Input and output order of recall as early markers of cognitive decline

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Glossary

AD = Alzheimer’s Disease

AVLT = Auditory Verbal Learning test

CMT = Context Maintenance and Retrieval model

CRIq = Cognitive Reserve Index questionnaire

CRP = Conditional Response Probability model

CRUNCH = Neural Circuits Hypothesis

CUD = Cognitively Unimpaired Declining

CUS = Cognitively Unimpaired Stable

DA = Divided Attention

DLPF = Dorsolateral Prefrontal

DSS = Digit Symbol Substitution test

fNIRS = functional Near-Infrared Spectroscopy

HAROLD = Hemispheric Asymmetry Reduction in Older adults

HERA = Hemispheric Encoding Retrieval Asymmetry model

LJMU = Liverpool John Moores University

LTM = Long-Term Memory

MCI = Mild Cognitive Impairment

MOCA = Montreal Cognitive Assessment

MTL = Medial Temporal Lobe

PFC = Prefrontal Cortex

PHQ = Patient Health Questionnaire

RBANS = Repeated Battery for the Assessment of Neuropsychological Status

STAI = State Trait Anxiety Inventory

STeM = Spatio-Temporal Memory test

STM = Short-Term Memory

TCM = Temporal Context Model

TMT = Trail Making Test

WRAP = Wisconsin Registry for Alzheimer’s Prevention

Abstract

This thesis explored the effects of age on free recall patterns in episodic memory. Neuropsychological and neuroimaging instruments were used to investigate the input (i.e., serial position effects) and output (i.e., temporal vs. spatial contiguity) of free recall in younger vs. healthy older individuals and in older adults with cognitive decline.

In study 1 (Chapter 4), primacy (intended as the tendency to better remember items presented at the beginning of a list compared to the middle) at delayed recall was the most accurate serial position effect in predicting conversion to early stage Mild Cognitive Impairment (MCI), from a baseline of cognitively functioning older adults.

In study 2 (Chapter 5), age differences in the use of spatial vs. temporal contiguity (intended as the tendency to retrieve items following the temporal, or spatial, context in which they have been learned) were explored in younger vs. healthy older adults. It was found that temporal contiguity was the most utilised associative process in both groups, although older adults showed lower temporal contiguity compared to younger adults.

In study 3 (Chapter 6), the universality of temporal contiguity and the relationship between attentional processes and the output order of free recall were examined. Temporal vs. spatial contiguity were investigated during tasks meant to interfere with encoding processes, that is Divided Attention (DA) tasks and tasks involving presentation of verbal vs. pictorial material. Results showed consistent use of temporal contiguity in all experimental conditions, therefore suggesting the ubiquity of temporal contiguity and its involvement in retrieval processes.

In study 4 (Chapter 7), the output order in free recall was investigated in younger and older adults in relation to prefrontal blood oxygenation, by means of functional Near-Infrared Spectroscopy (fNIRS). It was found that areas involved during temporal contiguity change with age, as younger adults showed greater activity of the right prefrontal cortex, whilst older adults engaged alternative or opposite regions.

In study 5 (Chapter 8) the use of unrelated memory lists was investigated as a sensitive measure to detect age-related differences on the use of temporal vs. spatial contiguity. Moreover, age-associated differences in the use of temporal contiguity were explored at immediate vs. delayed recall. It was found that unrelated lists are able to detect age-related changes in the use of contiguity effects, and that temporal contiguity is negatively affected in both younger and older adults at delayed recall.

In study 6 (Chapter 9) temporal clustering was investigated as potential predictor of conversion to Cognitive Unimpaired Declining (CUD) status, from a baseline of cognitively functioning older individuals. Results supported the hypothesis that temporal contiguity is a marker of cognitive decline, also when controlling for genetic information and for variables typically used in clinical practice.

In summary, the findings of this thesis show that the input and output order of free recall, although quite stable, decline with age and that they may be added as a potential tool for early detection in clinical settings, and in the research field.

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Last, but not least, to my family, to whom this thesis is dedicated. Mamma, babbo, Alessio: siete un sole nei momenti bui e una bussola quando mi sento persa.

Chapter 1 Memory in humans

One of the most unique aspects of the human mind is the capacity to travel mentally through time, by re-experiencing past events (Tulving, 2002). The assumption that memory and time are related to one another dates back at least to Aristotle, who stated that only animals which perceive time can remember (Aristotle, 449/2015). In the nineteenth and twentieth century, empirical studies of memory provided the foundation of research in memory and learning (Ebbinghaus, 1913), and consolidation (Müller & Pilzecker, 1900). These studies introduced the notion that different types of memory (Tulving, 1984) and processing (Melton, 1963) exist.

1.1 Memory systems and processes

Memory involves three forms of information processing: encoding, storage and retrieval. Although early studies emphasised the importance of one process over another, all of them play a fundamental role in memory, as expressed by the encoding specificity principle: “What is stored is determined by what is perceived and how it is encoded, and what is stored determines what retrieval cues are effective in providing access to what is stored” (Tulving & Thomson, 1973, p. 353).

1.1.1 Encoding

Encoding involves the processing of incoming information in order to create representations in the memory system. Attentional processes permit selected information to enter the memory system (selective attention; Johnston & Dark, 2012) through automatic or effortful processes. In both cases, encoding involves recoding, that is translating and elaborating perceived events in memory representations. The concept that memory is elaborative, or rather re-constructive, was first introduced by Bartlett (1932), who subverted the prominent behaviourist approach, wherein memory was merely a repetitive process. Thanks to Bartlett's work, encoding was recognised as playing a determinant role in memorization, depending on the level of processing perceived stimuli receive (Craik & Lockhart, 1972). Craik and Lockhart (1972), who looked at memory mainly from the encoding prospective, postulated that the greater the depth of elaboration, the more memory representations were likely to be persistent. According to their view, attention helps maintaining perceived information at a constant Level Of Processing (LOP) called Primary Memory (PM), or Type I processing, where repetition permits that items are kept at the conscious level. However, given that PM keeps the information at a fixed level of processing, it cannot be involved in deeper analyses, which are fundamental to the formation of permanent traces and to improve memory performance. This role is covered by the Type II processing, which involves more complex and semantic analyses of stimuli. Type I processing may be applied when repeating a telephone number before composing it on the 'phone, whilst semantic processing occurs when linking the meaning of concepts together. Although showing the importance of encoding in memory, the LOP theory has received criticism, mostly concerning the objective measure of deep processing and how this is directly related to greater memory performance (Eysenck, 1978). Indeed, Craik and Lockhart associated deep processing with long-term memory, but failed to provide evidence or instruments to test this relationship. This limitation leads to a circularity problem, wherein deeply processed information is predicted to be better remembered, by measuring how well information is remembered.

An alternative theory of encoding, that highlights processing focus rather than processing depth (Braisby & Gellatly, 2012), was suggested by Mandler (1979), who distinguished between item-specific (integration) and relational (elaboration) processing. Whilst the first focuses on how the cognitive processes that carry mental representations are enhanced, the second concerns the creation of connections between items. Mandler (1979) also distinguished between recognition, which is based on the familiarity of a stimulus, and identification, that involves evaluation of contextual information and familiarity (essentially what today is known as recollection). Mandler believed that whilst recognition would benefit from item-specific, rather than relational processing, free recall would derive mostly from relational processing. His theories were later investigated by Hunt and Einstein (1981), who provided evidence regarding Mandler's hypothesis of recognition, but contrasted his assumption on free-recall, which they found to be benefitting from both relational and item-specific processing. On this view, encoding of the to-be-remembered events is guided by both similarities (relational) and differences (item-specific) of the material. These processes can therefore be used reciprocally during encoding, depending on the type of material and instructions provided.

1.1.2 Storage

Storage refers to the maintenance of specific memory information over time. The concept that there are several forms of memory was first introduced by James in 1890, who distinguished between primary and secondary memory, and was successively reorganised in the multi-store model (Atkinson & Shiffrin, 1968, Figure 1.1), where information is sequentially stored into three main storage areas: sensory memory, short-term memory (STM) and long-term memory (LTM).

1.1.2.1 Sensory memory

The sensory store holds information briefly and it is limited to specific sensory modalities, which are mostly visual (iconic store) or acoustic (echoic store). A classic example of iconic (or sensory) memory is given by Sperling's (1960) study, wherein participants were presented with a visual array of letters for a duration of 50ms and, when asked to report the letters they were able to see, they reported 4/5 letters although they claimed to have seen more. This pioneering study provided evidence for the first time that sensory memory decays within 50ms, although more recent studies suggest a duration of up to 1600ms (Landman, Spekreijse, & Lamme, 2003). Information within the echoic store has a duration of typically 2 – 4 seconds (Treisman, 1964).

1.1.2.2 Short-Term memory and Working memory

The duration of STM is between 15 and 30 seconds according to Atkinson and Shiffrin (1971), although Peterson and Peterson (1959) have suggested shorter durations when studying STM, with a 50% reduction in memory performance after 6 seconds and complete forgetting after 18 seconds. STM is limited in storage capacity to seven pieces (or chunks) of information, plus or minus two (Miller, 1956).

In 1974, Baddeley and Hitch introduced the concept of working memory (WM) as an active replacement to the more static and simplistic STM. WM is necessary for cognitively complex tasks and acts through four components: (a) phonological loop, which stores and retrieves spoken and written material and is fundamental in language learning; (b) visuo-spatial sketchpad, which is involved in spatial and visual manipulation; (c) central executive, which is considered an attentional-controlling system, as it monitors and coordinates the other components and relates them to the LTM; and (d) the episodic buffer, introduced more recently as an attempt to create a more unitary representation of WM, and it is assumed to integrate, briefly store and combine multi-dimensional representations coming from the phonological loop, the visuo-spatial sketchpad and LTM (Baddeley, 2000).

