBT with degree as a predictor.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.43	.29	11.70	**<.001**
Proportion correct	Degree	-.16	.29	-.56	.56
	Group (MCI)	-1.18	.37	-3.14	**.001**
	Condition (Binding)	-1.66	.24	-6.80	**<.001**
	Degree x Group	-.01	.39	-.04	.96
	Degree x Condition	-.10	.24	-.41	.67
	Group x Condition	.22	.29	.77	.44
	Degree x Group x Condition	.61	.32	1.86	.06

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (Healthy controls, MCI patients), Condition (Shape Only, Binding). Planned comparisons were: Healthy controls vs MCI patients, and Shape Only vs Binding in relation to the variable 'Degree'.

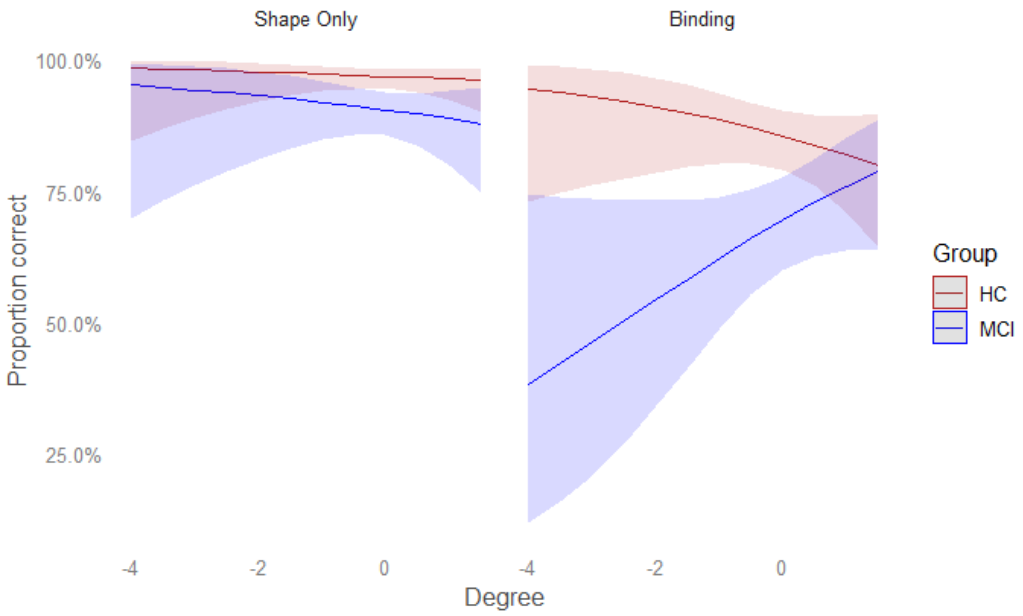


Figure 13 *- Trends in performance for healthy controls and MCI patients in both experimental conditions as predicted by degree.*

Degree. *Table 13* shows the significant main effect of group on the performance in association with node density, meaning that the number of connected links decreased in MCI patients compared to healthy controls. A similar conclusion can be achieved for the Binding condition compared to the Shape Only condition too. *Figure 13* depicts accuracy trends, depending on node density, for both groups and in both conditions.

Table 14 *– Generalised linear mixed-effects model output for accuracy in the WMBT with strength as a predictor.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.47	.30	11.55	**<.001**
Proportion correct	Strength	.21	.28	.76	.44
	Group (MCI)	-1.20	.38	-3.13	**.001**
	Condition (Binding)	-1.70	.24	-6.91	**<.001**
	Strength x Group	-.45	.38	-1.20	.22
	Strength x Condition	-.29	.23	-1.28	.20
	Group x Condition	.24	.29	.81	.41
	Strength x Group x Condition	.75	.30	2.48	**.01**

Significant (p< 0.05) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (Healthy controls, MCI patients), Condition (Shape Only, Binding). Planned comparisons were: Healthy controls vs MCI patients, and Shape Only vs Binding in relation to the variable 'Strength'.

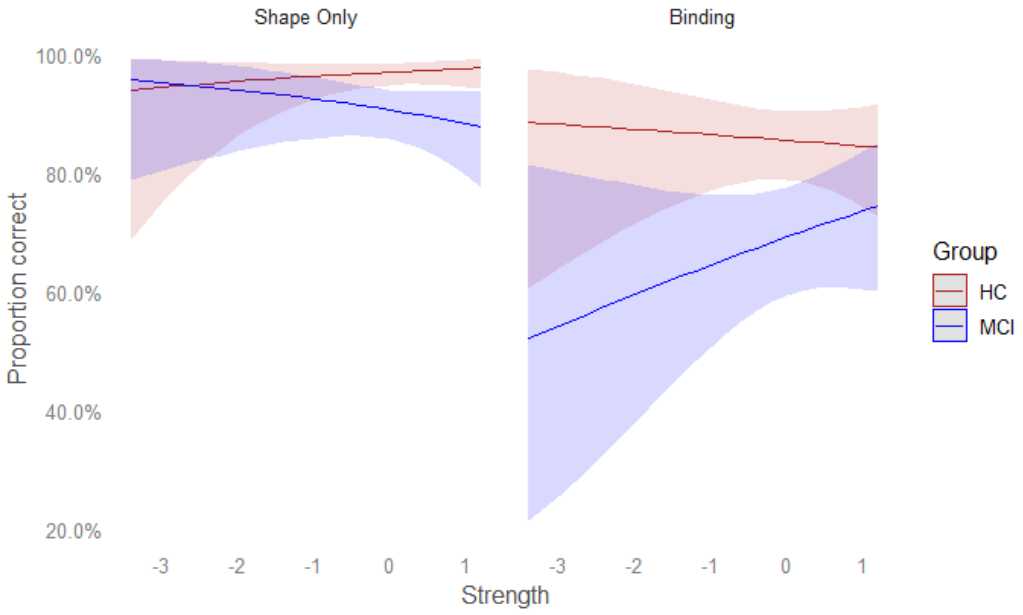


Figure 14 *- Trends in performance for healthy controls and MCI patients in both experimental conditions as predicted by strength.*

Strength. When strength was entered in the model (see *Table 14* and *Figure 14*), group and condition were significant predictors of the performance in the WMBT: MCI patients exhibited lower levels of strength compared to healthy controls; in addition, decreasing strength was associated with the Binding condition more than with the Shape Only condition. Strikingly, the interaction among the three factors, the strength*group*condition interaction, revealed that MCI patients needed stronger white matter connections among brain areas to perform the Binding condition of the WMBT.

Table 15 *– Generalised linear mixed-effects model output for accuracy in the WMBT with mean shortest path as a predictor.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.46	.30	11.53	**<.001**
Proportion correct	Mean Shortest Path	-.15	.29	-.54	.58
	Group (MCI)	-1.21	.38	-3.13	**.001**
	Condition (Binding)	-1.69	.24	-6.92	**<.001**
	Mean Shortest Path x Group	.36	.38	.95	.33
	Mean Shortest Path x Condition	.23	.23	1.00	.31
	Group x Condition	.23	.29	.78	.43
	Mean Shortest Path x Group x Condition	-.54	.29	-1.82	.06

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (Healthy controls, MCI patients), Condition (Shape Only, Binding). Planned comparisons were: Healthy controls vs MCI patients, and Shape Only vs Binding in relation to the variable 'Mean Shortest Path'.

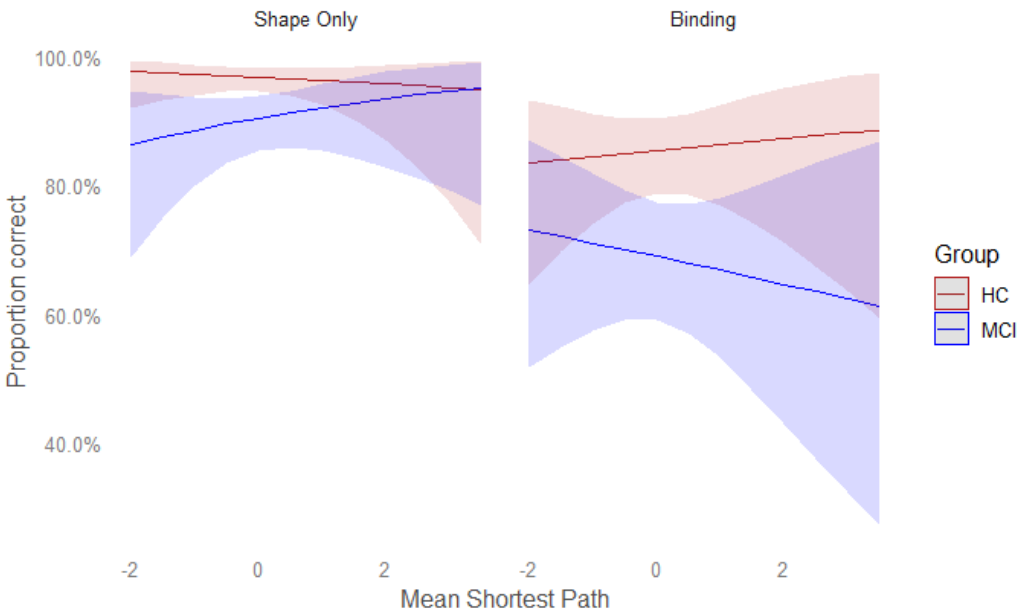


Figure 15 *- Trends in performance for healthy controls and MCI patients in both experimental conditions as predicted by mean shortest path.*

Mean Shortest Path. Significant main effects of group and condition were yielded by the model including mean shortest path as a predictor for the WMBT. Reduced amount of short paths was found in the MCI group, as well as in the Binding condition compared to the Shape Only condition. *Table 15* and *Figure 15* illustrate these trends.

Table 16 *– Generalised linear mixed-effects model output for accuracy in the WMBT with global efficiency as a predictor.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.48	.30	11.51	**<.001**
Proportion correct	Global Efficiency	.25	.28	.87	.38
	Group (MCI)	-1.22	.38	-3.15	**.001**
	Condition (Binding)	-1.71	.24	-6.9	**<.001**
	Global Efficiency x Group	-.50	.37	-1.33	.18
	Global Efficiency x Condition	-.25	.22	-1.13	.25
	Group x Condition	.24	.30	.81	.41
	Global Efficiency x Group x Condition	.57	.28	1.99	**.04**

Significant (p< 0.05) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (Healthy controls, MCI patients), Condition (Shape Only, Binding). Planned comparisons were: Healthy controls vs MCI patients, and Shape Only vs Binding in relation to the variable 'Global Efficiency'.

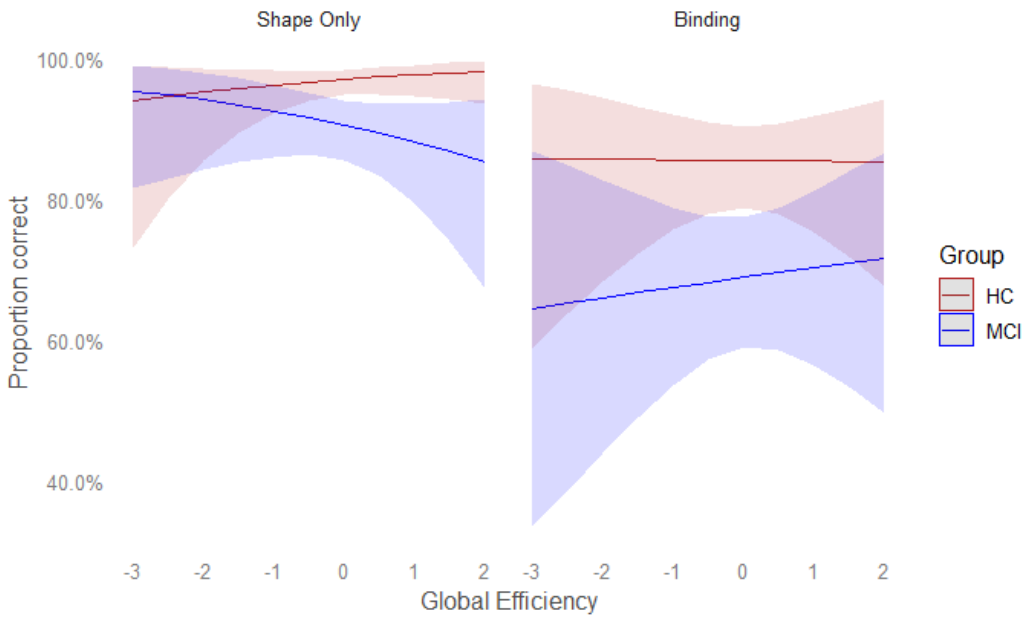


Figure 16 *- Trends in performance for healthy controls and MCI patients in both experimental conditions as predicted by global efficiency.*

Global Efficiency. *Table 16* reports that, by entering global efficiency as a predictor, group and condition were confirmed to have a significant effect on the level of performance in the WMBT. MCI patients' structural network was observed to be less efficient than expected in normal cognition, and this decrease of efficiency was registered in the Binding condition more than in the Shape Only condition. The significant global efficiency*group*condition interaction suggested that relative to healthy controls, MCI patients' performance on the Binding condition was more reliant on communication among the brain nodes, which, based on the effects above reported, was not sufficiently efficient (see *Figure 16*).

Table 17 *– Generalised linear mixed-effects model output for accuracy in the WMBT with clustering coefficient as a predictor.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.54	.31	11.41	**<.001**
Proportion correct	Clustering Coefficient	.43	.29	1.46	.14
	Group (MCI)	-1.26	.39	-3.23	**.001**
	Condition (Binding)	-1.76	.25	-6.87	**<.001**
	Clustering Coefficient x Group	-.73	.39	-1.92	.05
	Clustering Coefficient x Condition	-.46	.24	-1.91	.05
	Group x Condition	.29	.30	.94	.34
	Clustering Coefficient x Group x Condition	.80	.29	2.71	**.006**

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (Healthy controls, MCI patients), Condition (Shape Only, Binding). Planned comparisons were: Healthy controls vs MCI patients, and Shape Only vs Binding in relation to the variable 'Clustering Coefficient'.

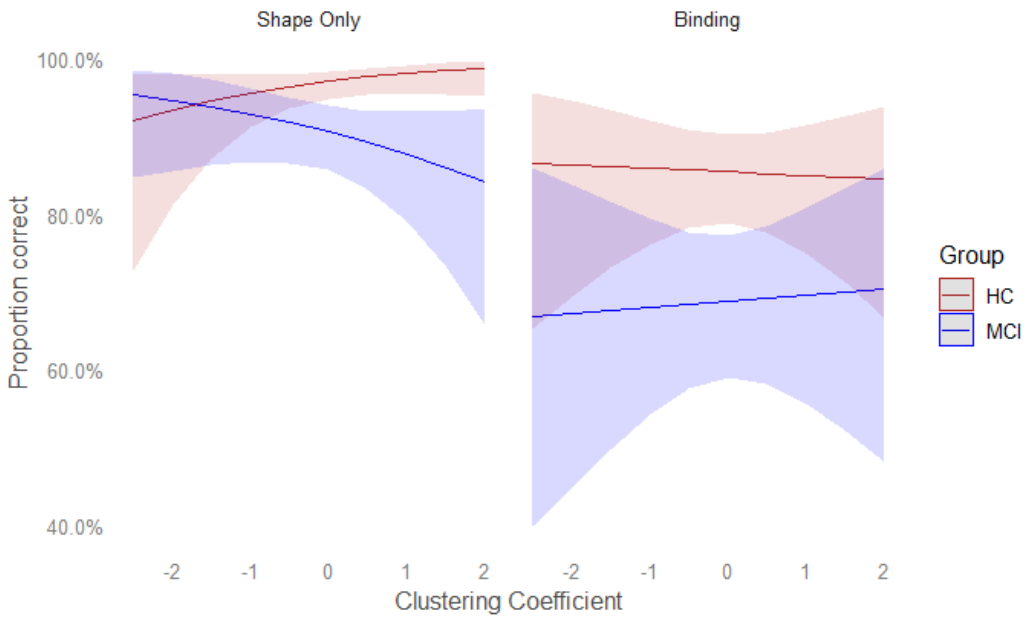


Figure 17 *- Trends in performance for healthy controls and MCI patients in both experimental conditions as predicted by clustering coefficient.*

Clustering Coefficient. Finally, as displayed in *Table 17*, group and condition also showed significant slopes in the model involving clustering coefficient as a predictor. Again, MCI was associated with fewer engaged clusters of nodes compared to their healthy counterparts, and this was true especially for encoding and retaining bound material rather than single features. The three-way interaction acknowledged that MCI patients' impaired ability to hold colour-shape conjunctions in WM was driven by greater functional segregation, as also evident in *Figure 17*.

3.4.6.2.2 Performance in the FCSRT as predicted by connectome metrics

Table 18 *– Linear multiple regression model outputs for accuracy in the FCSRT with mean edge weight as a predictor.*

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
	Intercept	27.88	1.87	14.91	**<.001**
IFR score	Mean Edge Weight	-2.32	1.92	-1.20	.23
	Group	-15.72	2.64	-5.94	**<.001**
	Mean Edge Weight x Group	3.94	2.72	1.44	.15

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
	Intercept	47.66	2.55	18.62	**<.001**
ITR score	Mean Edge Weight	-.06	2.63	-.02	.98
	Group	-14.44	3.61	-3.99	**<.001**
	Mean Edge Weight x Group	-1.45	3.72	-.39	.69

Significant ($p < 0.05$) effects are highlighted in bold.

Mean edge weight. Linear regression models including mean edge weight as a predictor, as displayed in *Table 18*, showed a meaningful effect of group on the performance in the FCSRT-IFR and FCSRT-ITR. This indicated that decreasing edge weights are associated with lower scores in MCI.

Table 19 *– Linear multiple regression model outputs for accuracy in the FCSRT with density as a predictor.*

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
IFR score	Intercept	27.88	1.75	15.93	**<.001**
	Density	.22	1.80	.12	.90
	Group	-15.72	2.47	-6.35	**<.001**
	Density x Group	4.53	2.54	1.78	.08

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
ITR score	Intercept	47.66	2.41	19.73	**<.001**
	Density	-.13	2.48	-.05	.95
	Group	-14.44	3.41	-4.22	**<.001**
	Density x Group	5.28	3.51	1.50	.14

Significant ($p < 0.05$) effects are highlighted in bold.

Density. Lower global connectivity was registered in MCI patients when instructed to recall item-category associations, as revealed by the significant main effect of group resulting from the linear regression models including density as a factor (see *Table 19*).

Table 20 *– Linear multiple regression model outputs for accuracy in the FCSRT with degree as a predictor.*

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
IFR score	Intercept	27.88	1.75	15.93	**<.001**
	Degree	.22	1.80	.12	.90
	Group	-15.72	2.47	-6.35	**<.001**
	Degree x Group	4.53	2.54	1.77	.08

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
ITR score	Intercept	47.66	2.41	19.73	**<.001**
	Degree	-.13	2.48	-.05	.95
	Group	-14.44	3.41	-4.22	**<.001**
	Degree x Group	5.28	3.51	1.50	.14

Significant ($p < 0.05$) effects are highlighted in bold.

Degree. *Table 20* shows that the number of connected links decreased in MCI patients compared to healthy older controls when performing both FCSRT-IFR and FCSRT-ITR.

Table 21 *– Linear multiple regression model outputs for accuracy in the FCSRT with strength as a predictor.*

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
IFR score	Intercept	27.88	1.75	15.90	**<.001**
	Strength	-1.61	1.80	-.89	.37
	Group	-15.72	2.48	-6.33	**<.001**
	Strength x Group	6.04	2.55	2.36	**.02**

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
ITR score	Intercept	47.66	2.49	19.11	**<.001**
	Strength	-.13	2.56	-.05	.95
	Group	-14.44	3.52	-4.09	**<.001**
	Strength x Group	3.81	3.62	1.05	.30

Significant ($p < 0.05$) effects are highlighted in bold.

Strength. Linear regression models assessing the relationship between FCSRT-IFR and FCSRT-ITR scores and strength yielded a significant main effect of group, with MCI patients recalling fewer words than healthy controls. Also, a strength*group interaction was found for the FCSRT-IFR score only, indicating that stronger connections were needed by MCI patients to carry out the immediate free recall sub-test (see *Table 21*).

Table 22 *– Linear multiple regression model outputs for accuracy in the FCSRT with mean shortest path as a predictor.*

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
IFR score	Intercept	27.88	1.77	15.70	**<.001**
	Mean Shortest Path	2.21	1.82	1.21	.23
	Group	-15.72	2.51	-6.26	**<.001**
	Mean Shortest Path x Group	-6.05	2.58	-2.34	**.02**

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
ITR score	Intercept	47.66	2.54	18.74	**<.001**
	Mean Shortest Path	.02	2.61	.009	.99
	Group	-14.44	3.59	-4.01	**<.001**
	Mean Shortest Path x Group	-2.27	3.70	-.61	.54

Significant ($p < 0.05$) effects are highlighted in bold.

Mean Shortest Path. Regression models measuring the predictive role of mean shortest path on FCSRT performance, depicted in *Table 22*, presented a significant main effect of group for both IFR and ITR scores. The mean shortest path*group interaction reached significance for the FCSRT-IFR score only, revealing that patients' immediate free recall was associated with disrupted communication among neighbouring brain regions.

Table 23 *– Linear multiple regression model outputs for accuracy in the FCSRT with global efficiency as a predictor.*

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
IFR score	Intercept	27.88	1.78	15.63	**<.001**
	Global Efficiency	-2.23	1.83	-1.21	.23
	Group	-15.72	2.52	-6.23	**<.001**
	Global Efficiency x Group	5.93	2.59	2.28	**.02**

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
ITR score	Intercept	47.66	2.55	18.66	**<.001**
	Global Efficiency	-.03	2.62	-.01	.99
	Group	-14.44	3.61	-4.00	**<.001**
	Global Efficiency x Group	1.88	3.71	.50	.61

Significant ($p < 0.05$) effects are highlighted in bold.