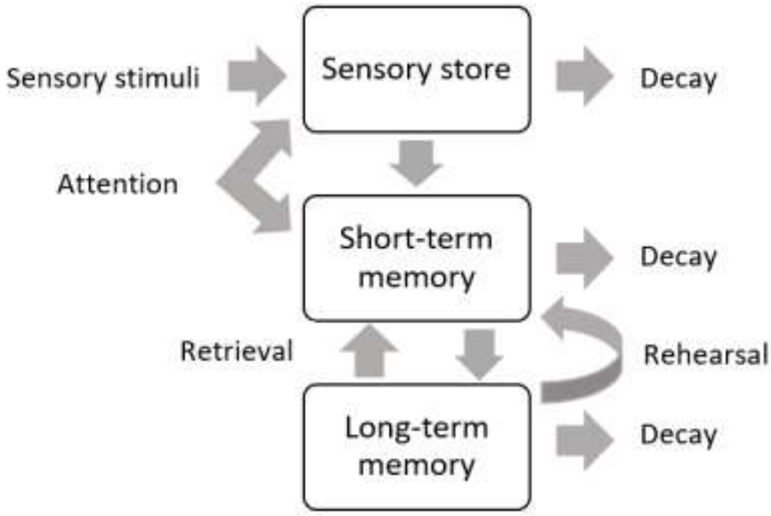


Figure 1.1 Atkinson & Shiffrin's Multi-store model of human memory.

1.1.3 Consolidation

Short-term memories can become long-term memories via consolidation, a process based on the concept that short-term traces are fragile, but become more robust with time (Müller & Pilzecker, 1900). Evidence of memory consolidation provided an explanation for retrograde amnesia, which involves disruption of past memories (Ribot, 1882), and has been found in various animal species (Muller, 1996). Hebb and Gerard's physiological studies (Gerard, 1949; Hebb, 1949) provided the first evidence of a neural basis of consolidation, which will be further discussed in Paragraph 1.3.1.2.

1.1.3.1 Long-Term Memory

LTM is the depository of enduring knowledge and skills and its storage capacity is believed to be unlimited. LTM memories are stored in two systems (Cohen & Squire, 1980): declarative and non-declarative systems (Figure 1.2).

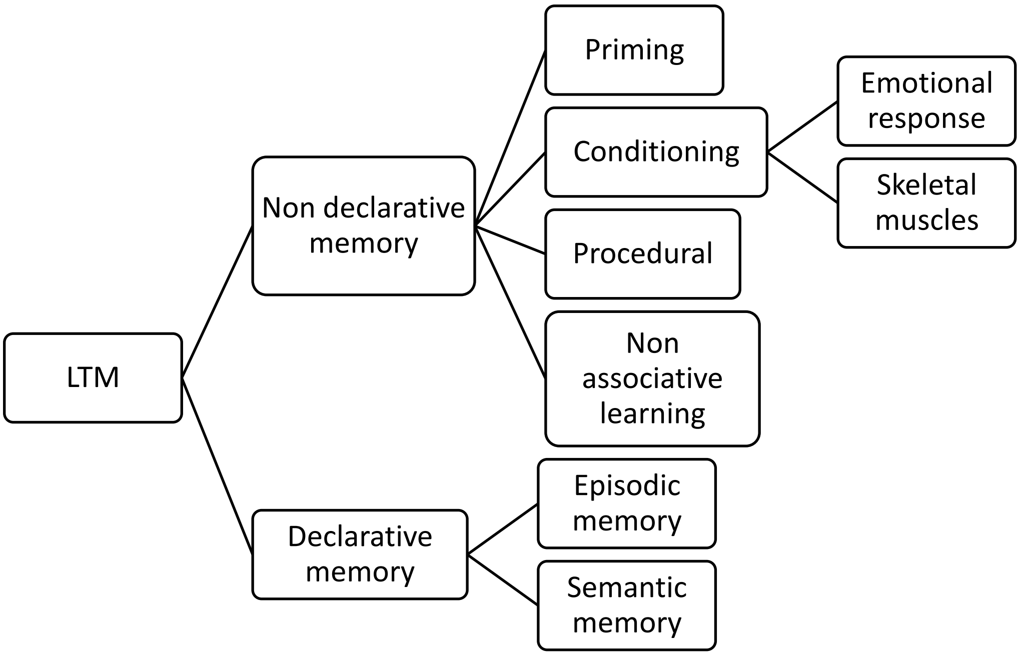


Figure 1.2 Taxonomy of declarative and nondeclarative memory systems.

Declarative (or explicit) memory is flexible, representational and explicit. In this respect, it differs from other non-declarative (implicit) memory systems, which are unconscious (Squire, 2004). Various memory systems can be distinguished in terms of the different kind of information they process and the principles by which they operate. Tulving (1984) divided declarative memory into episodic memory, which is the ability to recall and mentally re-experience a personal event in the context wherein it originally occurred, and semantic memory, which is knowledge about the world.

Non-declarative (or implicit) memory is a type of LTM that does not require consciousness and includes procedural memory, which refers to the sensorimotor habits and automatic skills, and the perceptual representation system, a group of domain-specific modules regarding perceptual information contained within stimuli. An example of these modules is repetition priming, which refers to the implicit impact that prior exposure to a stimulus has on later responses to similar stimuli (Baars & Gage, 2010). Associative (or conditioning) and non-associative learnings also lead to formation of non-declarative memories. Whilst the associative learning involves learning to associate a stimulus with another (classical conditioning, e.g. Pavlov's experiments with dogs; Pavlov, 1927) or with a new response (instrumental conditioning, e.g. Thorndike's experiments with puzzle boxes; Thorndike, 1911), non-associative learning includes learning one stimulus at a time.

1.1.4 Retrieval

Retrieval is remembering stored information. Retrieval completes the process of remembering and has been argued by Tulving to be "the key process of memory" (Gazzaniga, 2008, p. 91). Retrieval can be an automatic process, as shown by studies where distractors or divided attention do not influence the retrieval process (Naveh-Benjamin, Craik, Gues, & Dori, 1998), or a strategic process, as emphasised by the findings that study strategies are used to optimise retrieval (Hunt & McDaniel, 1993). For instance, retrieval practice, based on repetition, increases accurate retrieval (Pyc & Rawson, 2009), whilst inducing forgetting of related information (Anderson, Bjork, & Bjork, 1994). Distraction at encoding may, on the other hand, impair consequent retrieval. Moreover, whilst information retrieved from STM tends to be recalled verbatim, retrieval of LTM requires cognitive re-elaboration and construction of encoded stimuli which are modified by already existing knowledge. Different types of analyses of retrieval (or recall) are used in neuropsychological assessment to test episodic memory.

1.2 Universal principles of memory processes

The most common explicit tests of memory retrieval, that involve asking participants to recall specific events, are recognition, where an outside stimulus is utilised as a cue for related encoded information, and recall, where memories are retrieved without a cue. Recall can in turn be divided in: (a) serial recall, wherein information is retrieved following a specific order; (b) cued recall, where a cue is provided as an associate of a previously studied item; (c) and free recall, which permits autonomous retrieval. Free recall tasks consist of reading or listening to a list of words and freely recalling as many items as possible, after a variable period of time. Given the absence of overt cues, free recall is the most context-dependent memory test, because it relies exclusively on the circumstances under which items have been studied. For this reason, it requires participants to efficiently organise information at encoding, and to select appropriate memory strategies at retrieval in order to increase memory performance. Given that retrieval is spontaneous in free recall, the order of items recalled should reflect the order in which those items come to mind. Therefore, the response order should reflect the internal organization of memory, which is made of various encoding and retrieval strategies and guided by general universal principles (Healey & Kahana, 2014).

1.2.1 Input order of free recall: the serial position paradigm

While writing logarithms, Nipher (1878) observed that figures in the middle of the numbers are more difficult to remember than those at the extremes. After Nipher's observation, the serial position effect has become one of the most established generalizations in the study of verbal learning and has been hailed as a universal principle, since it is extremely consistent across healthy participants from several age groups. On list-learning tasks, the probability of retrieving an item depends on the item's position in the study list. That is, items are more likely to be recalled when presented at the beginning (primacy effect) or at the end (recency effect) of the list (Deese & Kaufman, 1957). In 1913, Ebbinghaus pioneered experimental studies on verbal memory involving serial learning (Ebbinghaus, 1913) and first coined the term "serial position effect". Since then, several experiments have shown that primacy and recency of serial position facilitate memorization during free recall tasks, independently of list length and presentation rate. Specifically, Murdock (1962) compared six groups of participants who were tested on verbal memory tasks composed of lists of 10, 15, 20 and 30 unrelated words, where each item was presented every 1 or 2 seconds. His findings confirmed results from similar studies (Keith, 2013; Robinson & Brown, 1926): all serial position curves share certain general characteristics so that a U-shaped curve is formed. For instance, in a list of 25 unrelated words, the primacy effect extends over the first three or four words in the list, the recall of the middle of the list is flattened, whilst recency extends over the last eight words of the list (see Figure 1.3). These effects have been interpreted as reflecting the action of two different systems.

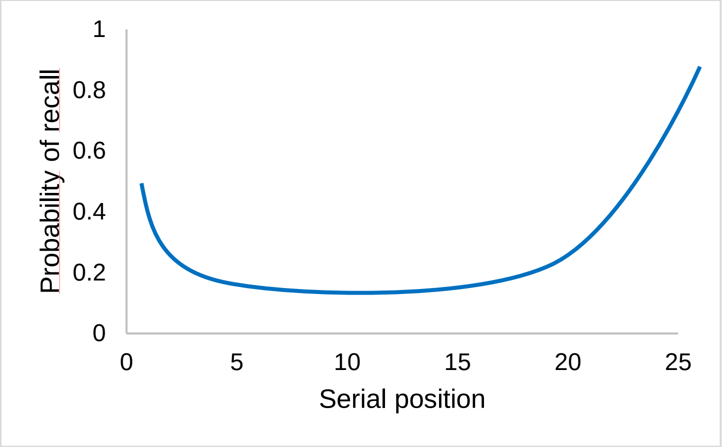


Figure 1.3 Idealised serial position curve. Words at the beginning (primacy) and at the end (recency) are recalled better than words in the middle of the list.