Global Efficiency. FCSRT-IFR and FCSRT-ITR scores were better predicted by the group membership. MCI patients required more efficient connections among brain areas to succeed in the immediate free recall sub-test (see *Table 23*), as indicated by the significant global efficiency*group interaction.

Table 24 *– Linear multiple regression model outputs for accuracy in the FCSRT with clustering coefficient as a predictor.*

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
IFR score	Intercept	27.88	1.84	15.14	**<.001**
	Clustering Coefficient	-1.93	1.89	-1.02	.31
	Group	-15.72	2.60	-6.03	**<.001**
	Clustering Coefficient x Group	4.72	2.68	1.76	.08

Dependent Variable	Effects	β	SE	t-value	Pr(>|t|)
ITR score	Intercept	47.66	2.56	18.55	**<.001**
	Clustering Coefficient	-.09	2.64	-.03	.97
	Group	-14.44	3.63	-3.97	**<.001**
	Clustering Coefficient x Group	.87	3.73	.23	.81

Significant ($p < 0.05$) effects are highlighted in bold.

Clustering Coefficient. The regression analyses on the rates of recalled (both free and total) items yielded a significant difference between healthy controls and MCI patients overall, as reported in *Table 24*.

3.4.6.3 Further analysis and results

Further analyses were carried out to investigate the relationship between connectome metrics and behavioural performance in the WMBT in those MCI patients who showed a more compatible profile with AD, namely, those displaying a severe impairment to temporarily process colour-shape conjunctions. These were patients whose performance was - 1.5 SD away from the mean of the control group (HC). Thus, the MCI group, accounting for eighteen patients in total, was divided in two sub-groups of nine patients each: patients with good WMB capacities, named “MCI – Good Binders” (MCI-GB), and patients with poor WMB capacities, called “MCI – Poor Binders” (MCI-PB).

The relationship between WMBT performance and connectome metrics, depending on task conditions and group membership, was examined with generalised linear mixed-effects models (Bates et al., 2015) running in R Studio (version 1.1.456; R Core Team, 2013). As for previous analyses, the fixed effects were: Connectome metrics (i.e., mean edge weight, density, degree, strength, mean shortest path, global efficiency, and clustering coefficient), Group (HC, MCI-GB, MCI-PB), and Condition (Shape Only, Binding). Connectome metrics were entered one by one in the model and centred to reduce co-linearity. The random effect included in the models, both as intercept and slope, was Subject (36).

3.4.6.3.1 Relationship between connectome metrics and the WMBT in MCI-Poor Binders

Table 25 *– Proportion of correct responses in the WMBT as predicted by mean edge weight.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
Proportion correct	Intercept	3.47	.28	12.12	**<.001**
	Mean Edge Weight	.41	.26	1.57	.11
	Group (MCI-Good binders)	-.92	.42	-2.17	**.02**
	Group (MCI-Poor binders)	-1.49	.42	-3.56	**<.001**
	Condition (Binding)	-1.74	.25	-6.83	**<.001**
	Mean Edge Weight x Group (MCI-Good binders)	-.36	.41	-.90	.36
	Mean Edge Weight x Group (MCI-Poor binders)	-1.08	.42	-2.57	**.01**
	Mean Edge Weight x Condition	-.29	.22	-1.30	.19
	Group (MCI-Good binders) x Condition	.64	.36	1.77	.07
	Group (MCI-Poor binders) x Condition	-.04	.35	-.14	.88
	Mean Edge Weight x Group (MCI-Good binders) x Condition	-.15	.34	-.45	.64
	Mean Edge Weight x Group (MCI-Poor binders) x Condition	.98	.34	2.80	**.005**

Significant (p< 0.05) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (HC, MCI-GB, MCI-PB), Condition (Shape Only, Binding). Planned comparisons were: HC vs MCI-GB and HC vs MCI-PB, and Shape Only vs Binding in relation to the variable 'Mean Edge Weight'.

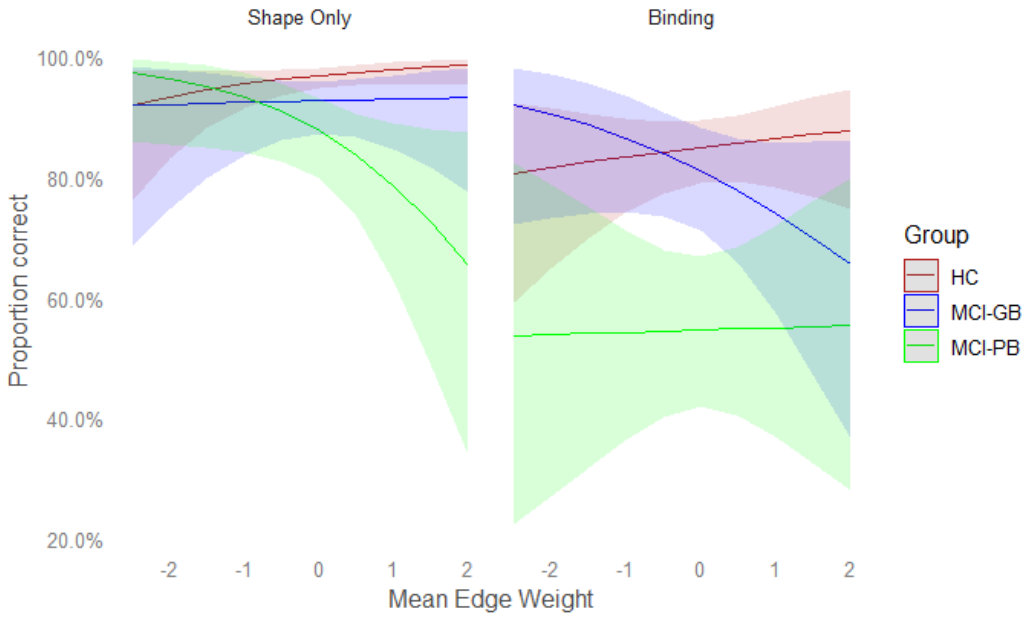


Figure 18 *- Trends in performance for healthy controls, MCI-Good Binders and MCI-Poor Binders in both experimental conditions as predicted by mean edge weight.*

Mean Edge Weight. When mean edge weight was entered in the model, as in *Table 25*, the Shape Only condition appeared to be carried out more easily by the three groups compared to the Binding condition. The mean edge weight*group interaction was significant, suggesting that weights of white matter connections tended to decrease in MCI patients who had a severe WMB deficit (i.e., MCI-Poor Binders). Puzzlingly, the meaningful mean edge weight*group*condition interaction revealed that, when engaged in the Binding condition of the WMBT, weights of connections increased in MCI-Poor Binders. This is also highlighted in *Figure 18*.

Table 26 *– Proportion of correct responses in the WMBT as predicted by density.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
Proportion correct	Intercept	3.4	.27	12.31	**<.001**
	Density	-.16	.27	-.59	.55
	Group (MCI-Good binders)	-.84	.41	-2.02	**.04**
	Group (MCI-Poor binders)	-1.46	.40	-3.58	**<.001**
	Condition (Binding)	-1.65	.24	-6.77	**<.001**
	Density x Group (MCI-Good binders)	.25	.44	.58	.55
	Density x Group (MCI-Poor binders)	-.36	.44	-.82	.41
	Density x Condition	-.10	.24	-.41	.67
	Group (MCI-Good binders) x Condition	.55	.35	1.57	.11
	Group (MCI-Poor binders) x Condition	-.09	.33	-.27	.78
	Density x Group (MCI-Good binders) x Condition	.43	.38	1.10	.26
	Density x Group (MCI-Poor binders) x Condition	.65	.38	1.69	.08

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (HC, MCI-GB, MCI-PB), Condition (Shape Only, Binding). Planned comparisons were: HC vs MCI-GB and HC vs MCI-PB, and Shape Only vs Binding in relation to the variable 'Density'.

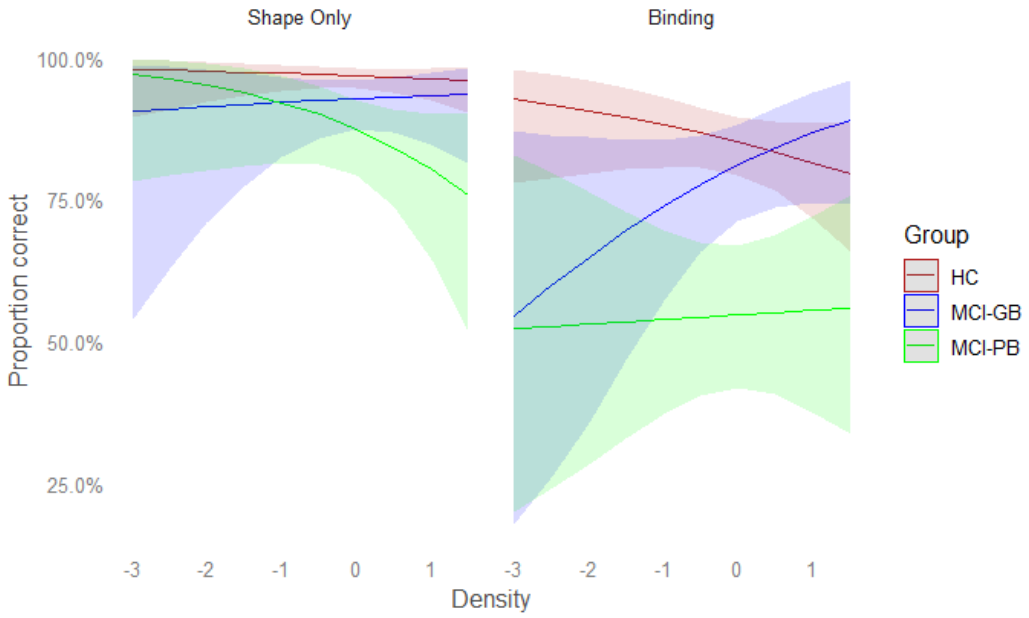


Figure 19 *- Trends in performance for healthy controls, MCI-Good Binders and MCI-Poor Binders in both experimental conditions as predicted by density.*

Density. Results showed that node density levels were lower for both MCI-Good Binders and MCI-Poor Binders compared to healthy controls. The difference was also significant between Shape Only and Binding conditions overall (see *Table 26* and *Figure 19*).

Table 27 *– Proportion of correct responses in the WMBT as predicted by degree.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.40	.27	12.31	**<.001**
Proportion correct	Degree	-.16	.27	-.59	.55
	Group (MCI-Good binders)	-.84	.41	-2.02	**.04**
	Group (MCI-Poor binders)	-1.46	.40	-3.58	**<.001**
	Condition (Binding)	-1.65	.24	-6.77	**<.001**
	Degree x Group (MCI-Good binders)	.25	.44	.58	.55
	Degree x Group (MCI-Poor binders)	-.36	.44	-.82	.41
	Degree x Condition	-.10	.24	-.41	.67
	Group (MCI-Good binders) x Condition	.55	.35	1.57	.11
	Group (MCI-Poor binders) x Condition	-.09	.33	-.27	.78
	Degree x Group (MCI-Good binders) x Condition	.43	.38	1.10	.26
	Degree x Group (MCI-Poor binders) x Condition	.65	.38	1.69	.08

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (HC, MCI-GB, MCI-PB), Condition (Shape Only, Binding). Planned comparisons were: HC vs MCI-GB and HC vs MCI-PB, and Shape Only vs Binding in relation to the variable 'Degree'.

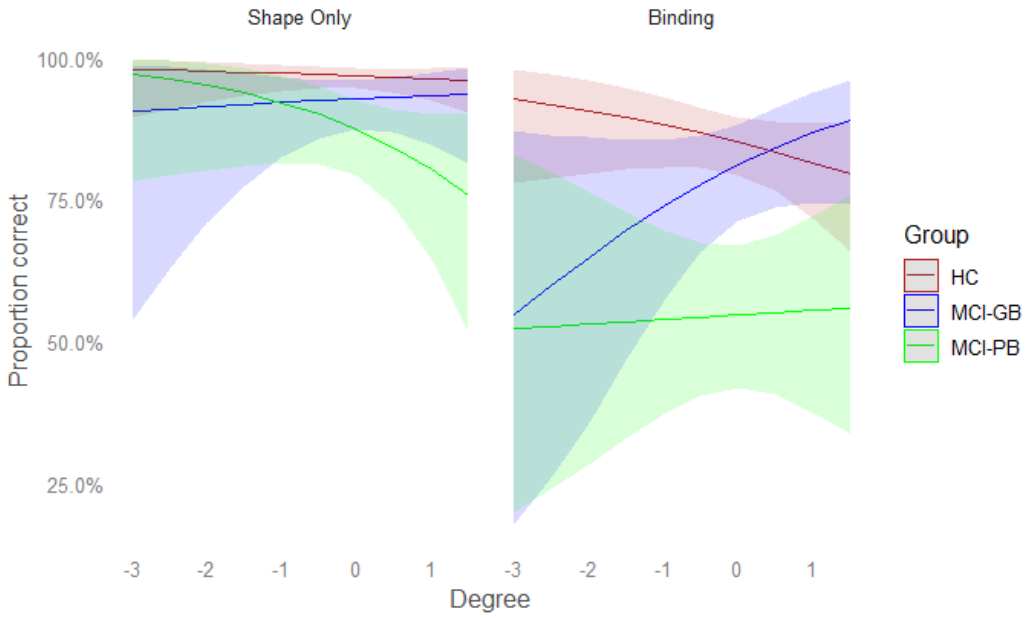


Figure 20 *- Trends in performance for healthy controls, MCI-Good Binders and MCI-Poor Binders in both experimental conditions as predicted by degree.*

Degree. *Table 27* reports the significant main effect of group, suggesting that the number of connected links was reduced in both MCI-Good Binders and MCI-Poor Binders compared to healthy controls. Also, this occurred in the Binding condition compared to the Shape Only condition as indicated by the significant main effect of condition. *Figure 20* illustrates trends in performance for the three experimental groups as predicted by the connectome metric of interest.

Table 28 *– Proportion of correct responses in the WMBT as predicted by strength.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.44	.28	12.11	**<.001**
Proportion correct	Strength	.22	.26	.83	.40
	Group (MCI-Good binders)	-.86	.43	-2.01	**.04**
	Group (MCI-Poor binders)	-1.47	.42	-3.47	**<.001**
	Condition (Binding)	-1.69	.24	-6.88	**<.001**
	Strength x Group (MCI-Good binders)	-.05	.43	-.12	.90
	Strength x Group (MCI-Poor binders)	-.84	.43	-1.95	.05
	Strength x Condition	-.29	.23	-1.26	.20
	Group (MCI-Good binders) x Condition	.55	.35	1.55	.12
	Group (MCI-Poor binders) x Condition	-.08	.34	-.24	.80
	Strength x Group (MCI-Good binders) x Condition	.09	.36	.27	.78
	Strength x Group (MCI-Poor binders) x Condition	.95	.36	2.62	**.008**

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (HC, MCI-GB, MCI-PB), Condition (Shape Only, Binding). Planned comparisons were: HC vs MCI-GB and HC vs MCI-PB, and Shape Only vs Binding in relation to the variable 'Strength'.

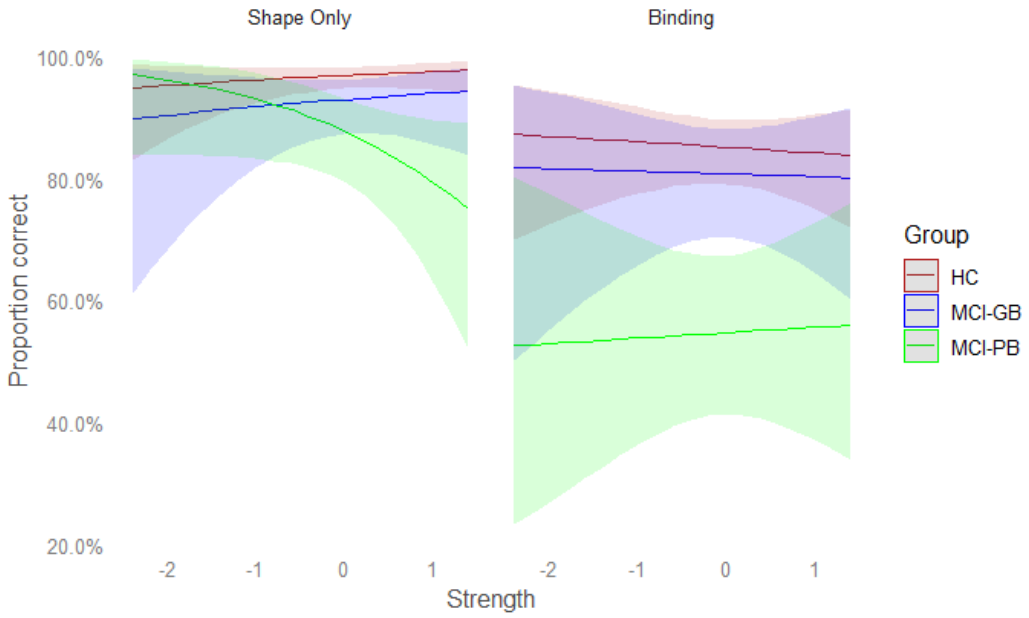


Figure 21 *- Trends in performance for healthy controls, MCI-Good Binders and MCI-Poor Binders in both experimental conditions as predicted by strength.*

Strength. By entering strength in the model as a predictor, as shown in *Table 28*, the significant main effects of group and condition were found. This means that white matter connections were not strong in both MCI samples in respect to healthy controls, as well as in the Binding condition compared to the Shape Only condition. The model also revealed a significant strength*group*condition interaction, indicating that the strength of brain connections was higher for the MCI-Poor Binders group only when processing colour-shape conjunctions in WM. A similar trend is evident in *Figure 21*.

Table 29 *– Proportion of correct responses in the WMBT as predicted by mean shortest path.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.43	.28	12.15	**<.001**
Proportion correct	Mean Shortest Path	-.16	.27	-.60	.54
	Group (MCI-Good binders)	-.86	.42	-2.01	**.04**
	Group (MCI-Poor binders)	-1.50	.41	-3.58	**<.001**
	Condition (Binding)	-1.68	.24	-6.84	**<.001**
	Mean Shortest Path x Group (MCI-Good binders)	.09	.43	.22	.82
	Mean Shortest Path x Group (MCI-Poor binders)	.66	.43	1.53	.12
	Mean Shortest Path x Condition	.23	.23	1.01	.31
	Group (MCI-Good binders) x Condition	.57	.35	1.63	.10
	Group (MCI-Poor binders) x Condition	-.05	.33	-.17	.86
	Mean Shortest Path x Group (MCI-Good binders) x Condition	.20	.37	.56	.57
	Mean Shortest Path x Group (MCI-Poor binders) x Condition	-.74	.36	-2.07	**.03**

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (HC, MCI-GB, MCI-PB), Condition (Shape Only, Binding). Planned comparisons were: HC vs MCI-GB and HC vs MCI-PB, and Shape Only vs Binding in relation to the variable 'Mean Shortest Path'.

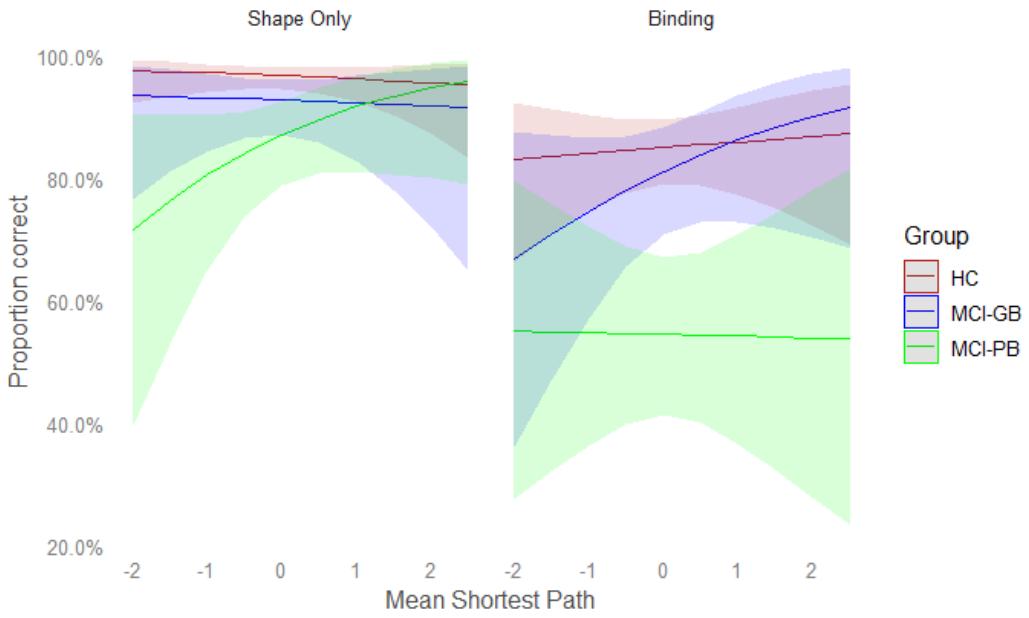


Figure 22 *- Trends in performance for healthy controls, MCI-Good Binders and MCI-Poor Binders in both experimental conditions as predicted by mean shortest path.*

Mean Shortest Path. Similar results emerged from the model including mean shortest path as a predictor for WMBT performance (see *Table 29* and *Figure 22*). The significant main effect of group showed that MCI groups displayed a reduced amount of connections among neighbouring brain regions; also, this was verified in the Binding condition only for all participants. The three-way interaction strengthened the evidence that longer connections, hence, more distant and various areas are recruited by MCI-Poor Binders to temporarily bind features in WM.

Table 30 *– Proportion of correct responses in the WMBT as predicted by global efficiency.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.44	.28	12.13	**<.001**
Proportion correct	Global Efficiency	.25	.26	.96	.33
	Group (MCI-Good binders)	-.88	.42	-2.05	**.03**
	Group (MCI-Poor binders)	-1.49	.42	-3.54	**<.001**
	Condition (Binding)	-1.70	.24	-6.88	**<.001**
	Global Efficiency x Group (MCI-Good binders)	-.18	.42	-.42	.66
	Global Efficiency x Group (MCI-Poor binders)	-.83	.42	-1.96	.05
	Global Efficiency x Condition	-.26	.22	-1.13	.25
	Group (MCI-Good binders) x Condition	.59	.35	1.66	.09
	Group (MCI-Poor binders) x Condition	-.06	.34	-.17	.85
	Global Efficiency x Group (MCI-Good binders) x Condition	-.17	.35	-.48	.63
	Global Efficiency x Group (MCI-Poor binders) x Condition	.85	.35	2.43	**.01**

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (HC, MCI-GB, MCI-PB), Condition (Shape Only, Binding). Planned comparisons were: HC vs MCI-GB and HC vs MCI-PB, and Shape Only vs Binding in relation to the variable 'Global Efficiency'.

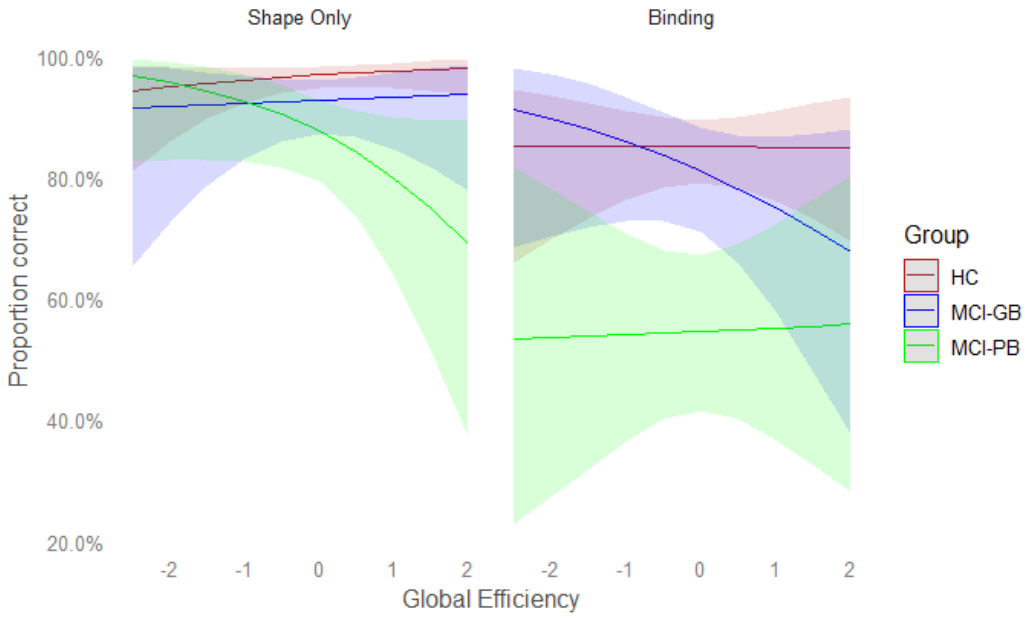


Figure 23 *- Trends in performance for healthy controls, MCI-Good Binders and MCI-Poor Binders in both experimental conditions as predicted by global efficiency.*

Global Efficiency. Lower levels of global efficiency were registered in MCI-Good and –Poor Binders compared to healthy normals. This held true for the Binding condition compared to the Shape Only condition as well. The global efficiency*group*condition interaction was significant and the positive trend suggested that MCI-Poor Binders needed a better communication and information transfer among connected brain regions to carry out the Binding condition of the WMBT. *Table 30* and *Figure 23* report similar trends.

Table 31 *– Proportion of correct responses in the WMBT as predicted by clustering coefficient.*

Dependent Variable	Effects	β	SE	z-value	Pr(>|z|)
	Intercept	3.50	.29	11.96	**<.001**
Proportion correct	Clustering Coefficient	.44	.27	1.57	.11
	Group (MCI-Good binders)	-.92	.43	-2.14	**.03**
	Group (MCI-Poor binders)	-1.50	.42	-3.50	**<.001**
	Condition (Binding)	-1.75	.25	-6.83	**<.001**
	Clustering Coefficient x Group (MCI-Good binders)	-.29	.43	-.69	.48
	Clustering Coefficient x Group (MCI-Poor binders)	-1.11	.42	-2.60	**.009**
	Clustering Coefficient x Condition	-.46	.24	-1.91	.05
	Group (MCI-Good binders) x Condition	.62	.36	1.71	.08
	Group (MCI-Poor binders) x Condition	-.04	.35	-.12	.90
	Clustering Coefficient x Group (MCI-Good binders) x Condition	.17	.35	.49	.62
	Clustering Coefficient x Group (MCI-Poor binders) x Condition	1.16	.35	3.26	**.001**

Significant ($p < 0.05$) effects are highlighted in bold.

Note: Predictors are listed in the table as they were entered in the model. The predictors were: Connectome metric, Group (HC, MCI-GB, MCI-PB), Condition (Shape Only, Binding). Planned comparisons were: HC vs MCI-GB and HC vs MCI-PB, and Shape Only vs Binding in relation to the variable 'Clustering Coefficient'.

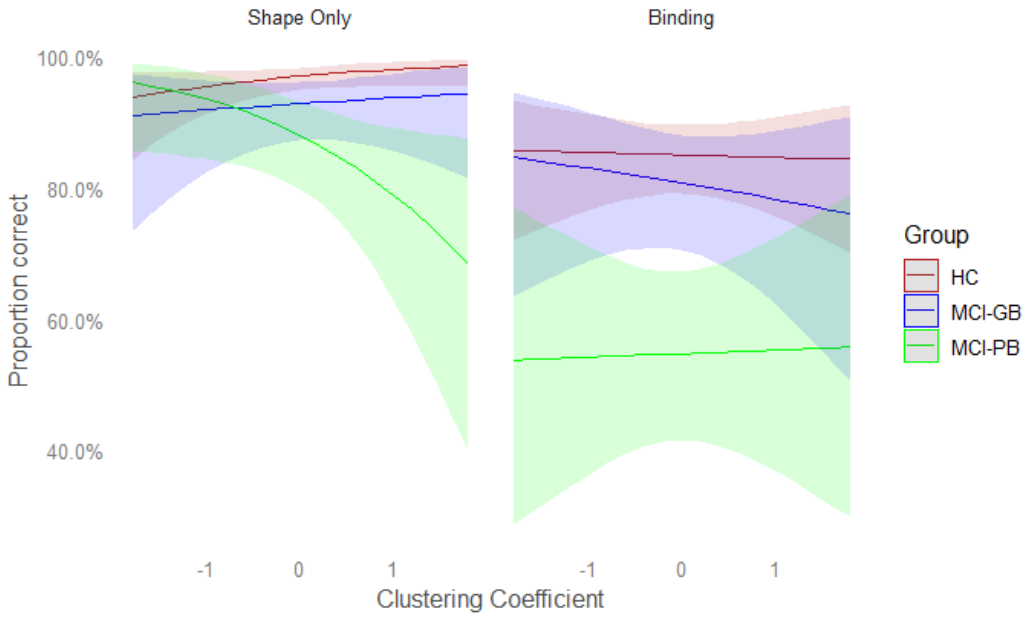


Figure 24 *- Trends in performance for healthy controls, MCI-Good Binders and MCI-Poor Binders in both experimental conditions as predicted by clustering coefficient.*

Clustering Coefficient. Finally, when clustering coefficient was entered in the model, as shown in *Table 31*, it determined both meaningful main effects of group and condition as discussed for other connectome metrics. In addition, the clustering coefficient*group interaction was significant, indicating that, when not accounting for behavioural performance, MCI-Poor Binders displayed fewer brain regions to be connected into clusters in respect to the other two groups. Lastly, the significant clustering coefficient*group*condition interaction revealed the opposite trend when the same participants were required to process feature conjunctions: MCI-Poor Binders recruited more clusters of regions to perform the task. *Figure 24* accounts for all these trends.

3.4.6.3.2 Summary of results

I think it may be worth summarising the core findings from analyses on MCI-Poor Binders (MCI-PB), since they are really informative of the relationship between conjunctive WMB deficits and loss of connectivity in prodromal AD.

It has been shown that MCI-PB relied on increasing levels of mean edge weight, strength, global efficiency and clustering coefficient to temporarily hold colour-shape conjunctions in WM (three-way interactions). This indicates that, in order to compensate for lower binding capacities, MCI-PB exhibit a structural brain organisation wherein more brain regions are connected.

Also, by looking at the model including mean shortest path as a predictor, it appears that levels of average shortest paths decrease in MCI-PB in the Binding condition. This suggests that brain regions underpinning conjunctive WMB need more long-distance connections to transfer and process information. I will better explain the implications of these results in the next section.

3.4.7 Discussion

The present study was designed to investigate whether changes in the structure of the brain connectome were associated with memory binding deficits in patients at risk of sporadic AD.

3.4.7.1 Behavioural findings

Neuropsychological findings were in line with those yielded in the prior chapter (see *Section 2.3.7.1*). Also, consistently with previous studies, current behavioural findings confirmed that

the WMBT and the FCSRT are reliable tools to detect early signs of cognitive impairment in people who show risk of developing AD (Koppara et al., 2015; Parra et al., 2019; Pietto et al., 2016).

A significant group x condition interaction was found, showing that MCI patients were worse than healthy older controls in the Binding condition.

It is noteworthy to specify that this pattern of results, as emerging from eighteen MCI patients and eighteen healthy controls assessed in the present DT-MRI paradigm, is the same obtained from the behavioural analysis on twenty-two MCI patients and twenty-two healthy controls involved in the fMRI study discussed in the previous chapter.

In addition, MCI patients showed lower free and total recall rates than healthy older adults in the FCSRT. Such evidence corroborates previous findings reporting the reliability of the test to detect subtle cognitive changes in people at risk of AD (Grober & Kawas, 1997; Grober et al., 2008; 2000; Lemos et al., 2014; Papp et al., 2015).

3.4.7.2 DT-MRI findings

The main findings yielded by DT-MRI analyses in relation to the behavioural performance were: (i) MCI patients exhibited disrupted topological organisation of white matter networks as revealed by decreasing values of mean edge weight, density, degree, strength, mean shortest path, global efficiency, and clustering coefficient compared to healthy older controls; (ii) increased levels of strength, global efficiency, and clustering coefficient were observed in MCI patients when undergoing the Binding condition of the WMBT; (iii) MCI patients showed increased strength and global efficiency, and decreased mean shortest path in association with the FCSRT-IFR score; (iv) performance in FCSRT-ITR was not significantly predicted by changes in brain connectivity.

Firstly, changes in the topological structure of the brain connectome, as expressed by metrics of interest, should be discussed in the light of group differences between MCI patients and healthy controls. It is well-known that the human structural connectome shares small-world properties, with an optimal balance between functional segregation (clustering coefficient) and global integration (mean shortest path). Pathology-related neural changes affect such structure to the extent that loss of small-worldness has been considered a hallmark of AD across its spectrum (Bai, Shu, Yuan, Shi, Yu, Wu et al., 2012; Daianu, Jahanshad, Nir, Toga, Jack Jr, Weiner, & Thompson, 2013; Liu, Zhang, Yan, Bai, Dai, Wei et al., 2012; Shu, Liang, Li, Zhang, Li, Wang et al., 2012; Wang, Zuo, Dai, Xia, Zhao, Zhao et al., 2013; Yao, Zhang, Lin, Zhou, Xu, & Jiang, 2010; see Dai & He, 2014 for a review).

Indeed, low levels of modularity (i.e., density and degree), strength and clustering coefficient are associated with increasing cortical amyloid burden characterising the pathology (de Haan, van der Flier, Koene, Smits, Scheltens, & Stam, 2012; Prescott, Guidon, Doraiswamy, Choudhury, Liu, & Petrella, 2014). Consistently, decreased clustering coefficient, strength, density and degree were observed in the MCI sample, but not in the healthy control group, involved in the present study.

Regarding the mean shortest path, well-functioning small-world networks imply a low path length to ensure effective integrity and rapid information propagation between and across remote regions of the human brain (Sporns, 2004). However, prior literature reported contrasting findings about changes related to this metric in the course of AD.

Several neuroimaging studies showed increased path length in MCI and AD patients during resting-state fMRI (Bai et al., 2012; He, Chen, & Evans, 2008; Liu et al., 2012; Lo, Wang, Chou, Wang, He, & Lin, 2010; Sanz-Arigita, Schoonheim, Damoiseaux, Rombouts, Maris, Barkhof, Scheltens, & Stam, 2010; Stam, Jones, Nolte, Breakspear, & Scheltens, 2007;

Wang et al., 2013; Yao et al., 2010), whereas others presented the opposite trend within the same cohorts (Daianu et al., 2013; De Haan, Pijnenburg, Strijers, Van Der Made, Van Der Flier, Scheltens, & Stam, 2009; Sanz-Arigita, Schoonheim, Daimoseaux, Rombouts, Barkhof, Scheltens, & Stam, 2008; Stam, de Haan, Daffertshofer, Jones, Nashaden, van Cappellen van Walsum et al., 2009; Supekar, Menon, Rubin, Musen, & Greicius, 2008; Tijms, Wink, De Haan, Van Der Flier, Stam, Scheltens, & Barkhof, 2013; Tijms, Yeung, Sikkes, Möller, Smits, Stam et al., 2014). Importantly, Buldu and colleagues (2011) indicated that, when assessed with a letter-probe memory task, MCI patients exhibited a decreasing path length. Authors have hypothesised that this discrepancy within scientific literature may be due to the fact that more connections may be required to cope with demanding cognitive tasks, whereas, during resting, fewer connections are maintained after essential interruption of spontaneous neural activity (Buldu, Bajo, Maestu, Castellanos, Leyva, Gil, Sendiña-Nadal, Almendral, Nevado, del-Pozo, & Boccaletti 2011; Wang et al., 2013). Current findings seem to clearly support this inference.

Moreover, a decrease in global efficiency has been seen in the MCI group. This likely indicates that the efficiency of information exchange between the nodes in MCI patients declined, and this evidence is consistent with previous research (Li, Qin, Chen, & Li, 2013; Liu, Yu, Zhang, Liu, Duan, Alexander-Bloch, Liu, Jiang, & Bullmore, 2013; Zhao, Liu, Wang, Liu, Xi, Guo, Jiang, Jiang, & Wang, 2012).

On a second level, the present findings should be examined in the light of the three-way interactions obtained from statistical analyses, as they reveal important differences in terms of connectome metrics depending on group membership and task condition.

MCI patients' performance on the Binding condition of the WMBT was better predicted by increasing strength, global efficiency and clustering coefficient. High clustering coefficient indicated that more brain regions were connected into networks to process colour-shape conjunctions. Also, increased binding-related global efficiency and strength revealed that

information transfer among nodes was served by stronger and more efficient connections across the whole involved network.

Since behavioural data showed that MCI patients were outperformed by healthy controls, such higher connectivity is believed to reflect atrophy-related hyper-connectivity registered in the course of AD (Bajo, Maestù, Nevado, Sancho, Gutiérrez, Campo et al., 2010; Bokde, Lopez-Bayo, Meindl, Pechler, Born, Faltraco et al., 2006; García-Cordero, Sedeño, Fraiman, Craiem, de la Fuente, Salamone et al., 2015; Gardini, Venneri, Sambataro, Cuetos, Fasano, Marchi, Crisi, & Caffarra, 2015; Gour, Felician, Didic, Koric, Gueriot, Chanoine et al., 2014; Palop & Mucke, 2016; Parra et al., 2013; 2017; Pasquini, Scherr, Tahmasian, Meng, Myers, Ortner et al., 2015; see also Jacobs, Radua, Luckmann, & Sack, 2013 for a meta-analysis). Specifically, MCI patients have been observed to recruit a larger functional network to compensate for initial structural defects (e.g., loss of axons), and this elicited a major connectivity to cope with demanding cognitive tasks. Of note, as the pathology progresses, the hyper-connection turns into disconnection (Delbeuck et al., 2003).

Regarding the FCSRT, although enhanced strength and global efficiency of white matter connections were necessary for the MCI group to carry out the IFR component of FCSRT, increasing clustering coefficient in relation to the same task was not found. This suggests that densely connected groups of brain regions are not involved when memory information is just associated rather than merged together.

Finally, evidence of decreasing mean shortest path associated with patients' performance under free recall was consistent with previously discussed findings on the recruitment of more connections to carry out cognitive tasks (Buldu et al., 2011; Daianu et al., 2013; De Haan et al., 2009; Sanz-Arigita et al., 2008; Stam et al., 2009; Supekar et al., 2008; Tijms et al., 2013). Lastly, the FCSRT-ITR score was not significantly predicted by changes in structural connectivity. This evidence is consistent with novel research supporting the

unreliability of this sub-test for diagnostic purposes (Frasson, Ghiretti, Catricala, Pomati, Marcone, Parisi, Rossini, Cappa, Mariani, Vanacore, & Clerici, 2011; Jonin et al., 2019; Killin et al., 2018).

3.4.7.3 Connectome changes in MCI patients with severe working memory binding deficits

In order to investigate the sensitivity and specificity, along with the predicting power, of WMB deficits – connectivity changes coupling, I split the MCI sample in two sub-groups on the basis of their WMB capacities (i.e., MCI-Good Binders and MCI-Poor Binders).
Main findings were (i) lower mean edge weight, density, degree, strength, mean shortest path, global efficiency and clustering coefficient in both MCI groups compared to the healthy controls; (ii) higher mean edge weight, strength, global efficiency and clustering coefficient in MCI-Poor Binders engaged in the processing of colour-shape conjunctions; (iii) decreasing mean shortest path in relation to performance of MCI-Poor Binders in the Binding condition.

Prior conclusions on changes in the topological structure of the brain connectome of MCI-Poor Binders, compared to healthy controls, are confirmed. More importantly, DT-MRI findings endorse the hyper-connectivity hypothesis by revealing that MCI patients with poorer WMB capacities do engage a wider neural network to cope with the high cognitive demand provided by the task (Bajo et al., 2010; Bokde et al., 2006; García-Cordero et al., 2015; Gardini et al., 2015; Gour et al., 2014; Palop & Mucke, 2016; Parra et al., 2013; 2017; Pasquini et al., 2015). These results foster the accuracy of the WMBT to detect structural changes due to AD pathology since prodromal stages.

3.4.7.4 Conclusive remarks and leading ideas for further research

The current DT-MRI study sheds further light on the dissociation between conjunctive and relational memory binding by revealing that the connectivity patterns underpinning the two functions are differentially affected by AD-related neuropathological changes.

Also, results from analyses on MCI-Poor Binders demonstrated that changes in brain connectivity, and loss of small-worldness, are more strongly coupled with WMB impairments. This evidence strengthens the notion that combining the WMBT with neuroimaging techniques, such as DT-MRI, may provide a very useful procedure to identify neurocognitive signatures of AD in at-risk individuals.

Further research should be focused on longitudinal trials as well as on larger samples to better test neurocognitive markers in the prediction of AD dementia.

So far, I have addressed how deficits to bind features, such as colours and shapes in visual WM, are specific to AD. Evidence of their occurrence since the very early stages of the pathology has supported the hypothesis that WMB impairments are a hallmark of the disease. This generalisation may be premature as current research has focused on WMB deficits for material processed in the visual domain only.

Since we live in a multimodal world, we regularly integrate various information coming from all our senses to construct our reality. Similar binding disruptions will interfere with the ability to interact with the environment and be independent on daily basis. Therefore, whether or not binding colours and shapes, presented through different modalities, is also affected by AD is a question that needs investigation. I will address it in the following chapter.

CHAPTER IV

UNIMODAL AND CROSSMODAL WORKING MEMORY BINDING IS NOT DIFFERENTIALLY DISRUPTED BY AGE OR SPORADIC ALZHEIMER'S DISEASE

4.1 Introduction

This PhD project has so far focused on investigating the neural and connectivity underpinnings of WMB deficits in people at risk of sporadic AD, that is, MCI patients. Results discussed in Chapter II and III showed that such impairments are coupled with neuropathological changes characterising AD and appear in people who hold a risk for this type of dementia. These neurocognitive findings add to the evidence that the WMBT is a reliable screening tool.

It is worth highlighting that the WMBT used in previous chapters requires participants to bind and temporarily maintain colours and shapes presented across one single modality at a time (i.e., the visual modality). In the present chapter, I will refer to this mechanism as *unimodal WMB*. However, in Chapter I, I have outlined that WMB can also occur across diverse modalities at the same time, a mechanism known as *crossmodal WMB* (see *Section 1.4.4*). Exploring crossmodal WMB functions in both healthy and pathological cohorts appears to be fundamental. The reality we live in is multimodal in nature, and we constantly recognise objects from the sound they make or how they appear to the touch, for instance. Functions, such as keeping track of conversations, require integrating visuospatial (face-location) and auditory (voice) information and this function is affected by AD (Alberoni, Baddeley, Della Sala, Logie, & Spinnler, 1992). Disruptions to bind crossmodal information may undermine our independence in daily living activities.