1.2.1.1 The dual-store approach to serial position

Based on the dual-store interpretation, the recency effect is dependent on STM, as it is susceptible to rapid decay but not to storage capacity, whilst primacy depends on LTM, as it is relatively unaffected by delay (Glanzer & Cunitz, 1966). Subsequent studies provided further evidence that variables known to facilitate retrieval from LTM, including slower presentation rate, using familiar or concrete words, positively impacted primacy, but not recency (Glanzer, 1972). On the other hand, using distractors during the retention period seems to attenuate the recency effect. Although items encoded most recently in STM are usually easier to access and rehearse, in such conditions they can be retrieved exclusively from LTM, therefore they lose the advantage of greater accessibility.

1.2.1.2 The single-store approach to serial position

The assumption that recency is simply dependent on STM has been questioned by single-store theorists, who observed recency effects in conditions in which STM should be affected, such as when using 20-second distractor tasks during both encoding and retrieval (Bjork & Whitten, 1974) and in time-based decay, where long-term recency effects are found (Baddeley & Hitch, 1977). The fact that recency is persistent in both immediate and long-term conditions suggests that it may be common to primacy and to specific temporal or contextual retrieval strategies (Greene, 1986).

For instance, the ratio-rule models (Gillund & Shiffrin, 1984; Glenberg & Swanson, 1986; Shiffrin & Raaijmakers, 1981) suggest that serial position is based upon retrieval mechanisms based on the distinctiveness of information. Crowder (1976) underlined the importance of time as a retrieval cue in recency. That is, more recent encoded items share a temporal context (temporal distinctiveness model) most similar to the present context and therefore are remembered more easily. His theory was then extended by Neath (1993), who suggested that the discriminability can be applied to dimensions other than temporal, such as semantic, physical and spatial (dimensional distinctiveness model). Whilst these models consider the duration of the Retention Interval (RI) or of the Inter-Presentation Intervals (IPI) as a critical determinant of items' distinctiveness, the ratio-rule models predict the amount of recency by calculating the temporal ratios between the duration of IPI and RI (Nairne, Neath, Serra, & Byun, 1997). Based on the observation that items retrieved successively tend to come from neighbouring study positions, Howard and Kahana (1999) postulated a single-store model able to explain recency effects in immediate, delayed and continuous-distractor free recall. In their contextual variability model, context is used as a cue to retrieve subsequent recalls and the serial position curve is characterised by the probability of first recall and the Conditional Response Probability (CRP), or "how one recall follows another" (Howard & Kahana, 1999, p. 924), which are not completely dependent on rehearsal.

1.2.1.3 Dual-store versus single-store approaches

The dispute between dual-store and single-store memory models is still ongoing. Studies on patients with brain damage and studies using neuroimaging instruments are utilised to support one approach over the other. For instance, studies on patients with amnesia have shown that impairment of LTM affects primacy, but not recency (Baddeley & Warrington, 1973), whereas impairment of STM cancelled the recency effect, whilst preserving primacy (Basso, Spinnler, Vallar, & Zanobio, 1982). This last finding was in contrast with the dual-store model, for which STM is necessary for formation of LTM. However, other authors used neuroimaging techniques to provide support in favour of the dual-store model. Talmi, Grady, Goshen-Gottstein and Moscovitch (2005) found that the brain areas activated during retrieval of primacy items, but not of recency items, were those typically associated with LTM (e.g., the hippocampus). Innocenti et al. (2013) reported that primacy was worsened by stimulation aimed at suppressing activity in the dorsolateral PFC, whilst recency was affected by stimulation of the intraparietal lobe. Recent studies however have found evidence for the involvement of medial-temporal structures in rehearsal processes and in strengthening encoding (Bruno et al., 2015; Davachi & Wagner, 2002), whereas PFC contributes to rehearsal (Nee & Jonides, 2008). These findings observed relevant functional connectivity between PFC and medial-temporal structures, therefore suggesting a more unitary view of memory.

1.2.2 Output order of free recall

Compared to serial order recall, where tests are designed to emphasise recalling of serial order and specific instructions may be provided, free recall tasks have the advantage that no experimenter-imposed structure is forced upon the nature of the retrieval process. In learning lists of random items, participants seem to create a sort of “organization” of the materials, most probably aimed to optimise their performance on the type of test they expect. In this regard, Hintzman (2016) talked about a prospective component of memory processes, based on the assumption that participants utilise specific encoding strategies to enhance memory performance, as they anticipate a memory test. Some associations are clustered through semantic organization when lists include strong semantic associations, such as cat and dog. However, associations may also depend on the context in which items are presented, especially when they are not semantically related. The most common organizational strategy in free recall follows temporal associations: items presented close in time tend to be retrieved together. Temporal organization has been found to be remarkably consistent across participants and experimental paradigms, so it is suggested as a fundamental cognitive principle (Healey & Kahana, 2014). Lastly, when spatial context is introduced in memory tasks, associations are formed on the basis of where items are spatially located, therefore increasing recall for stimuli that are spatially close to each other. For the purpose of this thesis, the terms “contiguity”, “clustering”, “organization”, “output order” and “associative processes” will be used as synonyms.

1.2.2.1 Semantic organization

Semantic clustering happens when participants presented with lists of words from several semantic domains tend to recall items by clustering them by semantic category. Bousfield and Cohen (1953) analysed performance in an episodic memory test on 100 healthy participants. The 60 items presented were chosen from four different domains. The results showed that subjects tended to recall by semantically clustering the items. Following studies confirmed the existence of semantic proximity and its relationship with temporal organization (Romney, Brewer, & Batchelder, 1993). In this respect, Glanzer (1969) suggested that semantic association is strengthened in long-term memory when items are rehearsed together in the short-term storage (STS). However, as the STS has limited capacity, the probability that related words are in the STS simultaneously increases when there are fewer distractor words separating them. Therefore, he hypothesised that recall of semantic associates is enhanced when appearing in nearby list positions (Glanzer, 1969). More recently, Howard and Kahana (2002) simultaneously measured semantic and temporal influences on output recall and found that variations in semantic similarity have an effect on the way in which items are recalled (output order) specifically at delayed recall.

1.2.2.2 Temporal organization

Hook (1682) suggested that memories are stored in the brain as a chain of memory traces, which grows as new memories are acquired and old memories are pushed further back along the chain. Following this principle, Ribot (1882) showed that individuals with amnesia are more likely to lose new memories first, whereas old memories are the hardest to forget (graded forgetting).

Learning by contiguity is also the principle behind the Gestalt laws of perceptual organization (Goldstein, 2017) and conditional learning (Pavlov, 1927). Temporal contiguity is based on the concept that after recall initiation, associations between just-recalled items drive subsequent recall (Kahana, Howard, & Polyn, 2008). Temporal association refers to the general finding that recall is facilitated by the presentation or recall of another item that is close in time to the target item (Kahana, 1996) and it has been found to predict episodic memory performance, so that participants who use it more effectively perform better on recall tasks (Sederberg, Miller, Howard, & Kahana, 2010). To measure the influence of temporal association, Kahana (1996) introduced the lag-Conditional Response Probability function (CPR): the conditional probability that recall of an item from a given input position is followed by recall of an item from a given distance (or lag) from the first, in either a forward (positive) or backward (negative) direction. Lags can range from – (N – 1) to (N + 1), therefore it excludes lags that would fall outside the list boundaries. For instance, items A, B, C, D are presented in this order. If item C is recalled second (= 2), followed by D (= 3), then we would have a lag, D – C, of + 1. If plotted, the lag-CRP has a picked shape in the middle (around lag zero), indicating that recalls from nearby study positions are more likely.

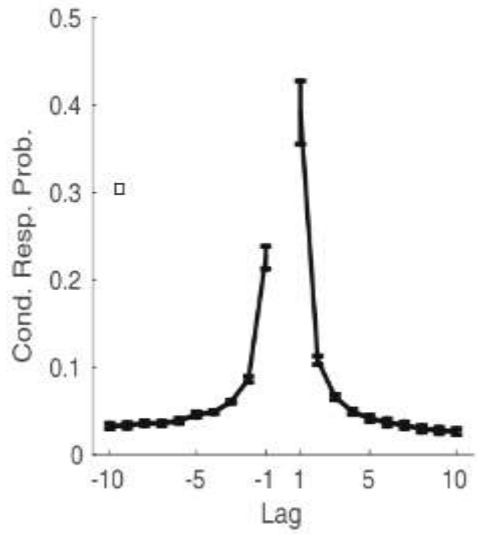


Figure 1.4 Example of CRP from Healey et al., 2018

Recalls are also more likely to be in the forward/positive, rather than backward/negative direction (see Figure 1.4), than recalls from greater distance.

The lag-CRP curve has been consistently shown across experiments and subjects (Healey & Kahana, 2014).

1.2.2.2.1 Models of temporal contiguity

More recently, a Temporal Context Model (TCM, Howard & Kahana, 2002a) was developed in order to eliminate the effects of recency (end-of-the-list context) in calculating lag-CRP in immediate, delayed recall and in continuous-distractor free recall. According to the TCM, the context in which items are studied during encoding changes depending on the positions of the items in the list. Items that are presented in nearby study positions share a similar context. At retrieval, this information is used as a probe for recall and each just-recalled item is used to update the context information and recall additional items. Since context changes gradually over time, the TCM can simultaneously explain contiguity and recency effect, as recent contexts are remembered better than previous ones. The TCM was questioned by Farrell and Lewandowsky (2008), who argued that serial position effects, especially recency, may increase the lag-CRP at extreme lags, therefore undermining the contiguity effect. However, Howard, Sederberg and Kahana (2009) showed that the TCM is not a simple confound of serial position effect and that it is able to predict the nonmonotonicity, suggested by Farrell and Lewandowsky (2008), in the lag-CRP. The TCM however lacked an explanation of the effect of non-temporal (i.e., semantic) factors in retrieval.

Therefore, the Context Maintenance and Retrieval (CMR) model was introduced, which accounts for the influence of semantic and source information in recall dynamics (Polyn, Norman, & Kahana, 2009). In the CMR, a distribution of temporal distances is generated from a specific recalled item to every other to-be-recalled stimulus. The distances are calculated as absolute values of the difference between the serial position of the just-recalled item and the to-be-recalled items. A percentile score is then calculated by comparing the temporal distance value of the following item to be retrieved to the rest of the distribution. Lastly, all values are averaged so that a temporal factor score is available per each participant. Temporal factor scores of .50 indicate absence of temporal organization, whereas values over .50 are representative of a tendency to temporally cluster items, where a value of 1 would represent exclusive and highest use of temporal associations. Temporal factor scores will be used in Chapters 5, 6, 7, 8 and 9.