Considering that WMB deficits, which are sensitive and specific to AD, have been mainly ascribed to the visual modality only, the question arises as to whether it is possible to generalise AD-related WMB impairments for material processed across different sensory channels.

Evidence from healthy younger adults showed that crossmodal and unimodal WMB are performed to equivalent accuracy and rely upon the same degree of attentional resources (Allen et al., 2009; Gao et al., 2017; see also *Section 1.4.4*), possibly implying similar cognitive and neural mechanisms for the two tasks. The perirhinal cortex has been identified as the neural site wherein perceptual material is bound across diverse modalities, as demonstrated by human and nonhuman primate research (Murray & Bussey, 1999; Murray & Richmond, 2001; Suzuki & Amaral, 1994; Taylor et al., 2006; Tyler, Stamatakis, Bright, Acres, Abdallah, Rodd, & Moss, 2004). Throughout higher cognitive processing, and regardless of sensory channels, the role of the perirhinal cortex also appears to be crucial to maintain unimodal bound representations in WM (Della Sala et al., 2012; Staresina & Davachi, 2010). WMB deficits are hypothesised to be caused by abnormal neurophysiological changes occurring in the perirhinal cortex from very early stages of AD (Didic et al., 2011; see also *Section 1.10*). However, there is currently a lack of behavioural studies comparing how these forms of binding might be affected by AD.

Before embarking on a similar examination, there is another pending question to tackle. Very little is known about how crossmodal WMB changes in healthy ageing, and the possibility that age might have a detrimental effect on such cognitive function should be ruled out to confirm that WMB deficits are a hallmark of AD.

To date, age-related changes in crossmodal binding processing have been investigated in perceptual attention tasks rather than in WM paradigms. In such perceptual paradigms, older adults benefit more from the provision of crossmodal rather than unimodal cues compared to

their younger counterparts, especially when temporal congruency between the stimuli is at play (Brooks, Chan, Anderson, & McKendrick, 2018; Laurienti, Burdette, Maldjian, & Wallace, 2006; Mozolic, Hugenschmidt, Peiffer, & Laurienti, 2012; Peiffer, Mozolic, Hugenschmidt, & Laurienti, 2007). Decline in attention observed in healthy ageing appears to have the effect of encouraging multisensory integration, as older people are slower at distinguishing relevant from irrelevant stimuli and find it difficult to keep them separated (Alain & Woods, 1999; Guerreiro, Anguera, Mishra, Van Gerven, & Gazzaley, 2014; Robinson & Sloutsky, 2010; Talsma & Woldorff, 2005). However, this evidence does not endorse any conclusions on whether older adults retain the ability to store crossmodal conjunctive bindings in WM.

The aim of the studies reported is in this chapter is twofold:

1. To investigate whether crossmodal WMB is differently affected by age compared to unimodal WMB, namely, if there is a significant difference between the two binding functions;

2. To assess the effect of AD on crossmodal WMB with respect to unimodal WMB.

Participants undertook the WMB tasks devised by Allen et al. (2009) and described in *Section 1.4.4* of this dissertation, but with two major modifications. Firstly, the number of experimental conditions was set to two instead of four, involving (i) the assessment of both visual unitised colour-shape and (ii) auditory colour–visual shape combinations. Secondly, the task was adapted to a cued-recall paradigm. I aimed at challenging participants' temporary binding capacities by employing a retrieval task wherein the study material is not re-presented in the test phase (Arenberg, 1973; Burke & Light, 1981; Craik, 1977; Craik & McDowd, 1987; Gajewski & Brockmole, 2006; Schonfield & Robertson, 1966), thus requiring

participants to initiate an effortful mental search of the target stimulus (Craik, 1983; Hasher & Zacks, 1979).

Study 1 and Study 2 addressed these premises by asking participants to carry out the tasks with and without Articulatory Suppression (AS). It is well-known that age-related detrimental effects are larger for visuospatial than for verbal WM (Jenkins, Myerson, Joerding, & Hale, 2000; Johnson, Logie, & Brockmole, 2010), hence, it has been predicted that older adults might benefit from the use of verbal material when recalling the colour-shape bindings. However, I expected that the prevention of verbal rehearsal by AS in Study 2 would cause a drop in the older group's accuracy.

Finally, Study 3 tested binding capacities in AD patients with both unimodal and crossmodal versions of the task. If single objects are formed through the binding mechanism and maintained as such in WM, it has been predicted that AD patients would show the same magnitude of impairment in carrying out any WMB tasks regardless of the modalities through which information is perceived and integrated. On the contrary, if the sensory features derived from distinct modalities are held in WM as separated entities, diverse cortical areas will be engaged to process auditory-visual rather than only visual material. As a result, AD patients will experience major difficulties in performing the crossmodal WMBT compared to the unimodal WMBT.

4.2 Methods

4.2.1 Study 1

4.2.1.1 Aims

Allen et al. (2009) demonstrated that younger participants are able to bind together colour and shape features across the visual and auditory modalities without requiring additional resources compared to the maintenance of visually presented combinations. Study 1 investigates whether there is evidence for an age-related crossmodal binding decline in WM.

4.2.1.2 Ethics statement

The current study was approved by the University of Edinburgh's Psychology Research Ethics Committee (Ref: 152-1718/8). All participants read the relevant information sheet and gave consent prior to participation.

4.2.1.3 Participants

Table 32 *– Demographics and average performance on the MMSE of the two groups of participants in Study 1.*

	Younger (N = 26)			**Older** (N = 26)			**Statistics**
	M	**±**	**SD**	**M**	**±**	**SD**	**T(50), p-value**
Age	18.57	±	.59	71.38	±	5.47	48.15, <.001
Years of Education	13.52	±	.58	15.30	±	2.31	3.45, .001
MMSE (range)	28.73 (25 - 30)	±	1.48	29.34 (26 – 30)	±	1.09	1.53, .13
Sex	5 men; 21 women			13 men; 13 women			$X^2(1)$= 5.43, .02

Note: N= Numerosity; M= Mean; SD= Standard deviation.

Following an *a priori* power analysis, based on a mixed ANOVA design with an effect size of .37 (as in Brown et al., 2017, Experiment 1) and power at .80 (G*Power 3.0.10; Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007), twenty-six younger adults (YA) and twenty-six older adults (OA)[5] took part in the experiment receiving either course credit or an honorarium. Younger participants were students from the University of Edinburgh, whereas older adults were recruited from the university volunteer panel. They were Europeans and Asians, and demographics are reported in *Table 32*. Participants had no known auditory problems, had normal or corrected-to-normal vision. The Mini Mental State Examination (MMSE - Folstein, Folstein, & McHugh, 1975) indicated that none of the participants showed signs of cognitive impairment (see *Table 32***)**.

4.2.1.4 Materials and apparatus

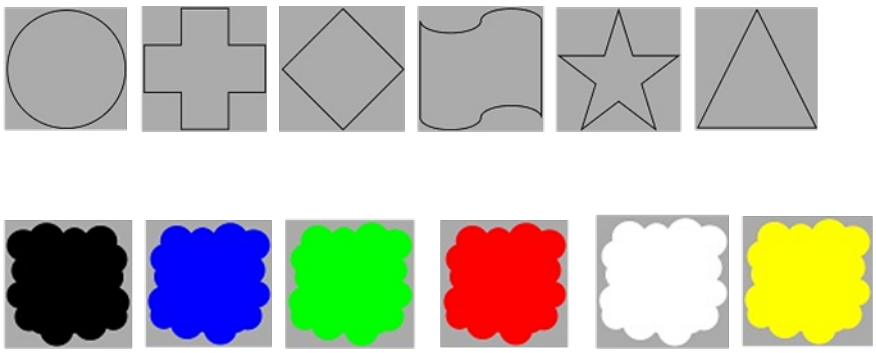


Figure 25 *- Experimental stimuli – Coloured blobs and blank shapes taken from Allen et al., 2006.*

[5] I use a different nomenclature for control groups, by employing “healthy controls” in Chapter II and III and “older adults” in Chapter IV. This is to keep consistency with prior relevant scientific literature.

Visual stimuli utilised a set of six simple shapes (circle, cross, diamond, star, flag, triangle) and six colours (green, red, blue, yellow, black, white) derived from Allen, Baddeley, and Hitch (2006; see *Figure 25*). Two changes were made compared to the original pool of material: 1) Among the colours, "white" was used instead of "grey", since all stimuli were presented against a grey background; 2) Only the more easily nameable items, selected on the basis of the results obtained by Allen et al. (2006) when testing for ease of discriminability, were included. Each colour was depicted as a formless shape (i.e., a "blob"), while each shape was displayed as an unfilled black outline. All visual stimuli were displayed at the centre of the screen, with an item size of 124 x 124 mm and subtending a visual angle of approximately 17°. Auditory stimuli were obtained from the website http://www.fromtexttospeech.com/ by converting text files into recordings. A male English voice (British accent) was used, and the material was presented via headphones. Arrays were made of three items presented one by one. The choice of using a set size three was in accord to previous studies (Allen et al., 2009; Brown & Brockmole, 2010) accounting for the assessment of healthy participants' WMB capacities. Testing was controlled on a Macintosh iMac with a 13.5-inch screen, placed at approximately 40 cm from the subject, and "PsychoPy" program (version 1.85.1 - Peirce, 2007; 2009) was used to run the experiment.

4.2.1.4.1 Pilot study 1

A pilot study was conducted prior to the experiment to ascertain that participants were able to recognise and name all the colours and shapes used as experimental stimuli. Moreover, it checked the possibility that the tasks could have been too difficult to perform. Nine healthy younger adults (Age: M= 29.66, SD= 3.04; YoE: M= 18.44, SD= .52; 6 men and 3 women) were tested with the WMB tasks. Results from a paired sample t-test revealed that the

performance in the unimodal condition (M= .83, SD= .13) and that in the crossmodal condition (M= .79, SD= .10) were not significantly different (*t*(8)= -.99, p= .34, d= .32).

4.2.1.5 Design and procedure

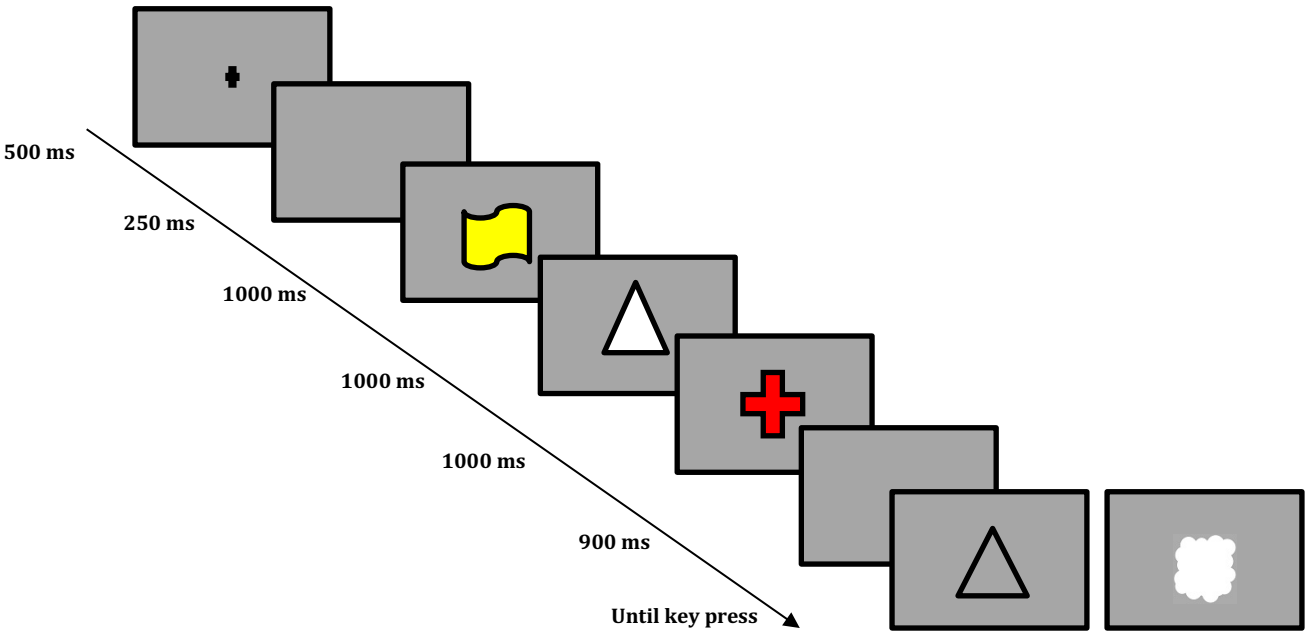


Figure 26 *- Example of a trial in the unimodal condition. After observing the sequence of three visual colour-shape bindings appearing on the computer screen, participants were instructed to recall the missing feature as soon as the cue (i.e., either the unfilled shape or the coloured blob) was displayed. In the crossmodal condition the procedure was the same, with the three blank shapes visually presented and the three colour names delivered through headphones.*

The study presented two experimental conditions. In the *unimodal condition*, a series of three visual colour-shape conjunctions was presented in sequence on the computer screen. In the *crossmodal condition*, a series of three blank shapes was visually presented while three colour names were delivered in synchrony through headphones. In each case, after a brief

delay, either a shape or a colour probe appeared. Participants were instructed to recall the feature that was originally paired with the test probe feature.

At the beginning of the experiment, both age groups were screened for potential colour vision deficiency. They were presented with two separate arrays, one consisting of the six experimental shapes and the other consisting of the six experimental colours. They were asked to name the stimuli one by one in order to ensure that every feature was known and recognised. Participants were then invited to carefully read instructions displayed on the computer screen, and to ask for elucidations if necessary.

In the unimodal condition, participants read "*You are going to see a sequence of three coloured shapes on the screen. After a brief delay interval, either one coloured blob or one blank shape will be presented. If you see a coloured blob, try to recall out loud the shape it was presented in. If you see a blank shape, try to recall out loud the colour it was*".

In the crossmodal condition, they read "*You are going to see a sequence of three blank shapes on the screen while listening to colour names at the same time. After a brief delay interval, either one coloured blob or one blank shape will be presented. If you see a coloured blob, try to recall out loud the shape it was associated with. If you see a blank shape, try to recall out loud the matching colour*".

The experimental session then started. Each experimental trial began with a fixation cross depicted at the centre of the screen for 500ms, followed by a 250ms blank screen delay. Each visual item was presented at the screen centre for 1000ms. A 900ms blank screen delay followed the presentation of the three feature pairs. The test probe was then shown at the centre of the screen. *Figure 26* illustrates the example of a trial run.

On 50% of the trials, the shape was the to-be-recalled feature, whereas, on the remaining 50% of the trials it was the colour to be recollected. This occurred in a randomly intermixed fashion. Conditions were blocked and their order was counterbalanced. Responses were

recorded through a microphone. There was no limit on the time available to recall the information. Participants could perform the tasks at their own pace by pressing space bar when they were ready to proceed with the following trial. Nonetheless, they were explicitly invited to take a break twice throughout the session. Each block consisted of 6 practice trials and 36 test trials divided in two blocks of 18 trials each. This allowed the three serial positions to be tested the same amount of times in both conditions. Conjunctions were repeated within the same block but not within the same array.

4.2.1.6 Data analysis

Percentage of correct responses (overall accuracy), percentage of correct responses for each serial position (SP), and percentage of errors were calculated through mixed ANOVAs. For overall accuracy, the mixed ANOVA included condition (unimodal condition vs crossmodal condition) as the within-subjects factor and group (older adults vs younger adults) as the between-subjects factor. The ANOVA model for the serial position analysis included condition (unimodal condition vs crossmodal condition) as the within-subjects factor, SP as the within-subjects factor (SP1 vs SP2 vs SP3), and group (older adults vs younger adults) as the between-subjects factor.

Finally, the error analysis was conducted in order to investigate what type of errors participants were more inclined to make. Error types were divided into two categories, based on Hu et al. (2014; see also *Section 1.3.4.4*): (i) *within-series confusions*, participants recalled a feature from the to-be-studied array that did not match with the test probe. These errors can be considered as reflecting an error in WMB; (ii) *extra-series intrusions*, participants recalled a feature that was not displayed in the to-be-studied array. Mixed ANOVAs for the analysis on within-series confusions and extra-series intrusions, separately,

included condition (unimodal condition vs crossmodal condition) as the within-subjects factor and group (older adults vs younger adults) as the between-subjects factor.

ANOVAs were run by means of both frequentist (alpha level set at .05) and Bayes Factor (BF) analyses. Frequentist analysis was run in R Studio (version 1.1.456; R Core Team, 2013) and IBM SPSS Statistics 21, whereas BF analysis was run in JASP (version 0.9.2; JASP Team, 2019). BF analysis quantifies the predictive strength of the alternative hypothesis (H_1) compared to the null hypothesis (H_0). All possible models were assessed by accounting for interactions even when the main effect was not included. The inclusion BF, "BF", indicates the extent to which the data support inclusion of the factor of interest, taking all models into account. BF and BF_{10} indicate the likelihood of H_1 over H_0, and the larger BF and BF_{10} the greater support for H_1. BFs for all main effects and interactions are reported afterwards. The default priors were set as described in Rouder, Morey, Speckman and Province (2012), and the number of iterations was set at 500,000 to guarantee a smaller percentage of errors.

4.2.1.7 Results

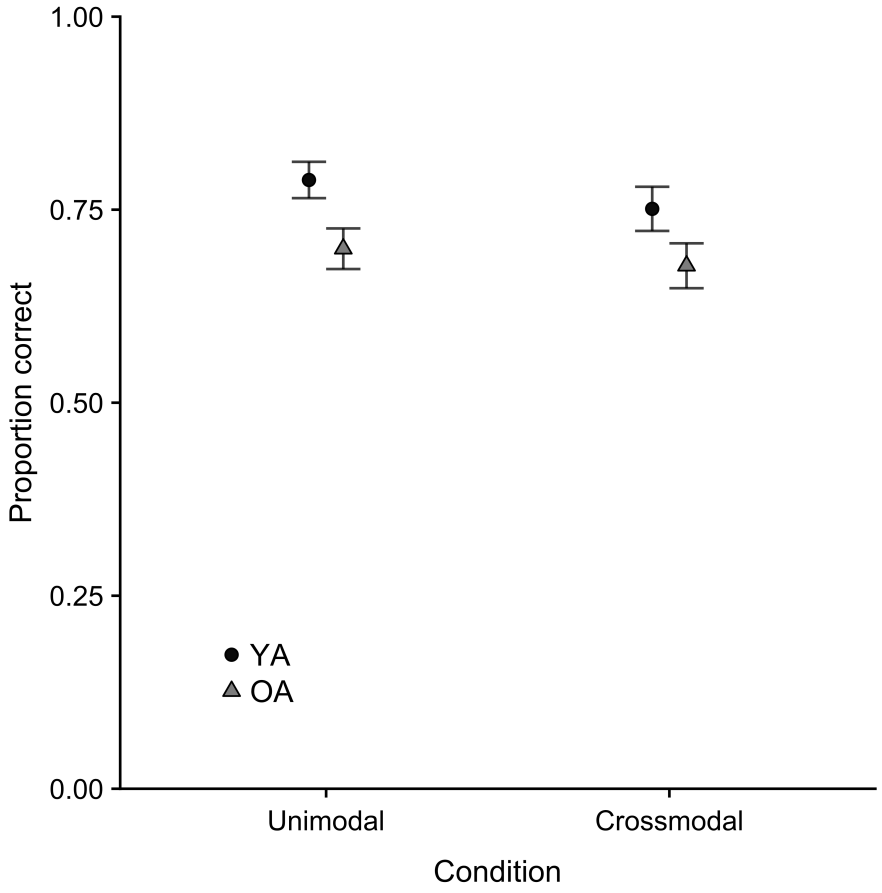


Figure 27 *- Percentage of correct responses in the unimodal and crossmodal conditions for both younger and older adults.*

Accuracy. A 2 x 2 mixed ANOVA yielded no significant effect of condition ($F(1,50)= 3.05$, $p= .08$, $\eta^2p= .05$, $BF= .78$). *Figure 27* illustrates the significant age effect ($F(1,50)= 5.68$, $p= .02$, $\eta^2p= .10$, $BF= 3$), showing a higher accuracy level for younger adults compared to older adults in both unimodal (YA: $M= .78$, $SD= .11$; OA: $M= .69$, $SD= .13$) and crossmodal (YA: $M= .75$, $SD= .14$; OA: $M= .67$, $SD= .14$) conditions. No interaction effect was found ($F(1,50)= .20$, $p= .65$, $\eta^2p= .004$, $BF= .30$). These results were supported by the BF analysis, showing

that the most likely model to explain our data included the main effect of group (BF_{10}= 2.83 relative to the null model including only participant).