1.2.2.3 Spatial organization

In the domain of spatial memory, the study of spatial priming has a short history, although the concept that spatial information can be intentionally encoded and retrieved has been long-established (Campbell & Warren, 2006). Given the difficulty of isolating temporal contiguity when investigating the spatial contributes in memory for spatial context, spatial clustering was originally believed to occur as a consequence of temporal clustering (Clayton & Habibi, 1991; McNamara, Halpin, & Hardy, 1992; Sherman & Lim, 1991). That is, when two items are presented in neighbouring locations, they also tend to be perceived as close in time. For instance, McNamara et al. (1992) had participants learn objects' names and their locations in a two-dimensional spatial array and found that both object-recognition and location judgments were faster and more accurate when items were presented in both spatial and temporal proximity. However, whilst previous experiments investigated the intentional component of spatial clustering, by specifically instructing participants to encode the spatial contributes of presented items and to consequentially recall their spatial location, Miller, Lazarus, Polyn, and Kahana (2013) made a considerable contribution to the study of spatial priming, by exploring the spontaneous utilization of temporal and spatial priming in free recall. In Miller et al.'s (2013) study, participants played a game in which, after a practice training, they were asked to deliver objects to specific buildings in a virtual environment (encoding phase) and then freely recall them (recall phase). By analysing both temporal and spatial CRP, spatial clustering was reported, alongside temporal clustering. The study showed that spatial contiguity during item presentation is a strong predictor of the order in which items are then freely recalled. These findings support the hypothesis that spatiotemporal contributions are utilised conjointly during encoding and that these associations are conserved at retrieval. Moreover, Pacheco and Verschure (2018) recently reported that spatial clustering can be maintained up to 24h, therefore providing evidence for spatial clustering's persistence over time.

No study however has so far investigated clustering preferences when temporal and spatial priming are used in opposition, rather than in association, which will be addressed in Chapters 5, 6, 7 and 8.

1.3 Human memory and the brain

Several approaches have been used to understand the relationship between brain and memory and to support the cognitive theories on memory's components. Over the years, studies on patients with brain injuries, memory problems and, more recently, studies using neuroimaging methods have provided insights on the anatomical locations of memory processes and functions.

1.3.1 Neurological basis of memory processes

In the following paragraphs, the neural substrates of encoding, consolidation, storage and retrieval will be addressed.

1.3.1.1 Encoding

Frontal and prefrontal cortexes have been found to play a critical role in memory encoding. Functional Magnetic Resonance Imaging (fMRI) and Positron-Emission Tomography (PET) studies have shown that intentional encoding of new memories involves activation of the left prefrontal cortex (corresponding to Brodmann areas 9, 10 and 46), compared to right prefrontal areas which are instead activated during retrieval (Hemispheric Encoding/Retrieval Asymmetry, HERA model, Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). This pattern is found for both verbal and nonverbal material (Buckner, 1996) and will be discussed thoroughly in Chapter 6. Encoding has also been related to the activation of anterior hippocampal regions (Lepage, Habib, & Tulving, 1998), therefore suggesting that these areas, which are typically responsible for consequent memory processes (e.g., consolidation), play a role in encoding.

1.3.1.2 Consolidation

Studies on patients with retrograde and anterograde amnesia provided support to the view that the hippocampus is fundamental to memory consolidation, whilst permanent memories are stored elsewhere. For instance, findings from the well-known case of H.M. (Scoville & Milner, 1957), who suffered severe memory impairment as a consequence of bilateral Medial Temporal Lobe (MTL) resection, provided the basis for modern memory research. H.M.'s peculiar inability to form new memories, whilst conserving intact intellectual and perceptual functions, provided evidence that MTL, including the hippocampal complex, were distinct memory cerebral functions and motivated the application of animal models in human memory research. It was also demonstrated that there are different types of memories in the brain and that some of them do not necessitate the involvement of the MTL. Recently, it has been shown that consolidation processes permit retrieval even without hippocampus involvement (Dudai, 2004). This is known as the standard consolidation theory (Sekeres, Moscovitch, & Winocur, 2017). Debate on the role of the hippocampus in memory consolidation is currently ongoing (Nadel, Hupbach, Gomez, & Newman-Smith, 2012). For instance, according to an alternative theory of multi memory trace (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006), the hippocampus plays an active role in consolidation and it never becomes completely independent from the other structures. Alternatively, other brain regions, such as the amygdala, have been included as part of the neurobiological systems regulating consolidation (Mcgaugh, 2000), therefore underlining the influence of emotional arousal on memory (Cahill et al., 1996).

1.3.1.3 Storage

Brain substrates of memory storage mostly involve the MTL, including the hippocampus and the amygdala, and nearby areas, such as the entorhinal and perirhinal cortexes and the parahippocampal region. Whilst the perirhinal cortex receives information on the specific stimulus (the what), the parahippocampal cortex receives information about the context (the where) and the hippocampus binds all the information together (Diana, Yonelinas, & Ranganath, 2007). Similar to consolidation processes, the amygdala seems to be involved in storage processes, by modulating release of hormones and neurotransmitters, which in turn influences long-term memory (McGaugh, Cahill, & Roozendaal, 1996). These findings suggest that memory storage involves the cooperation of different brain substrates, mostly located in the temporal lobe.

1.3.1.4 Retrieval

Different brain substrates are activated when memories are retrieved. Other than the temporal lobes, several studies support the involvement of the frontal cortex. Specifically, the ventrolateral prefrontal cortex appears to be involved in passive rehearsal and maintenance functions, whereas the monitoring and manipulation of memory has been associated with activation of the dorsolateral prefrontal cortex (DLPF; Petrides, Alivisatos, Evans, & Meyer, 1996). In fact, DLPF areas are believed to be activated during retrieval of past events (Nyberg, Cabeza, & Tulving, 1996). However, as these areas are particularly involved in inhibition, cognitive and emotional control, they are also crucial in active forgetting processes (Anderson et al., 2004).

1.3.1.5 Neural substrates of the input order of free recall

As mentioned in paragraph 1.2.1.3, the primacy effect has been linked to activation of hippocampal areas. These include anterior hippocampus, bilateral parahippocampus, together with the posterior fusiform cortex (Strange, Otten, Josephs, Rugg, & Dolan, 2002). The recency effect has been related to activation of left PFC, whereas retrieval of middle list words seems to activate a wider range of brain areas, including basal ganglia, dorsal cerebellum, left parietal cortex and visual cortex (Li et al., 2003).

1.3.1.6 Output order of free recall and its neural features

Semantic clustering has been linked to activation of MTL, especially the left hippocampus, and PFC, with left ventrolateral PFC activation during encoding of semantically related items, and left dorsolateral and anterior PFC activation during retrieval (Prince, Daselaar, & Cabeza, 2005).

fMRI studies investigating the neural substrates of temporal organization consistently reported the influence of MTL brain structures in long-term temporal memory and PFC areas' involvement in temporal context encoding. Specifically, the posterior hippocampus and adjacent parahippocampal areas were found to increase their activity when items were recalled from nearby study positions, linking these regions to temporal organization for long-term retention (Kragel, Morton, & Polyn, 2015; Tubridy & Davachi, 2011). Jenkins and Ranganath (2010) also reported activation of rostrolateral, dorsolateral and ventrolateral PFC during short-term temporal context encoding. Literature on this specific topic is however still scant; therefore, further research is crucial for a better understanding of the neural mechanisms underlying temporal organization.

Although there is currently no research on the neural substrates of spatial clustering, it is plausible that the same areas involved in free recall and temporal contiguity may be activated during spatial clustering. Neuroimaging research emphasises the role of the parahippocampus for processing of spatial attributes (Burgess, Maguire, & O'Keefe, 2002), whereas the right hippocampus is involved in retrieval of spatial context (Burgess, Maguire, Spiers, & O'Keefe, 2001; Maguire, Frackowiak, & Frith, 1997). Nevertheless, DLPF regions have also been related to retrieval of contextual information, both spatial and non-spatial (Hayes, Ryan, Schnyer, & Nadel, 2004). The neural substrates of spatial clustering are discussed in Chapter 6.

Chapter 2 Ageing and memory

The ageing process causes deleterious changes in the brain (Craik & Salthouse, 2016; Hasher & Zacks, 1988; Salthouse, 1991). These changes include cerebral blood flow reductions in frontal and parietal areas (Agbangla, Audiffren, & Albinet, 2017; Bertsch et al., 2009), reduced hemispheric specialization (Cabeza, 2002) and loss of volume and weight of brain tissues (Jernigan et al., 2001; Pakkenberg et al., 2003), including losses in myelination and reduced dendritic branching. Given these changes, it is not surprising that older adults also exhibit age-related cognitive deficits in several cognitive domains including perception, attention, executive functions and several types of memory (Craik & Salthouse, 2016; Luo & Craik, 2008) in both laboratory and natural settings (Salthouse, 1991).

2.1 Cognitive ageing

Cognitive deficits are not however imperative in older adulthood. Researchers have shown that some older adults perform as well as younger adults on a variety of cognitive tasks (Christensen et al., 1999). New evidence from neuroimaging studies (Reuter-Lorenz & Lustig, 2005) shows that, although older adults may experience neural decline in typical areas related to specific cognitive functions, they also often tend to activate alternative networks, potentially for compensation or neurocognitive reorganization (Cabeza, 2002). This suggests that optimising some processes may counteract cognitive decline and contribute to successful ageing.