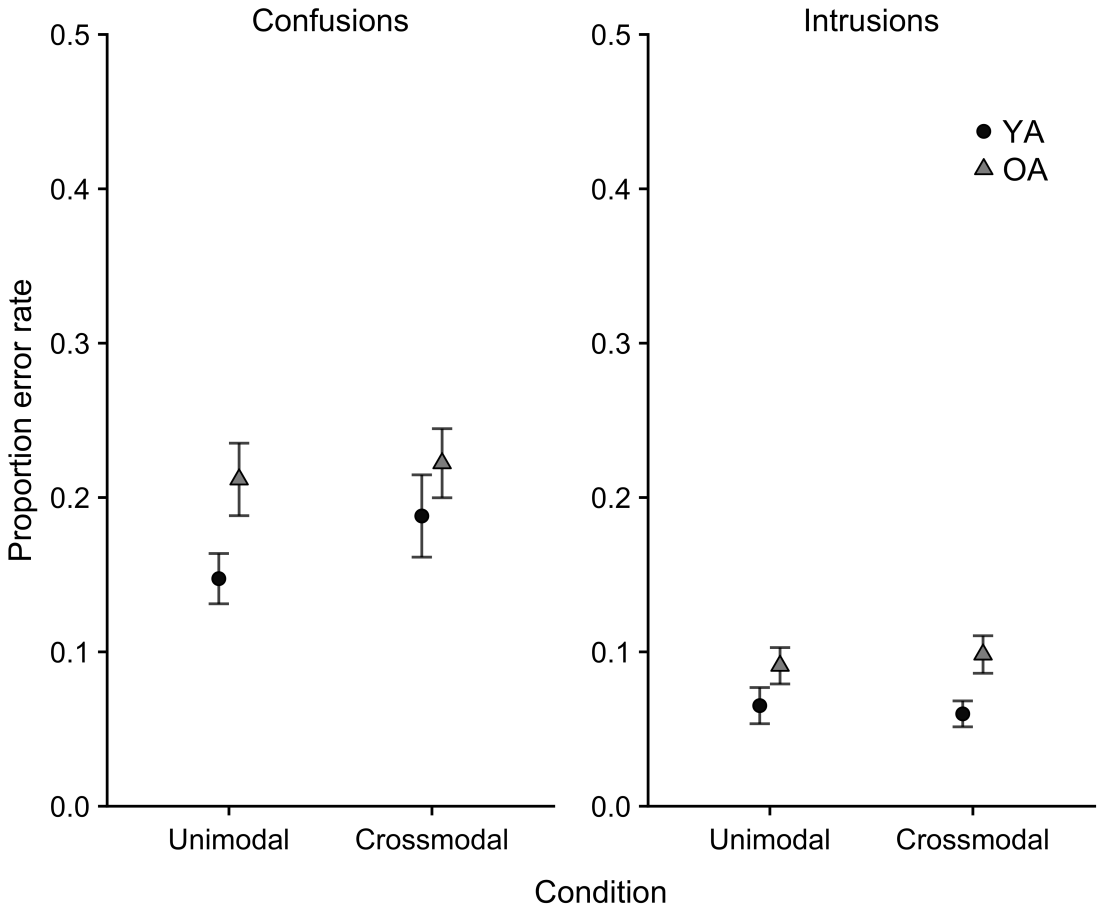


Figure 28 *- Rates of within-series confusions and extra-series intrusions for both age groups in both binding conditions.*

Error Analysis. A 2 x 2 mixed ANOVA on within-series confusions revealed no significant main effect of condition ($F(1,50)= 2.29$, $p= .13$, $\eta^2p= .04$, $BF= .44$) as well as of group ($F(1,50)= 3.32$, $p= .07$, $\eta^2p= .06$, $BF= .89$); furthermore, no condition*group interaction

(F(1,50)= .79, p= .37, η^2p= .01, BF= .28) was found. All participants were equally prone to recalling a feature not matching the test probe but belonging to the same visual array across both experimental conditions. According to BF analysis, the most likely model included the main effect of group (BF_{10}= 1.12 relative to the null model including only participant).

In addition, a 2 x 2 mixed ANOVA on extra-series intrusions yielded a significant main effect of group (F(1,50)= 6.70, p= .01, η^2p= .11, BF= 2.49): older adults made a higher extra-series intrusions rate compared to their younger counterparts, and this held true in both unimodal (YA: M= .06, SD= .05; OA: M= .09, SD= .06) and crossmodal (YA: M= .05, SD= .04; OA: M= .09, SD= .06) conditions. Main effect of condition (F(1,50)= .01, p= .92, η^2p= .0002, BF= .17) and condition*group interaction (F(1,50)= .42, p= .51, η^2p= .008, BF= .17) were not significant. As before, the most likely model included main effect of group (BF_{10}= 4.43 relative to the null model including only participant). *Figure 28* shows the proportion of errors made by both younger and older adults in both conditions.

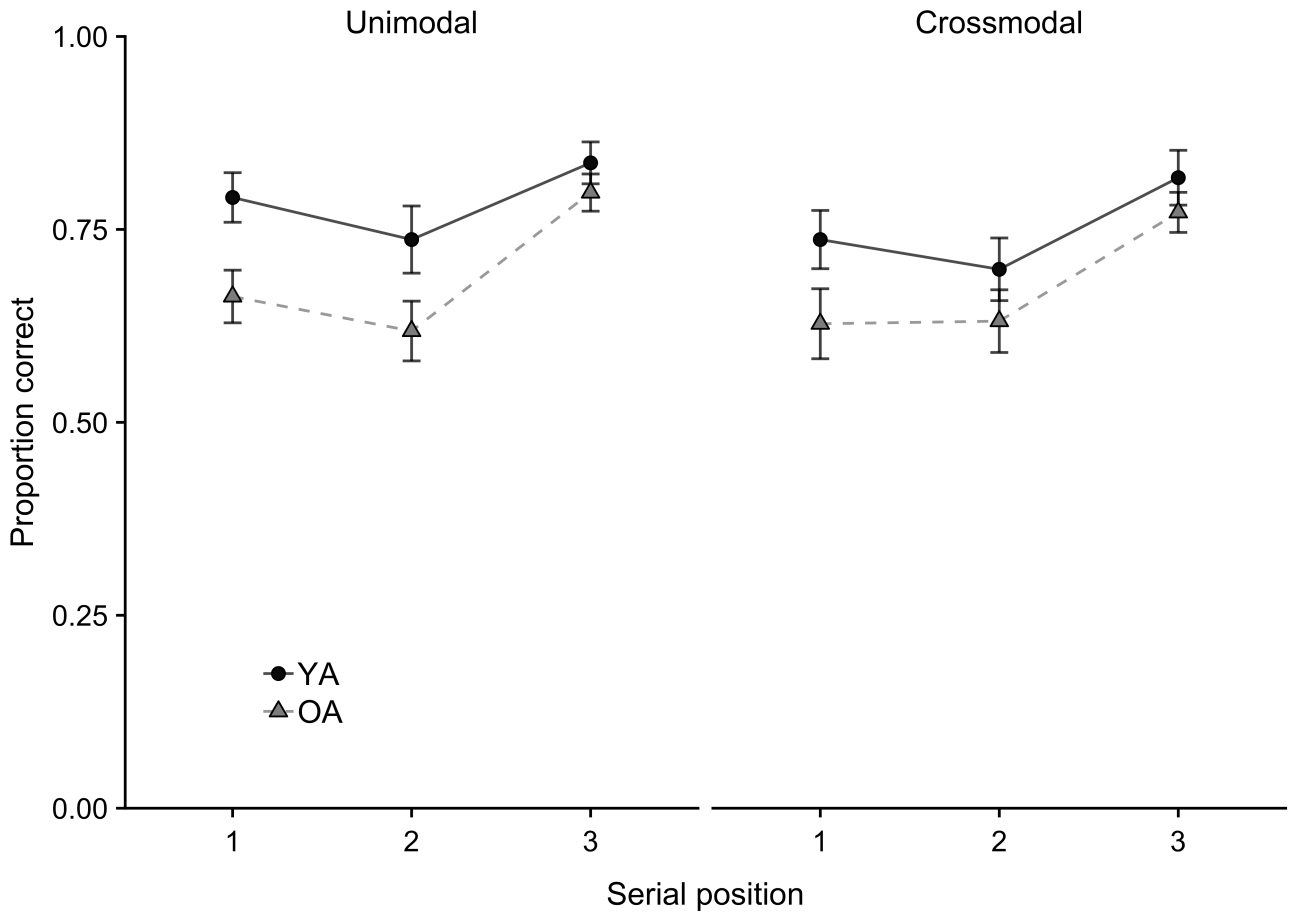


Figure 29 *– Proportion correct across serial positions for each age group and task condition.*

Table 33 *– Mean accuracy and SD as a function of Serial Position (SP) for both age groups in* Study *1.*

	Younger (N = 26)		**Older** (N = 26)	
	Unimodal	**Crossmodal**	**Unimodal**	**Crossmodal**
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**
SP 1	.79 ± .16	.73 ± .19	.66 ± .17	.62 ± .23
SP 2	.73 ± .22	.69 ± .20	.61 ± .19	.63 ± .20
SP 3	.83 ± .13	.81 ± .20	.79 ± .12	.77 ± .13

Note: N= Numerosity; M= Mean; SD= Standard deviation; SP= Serial position.

Serial Position Analysis. A 2 x 2 mixed ANOVA yielded a main effect of serial position ($F(2, 100)= 17.31$, $p< .001$, $\eta^2p= .25$, $BF> 10,000$). *Figure 29* shows the recall rates in both the unimodal and crossmodal conditions (see also *Table 33*). There was a significant difference due to age ($F(1,50)= 6.20$, $p= .01$, $\eta^2p= .11$, $BF= 2.95$) as seen previously. The effect of condition was not significant ($F(1,50)= 2.41$, $p= .12$, $\eta^2p= .04$, $BF= .40$), and no two-way or three-way significant interactions were found ($p= .26$, $\eta^2p= .02$, $BF= .28$). The BF analysis indicated that the most likely model was the one including the main effect of group and SP, as well as the group*condition interaction ($BF_{10}> 10,000$ relative to the null model including only participant).

4.2.1.8 Discussion 1

Study 1 revealed the expected age effect on cued recall, with older participants being less accurate than their younger counterparts in both experimental conditions. However, the performance in the crossmodal condition did not differ significantly from that in the unimodal condition, for both older and younger adults. This suggests that age does not have any differential effect on crossmodal relative to unimodal WMB, discarding the hypothesis that crossmodal binding mechanisms are sensitive to normal ageing. The error analysis showed a common trend to recall a feature presented in the study sequence but not matching the test probe (i.e. a WMB error) that emerged throughout the tasks, and that was elevated in the older adult group. Finally, the serial position analysis highlighted a general tendency for improved recall of the final item in the sequence in both conditions, as previously observed in Allen et al.' studies (Allen et al., 2006; Allen, Baddeley, & Hitch, 2014).

4.2.2 Study 2

4.2.2.1 Aims

All colours and shapes used in the WMB tasks in Study 1 were potentially nameable. This may have elicited recoding and rehearsal of the information as a strategy for better recall, a mechanism that is possibly more prominent in younger adults (Brown & Wesley, 2013; Bunce & Macready, 2005). Study 2 was carried out in order to address the possibility that overt repetition of the item names could have modulated the performance of either younger or older adults.

4.2.2.2 Participants

Table 34 *– Demographics and average scores in the MMSE for* Study *2.*

	Younger (N = 35)	**Older** (N = 35)	**Statistics**
	M ± SD	**M ± SD**	**T(68), p-value**
Age	18.60 ± .84	68.11 ± 11.24	25.97, <.001
Years of Education	13.42 ± .73	15.60 ± 1.73	6.81, <.001
MMSE (range)	29.22 ± .80 (27 - 30)	29.17 ± 1.29 (25 - 30)	-.22, .82
Sex	11 men; 24 women	8 men; 27 women	$X^2(1)$= .65, .42

Note: N= Numerosity; M= Mean; SD= Standard deviation.

In Study 2, thirty-five younger adults and thirty-five older adults were recruited receiving either course credit or an honorarium. They were Europeans and Asians, and none of them had participated in Study 1. Demographics of the two age groups are reported in *Table 34*. Younger participants were students from the University of Edinburgh, whereas older adults

were recruited from the university volunteer pool. Participants had no known auditory problems, had normal or corrected-to-normal vision. The MMSE (Folstein et al., 1975) indicated that no participants showed signs of cognitive impairment (see *Table 34*).

4.2.2.3 Materials and procedure

Material and experimental procedure were the same as in Study 1, except for the use of articulatory suppression (AS). Participants were instructed to repeat the digits "*one, two, three, four*" constantly and aloud from the first fixation cross at the beginning of the study display until the appearance of the test probe. The text message "*Repeat out loud: "ONE, TWO, THREE, FOUR". Press SPACE to go on"* reminded them to do so before starting every new experimental trial. Furthermore, each session was monitored to ensure that this occurred and the experimenter occasionally reminded participants to verbally rehearse the digits as well.

4.2.2.4 Data Analysis

Both frequentist and Bayes Factor data analyses were conducted in R Studio (version 1.1.456; R Core Team, 2013), IBM SPSS Statistics 21, and JASP (version 0.9.2; JASP Team, 2019). Percentage of correct responses as well as errors were analysed by means of mixed ANOVAs. Bonferroni pairwise comparisons were used to examine further specific differences between groups in the two experimental conditions.

4.2.2.5 Results

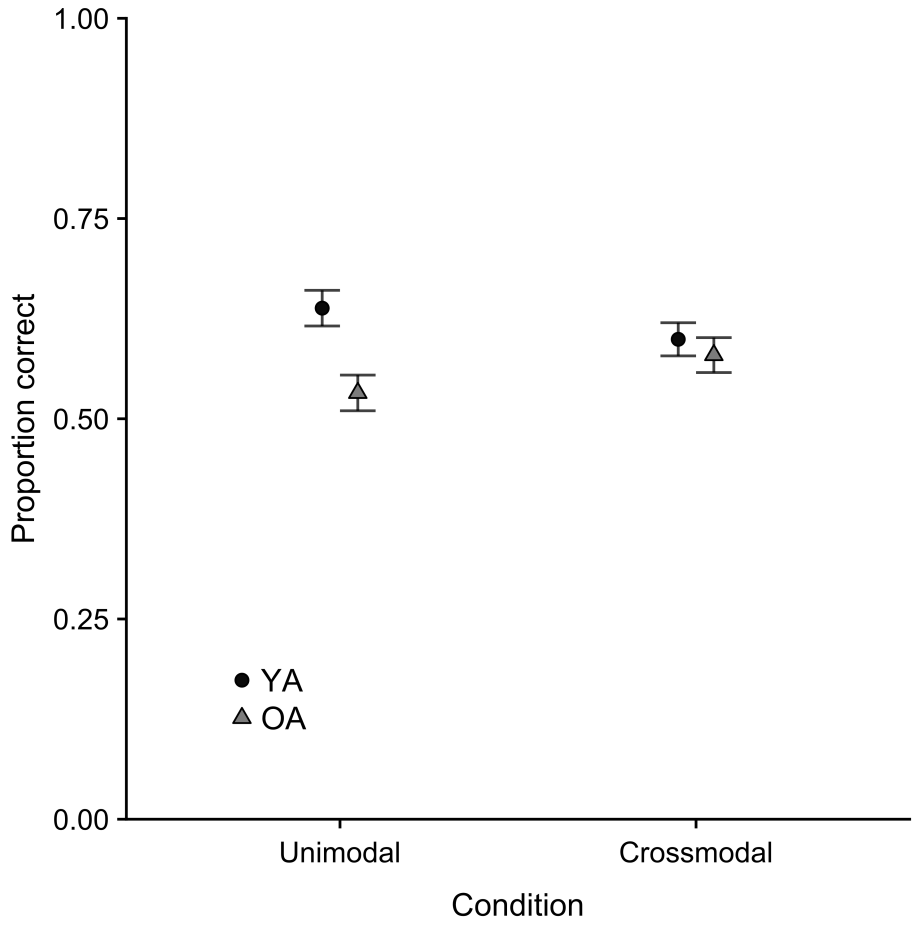


Figure 30 *– Level of accuracy in the Unimodal and Crossmodal conditions reached by both younger and older adults.*

Accuracy. A 2 x 2 mixed ANOVA showed no main effect of condition ($F(1,68)= .06$, $p= .79$, $\eta^2p= .001$, $BF= .18$); there was a main effect of group ($F(1,68)= 5.70$, $p= .02$, $\eta^2p= .07$, $BF= 2.79$) on the performance instead. A condition*group interaction ($F(1,68)= 7.19$, $p= .009$, $\eta^2p= .09$, $BF= 5.04$) was also found (see *Figure 30*). Bonferroni pairwise comparisons reported that younger and older adults were significantly different at performing the unimodal condition (YA: $M= .63$, $SD= .13$; OA: $M= .53$, $SD= .13$; $t(68)= -3.35$, $p< .001$, $d= -.80$, $BF_{10}=$

24.83) but not the crossmodal condition (YA: M= .59, SD= .12; OA: M= .57, SD= .12; t(68)= -.65, p= .51, d= -.15, BF_{10}= .29). BF analysis indicated the model comprising the main effect of group as the most likely one (BF_{10}= 2.80 relative to the null model including only participant).

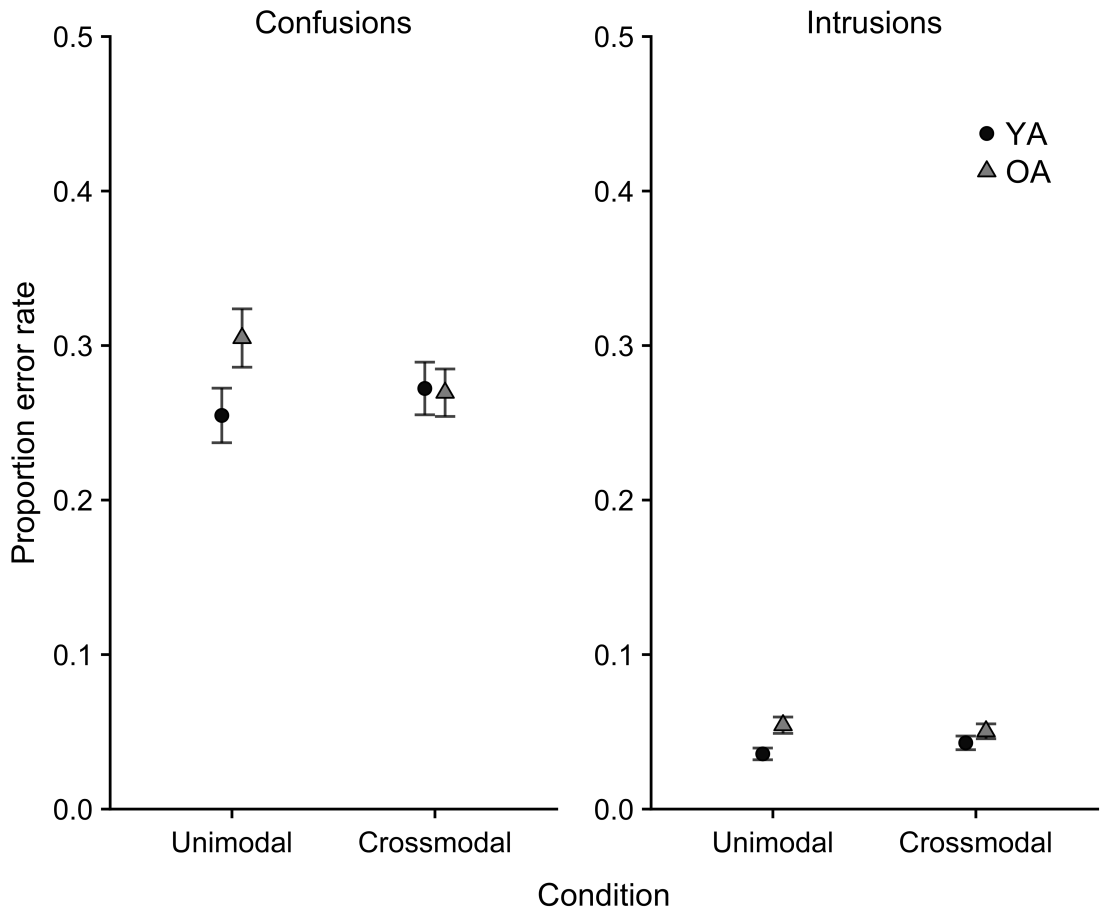


Figure 31 *- Percentage of within-series confusions and extra-series intrusions made by younger and older participants in both binding conditions.*

Error Analysis. Types of error were classified as in Study 1 and percentages of within-series confusions and extra-series intrusions for both age groups and conditions are depicted in *Figure 31*.

A 2 x 2 mixed ANOVA on within-series confusions reported neither significant effect of condition ($F(1,68)= .38$, $p= .53$, $\eta^2p= .006$, $BF= .21$) nor group ($F(1,68)= 1.43$, $p= .23$, $\eta^2p= .02$, $BF= .43$). Also, a significant condition*group interaction ($F(1,68)= 3.38$, $p= .07$, $\eta^2p= .04$, $BF= 1.04$) was not found. On average, older adults made the same amount of within-series confusions as their younger counterparts in both unimodal (YA: M= .25, SD= .10; OA: M= .30, SD= .11) and crossmodal (YA: M= .27, SD= .10; OA: M= .26, SD= .09) conditions. The BF analysis revealed that the most likely model accounted for the main effect of group ($BF_{10}= .43$ relative to the null model including only participant).

Analysis on extra-series intrusions yielded no significant main effect of condition ($F(1,68)= .16$, $p= .68$, $\eta^2p= .002$, $BF= .19$) and no condition*group interaction ($F(1,68)= 2.02$, $p= .16$, $\eta^2p= .02$, $BF= .61$). The effect of group was significant ($F(1,68)= 6.19$, $p= .01$, $\eta^2p= .08$, $BF= 2.96$): overall, older adults recalled more features seen across the task but not actually presented in the to-be-studied array compared to younger participants in both unimodal (YA: M= .03, SD= .02; OA: M= .05, SD= .03) and crossmodal (YA: M= .04, SD= .02; OA: M= .05, SD= .02) conditions. The most likely model, as indicated by the BF analysis, was the one including the main effect of group ($BF_{10}= 2.95$ relative to the null model including only participant).