Moreover, individual differences need to be accounted for when considering the factors that determine cognitive ageing and dementia risk. For instance, higher levels of education, IQ and occupation, as well as engagement in leisure activities and having a healthy and balanced lifestyle, have been linked to greater neural connectivity and cognitive reserve (Stern, Alexander, Prohovnik, & Mayeux, 1992), and contribute to how efficiently individuals cope with age-related brain and cognitive changes. In turn, factors like changes in social life (i.e., loss of partners or family members), poor circadian rhythms or health (Baltes & Baltes, 1993; Hess, 2005) and stereotypes about ageing (Cavanaugh & Poon, 1989), may cause or intensify the age-related decline (Craik & Salthouse, 2016). Among these individual differences, some factors are considered modifiable and others non-modifiable, in the sense that individuals may or may not control them in order to influence the ageing process. For instance, a Mediterranean diet, mild-to-moderate physical activity, use of supplements such as the soy isoflavone and cognitive trainings may ameliorate cognitive ageing (Lehert, Villaseca, Hogervorst, Maki, & Henderson, 2015). Non-modifiable variables may include ethnic differences, genetic components, such as presence of alipoprotein E (ApoE) gene for Alzheimer's Disease (AD) risk, and clinical factors, such as diabetes or stroke (Ritchie et al., 2010).

2.2 Neurocognitive features of ageing memory

Each type of memory shows different trajectories in the elderly. Whilst performance at tasks involving non-declarative memory (procedural and implicit learning) resembles that of younger adults, deficits in declarative memory have been consistently reported (Hoyer & Verhaeghen, 2006) and have been related to age-related brain changes in areas linked to these memory functions, such as the hippocampus and surrounding medial temporal regions (Squire, 2004) and regions of the PFC (Cabeza, Nyberg, & Park, 2004).

Based on the multi-store model (Chapter 1, Paragraph 1.1.2), age-related decline can be observed in episodic LTM, STM, WM (Park et al., 2002) and prospective memory (Maylor, Smith, Della Sala, & Logie, 2002), but not in vocabulary and general knowledge (as part of semantic memory), which appears to increase up to the age of 60 years and to decrease thereafter (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). This difference may be explained by the fact that retrieval of semantic information is linked to different cortical regions compared to other types of memory (Hoyer & Verhaeghen, 2006). For instance, whereas episodic memories rely mainly on how efficiently associations between events are built and on the integrity of medial-temporal functions, semantic memories mostly depend on the ability to maintain mental representations (Eichenbaum, 2003) and appear to be related to distributed patterns of neural activity, including temporal, prefrontal and occipital cortices (Manning, Sperling, Sharan, Rosenberg, & Kahana, 2012). These shared patterns therefore allow the employment of alternative pathways in case of age-related neural decline.

2.3 Episodic memory in older adulthood

Episodic memory begins a steady decline throughout the adult years (Nilsson, 2003). Although the age-related decline has been reported consistently (Cabeza et al., 2004), and an extensive number of studies and theories have been suggested (McDaniel, Einstein, & Jacoby, 2016), a definitive explanation of episodic memory decline in older adults is to date missing. Researchers have proposed several mechanisms that may undermine memory performance, both cognitive and neuroscientific. Cognitive hypotheses that are relevant for the purpose of this thesis include changes in sensorial and perceptive abilities (McCoy et al., 2005), slowing of processing speed (Salthouse, 1996), loss of inhibitory functions (Hasher & Zacks, 1988), reduced processing resources (Craik, 1982), and deficiencies in forming associations (Naveh-Benjamin, 2000). Neuroscientific theories relevant for the present thesis include the Hemispheric Asymmetry Reduction in Older Adults (HAROLD; Cabeza, 2002) experienced in the PFC, and the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter-Lorenz & Cappell, 2008). These theories will be discussed below.

2.3.1 Effortfulness hypothesis

Sensory functioning, such as auditory and visual acuity, has been reported as a strong predictor of individual differences in cognitive performance (Lindenberger & Baltes, 1994a). The effortfulness hypothesis suggests that sensory problems, such as hearing or visual loss, may cause memory deficits in some older adults, due to limited encoding. This hypothesis assumes that individuals with such deficiencies require extensive resources for perceptual processing, therefore burdening resources for elaboration, organization and retrieval of memories. For instance, McCoy et al. (2005) investigated the effects of hearing loss on older adults in word-list recall tasks. Participants were presented with auditory list of words and asked to recall the last three words heard when presentation stopped at random points. Whilst recalling nearly perfectly the last word of the three-words set, suggesting that all participants were able to perceive the items, older adults with mild to moderate hearing loss exhibited statistically fewer recall of the other two words. The authors concluded that the extra processing resources employed by older participants with hearing impairment to perceive items effectively caused the poor processing of memory encoding. Although this hypothesis does not provide a general explanation of memory decline in older adults, it emphasises the interdependence between sensory deficits and cognitive deficits, which tended to be ignored in past research and in clinical settings (McDaniel et al., 2016; Schneider & Pichora-Fuller, 2000).

2.3.2 Inhibitory deficit hypothesis

Hasher and Zacks (1988) proposed this theory on the observation that age-related differences on memory tasks are larger under conditions of high interference. The vulnerability to interference in older years was linked to the older adults' deficit in inhibiting irrelevant information in favour of relevant information. This tendency can be observed in the greater amount of false recognitions and intrusions associated with ageing and to older adults' difficulty in dealing with distracting tasks (Healey & Kahana, 2016). Consistent with this theory, Kahana, Dolan, Sauder and Wingfield (2005) found that older adults were more susceptible to intrusions during free recall tasks compared to younger individuals and interpreted as effect of the age-related deficit in inhibitory functions. Waldie and Kwong See (2004) reported similar results and conclusions by using recognition tests in the domain of false memories. The inhibitory deficit hypothesis however fails to explain age differences in memory tasks that require initiating, other than inhibiting, an action (i.e., prospective memory) (Henry, MacLeod, Phillips, & Crawford, 2004; Luo & Craik, 2008).

2.3.3 Slowing of processing speed hypothesis

According to this hypothesis, the general decline in processing speed may account for deficits in several cognitive functions, including memory. This theory comes from a variety of studies showing that a large percentage of age-related variance in a range of memory variables is associated with processing speed

(Hoyer & Verhaeghen, 2006). Despite these findings however, the slowing of processing speed hypothesis cannot explain those conditions where memory performance is unimpaired, and processing speed decreases. For instance, Lemke and Zimprich (2005) observed no decline in free recall memory tasks in older adults over a period of 4 years, whilst a slowing of processing speed was reported. Therefore, it is possible that other factors may be involved.

2.3.4 Reduced processing resources hypothesis

The processing resources framework focuses on the decline of attentional resources during ageing as a reason for the age-related decline of episodic memory. As a result of reduced processing resources, older adults are less effective in carrying out encoding and retrieval processes, resulting in poor memory performance. Evidence for this theory comes from studies using divided attention tasks to investigate age differences in episodic memory. Poorer memory performance was observed in older adults especially when the divided attention task was performed at retrieval rather than at encoding (Naveh-Benjamin, Craik, Guez, & Kreuger, 2005). The processing resources hypothesis also explains why age-related decrements are more pronounced in free recall than in recognition or cued recall (Baddeley, Eysenck, & Anderson, 2015). Free recall tasks, which are resource demanding, require individuals to self-initiate retrieval, whereas tasks of recognition or cued recall reduce the load of self-initiate processes, therefore simplifying retrieval, and are therefore typically less demanding tasks (Craik & McDowd, 1987). Although these studies provide adequate support for the processing resources framework, other factors may be associated with ageing, such as the impairment in forming associations between unrelated information (Naveh-Benjamin, 2000).

2.3.5 Associative deficit hypothesis

Naveh-Benjamin (2000) presented younger and older adults with lists of semantically related and unrelated words, which were then retrieved through recognition. Results showed that, whilst participants performed alike on associated pairs, they differed on unrelated items. Naveh-Benjamin's (2000) initial hypothesis was that impaired attentional abilities caused the older group to be less efficient in forming associations between items. However, following studies (Linden & Naveh-Benjamin, 2007; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003) showed that the associative deficit could not be explained in terms of attentional difficulties and was rather related to a deficit in learning capacity. For instance, Linden and Naveh-Benjamin (2007) tested older and younger adults' attentional costs on learning components (individual features of associations) and learning pairs (associations between two items) in two experimental conditions wherein the learning tasks were simultaneous or separate. Linden and Naveh-Benjamin's (2007) hypothesis was, according to the reduced attentional resources view, that separating the tasks would allow more resources to be used per each task, thus increasing older adults' performance. However, older adults exhibited comparable associative deficits independent of the experimental condition. These results were therefore in line with the associative deficit hypothesis, suggesting that age-related memory decline is caused by the inability to form associations between unrelated stimuli, rather than by reduced attentional resources.

2.3.6 HAROLD model

In younger adults, neuroimaging studies have associated learning and retrieval of episodic memories with PFC activation (Cabeza & Nyberg, 2000). PFC activity tends to be lateralised following a pattern known as Hemispheric Encoding/Retrieval Asymmetry (Habib, Nyberg, & Tulving, 2003; Tulving et al., 1994). In both verbal and non-verbal tasks (Nyberg et al., 1996), younger adults have been repeatedly found to activate the left PFC during encoding and the right PFC during retrieval. In contrast, healthy older adults display different patterns that suggest a reduction in hemispheric specialization with increased bilateral activation during retrieval of both pictorial and verbal stimuli (Grady, Bernstein, Beig, & Siegenthaler, 2002), during both cued recall (Cabeza et al., 1997) and recognition (Madden et al., 1999) tasks. Left rather than right PFC activation during retrieval has also been reported in older adults (Cabeza, 2002). Evidence for age-related reductions of PFC lateralization during episodic encoding has shown that older adults may experience an increase of right relative to left PFC activation, or decreased left PFC activation (Stebbins et al., 2002). PFC overactivation or under-activation in older adults has been explained in the HAROLD model in two different, but compatible ways. According to the dedifferentiation view, HAROLD is the result of a progressive difficulty in recruiting specific neural circuits, given by the observation that correlations across cognitive and sensory measures increase with age (Lindenberger & Baltes, 1994). According to the compensation view, reduction of hemispheric specialization helps to counteract age-related neural decline. This hypothesis was confirmed in studies showing that bilateral PFC activity in older adults was positively correlated with normal, rather than impaired, cognitive performance (Reuter-Lorenz et al., 2000) and specifically in cognitively high-performing older adults than in low-performing individuals (Cabeza, Anderson, Locantore, & Mcintosh, 2002). This evidence makes the compensation account the most plausible of the HAROLD model's explanations (Dennis & Cabeza, 2011).

2.3.7 CRUNCH model

Following Cabeza's (2002) compensatory hypothesis, Reuter-Lorenz and Cappell (2008) proposed the CRUNCH model, where overactivation of brain areas, especially of the PFC, in older adults is explained by increased cognitive load that compensates for the experienced functional decline. According to this model, older adults recruit more neural resources than their younger counterparts in order to achieve equivalent performances. The beneficial effect of this activity is explained by the fact that overactivation is typically linked to age-equivalent performance. Cappell, Gmeindl and Reuter-Lorenz (2010) used verbal working memory tasks to investigate PFC activation in younger and older individuals. They found that, although performing alike to their younger peers, older adults activated PFC regions during low demand tasks that younger adults activated exclusively during tasks requiring higher demand loads. The CRUNCH model also suggests that compensatory activation is effective exclusively at tasks with lower cognitive demands, whereas, in tasks with high demand levels, the compensation strategy becomes insufficient and older adults fail to match younger adults' performance. Evidence of this assumption comes from Mattay et al. (2006), who examined PFC activity in younger and older adults during "n-back" working memory tasks. Whilst performing alike at the 1-back, older adults showed greater bilateral activity of the PFC compared to younger adults. However, during the 2- and 3-back older adults exhibited reduced activity of these areas and performed poorer than the younger group, thus indicating the limit of the brain's compensatory activity.

2.4 Pathological ageing

Whilst decline in certain cognitive abilities is considered normal during the ageing process (Harada, Love, & Triebel, 2013), neurodegenerative conditions bring progressive pathological decline, typically characterised by pathological changes in the brain, cognitive and physical impairment, and by a severe impact on individuals' quality of life and autonomy (Craik & Salthouse, 2016). Dementia is the umbrella term used to describe these conditions and it includes AD, the most common form of dementia; vascular dementia; frontotemporal dementia; dementia with Lewy bodies; mixed dementia; and Parkinson Disease. For the purpose of the present thesis, attention will focus solely on AD and Mild Cognitive Impairment (MCI), the prodromal stage of dementia.

2.4.1 Alzheimer's Disease

AD accounts for approximately 62% of dementia cases in individuals older than 65 years old (Knapp & Prince, 2007). Difficulties with learning and retaining new information (episodic memory) are typically the first cognitive symptoms in patients with AD, followed by impairments in language and spatial functions (Welsh, Butters, Hughes, Mohs, & Heyman, 2011). In addition, individuals with AD experience deficits in other domains including executive functions, visuospatial abilities and behavioural changes. Although neurogenesis still persists in AD (Tobin et al., 2019), degeneration of the brain is typical in this population and is associated with cognitive decline and memory loss. For instance, deposition of β-amyloid plaques (Aβ42), neurofibrillary tangles (NFT) with elevated amounts of tau protein in the cerebrospinal fluid (CSF), probably start 20 to 30 years before the clinical onset of AD (Bateman et al., 2012; Reiman et al., 2012). These changes are related to brain atrophy, and to synapse and neuron loss. Tau deposition is believed to typically begin in the trans-entorhinal cortex, whereas Aβ is frequently found in neocortical regions, such as in the basal regions of temporal and frontal lobes (Braak & Braak, 1998; Braak, Alafuzoff, Arzberger, Kretzschmar, & Tredici, 2006; Sepulcre, Sabuncu, Becker, Sperling, & Johnson, 2013). These accumulations gradually spread to all cortical regions (Sepulcre et al., 2016; Villemagne, Fodero-Tavoletti, Masters, & Rowe, 2019), as shown in Figure 2.1.

Figure 2.1 Progression of Aβ and tau deposition in: a) Normal ageing; b) Prodromal Alzheimer's disease; c) Alzheimer's disease. Adapted from Villemagne et al., 2015.

The discovery of deposition of β-amyloid plaques contributed to the development of the amyloid cascade hypothesis (Hardy & Higgins, 1992), wherein a mutation of amyloid β protein was suggested as a causative agent of AD, followed by other markers of neurodegeneration (i.e., neurofibrillary tangles) that lead to cognitive decline (Figure 2.2).

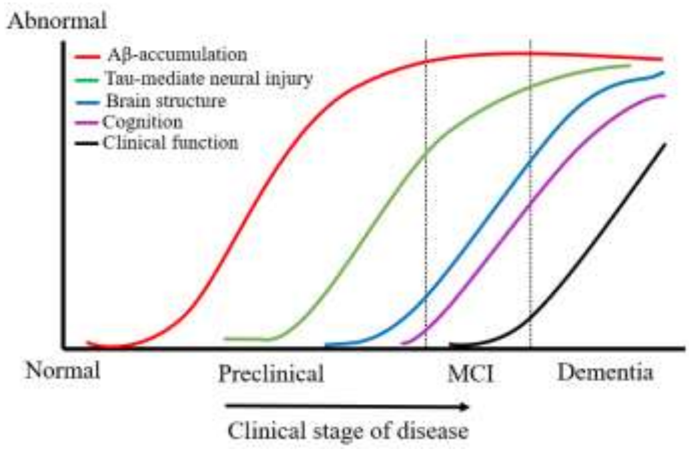


Figure 2.2 Hypothetical model of biomarkers of AD's pathology. Adjusted from Jack et al., 2010*.*

This hypothesis has been debated given that several post-mortem studies showed that the density of Aβ plaques is not necessarily associated with cognitive scores or neurodegeneration in all AD patients (Nelson et al., 2012; Snowdon, 1997), probably due to greater compensatory mechanisms in these individuals, such as the cognitive and neural reserve (Stern, 2012). Moreover, failed amyloid clinical trials have also brought into question the amyloid cascade hypothesis (Reitz, 2012). Consequently, a new classification scheme based on 3-class biomarkers, called the ATN system, has been proposed (Jack et al., 2016). In the ATN system, where A refers to Aβ42, T refers to values of tau biomarkers, and N to neurodegeneration or neural injury, several biomarkers are considered essential for the AD pathology.

Genetic biomarkers have also been suggested in AD risk. For example, the ApoE alleles ε2, ε3 and ε4, detected in blood and CSF, seem to be the most significant risk factor among the genes related to AD; they are associated with greater hippocampal atrophy in AD and with lower neuropsychological scores on tests assessing AD (Schuff et al., 2009).

Given these factors, the diagnosis of AD is clinic-pathophysiological, in the sense that it cannot be certified clinically and necessitates post-mortem confirmation (McKhann et al., 2011).

The probable diagnosis of AD is based on the following criteria (Dubois et al., 2007; Mckhann et al., 1984):

- Progressive and significant decline in memory functions and at least one additional cognitive domain, which interfere with activities of daily living and are not caused by other central nervous system, systemic or substance-induced conditions;

- Cognitive decline is steady and gradual, based on history or trials of neuropsychological testing;
- Evidence of casual AD genetic mutation based on family history or genetic testing.

Biomarker tests, although not necessary for routine diagnostic purposes, may also be used in the evaluation of patients with suspected dementia, in order to increase the certainty of AD diagnosis (Jack et al., 2011; McKhann et al., 2011).

Life expectancy, after diagnosis, varies, although the average duration is approximately 10 years. To date no cure exists for AD, although drug treatments and alternative therapies are used to attempt lessening the severity of some of the symptoms (Rebok et al., 2014; Ströhle et al., 2015). Cholinesterase inhibitors and memantine have shown modest therapeutic effects in clinical trials and are administered to manage AD symptoms at mild to moderate stages, and at severe stages (Bazzari, Abdallah, & El-Abhar, 2019; Di Santo, Prinelli, Adorni, Caltagirone, & Musicco, 2013). Other AD therapies under investigation include physical exercise programs (Forbes, Thiessen, Blake, Forbes, & Forbes, 2013) and cognitive trainings (Ngandu et al., 2015).

2.4.2 Mild Cognitive Impairment

Before receiving a diagnosis of AD, individuals typically transition from the asymptomatic phase to a predementia phase, referred to as Mild Cognitive Impairment (MCI; Petersen et al., 1999). This impairment is not considered a part of normal ageing, but a progression towards pathology (Sperling et al., 2011), as shown in Figure 2.3. MCI cannot be diagnosed through laboratory tests (Albert, et al., 2011), but requires clinical evaluation. Cognitive decline in MCI is greater than expected for a person's age and level of education (typically 1 to 1.5 standard deviations below the mean) but does not interfere particularly with daily activities. For this reason, although probable, MCI does not always develop to dementia (Petersen & Negash, 2008) and individuals could return to normal functioning overtime (Gauthier et al., 2006).

A person with MCI fulfils the following criteria:

- Concern about change in cognition, reported by the patient, an informant or a clinician;
- Impairment in at least one cognitive domain, such as memory (most common for those who develop AD dementia), executive function, attention, language and visuospatial skills;
- No impact on everyday living, with minor problems when performing complex tasks, but not severe enough for a diagnosis of dementia.

Although there are currently several classifications, MCI is commonly divided into two subtypes: amnestic, which comprises memory complaints and impairment, and non-amnestic, involving domains other than memory, such as language, executive functions or visuospatial skills. Each of these subtypes is then divided into single- or multi-domain, depending on how many cognitive functions are impaired (Petersen, 2004). Patients showing more severe episodic memory deficits, exhibited by abnormal performance on cued and delayed memory tasks, are more likely to progress to AD dementia at rates of approximately 10% per year (Petersen, 2004; Petersen & Negash, 2008).