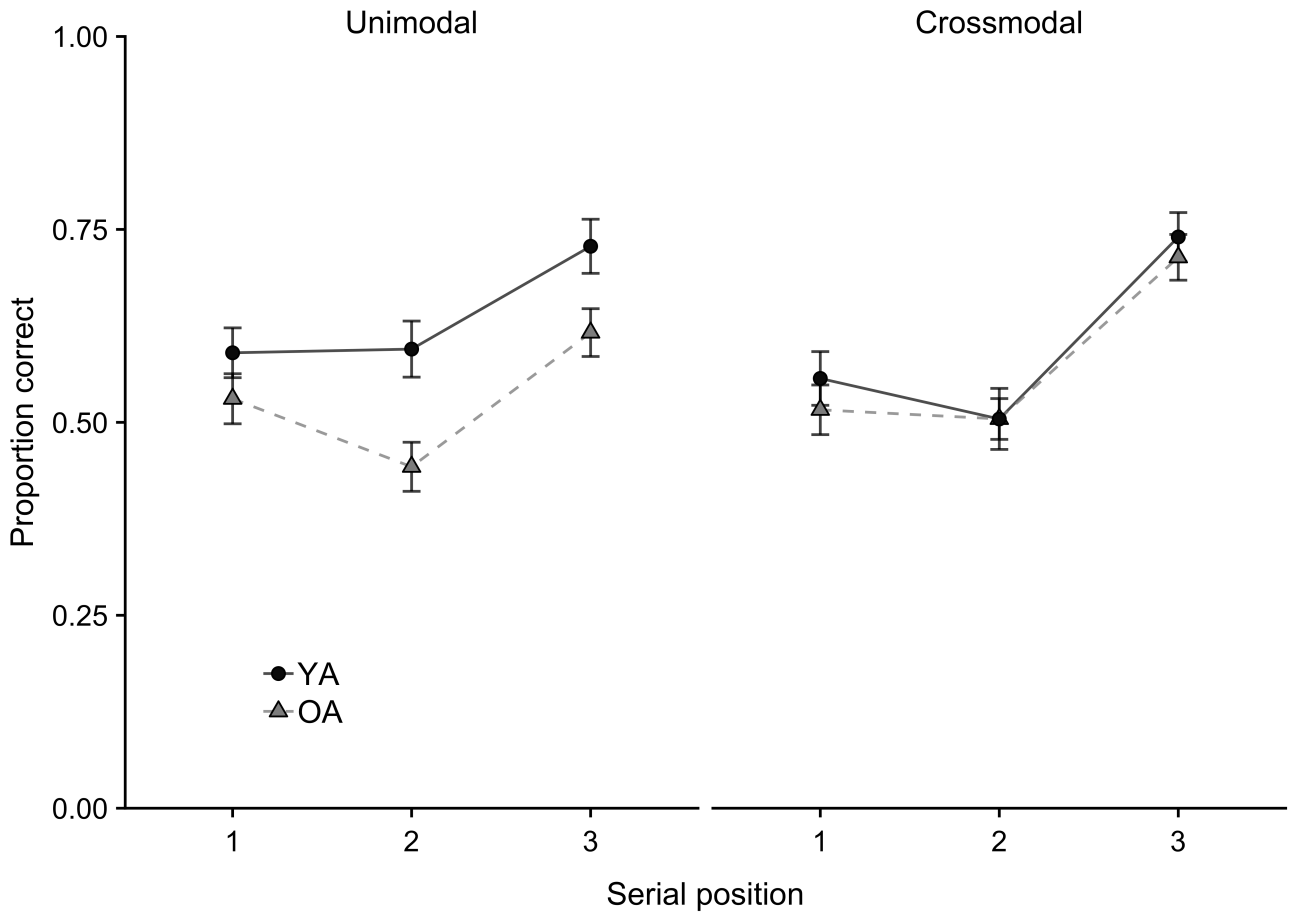


Figure 32 *– Correct responses (%) across serial positions for each age group and task condition.*

Table 35 *– Mean accuracy and SD according to SP for both age groups in* Study *2.*

	Younger (N = 35)		**Older** (N = 35)	
	Unimodal	**Crossmodal**	**Unimodal**	**Crossmodal**
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**
SP 1	.59 ± .19	.55 ± .20	.53 ± .19	.51 ± .19
SP 2	.59 ± .21	.50 ± .15	.44 ± .18	.50 ± .23
SP 3	.72 ± .20	.74 ± .18	.61 ± .18	.71 ± .17

Note: N= Numerosity; M= Mean; SD= Standard deviation; SP= Serial position.

Serial Position Analysis. A further analysis on serial position was carried out as in Study 1. A 2 x 3 x 2 mixed ANOVA presented a significant effect of serial position ($F(2,136)= 38.43$, $p< .001$, $\eta^2p= .36$, BF> 10,000). A main effect of group ($F(1,68)= 6.12$, $p= .01$, $\eta^2p= .08$, BF= 2.24) was also verified, since older adults recalled less than younger adults (see *Figure 32*; see also *Table 35*). The main effect of condition was not significant ($F(1,68)= .11$, $p= .73$, $\eta^2p= .002$, BF= .11), but a condition*group interaction was found ($F(1,68)= 7$, $p= .01$, $\eta^2p= .09$, BF= 2.48). Post-hoc t-tests yielded a significant difference between older and younger adults when recalling unimodally processed items presented in SP2 ($t(68)= -3.15$, $p= .002$, $d= -.75$, $BF_{10} = 14.85$) and SP3 ($t(68)= -2.39$, $p= .02$, $d= -.57$, $BF_{10}= 2.69$). Items presented in SP1 were equally recollected from both groups ($t(68)= -1.30$, $p= .19$, $d= -.31$, $BF_{10}= .50$).

On the contrary, in the crossmodal condition, there were no significant differences between younger and older participants independently of the serial position of each binding: SP1 ($t(68)= -.85$, $p= .39$, $d= -.20$, $BF_{10}= .33$), SP2 ($t(68)= .002$, $p= .99$, $d= .004$, $BF_{10}= .24$), SP3 ($t(68)= -.60$, $p= .54$, $d= -.14$, $BF_{10}= .28$). Neither two-way nor three-way interactions were revealed ($p= .10$, $\eta^2p= .03$, BF= .31). Both main effect of group and SP were included in the most likely model, as well as the interaction between SP and condition (BF_{10}> 10,000 relative to the null model including only participant).

4.2.2.6 Discussion 2

Study 2 confirmed the age-related decline previously revealed and, in addition, an interaction effect was found. Older and younger adults significantly differed in the unimodal condition only, especially when visual bindings were presented in SP2 and SP3 within the study array. As before, the error analysis corroborated the tendency to swap the features within the study

items when recalling, suggesting the occurrence of WMB errors. The serial position curve highlighted a trend to better remember the last conjunction of the series across conditions.

Cross-Experiment Analysis. Finally, a 2 (unimodal condition vs crossmodal condition, within factor) x 2 (AS vs No AS, between factor) x 2 (older adults vs younger adults, between factor) mixed ANOVA tested the role of preventing participants' overt rehearsal on their performance. Condition did not appear to be a significant factor ($F(1,118)= 1.16$, $p= .28$, $\eta^2p= .01$, $BF= .19$), whereas group ($F(1,118)= 11.58$, $p< .001$, $\eta^2p= .08$, $BF= 31.05$) and AS ($F(1,118)= 44.84$, $p< .001$, $\eta^2p= .27$, $BF> 10,000$) were both significant. The latter finding indicates that AS led to reduced accuracy overall. Nonetheless, a group*AS interaction was not found ($F(1,118)= .19$, $p= .66$, $\eta^2p= .002$, $BF= .35$), suggesting that both groups performed worse when AS was required despite their age.

Results also yielded a condition*group interaction ($F(1,118)= 4.57$, $p= .03$, $\eta^2p= .03$, $BF= 1.94$), and Bonferroni comparisons confirmed that older and younger adults showed a significantly different performance in the unimodal ($t(120)= -3.60$, $p< .001$, $d= -.65$, $BF_{10}= 56.64$) but not in the crossmodal ($t(120)= -1.59$, $p= .11$, $d= -.28$, $BF_{10}= .60$) conditions. The other interactions (i.e., condition*AS and condition*group*AS) were not significant ($p= .13$, $\eta^2p= .01$, $BF= .69$). The most likely model included the main effect of AS and the condition*AS interaction ($BF_{10}> 10,000$ relative to the null model including only participant).
This cross-experiment comparison demonstrates that both younger and older adults were challenged by the prevention of overt rehearsal of the stimuli to the extent that the overall accuracy decreased from the first to the second experiment.

4.2.3 Study 3

4.2.3.1 Aims

Study 3 investigates whether patients in the mild to moderate stages of AD are able to hold bound information coming from diverse sensory modalities in WM. It also investigates whether any deficit in maintaining crossmodal bound features would reflect an impairment over and above temporary memory problems for conjunctive binding as tested solely within the visual domain (Cecchini et al., 2017; Della Sala et al., 2012; Parra et al., 2009a; 2010b).

4.2.3.2 Participants

Table 36 *– Demographics of participants in* Study *3.*

	AD (N = 24)	**Older adults (set size 2)** (N = 24)	**Older adults (set size 3)** (N = 24)	**Statistics T(46), p-value**		
	M ± SD	**M ± SD**	**M ± SD**	**AD vs OA2**	**AD vs OA3**	**OA2 vs OA3**
Age	76.29 ± 5.18	74.54 ± 4.12	74.75 ± 3.92	1.29, .20	-1.16, .25	.17, .85
Years of Education	9.08 ± 1.18	10.20 ± 3.47	9.56 ± 2.90	-1.29, .20	.70, .48	-.63, .52
Sex	13 men; 11 women	9 men; 15 women	11 men; 13 women		$X^2(2)= 1.34$, .51	

Note: N= Numerosity; M= Mean; SD= Standard deviation.

According to an *a priori* power analysis based on Study 1, with an effect size of .004 and a power of .80 ($p< .05$) (G*Power 3.0.10; Faul et al., 2009; 2007), twenty-four AD patients and forty-eight older adults (OA) undertook the WMB tasks. All participants were Europeans. Patients were diagnosed with AD dementia according to the diagnostic criteria established by the DSM-IV-TR, and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), and the Alzheimer's Disease and Related Disorders Association (ADRDA)

workgroups (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984; McKhann et al., 2011). They were recruited at the "Unitá operativa di valutazione Alzheimer" in the Distretto Sanitario di Mercato San Severino – Azienda Sanitaria Locale (ASL) Salerno, Italy.

Among forty-eight healthy controls, three were spouses and two were carers of the patients while the others were recruited through word of mouth. They were divided in two groups of twenty-four subjects each (i.e. OA2 and OA3) in order to account for an experimental manipulation. Specifically, OA2 performed the tasks with the same set size as AD patients, whereas OA3 were shown an increased set size. The three groups were matched for age and years of education, and demographics are reported in *Table 36*. Participants had no known auditory problems, and normal or corrected-to-normal vision. They were screened for colour blindness by asking them for naming the stimuli before the starting of the experimental session, as explained previously (see *Section 4.2.1.5*). Reading the information sheet and giving written consent were necessary steps to fulfil prior to participation.

4.2.3.3 Neuropsychological assessment

AD patients underwent a neuropsychological assessment in order to characterise the sample. The same neuropsychological battery was administered to healthy controls to test all groups under the same circumstances. The neuropsychological battery comprised tests of global cognitive functioning (*ACE-R*– Mioshi et al., 2006; Siciliano, Raimo, Tufano, Basile, Grossi, Santangelo, Trojano, & Santangelo, 2016); memory (*FCSRT* – Frasson et al., 2011; Grober & Buschke, 1987); attention (*Digit Span forward* – Orsini, Trojano, Chiacchio, & Grossi, 1988); verbal fluency (*FAS* – Borkowski et al., 1967; *Word Fluency: Colours, Animals, Fruit, Cities* – Spinnler & Tognoni, 1987); depressive symptoms (*GDS short form* – Brink, Yesavage, Lum, Heersema, Adey, & Rose, 1982). AD patients' carers were also

asked to respond to the *Activities of Daily Living* (ADL) questionnaire (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963).

4.2.3.4 Materials and apparatus

The experimental material and apparatus were almost the same as in Study 1 and 2. Visual stimuli utilised a formless shape (i.e., a "blob") to depict the colours and unfilled three-point black outline for the shapes. They were displayed at the centre of the screen, presenting a size of 124 x 124 mm and subtending a visual angle of approximately 17°. Auditory stimuli were obtained from the website http://www.fromtexttospeech.com/ by converting text files into recordings. A male Italian voice was picked this time in order to pronounce the to-be-heard material.

AD patients were presented with two bindings in the test phase, whereas the OA3 group encountered three colour-shape conjunctions in the test array. These set sizes are consistent with those used in previous studies (Della Sala et al., 2012; Parra et al., 2009a), indicating that, at this memory load, the performance of both groups would be comparable and avoid ceiling and floor levels. Moreover, the OA2 group processed the same number of items per sequence as the patients, in order to test both experimental and control groups with the same memory load manipulation. Participants were assessed either at the ASL department or at their own home if they were unable to travel. Testing was controlled on a Macintosh iMac with a 13.5-inch screen, placed at approximately 40 cm from the subject, and "PsychoPy" (version 1.85.1 - Peirce, 2007; 2009) program was used to run the experiment.

4.2.3.4.1 Pilot study 2

A pilot study was conducted to ascertain that a longer time display would have not affected the level of performance. Six healthy older adults (Age: M= 72.33, SD= 4.80; YoE: M= 13.67, SD= 1.63; 4 men and 2 women) were tested with the 1000ms time display, whereas other six healthy elderly were tested with the 1500ms time display (Age: M= 72.83, SD= 6.31; YoE: M= 15.33, SD= 1.86; 1 man and 5 women). Results from a 2 x 2 mixed ANOVA yielded neither a main effect of condition ($F(1,10)= 1.02$, $p= .33$, $\eta^2p= .92$), nor of group ($F(1,10)= .07$, $p= .78$, $\eta^2p= .008$), nor a condition*group interaction ($F(1,10)= .007$, $p= 1$, $\eta^2p< .001$).

4.2.3.5 Design and procedure

A few adjustments were made to the design used in Study 1 and 2 in order to make it more suitable for AD patients. Firstly, conditions were blocked according to the probe type, that is, shape- and colour-probes were not intermixed in the test phase - accounting for the 50% of the test trials each - but they were presented across separate conditions. As a result, the task included four experimental conditions: 1) unimodal condition – shape probe; 2) unimodal condition – colour probe; 3) crossmodal condition – shape probe; 4) crossmodal condition – colour probe.

Secondly, the four conditions were grouped in two blocks, in order to collect data from all of the four conditions in case any patient could not stand the experimental session for a long time. Therefore, conditions were presented in a counterbalanced order and each accounted for 3 practice trials and 12 test trials per block so that every feature was repeated twice within it. Finally, the time display of each visual feature was set to 1500ms instead of 1000ms in order to give sufficient time for patients to encode the material.

4.2.3.6 Data analysis

Both frequentist and Bayes Factor data analyses were conducted in R Studio (version 1.1.456; R Core Team, 2013), IBM SPSS Statistics 21, and JASP (version 0.9.2; JASP Team, 2019). Percentage of correct responses as well as errors were analysed by means of mixed ANOVAs. Whenever significant interactions were found, group differences were inspected through planned comparisons between AD patients and OA3, AD patients and OA2, and OA3 and OA2.

Also, participants' WM capacity was calculated according to Cowan's formula (Chen & Cowan, 2013; Cowan, 2001) adapted to the current paradigm. Proportion correct (*c*) was related to capacity estimate (*K*), number of items per memory array (*N*), and number of response options, that is, number of items in the experimental set (*R*). The resulting formula read:

$$c = \frac{K}{N} + \left(1 - \frac{K}{N}\right) x \frac{1}{R}$$

This formula was transformed to obtain WM capacity estimate K:

$$K = \left(c - \frac{1}{R}\right) x \frac{R\ x\ N}{R - 1}$$

4.2.3.7 Results

Table 37 *– Neuropsychological profile of AD patients, OA2, and OA3 in* Study *3.*

	AD	OA2	OA3	T-test		
	(N=24)	(N=24)	(N=24)	T(46), p-value		
	M ± SD (range)	**M ± SD** (range)	**M ± SD** (range)	**AD vs OA2**	**AD vs OA3**	**OA2 vs OA3**
GDS	10 ± 8.26 (1 - 28)	8.45 ± 5.90 (1 - 24)	16 ± 2.82 (1 - 18)	.69, .49	1.21, .23	.66, .51
ACE	44 ± 15.84 (13 - 59)	89.37 ± 6.31 (82 - 100)	90.63 ± 5.19 (82 - 100)	**-14.37, <.001**	**-15.20,<.001**	-.74, .45
MMSE	16.60 ± 6.38 (8 - 22)	28.12 ± 1.91 (24 - 30)	28.38 ± 1.27 (26 - 30)	**-10.09, <.001**	**-10.66,<.001**	-.53, .59
FAS	10.50 ± 7.46 (0 - 26)	38.58±15.70 (20 - 73)	35.13 ± 9.79 (20 - 56)	**-7.62, <.001**	**-9.52, <.001**	.91, .36
SEMANTIC FLUENCY	5.41 ± 1.60 (2.25 – 6)	17.07 ± 4.19 (12 - 30)	16.60 ± 3.75 (12 - 27)	**-12.28, <.001**	**-13.06,<.001**	.48, .63
FCSRT-IFR	6.87 ± 6.41 (0 - 17)	27.75 ± 3.92 (20 - 35)	25.71 ± 5.08 (19 - 35)	**-13.62, <.001**	**-10.78,<.001**	1.62, .11
FCSRT-ITR	19.95 ± 12.59 (0 - 33)	35.87 ± .33 (35 – 36)	35.71 ± .46 (35 - 36)	**-6.18, <.001**	**-6.12, <.001**	1.42, .16
DIGIT SPAN	2.95 ± 1.11 (0 - 3)	5.58 ± 1.05 (4 - 7)	5.13 ± .74 (4 - 6)	**-8.10, <.001**	**-7.77, <.001**	1.73, .08
ADL	2.25 ± 1.77 (1 - 5)					

Significant ($p < 0.05$) tests highlighted in bold.
Note: N= Numerosity; M= Mean; SD= Standard deviation; GDS= Geriatric Depression Scale; ACE= Addenbrooke's Cognitive Examination; MMSE= Mini Mental State Examination; FCSRT= Free and Cued Selective Reminding Test (IFR= Immediate Free Recall; ITR= Immediate Total Recall); ADL= Activities of Daily Living

Neuropsychological results. *Table 37* shows the neuropsychological profile of participants who entered the study, as well as the pairwise comparisons for each test. Significant differences emerged between AD patients and OA2, and AD patients and OA3 in all neuropsychological tests included in the battery, except in the GDS (Brink et al., 1982). This indicates that all participants reported, on average, similar depressive traits. Importantly, the two control groups, OA2 and OA3, did not show any substantial discrepancies in performing the tests.

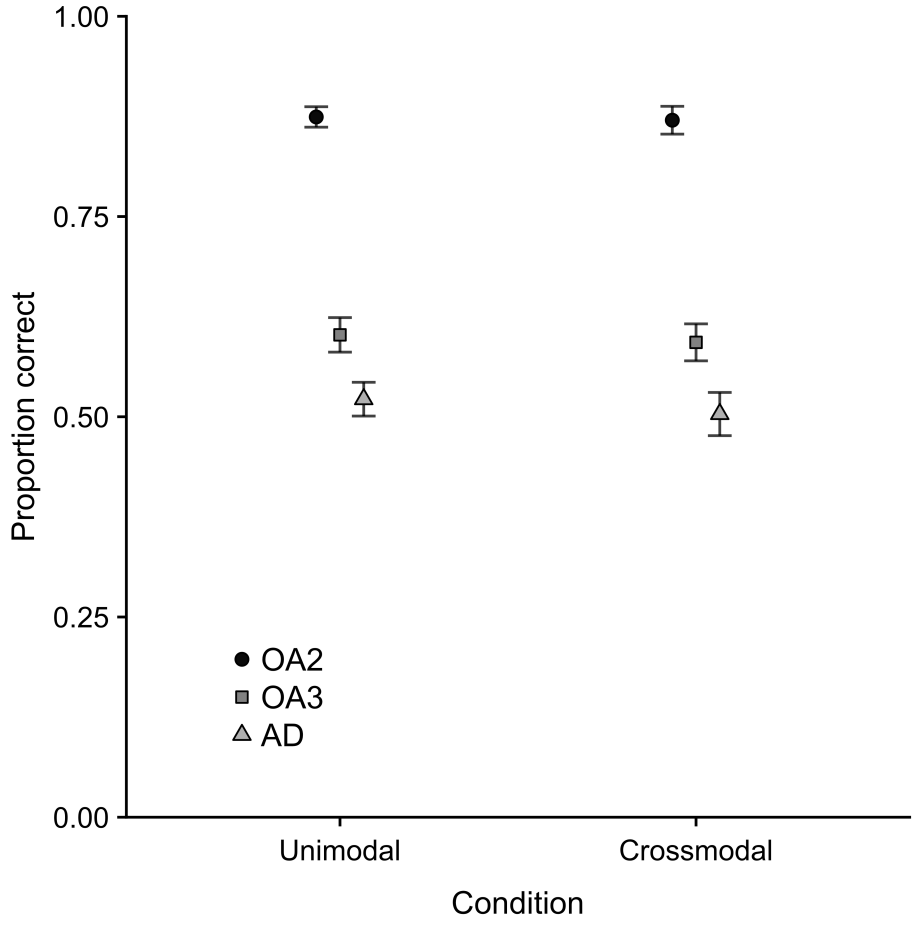


Figure 34 *- Percentage of correct responses in the unimodal and crossmodal conditions for OA2 and OA3 groups, and AD patients.*

Accuracy. A 2 x 3 mixed ANOVA yielded a significant main effect of group ($F(2,69)= 126.54$, $p< .001$, $\eta^2p= .78$, BF> 10,000) as evident from *Figure 34*. Bonferroni pairwise comparisons confirmed that AD (unimodal: M= .52, SD= .10; crossmodal: M= .50, SD= .13) were significantly different from both OA2 ($p< .05$) and OA3 ($p< .05$), as well as OA2 (unimodal: M= .87, SD= .06; crossmodal: M= .87, SD= .08) and OA3 (unimodal: M= .60, SD= .10; crossmodal: M= .59, SD= .11) showed a significantly different performance ($p< .05$). Neither a main effect of condition ($F(1,69)= .53$, $p= .46$, $\eta^2p= .008$, BF= .22) nor a condition*group interaction ($F(2,69)= .08$, $p= .91$, $\eta^2p= .002$, BF= .13) were found. The BF analysis endorsed

such evidence by revealing that the most likely model included the main effect of group (BF_{10}> 10,000 relative to the null model including only participant).