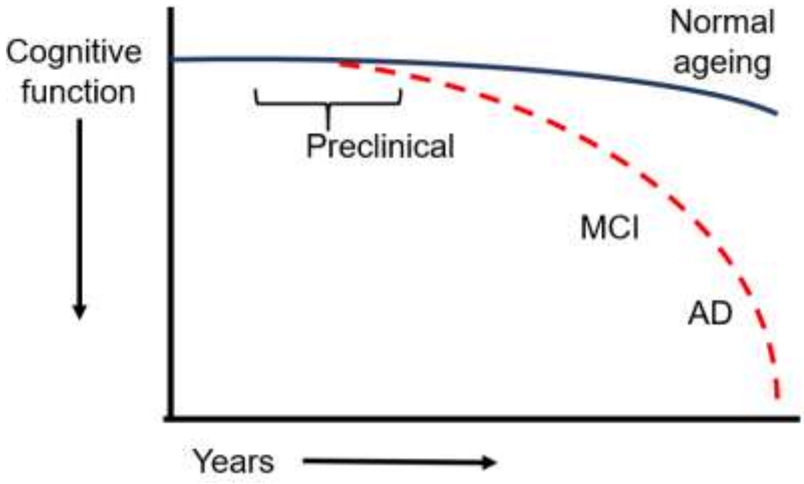


Figure 2.3 Model of the trajectory of Alzheimer's disease suggested by Sperling et al., 2011.

The importance of MCI classification is that it allows early diagnosis and treatment, as well as attempted prevention, of AD pathology, which to date has no definitive treatment. Prevention and early diagnosis permit individuals to have a longer period of normal cognitive functioning, time to settle financial and business affairs, and to retain independence and quality of life for longer. Neuroimaging studies on patients with MCI who converted to AD have shown that atrophy of specific brain areas, such as the hippocampus, predicts the progression (Jack et al., 1999). Early detection has also been investigated in MCI using cerebrospinal fluid (CSF) biomarkers, such as tau, Aβ and ApoE4 status (Hansson et al., 2006). In clinical assessment, a variety of memory tests have been shown to be useful and low-cost alternatives for early detection. Tests such as the Rey Auditory Verbal Learning Test (AVLT; Schmidt, 1996), the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) and the Logical Memory I and II of the Wechsler Adult Intelligence Scale (Wechsler, 1955) have been found to accurately predict conversion from MCI to AD (Albert et al., 2011). These tests are also fundamental in exploring early detection through serial position effects and temporal associative processes.

2.5 Input order of free recall

The serial position paradigm, covered in paragraph 1.2.1 of Chapter 1, has been used consistently in the ageing research to explain age-related memory decline and to provide evidence that supports dual-store models of memory, which suggest primacy and recency effects to depend on LTM and STM, respectively. Although total recall is reduced in older adults, the U-shaped pattern of recall is typically not affected in normal ageing and is consistent across the lifespan (Wright, 1982). Previous studies have however reported some differences in primacy and recency in older adults when compared to younger groups (Capitani, Della Sala, Logie, & Spinnler, 1992). For instance, experiments on lists varying in stimulus characteristics (related/unrelated words, animate/inanimate words), presentation rate and list length, showed that older adults remembered fewer items from primacy and middle positions, but were equal to younger groups for items recalled from the recency position (Craik, 1968; Raymond, 1971; Sanders, Murphy, Schmitt, & Walsh, 1980). These results were explained in terms of dual-store models, as the ageing process brings older adults to experience decline in LTM, underpinning the primacy effect, whilst maintaining approximately intact STM, responsible for the recency effect (Carlesimo, Sabbadini, Fadda, & Caltagirone, 1997; Craik, 1970). This explanation was supported by studies investigating the influence of time and rehearsals on serial position effects. For instance, when recency requires participation of LTM, such as at delayed recall, the effect is worse than at immediate recall (Bruno, Reichert, & Pomara, 2016). Similarly, in multi trials learning tasks, wherein repetition favours consolidation, recency is still more affected than primacy (Griffin et al., 2017; Ward & Maylor, 2005). These findings suggest that, with repeated exposures and adequate time, older adults are capable of transferring primacy words from STM to LTM and, by repetition and rehearsal, middle and recency words can be stored in STM, but cannot be easily transferred to LTM. From a neurological point of view, this is explained by the progressive decline of the MTL, including the hippocampal region, which has been related to consolidation of primacy items (Bruno et al., 2015).

2.5.1 Serial position and pathological ageing

Given its association with medio-temporal brain areas (Zola-Morgan & Squire, 1991), serial position has also been investigated in older adults who experience memory loss, such as in MCI and AD. Although Bennett, Golob, Parker and Starr (2006) found no differences between healthy older adults and those with MCI, several studies have shown that individuals with MCI tend to have poorer primacy compared to cognitively intact older adults, and greater primacy compared to patients with AD, whilst recency is typically greater than in cognitively intact older adults (Cunha, Guerreiro, De Mendonça, Oliveira, & Santana, 2012; Howieson et al., 2017; Shankle, Mangrola, Chan, & Hara, 2009). In patients with AD, primacy is notably reduced compared to cognitively functioning individuals and to those with MCI (Egli et al., 2015; Foldi, Brickman, Schaefer, & Knutelska, 2003), whilst the recency effect is unimpaired or exaggerated (Carlesimo, Fadda, Sabbadini, & Caltagirone, 1996; Gainotti, Marra, Villa, Parlato, & Chiarotti, 1998). These results have been explained by AD’s inability to transfer and consolidate information from the STM to the LTM and may be associated with AD’s neuropathological changes.

Serial position deficits may also be markers of cognitive vulnerability to AD (La Rue et al., 2008) and of cognitive decline (Bruno, Reiss, Petkova, Sidtis, & Pomara, 2013) in healthy populations. For instance, Egli et al. (2014) investigated which cognitive variables best predicted conversion to AD in a sample of individuals with MCI and found that increased recency and poor primacy increased risk of developing dementia, with the primacy effect being a stronger sensitive measure when progression to AD was slower.

Bruno et al. (2013) shifted the focus of attention to primacy at delayed recall, by suggesting that delayed primacy may be a stronger marker of cognitive decline than other serial position measures. Specifically, Bruno et al. (2013) found that delayed primacy predicted cognitive decline in 204 cognitively functioning older individuals, over a period of 7 years. The predictive effect of delayed primacy was stronger than immediate primacy and recency, delayed recency, and other standard variables, such as APOE ε4-carrier status. These findings have been repeated also in individuals who developed early symptoms of MCI and will be described in Chapter 4 (Talamonti, Koscik, Johnson, & Bruno, 2019).

2.6 Ageing and the output order of free recall

Literature on associative processes in older adulthood is relatively new considering that the associative deficit hypothesis was introduced only two decades ago (Naveh-Benjamin, 2000) and it is also considerably scarce compared to research in younger populations. Whilst semantic clustering remains relatively intact in older years, spatial clustering seems to partially decline, whereas temporal organization appears to be affected by ageing, thus suggesting that age-related associative deficits may be specific for this type of clustering.

2.6.1 Semantic organization

Similar to semantic memory, the ability to recall items clustered by semantic category tends to be relatively spared in older adulthood (Burke & MacKay, 1997), although older adults experience impairment in accessing relevant categories (Wingfield, Lindfield, & Kahana, 1998). Wingfield and Kahana (2002) however observed that whilst younger and older adults are equally able to create semantic associations when a pre-existing semantic list is presented, older adults experience a marked deficit when, given a words' list, new semantic associations must be created. These findings were explained by the fact that, even when lists are organised semantically, temporal clustering, which is impaired with ageing, is implicated in guiding retrieval in semantic memory, as it provides further information on when items are temporally encountered. More recently, Golomb, Peelle, Addis, Kahana, and Wingfield (2008) explored implicit semantic organization, by testing younger and older adults with a list of randomly selected words. Results showed that younger and older participants utilised semantic clustering during recall in both free and serial recall tasks, with older adults persistently using semantic organization, even when alternative associations, such as temporal, may have been more advantageous for the task, resulting in a lower general performance. Golomb et al.'s (2008) findings supported previous hypotheses of unimpaired semantic organization of memory in older adulthood (Wingfield & Kahana, 2002) and suggested that semantic organization may be used to compensate for the temporal association deficit.

Semantic organization also seems to remain intact even when individuals are diagnosed with AD. Indeed, Herlitz and Viitanen (1991) found that, in recall tasks of semantically organizable words, both healthy controls and participants with mild AD showed a greater performance than individuals with moderate AD, which seemed to use semantic clustering to facilitate recall. This pattern should be considered when using semantically related lists (i.e., CVLT) to investigate memory performance in older adults, as it may mask age-related memory deficits. Taken together, these results are consistent with previous research, showing that semantic clustering, as well as semantic memory, are relatively spared in older adulthood and they suggest that, contrary to serial position effects, they may be an improbable marker for early detection of cognitive decline.

2.6.2 Spatial organization

Although the current literature on spatial memory suggests that age-related declines are evident only in complex tasks and, probably, as a consequence of reduced attentional/executive resources (Klencklen, Després, & Dufour, 2012), research on spatial organization in older adults is to date surprisingly scarce. Age-related declines of spatial contextual information has been shown in older adults aged at least 60, when assessed in real-life situations (Uttl & Graf, 1993). In laboratory settings, Meulenbroek et al. (2010) investigated free recall of object location associations in younger and older adults and found no effect of age on performance, although younger adults made greater use of spatial contiguity cues than older adults. Similarly, Kukolja, Thiel, Wilms, Mirzazade, and Fink (2009) explored memory for spatial context information in younger and older participants and found that both groups recognised and correctly attributed objects' locations, although the spatial context memory was superior among younger participants. These and previous findings (Parkin, Walter, & Hunkin, 1995) suggest that age-related deficits in spatial organization are not imperative. Therefore, it is possible that this strategy may be used to compensate for other age-dependent deficits of memory associative processes, such as temporal organization.