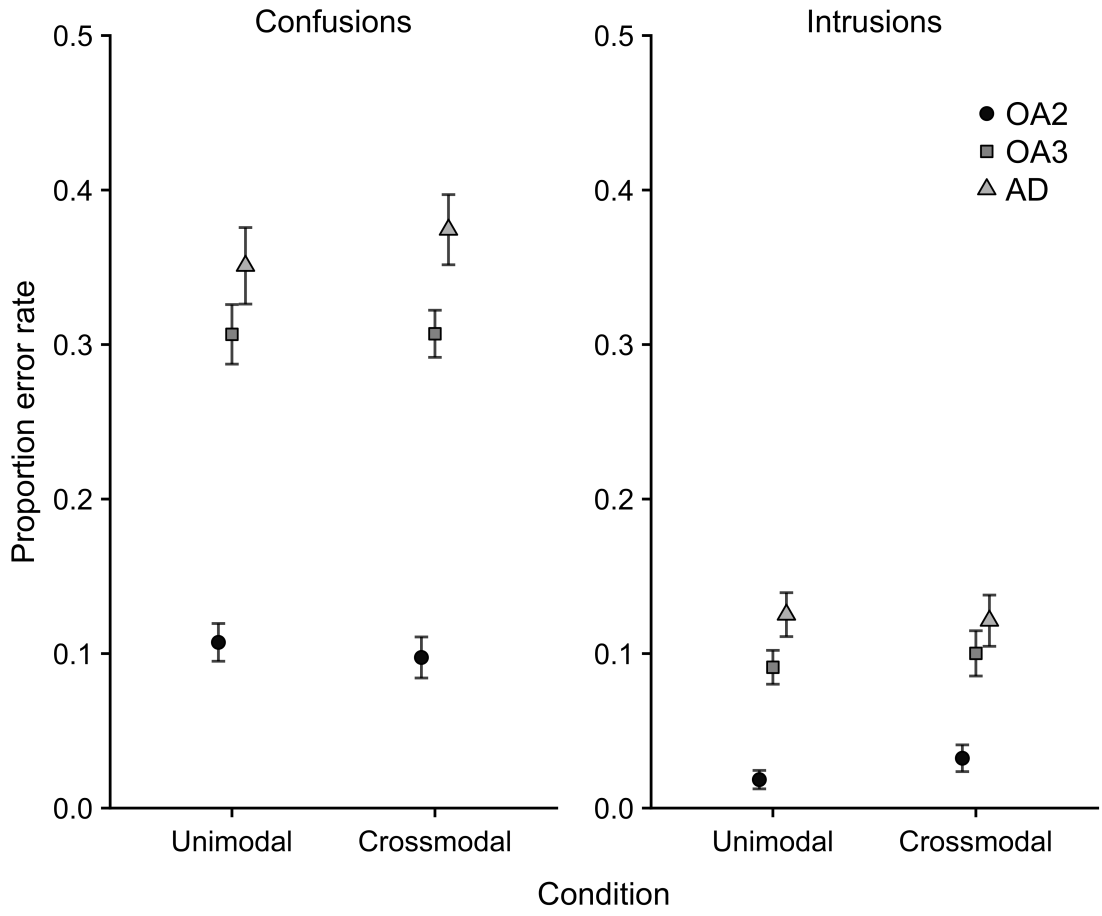


Figure 35 *– Error rates as a function of within-series confusions and extra-series intrusions for OA2, OA3, and AD patients.*

Error Analysis. Neither a significant effect of condition ($F(1,69)= .16$, $p= .68$, $\eta^2p= .002$, $BF= .15$) nor a condition*group interaction ($F(2,69)= .74$, $p= .47$, $\eta^2p= .02$, $BF= .12$) were shown by the analysis on within-series confusions. The difference among groups was significant

(F(2,69)= 76.33, p< .001, η²p= .68, BF> 10,000), as displayed in *Figure 38*. The rate for within-series confusions in AD patients (unimodal: M= .35, SD= .12; crossmodal: M= .37, SD= .11) was higher compared to both OA2 (unimodal: M= .10, SD= .05; crossmodal: M= .09, SD= .06) and OA3 (unimodal: M= .30, SD= .09; crossmodal: M= .30, SD= .07). The most likely model, resulted from the BF analysis, included the main effect of group and the condition*group interaction (BF_{10}> 10,000 relative to the null model including only participant).

The ANOVA on extra-series intrusions revealed a similar pattern (see also *Figure 35*). Just the main effect of group was significant (F(2,69)= 26.58, p< .001, η²p= .43, BF> 10,000), with AD patients' recall memory showing more intrusion of trial-irrelevant features (unimodal: M= .12, SD= .06; crossmodal: M= .12, SD= .08) compared to both OA2 (unimodal: M= .01, SD= .02; crossmodal: M= .03, SD= .04) and OA3 (unimodal: M= .09, SD= .05; crossmodal: M= .10, SD= .07). The main effect of condition (F(1,69)= .51, p= .47, η²p= .007, BF= .17) and the two-way interaction (F(2,69)= .36, p= .69, η²p= .01, BF= .10) did not account for a significant proportion of variance. The BF analysis suggested that the most likely model included the main effect of group only (BF_{10}> 10,000 relative to the null model including only participant).

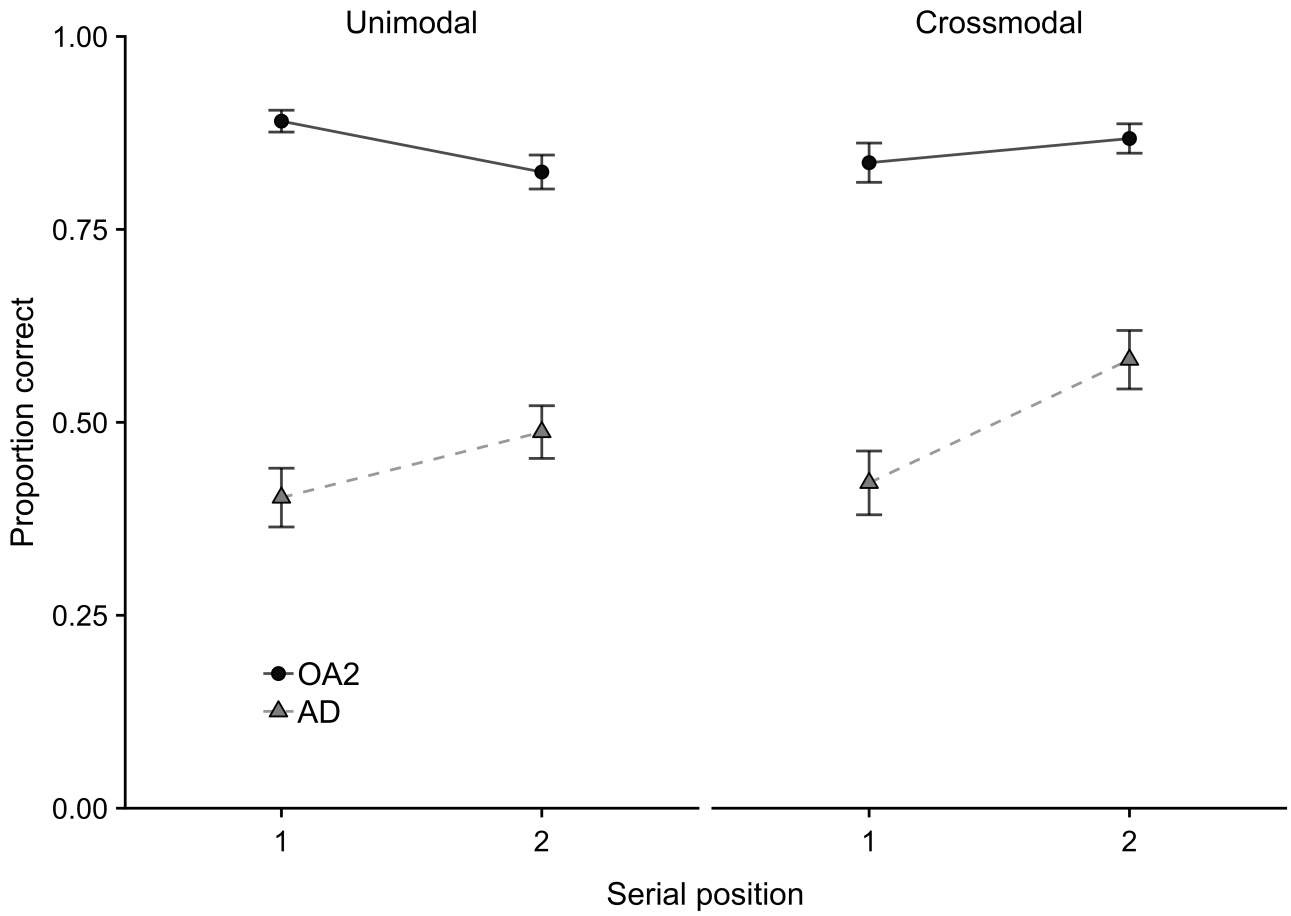


Figure 36 *– Proportion correct across serial positions for each task condition in OA2 and AD groups.*

Table 38 *– Proportion correct recall and SD as a function of SP for AD patients and OA2 in Study 3.*

	AD (N = 24)				**OA 2** (N = 24)			
	Unimodal		**Crossmodal**		**Unimodal**		**Crossmodal**	
	M ± SD		**M ± SD**		**M ± SD**		**M ± SD**	
SP 1	.40 ± .18		.42 ± .20		.89 ± .06		.83 ± .12	
SP 2	.48 ± .16		.58 ± .18		.82 ± .10		.86 ± .09	

Note: N= Numerosity; M= Mean; SD= Standard deviation; SP= Serial position.

Serial Position Analysis. Lastly, the serial position analysis was run for the two groups that processed two bindings only, namely, AD and OA2. A 2 x 2 x 2 mixed ANOVA did not present a significant main effect of condition ($F(1,46)= 1.62$, $p= .20$, $\eta^2p= .03$, $BF= .52$), conversely, the serial position factor played a significant role ($F(1,46)= 4.22$, $p= .04$, $\eta^2p= .08$, $BF= 64.18$). The main effect of group was also significant ($F(1,46)= 244.64$, $p< .001$, $\eta^2p= .84$, $BF> 10,000$). The group*SP ($F(1,46)= 7.46$, $p= .009$, $\eta^2p= .14$, $BF= 70.09$) as well as the condition*SP interactions ($F(1,46)= 8.64$, $p= .005$, $\eta^2p= .15$, $BF= 1.27$) reached significance. AD patients and OA2 showed a difference in recalling the items in SP1 ($t(46)= -8.54$, $p< .001$, $d= -2.46$, $BF_{10}> 10,000$) and SP2 ($t(46)= -6.75$, $p< .001$, $d= -1.95$, $BF_{10}= 439,949$) in the unimodal condition, and in SP1 ($t(46)= -12.00$, $p< .001$, $d= -3.46$, $BF_{10}> 10,000$) and SP2 ($t(46)= -8.29$, $p< .001$, $d= -2.39$, $BF_{10}> 10,000$) in the crossmodal condition.

Furthermore, OA2 were better at recalling bindings presented as first rather than as second ($t(23)= 3.01$, $p= .006$, $d= .61$, $BF_{10}= 7.29$) in the unimodal condition, but no difference between the two serial positions was worth of being noticed in the crossmodal condition ($t(23)= -1.48$, $p= .15$, $d= -.30$, $BF_{10}= .56$). On the contrary, AD patients showed a better memory when items appeared in SP2 compared to SP1 ($t(23)= -2.76$, $p= .01$, $d= -.56$, $BF_{10}= 4.49$) in the crossmodal condition, but not meaningful difference was registered ($t(23)= -1.64$, $p= .11$, $d= -.33$, $BF_{10}= .69$) in the unimodal condition. *Figure 36* illustrates all these trends (see also *Table 38*). No other interactions were meaningful ($p= .13$, $\eta^2p= .04$, $BF= .75$). The BF analysis showed that the most likely model comprised the main effect of group and SP, in addition to the group*SP interaction and the condition*group interaction ($BF_{10}> 10,000$ relative to the null model including only participant).

Working memory capacity. According to Cowan's formula, expressed in *Section 4.2.3.6*, WM capacity was calculated for OA2, OA3 and AD groups in both unimodal and crossmodal WMB conditions:

OA2

$$K(unimodal) = \left(0.87 - \frac{1}{6}\right) x \left(\frac{6\ x\ 2}{6-1}\right) = 0.71\ x\ 2.4 = 1.70$$

$$K(crossmodal) = \left(0.87 - \frac{1}{6}\right) x \left(\frac{6\ x\ 2}{6-1}\right) = 0.71\ x\ 2.4 = 1.70$$

OA3

$$K(unimodal) = \left(0.60 - \frac{1}{6}\right) x \left(\frac{6\ x\ 3}{6-1}\right) = 0.44\ x\ 3.6 = 1.58$$

$$K(crossmodal) = \left(0.59 - \frac{1}{6}\right) x \left(\frac{6\ x\ 3}{6-1}\right) = 0.43\ x\ 3.6 = 1.54$$

AD

$$K(unimodal) = \left(0.52 - \frac{1}{6}\right) x \left(\frac{6\ x\ 2}{6-1}\right) = 0.36\ x\ 2.4 = 0.86$$

$$K(crossmodal) = \left(0.50 - \frac{1}{6}\right) x \left(\frac{6\ x\ 2}{6-1}\right) = 0.34\ x\ 2.4 = 0.81$$

4.2.3.8 Discussion 3

Study 3 showed that WMB is impaired in patients affected by AD independently of the sensory modality through which the features integration occurs. Indeed, AD patients could recall unimodal and crossmodal colour-shape conjunctions to the same extent, suggesting that unimodal and crossmodal WMB are not differentially affected by pathological ageing. Also, the error analysis highlighted a greater tendency to recall a feature presented in the

study sequence but not matching the test probe in both tasks. This adds to the evidence that the poor performance on WMB is a characteristic of AD that may inform clinical judgements.

Finally, the last binding of the series was generally easier to be remembered for both AD patients and controls except for OA2 in the unimodal condition, where the first conjunction of the series was the best retained. Lastly, the estimation of WM capacity in both unimodal and crossmodal conditions revealed that older adults (both OA2 and OA3) could retain more than one conjunction per memory array, whereas AD patients held less than one conjunction in WM in each trial.

In summary, Study 3 endorsed the conclusion that WMB is a reliable cognitive marker for AD (Cecchini et al., 2017; Della Sala et al., 2012; Parra et al., 2009a; Parra et al., 2010b), regardless of modality of feature presentation.

4.3 General discussion

The three studies discussed in the present chapter examined whether unimodal and crossmodal WMB are similarly affected by healthy or pathological ageing. Study 1 and 2 addressed this question in a healthy ageing population. No greater age-related decline for unimodal WMB capacities, compared to single features memory, has been reported across the lifespan whenever participants were tested with a recognition task (Brockmole et al., 2008; Parra et al., 2009a). Consistently, results from Study 1 revealed that performance in crossmodal and unimodal conditions did not differ in either of the two age groups when using a cued-recall paradigm. This finding was confirmed by the outcome of Study 2, whereby participants were engaged in a concurrent interference task (i.e., articulatory suppression) while performing the WMB test.

Although articulatory suppression undermined global performance leading to a decrement in accuracy, younger adults outperformed the healthy older participants solely in the unimodal condition. Age-related slowness at processing information is more pronounced in the visuospatial compared to the verbal domain (Hale & Myerson, 1996; Jenkins et al., 2000; Lawrence, Myerson, & Hale, 1999; Lima, Hale, & Myerson, 1991). It is possible that older participants were less accurate at encoding the shapes of the present paradigm, which were displayed quite briefly, and thus tried to rely more upon what they heard because it was easier to process. Indeed, whenever auditory spoken material is processed, it enters the phonological store directly in the same order as it has been encoded (Baddeley, 2007); on the other hand, visual items must be phonologically coded beforehand. Perhaps, this increased the demand on older adults' capacity, especially when articulatory suppression interfered with such procedure. Similarly, a greater age-related deficit in visuospatial than verbal WM has often been reported (e.g., Jenkins et al., 2000; Johnson et al., 2010), and, it may be worth noticing that results from Study 2 show a higher accuracy for healthy older participants in the crossmodal condition compared to the unimodal condition (albeit the within-group performance did not differ significantly). Thus, age-related differences in WMB performance may be more pronounced in purely visual tasks, and reduced when the task has a verbal component (crossmodal WMB).

One caveat to note is that while the cross-experiment analysis produced a condition x group interaction, with an age-related difference in unimodal but not crossmodal WMB, articulatory suppression did not interact with other factors. Thus, follow-up work is needed to directly explore how verbal recoding and rehearsal might influence performance across age groups and WMB conditions. An additional possible limitation of the study is the recruitment of undergraduate university students as the younger participant group, as this may not be representative of the entire population. However, the younger group did not report more years of education, relative to the older group, in either Study 1 or 2. In addition, it is not clear

how any advantage for the younger groups of participants in the current studies (apart from their relative age) might manifest in the particular patterns of outcomes observed across the different WMB conditions.

Subsidiary analyses derived from both Study 1 and 2 shed light on other important aspects of the performance. The error analysis indicated a common bias for recalling a feature presented in the study sequence but not matching the test probe. This reflected the tendency of forgetting the exact targeted combination as the result of a WMB error (e.g. Hu et al., 2014; Ueno et al., 2011). Moreover, the serial position analysis yielded a general trend to recall the last item of the series better than earlier items (e.g. Allen et al., 2006; 2014). As emerged from the debriefing session, most participants used the same strategy to cope with their limited WM capacity: they reported to focus on a sub-set of the visual array, precisely on the first two items of the series, since the trace of the third one was more vivid in their memory. This is in line with recent findings (e.g. Atkinson, Baddeley, & Allen, 2018; Hu, Allen, Baddeley, & Hitch, 2016), suggesting that participants can strategically prioritise a subset of items in order to support performance.

In conclusion, both Study 1 and 2 support the hypothesis that the ability to form and temporarily store crossmodally bound representations does not decline with ageing, and that age does not have any differential effect on crossmodal relative to unimodal WMB. Similar evidence strengthens the lack of sensitivity and specificity of WMB deficits to normal ageing, a requisite that cognitive markers should have to reliably diagnose pathologies common in older age.

The second question that I was interested in addressing concerned crossmodal WMB performance in AD. Study 3 revealed that AD patients performed significantly less accurately than the healthy control group, even when the latter was challenged with a more demanding

task (i.e., increased set size). This proved equally true for both the crossmodal and the unimodal WMB task. Of note, participants' WM capacity was calculated based on Cowan's formula (Chen & Cowan, 2013; Cowan, 2001) adapted to the current paradigm. Both groups of older controls could retain, on average, approximately 1.6 items regardless of the memory set size or the binding condition. AD patients could maintain approximately 0.80 to 0.85 item (i.e., less than 1 item, on average) across the same conditions. The error analysis for this study also verified that AD patients showed an increased tendency to recall a feature that had been displayed in the study array but did not match the cue afterwards.

A potential caveat emerging from the background neuropsychological assessment is that the cognitive level of AD patients varied considerably. However, this may not constitute an issue as high variance is an index of the heterogeneity of the sample. Indeed, AD patients recruited for the study presented symptoms ranging from the mild to moderate stages of the pathology. Also, by looking at *Figure 34*, the error bars show that the dispersion of scores of AD patients was not hugely different from that of healthy controls in the binding task either. Taken together, these findings are consistent with those from previous studies demonstrating that the poor attainment shown by AD patients in WMB tasks is the result of a deficit related to the binding mechanism. Therefore, Study 3 endorses the diagnostic value of the WMB task as a sensitive test to discriminate between healthy and pathological ageing. Also, it provides evidence that such a function may be investigated using a variety of tasks applied to different scenarios, from clinical to real-life settings (Jonin et al., 2019; Parra, Butler, McGeown, Brown Nicholls, & Robertson, 2019; Yassuda et al., 2019).

The temporary retention of visual colour-shape conjunctions (unimodal conjunctive WMB) activates a cortical network involving the ventral stream (including the perirhinal cortex), the fusiform gyrus, the left inferior temporal lobe, the left superior and inferior parietal cortex, and the left dorsal premotor cortex (Parra et al., 2014). It has been claimed that some of these

regions (e.g., higher visual areas) reflected the type of stimuli used in the study (i.e., visual colour-shape conjunctions), with parietal regions engaged to provide the 'glue' that allowed the features to be maintained as bound during online processing (Parra et al., 2014; Shafritz et al., 2002; Song & Jiang, 2006; Xu, 2007; Xu & Chun, 2007).

Importantly, the perirhinal cortex has been acknowledged as the neural locus wherein both crossmodal integration and complex visual processes occur (Della Sala et al., 2012; Staresina & Davachi, 2010; Taylor et al., 2006). In AD, abnormal neuropathological changes commence in the medial portion of the perirhinal cortex, sequentially spreading across parahippocampal cortices, to finally reach the whole medial temporal lobe and ultimately the entire brain (Didic et al., 2011). As a consequence, binding deficits are among the first signs of cognitive decline in AD, as revealed in studies with asymptomatic carriers of a gene mutation inevitably leading to AD (Parra et al., 2010b; 2017; 2015b). Moreover, the fact that perirhinal degeneration is a hallmark of AD would justify the reliability of WMB tasks to discriminate among AD and healthy older adults (Parra et al., 2009a), and AD and other types of dementia (i.e., Fronto-Temporal Dementia, Parkinson's Disease with Dementia, Vascular Dementia, Dementia with Lewy Bodies - Cecchini et al., 2017; Della Sala et al., 2012).

Although the current study was not designed to address the neural correlates of crossmodal WMB, it is possible to speculate that the WMB deficits observed in AD are ascribed to the integrative functioning of the perirhinal cortex. Consistently, the fMRI study discussed in Chapter II showed that patients in the prodromal stage of AD do not recruit regions of the parahippocampal cortex to process colour-shape conjunctions in visual WM compared to healthy elderly. Taken together, these results suggest that bound representations are formed at encoding and maintained in WM as single units, and that the modalities through which

sensory information is bound are secondary compared to the severe impairments encountered by AD patients in the binding process.

In addition, as previously outlined, the involvement of a wide neural circuit hints at the evidence that WMB functions rely upon effective connectivity among brain areas (Logie, 2011; Koenig, Studer, Hubl, Melie, & Strik, 2005; O'Reilly, Busby, & Soto, 2003). It has been postulated that AD leads to a disconnection syndrome (Bozzali & Cherubini, 2011; Chua et al., 2008; Delbeuck et al., 2003; Gili et al., 2011; Stahl et al., 2007), and Chapter III has revealed that WMB deficits are underpinned by it since the early stages of the AD spectrum.

To conclude, I maintain that the disruption of connections among cortical areas, originated in the perirhinal cortex, is a hallmark of both preclinical and clinical AD and serves temporary binding functions despite any specific to-be-bound material. Study 3 is consistent with the conclusion that WMB deficits are sensitive and specific to AD independently of the modality through which information is integrated, hence, upholding the generalisation of WMB impairments in AD. Future research should analyse whether a similar generalisation may be accounted for in people en route to AD, or at-risk individuals may still benefit from particular types of sensory material to process feature conjunctions.

CHAPTER V

GENERAL CONCLUSIONS

5.1 Summary of outcomes

The main aim of this PhD project was to provide novel neuroimaging, behavioural and clinical evidence on the nature of WMB deficits, by giving particular emphasis to their usefulness in aiding the detection of cognitive impairment in the course of AD. By investigating underlying brain activation and white matter connections, as well as the effect of diverse engaged sensory modalities on performance, this PhD thesis shed further light on the processing of bound information in WM to form coherent object representations (or conjunctions) and the vulnerability of such cognitive function to age- and AD-related decline.

In achieving such aims, some relevant contributions have been made. Firstly, the literature review outlined in Chapter I showed that neuroimaging research on WMB has so far focused on people with genetic mutations who will inevitably develop familial AD (FAD), but do not present with symptoms at the moment of assessment (preclinical AD). Conversely, this PhD project dealt with the investigation of WMB functions in people with or at risk of non-genetic variants of AD dementia. These individuals have developed or will develop AD in the course of ageing (sporadic AD). Before full-blown conversion, they typically undergo a stage of transition between healthy and pathological ageing, also known as MCI or prodromal AD. Therefore, the present studies may contribute to a broader understanding of the neuropathological changes most likely linked to the transition from normal to abnormal ageing.

Secondly, findings from Chapter II and III offered insights into neural and connectivity underpinnings of temporary memory for feature (i.e., colour and shape) conjunctions in prodromal AD. Specifically, in Chapter II, the investigation of the neural correlates of conjunctive WMB deficits has endorsed prior evidence on the lack of hippocampal involvement in such mechanisms. Further contribution has been given in Chapter III by demonstrating that network connectivity among binding-specific brain regions is subject to abnormal changes in prodromal AD, especially in those patients who exhibit more severe deficits when temporarily holding colour-shape conjunctions.

Thirdly, another area of discussion has concerned the integration of information across diverse modalities (crossmodal WMB). Available cognitive and clinical research on WMB has largely addressed how unique representations are formed and stored when features are encoded through the visual modality only (unimodal WMB). In Chapter IV, three studies have examined how WMB functions operate when features are simultaneously delivered through auditory and visual sensory channels in both healthy ageing and clinical AD. Results contribute to our understanding of how crossmodal WMB mechanisms operate in such cohorts. Moreover, they add to the evidence on how WMB mechanisms can be mapped onto the Multicomponent Model of WM (Baddeley, 2000; Baddeley & Hitch, 1974). The proposal of the Episodic Buffer (EB) has been fundamental to account for the maintenance of bound information processed through diverse memory domains and sensory modalities. Results emerging from Chapter IV further support this notion.

Lastly, a final outstanding issue that this PhD project addressed is whether more retrieval-demanding tasks, such as recall tasks, affect temporary memory for conjunctive bindings in both healthy older adults and AD patients. In Chapter IV, the well-known change detection paradigm (the WMBT) assessing conjunctive WMB capacities has been adapted to a cued recall paradigm. It has been shown that neither normal ageing nor AD have a differential

effect on unimodal and crossmodal WMB, ruling out the possibility that a similar outcome might have been ascribed to the retrieval strategy used.

In the next sections, I shall better discuss these points in turn.

5.2 Neuroimaging research on working memory binding deficits is robust in both preclinical and prodromal stages of Alzheimer's disease

So far, electrophysiological and neuroimaging research on WMB has mainly focused on carriers of FAD (Parra et al., 2017; 2015b). This aimed at showing structural and functional changes in individuals who will inevitably develop AD dementia, and identifying mechanisms underpinning such a sensitive function as the disease progresses. However, AD in the course of ageing (sporadic AD) is the most common form of the disease worldwide, and the neural and connectivity correlates of WMB in patients with or at risk of non-genetic variants of AD dementia needed to be explored. Thus, one of the main objectives of the studies reported in Chapter II and III was the investigation of conjunctive WMB deficits in patients at risk of developing AD in the absence of a predisposition due to genetic factors.

By investigating the biological underpinnings of WMB deficits in MCI relying on pattern of functional activation (Chapter II) and structural connectivity methods (Chapter III), novel evidence has been brought to light about the links between neural drivers of such cognitive impairments and current understanding of the prodromal stage of AD. Current results support the evidence that neuroimaging research on WMB deficits is capable of detecting structural-functional abnormal coupling in early stages of dementia, hence being robust in both preclinical and prodromal AD.

Importantly, studies discussed in Chapter II and III also contribute to a more complete account on the expression of WMB deficits in the course of pathological ageing, and unveil neuropathological changes which would be worth monitoring as they may likely inform on risk of progressing to dementia stages in future.

5.3 Working memory binding in people at risk of sporadic Alzheimer's disease: Neural correlates do not include the hippocampus

Damage to the hippocampus and subsequent memory deficits for associated events stored as complex episodic memories (relational WMB) have always been considered an important hallmark of AD. Although this holds true at clinical stages of the AD spectrum, we have learned that cognitive decline due to hippocampal dysfunction is not among the first symptoms to occur. It has been hypothesised that amyloid plaques and neurofibrillary tangles firstly deposit in anterior MTL structures (including perirhinal and entorhinal cortices), and, as a result, cognitive functions relying upon them (conjunctive WMB) are the first to be disrupted in preclinical and prodromal AD (Berron, van Westen, Ossenkoppele, Strandberg, & Hansson, 2020; Didic et al., 2011).

The controversy is that consensus papers still promote neuropsychological tests assessing hippocampus-dependent relational deficits as reliable cognitive markers for AD. They seem to neglect that, because of its vulnerability to normal ageing, hippocampal dysfunction presents as a late clinical expression of neurodegeneration in both AD and other dementias. Hence, such abnormalities are specific to AD compared to neither normal ageing nor other age-related dementias. By contrast, the WMBT has been proved to meet core criteria of a good marker and, thus, can be considered a reliable test to be used for diagnostic purposes in the course of AD (see *Section 1.9.3*).

Following Didic et al.'s (2011) hypothesis and a prior fMRI study (Parra et al., 2014), which demonstrated the involvement of a specific neural network in the processing of colour-shape conjunctions in the healthy young population, Chapter II provide novel fMRI evidence on the identification of the neural correlates of WMB deficits in prodromal AD.

Results report the recruitment of a network comprising frontal, temporal and parietal areas, which partially overlaps with binding-specific regions found in healthy younger adults (Parra et al., 2014), and, more importantly, does not include the hippocampus. These findings not only endorse the lack of hippocampal activation in conjunctive WMB mechanisms, but also show that the hippocampus is not recruited in patients who are seemingly advancing along the AD spectrum. Nevertheless, it may be argued that such conclusion is premature, and more evidence should be gathered in order to purposely examine the role of the hippocampus in a similar paradigm.

In addition, results from Chapter II report the recruitment of the putamen and the cerebellum during the processing of colour-shape bindings. It has been recently suggested to shift our attention away from the MTL and focus on alternative structures, such as those within the basal ganglia, thought to support motor control (Valdes Hernandez et al., 2020). This may expand our understanding of the neural substrates of cognitive functions, which are revealing subtle yet detectable changes in the early stages of AD, being conjunctive WMB an example. Indeed, the fact that similar evidence has been reported by earlier neuroimaging research studies (Grot et al., 2018; Hanseeuw, Betensky, Mormino, Schultz, Sepulcre, Becker et al., 2018; Meier et al., 2014; Valdes Hernandez et al., 2020) may point at the need to revise the earliest neuropathological trajectory of AD, and its implication for our understanding of cognitive decline and cognitive assessment along the continuum of the disease.

5.4 Changes in network connectivity subtending working memory binding deficits predict sporadic Alzheimer's disease

Chapter III contributes more specifically to the dissociation between relational and conjunctive WMB mechanisms at large-scale brain level. The DT-MRI study here discussed is the first to investigate the relationship between memory binding and network connectivity in patients at risk of sporadic AD. Specifically, both relational and conjunctive WMB functions have been examined in the current study, and results reveal that deficits in temporarily holding word-word associations (FCSRT) and colour-shape conjunctions (WMBT) in prodromal AD are coupled with abnormal changes in brain connectivity. However, the structural connectivity changes linked to either task appear to be different.

Connectome metrics, such as strength, global efficiency and clustering coefficient, significantly interact with MCI patients' performance on the WMBT. More precisely, higher clustering coefficient indicates that more brain regions are connected into networks to process colour-shape conjunctions. Also, increased global efficiency and strength reveal that to-be-bound information transfer among nodes is served by stronger and more efficient connections across the whole involved network. Of note, these changes did not lead to better performance, hence suggesting that structural reorganisation is not compensating for the impact of pathology at this stage of the disease.

Importantly, these results have been also confirmed in a sub-set of MCI patients with more pronounced conjunctive WMB impairments (MCI-Poor Binders). This evidence further supports the accuracy of the WMBT to detect AD-related structural changes since the prodromal stage.

Regarding the FCSRT (Buschke, 1984; Grober & Buschke, 1987), better immediate recall of word-word associations was predicted by increasing levels of strength and global efficiency

in MCI patients. Increasing clustering coefficient in relation to the same task was not found. This suggests that, besides the establishment of stronger and more efficient communication between engaged brain regions, no densely connected neural clusters were recruited to carry out the FCSRT in prodromal AD.

In conclusion, findings from both Chapter II and III support the recent proposal by Costa and collaborators (2017) regarding the adoption of tests assessing conjunctive WMB capacities in clinical settings in order to screen for patients at risk of dementia. It has been envisaged that introducing these tests early in the healthcare pathway will support the development of suitable and effective interventions, which can help to either slow down or halt the progression of AD with treatments becoming available (Costa, Bak, Caffarra, Caltagirone, Ceccaldi, Collette et al., 2017).

5.5 Working memory binding is impaired in Alzheimer's disease despite the modality of presentation of to-be-bound material

The contribution made by Chapter IV adds to the knowledge delivered in previous chapters, by documenting, for the first time, the presence of impaired WMB functions serving crossmodal binding. It has been previously suggested that WMB mechanisms in AD are independent of the task used to assess the function and of the memoranda (Parra et al., 2009a; 2010a; 2010b). However, whether this held for crossmodal binding was an outstanding issue. In Chapter IV, I have addressed the integration of information processed across the auditory and visual modalities at the same time (crossmodal WMB) in healthy older adults and clinical AD patients. To my knowledge, no research study has previously investigated the effect of healthy and pathological ageing on the short-term maintenance of crossmodal bindings in respect to unimodal bindings.

Results show no differential effect of healthy ageing on both crossmodal and unimodal WMB, and, more importantly, the same conclusion is valid for the impaired pattern of performance found in AD. Of note, since the lack of a significant difference between the two binding conditions has been discussed in favour of the null hypothesis (i.e., crossmodal WMB = unimodal WMB), reported Bayesian analyses are sound to quantify evidence for the null as for any other hypothesis. Therefore, I suggest that the mechanism of binding information and storing conjunctions in WM is sensitive and specific to AD, regardless of the modality of presentation of the to-be-bound features.

These findings may provide an account for disruptions occurring in real-life experiences wherein it is needed to rely on multimodal integration, such as remembering who said what in conversations (Alberoni et al., 1992). This hints at the potential involvement of temporary binding impairments in AD patients' daily activities, which we know to preclude their independent living.

5.6 Working memory binding and the Episodic Buffer

From a theoretical point of view, the study of WMB was prompted by the concept of the EB proposed by Baddeley (2000) as the fourth component of the Multicomponent Model of WM (Baddeley & Hitch, 1974).

The EB has been conceived as a limited capacity storage system whereby separate visuospatial and verbal information streaming from the visuospatial sketchpad and the phonological loop, respectively, is integrated. Originally, the EB was theorised to depend upon the Central Executive (CE), a control system needed to supply attention whenever WM tasks are undertaken. Since Baddeley's amendments to the model (2000), a wide corpus of

research has examined the relationship between these two systems. The rationale was: if the CE controls access to and from the EB, then an attentionally demanding concurrent task should negatively affect participants' performance in binding information in WM.

Results have confuted such expectations as it was shown that no greater attention is required to bind colours and shapes, for instance, than to process them separately (Allen et al., 2006; 2012), and this holds true for words bound into sentences compared to individual words as well (Allen & Baddeley, 2008; Baddeley et al., 2009). Also, concurrent demanding tasks have been observed to not disrupt participants' performance when features are presented as spatially and temporally separated and required to be retained as bound afterwards (Karlsen et al., 2010). Finally, Allen and colleagues (2009) have broadened these findings by suggesting that young individuals' capacity to integrate features delivered across diverse modalities does not rely on major attentional resources compared to unimodally bound material and single features. Finally, I have shown that the same applies to both healthy older adults and AD patients.

Taken together, it has been demonstrated that WMB can occur across locations, across time, and across modalities, and that the EB allows the temporary maintenance of bound information and potentially facilitates its long-term storage. The fact that WMB deficits are sensitive and specific to the whole AD continuum indicates that early neuropathological changes, characterising the pathology, make EB functioning fail more than verbal and visuospatial subsidiary systems. This not only supports the key role of the EB within a theoretical perspective, but also reflects the importance of a specific neural region or network underpinning binding mechanisms. The frontal lobes have been proposed as the neural correlates of the EB (Baddeley, 2000; Prabhakaran et al., 2000), but given my own finding and those gleaned from relevant previous studies I posit that the perirhinal cortex would be a suitable alternative (see Chapter IV).

Finally, Chapter III informs on the importance of the CE in binding mechanisms. MCI patients recruit more brain regions to maintain feature conjunctions over short periods of time, producing a (dysfunctional) hyperconnectivity. This reflects the demand for more resources, which seem to be provided by increasing activation in the parietal regions (Parra et al., 2014; see Chapter II).

Altogether, this dissertation proposes an integrated view of the Multicomponent Model of WM along with some neuroanatomical and connectivity evidence, on which focusing to develop screening tools to assess pharmaceutical and rehabilitative interventions.

5.7 Cued recall of bound information held in working memory is unimpaired by age and AD pathology

The final outstanding issue this PhD project addressed is whether age and AD impact on the ability to recall bound features held in WM.

Prior studies have shown that AD patients are worse than healthy controls and non-AD dementia patients to hold visual colour-shape bindings in a free recall task (Cecchini et al., 2017; Della Sala et al., 2012; Parra et al., 2009a). Also, a more recent study has demonstrated that healthy elderly, with poor level of schooling, can temporarily maintain colour-shape conjunctions within a free recall paradigm (Yassuda et al., 2019). The authors concluded that, whenever recalling context-related information is not relevant, such as for colour-shape conjunctions, age has a less detrimental effect on performance (Danckert & Craik, 2013; Yassuda et al., 2019).

Results from Chapter IV revealed that, by using a cued recall paradigm, healthy older adults and AD patients could retain unimodally and crossmodally bound colour-shape conjunctions in WM to the same extent. Such results broaden previous conclusions, indicating that the

effect of age and AD pathology on recall of bound information is not influenced by the type of task.

In sum, current findings suggest that conjunctive WMB deficits are (i) age insensitive and (ii) AD sensitive and specific regardless of the modality of presentation of to-be-bound material and the retrieval strategy used to assess the binding function.

5.8 Leading ideas for future research

Further questions may derive from conclusions drawn thus far:

1. Can functional and structural changes associated with WMB deficits in prodromal AD predict progression to dementia and if so, at what specific stage of the disease continuum?

Longitudinal studies need to be carried out to ascertain that those MCI patients displaying neuropathological changes associated with WMB deficits will convert to AD dementia. Systematic evidence resulting from a longitudinal approach may also unveil when the conversion is most likely to occur.

2. Do measures of white matter integrity in relation to the WMBT show abnormalities in prodromal AD patients?

3. Since no loss of white matter integrity was observed in asymptomatic carriers of FAD compared to healthy controls, will network connectivity analysis reveal abnormal changes in the same cohort?

In a previous DT-MRI study (Parra et al., 2015b), loss of white matter integrity, as expressed by fractional anisotropy and mean diffusivity levels in specific ROIs, has been observed in FAD patients compared to healthy controls when performing the WMBT. Asymptomatic FAD carriers were not found to exhibit the same neurophysiological abnormalities. This may raise the question of when these changes commence within the AD continuum. A similar investigation in prodromal stages of AD may provide relevant contribution in this regard.
Also, investigating integrity of white matter tracts linking regions of interest in MCI patients while undergoing conjunctive and relational memory binding tasks may (i) further contribute to the identification of key areas involved in such WMB mechanisms and (ii) better clarify conversion trajectories in people at risk of sporadic AD.

On the other hand, network connectivity analysis at large-scale brain level, as the one described in Chapter III, may be an outstanding approach to unveil abnormal changes coupled with disruptions in the WMBT in preclinical AD and confirm, through a more sophisticated technique, the brain reorganisation prior observed (Parra et al., 2017).

4. Is there a binding cost when integrating information across modalities?

Crossmodal WMB is not more impaired than unimodal WMB in both healthy ageing and AD; however, whether there is a cost of such mechanism is yet unknown. In order to avoid fatigue in the AD sample who took part in my research, single feature conditions were not included in the paradigm. It is however worth claiming that further studies should assess whether crossmodal bindings are more difficult to maintain compared to single colours and single shapes perceived through the auditory and visual channels. This would highlight that holding crossmodal conjunctions in memory does require additional neural resources.

5. Do unimodal and crossmodal WMB mechanisms share neural structures and resources?

In line with the previous question, an fMRI study investigating neural activation underpinning both unimodal and crossmodal WMB would shed light on activated regions which may be common to both mechanisms. This would possibly identify a specific area or network responsible for binding per se, despite the type of material to be integrated. According to crossmodal sensory integration literature (Taylor et al., 2006; Tyler et al., 2004) and Didic et al.' s (2011) hypothesis, the perirhinal cortex may be a promising candidate to subtend the binding function, and further research should verify this.

6. Is it sound to definitely claim lack of hippocampal activation in conjunctive WMB?

This question may seem a bit controversial, considering that the lack of hippocampal activation in conjunctive WMB tasks has been often highlighted as one of the take-home messages of this thesis (Didic et al., 2011; Parra et al., 2014; Valdes Hernandez et al., 2020; see also Chapter II). However, the fMRI study that I conducted did not purposely account for the role of the hippocampus during colour-shape binding processing. Thus, further studies should examine this hypothesis in depth to permanently ascertain whether or not the hippocampus is recruited by patients progressing to AD dementia.

To conclude, this PhD thesis addressed some pending questions in the available scientific literature by contributing with novel neuroimaging, behavioural and clinical evidence on the role of WMB deficits. Results further support the sensitivity and specificity of conjunctive WMB mechanisms to AD pathology as well as their reliability to detect early signs of AD dementia. Similar evidence acknowledges that WMB deficits are a hallmark of AD since the initial stages of the spectrum, and that the WMBT should be used in clinical settings for

diagnostic and prognostic purposes. I expect that the results reported here will motivate further research into these topics, which have important implications for theories of cognition in ageing and for applications and procedures in clinical settings.

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