2.6.3 Temporal organization

As explained in Chapter 1, temporal organization of memories reflects the ability to place events in their temporal context. Whilst being extremely common in younger adults (Healey & Kahana, 2014) and believed to be a fundamental organizational factor in memory formation (Polyn & Cutler, 2017), temporal clustering may be affected by the ageing process. For instance, Kahana, Howard, Zaromb and Wingfield (2002) showed that whilst younger and healthy older adults tended to begin recall in the same way, older adults were less likely to recall items through temporal associations. Specifically, age differences were found to be more pronounced for close temporal transitions (CRP-lags of +1 and -1), therefore suggesting that older adults experience an impairment in using temporal information successfully. This suggestion was in line with previous research showing that memory for temporal order is particularly challenging for older adults (Kausler, 1994; Parkin et al., 1995), and it was consistent with the hypothesis of age-related deficits in associative memory (Naveh-Benjamin, 2000). The fact that temporal clustering decreases significantly in older adults was also reported in other studies (Golomb et al., 2008; Howard, Kahana, & Wingfield, 2006), where an age-related deficit for temporal organization of memory was hypothesised. Healey and Kahana (2016) suggested that the temporal contiguity deficit in older adults may undermine older adults’ ability to situate events in time, thus affecting autobiographical recall. This deficiency may also underlie the more general episodic memory impairment experienced during older adulthood (Wingfield & Kahana, 2002).

Correlations between temporal clustering and general cognitive abilities have also been observed. For instance, among healthy older adults, Bruno et al. (2016) showed that greater Mini-Mental State Examination (MMSE) scores were positively associated with greater use of temporal order information, highlighting the relationship between temporal clustering and general cognitive ability. Bruno et al.'s (2016) results also suggest that temporal clustering may be used as a marker of cognitive ability and decline in older populations. Implicit evidence of this assumption comes from previous studies (Bellassen, Igloi, De Souza, Dubois, & Rondi-Reig, 2012; Gillis, Quinn, Phillips, & Hampstead, 2013). When younger adults, cognitively intact older adults and those with MCI were compared on memory performance for temporal order, Gillis et al. (2013) found that older adults showed greater reduction in memory for context than content. Bellassen et al. (2012), who investigated behavioural cognitive markers of AD diagnoses, used a memory test in which both temporal and spatial order memories were utilised. They found that temporal order memory was the strongest measure in predicting AD diagnosis, thus suggesting its potential usage in clinical settings.

Bruno et al. (2016) also found that greater hippocampal size was associated with greater use of temporal organization in recall, whereas PFC has been related to temporal order memory (Fuster, 2001). As both of these brain areas are particularly sensitive to damage in AD, they suggest clinical relevance to investigating temporal clustering for early detection.

Chapter 3 Research aims and strategy

3.1 Background

The aim of the present thesis was to study the cognitive and neural substrates of input and output order in free recall and their potential applicability for early detection of cognitive decline.

Given the overall increase in life expectancy (United Nations, 2017), the number of people worldwide living with dementia and the economic cost that this diagnosis brings are estimated to increase exponentially over the following years. Reports published in 2018 by Alzheimer's Disease International estimated that nearly 50 million people worldwide were living with dementia, and the number was projected to increase to 152 million by 2050 (Patterson, 2018). In 2014 the total cost of dementia in the UK was estimated to be £26 billion a year (Prince et al., 2014). Although cognitive and pharmacological interventions are recommended in the National Institute for Health and Care Excellence (NICE) guidelines and by the Food and Drug Administration, the approved treatments show only minor therapeutic effects. It is therefore critical to ameliorate instruments that permit to detect cognitive decline in its very early stages and before AD manifestation, in order to prevent age-related decline.

The focus of the present thesis was on the use of cognitive measures for early detection given their valuable and distinctive attributes highlighted below. While biomarkers analysis is typically accurate in predicting MCI and AD pathologies decades before their appearance, this method is still not easily accessible, as it requires clinicians to use instrumentations such as FDG-PET (fluorodeoxyglucose-positron emission tomography), SPECT (single-photon emission CT), MRI or more invasive tools, such as lumbar puncture for cerebro-spinal fluid (CSF) analysis (NICE, 2018). The use of such costly machines also implicates a lack of affordability in biomarker analysis, especially when considering low-income countries. Therefore, cognitive tools, which are both accessible and affordable, were considered in this thesis as valid alternatives for early detection. However, the level of accuracy of cognitive tools used in clinical practice, such as total recall to measure episodic memory, is currently limited. Evidence of the relatively limited accuracy of these methods is given by the fact that cognitive symptoms are believed to be the last to emerge chronologically in the AD pathogenesis, when compared to changes detectable via biomarkers and gene analyses (Sperling et al., 2011). Nonetheless, analyses of recall patterns, rather than total recall, repeatedly have been shown to aid detection of cognitive changes from baselines of healthy older adults (Bruno et al., 2013; Egli et al., 2014). These findings suggest that, if accurate, cognitive instruments may be valuable tools for early detection. As part of the recall patterns, input and output order, which are the main topics of this thesis, have the potential to address the limitations of cognitive tools and be accessible, affordable and accurate diagnostic instruments.

Serial position effects (e.g., input order) have been extensively researched, but which measure of serial position is the most accurate for early detection remains an unanswered question. This question is also critical for the applicability of serial position effects in clinical practice. Furthermore, the potentiality of the output order in free recall (i.e., associative memory processes) for early detection has received very little attention to date. For example, temporal contiguity appears to decline with age. No study however has explored the neural changes underlying this decline. Moreover, it has not been examined whether cognitive decline may be masked by employing alternative forms of memory organization, such as when spatial information is provided.

Accordingly, the primary research aims of this thesis were to understand the cognitive and neural substrates of the output order, and to study input and output order in free recall for early detection of cognitive decline.

3.2 Research objectives and hypotheses

The aforementioned research aims were addressed through the following research objectives and hypotheses:

1) To investigate which measure of input order of free recall is the best for early detection of cognitive decline. In the previous Chapter, input order in free recall was reported as able to discriminate between normal and pathological ageing. However, research on delayed primacy as a potential cognitive marker for early detection is currently limited, compared to other serial position effects. Therefore, in Study 1 (Chapter 4), several measures of input order of free recall, (e.g., primacy, recency and delayed primacy) were assessed to explore the best predictor of conversion to early MCI from a baseline of healthy older adults, through the use of a secondary dataset provided by collaborators at the Wisconsin Alzheimer's Institute (USA). Given previous evidence that delayed primacy was able to predict cognitive decline in healthy older adults, the following hypothesis was formulated:

H1) Delayed primacy performance would be the strongest measure for predicting conversion to early MCI, compared to other measures of input order.

2) To assess age differences in the output order of free recall (i.e., temporal vs. spatial associative processes) in younger participants and in healthy, cognitively intact older adults, and to explore age-related temporal deficits and potential use of alternative associative processes. Whereas an age-related deficit has been reported in the literature for temporal organization, previous research showed that spatial clustering may be relatively spared in older adults; therefore, it may be used by older adults to compensate for the temporal deficit. Study 2 (Chapter 5) addressed this question by utilising neuropsychological, psychological and cognitive measures. The following predictions were defined:

   H2) Younger adults would show greater use of temporal, over spatial clustering, compared to older adults, in accordance with previous research;

   H3) Spatial clustering would be preferred over temporal clustering in older adults, compared to younger participants.

3) To investigate age differences in output order during divided attention and different types of material (pictorial vs. verbal) in order to determine whether attentional processes influence associative processes. Research on episodic memory has used divided attention tasks and various materials in order to investigate their effect on memory processes. It is to date not clear whether associative memory is linked to attentional processes, although previous studies suggest that it may be affected by divided attention. Study 3 (Chapter 6) addressed this research question by

measuring neuropsychological and cognitive performance in younger and healthy older individuals. The following hypotheses were formulated:

H4) Performing a secondary task during encoding would affect use of contiguity effects and total recall in all participants;

H5) Type of material would not negatively affect use of contiguity in all participants, given that contiguity effects are found with both pictorial and lexical material;

H6) Older adults, compared to younger adults, would show decreased temporal organization, particularly in challenging conditions.

4) To examine the neural substrates of memory associative processes (temporal vs. spatial output order) and to determine their relationship to ageing. In Chapter 1, the involvement of PFC during temporal and spatial clustering was explained in younger adults. However, as specified in Chapter 2, older adults may show different patterns of cortical activity, given the neural decline experienced with age. These questions were explored in Study 4 (Chapter 7) by investigating changes in haemodynamic response of the PFC during use of associative processes, in younger adults and in cognitively low-/high-performing older adults. It was hypothesised that:

H7) Compared to younger adults, older individuals would show decreased hemispheric specialization in the PFC during memory associations, in line with neuroscientific models of cognitive ageing;

H8) This decrement would be more evident in cognitively low-performing older adults compared to high-performers;

5) To explore memory associative processes at immediate and delayed recall, and to determine whether the use of uncategorical lists affected clustering type in different age groups. As addressed at Point 1, analyses of recall patterns at delayed recall may be more sensitive than immediate recall. In Study 5 (Chapter 8), the influence of age on associative memory processes was explored at immediate and delayed recall in younger and healthy older adults. Moreover, given that in the previous studies temporal and spatial contiguity were examined using a categorised memory test, in Study 5 these effects were investigated utilising unrelated, rather than categorical, lists. The following predictions were considered:

   H9) Younger adults would show greater use of temporal clustering, compared to older adults;

   H10) Older adults would exhibit alternative associative processes, other than temporal clustering, in order to compensate for the age-related temporal deficit;

   H11) Given that delayed memory performance is particularly challenging for older adults, temporal clustering at delayed recall would decrease consistently as a consequence of the ageing process.

6) To determine the potential use of output order in free recall for early detection of cognitive decline. Given the aforementioned importance of delayed recall of the input order in detection of cognitive decline, it is possible that the output order in delayed tasks may be a valuable measure of cognitive decline. This research objective was addressed in Study 6 (Chapter 9), by utilising a secondary dataset from collaborators at the Wisconsin Alzheimer’s Institute (USA). It was hypothesised that:

H12) Delayed temporal clustering would predict cognitive decline, from a baseline of cognitively functioning older adults;

H13) Delayed temporal clustering would be a stronger predictor, compared to other established diagnostic methods.

3.3 Overview of the experimental design

Below are outlined the main methodologies of the studies. More details will be provided in each relevant chapter.

Neuropsychological measures, including both standardized and ad hoc cognitive tests, psychological measures and neuroimaging technique (fNIRS) were utilised on younger participants, on cognitively intact older participants and on individuals experiencing cognitive decline. Ethical approvals were obtained by the Liverpool John Moores University (LJMU) Research Ethics Committee on December 2016 for all studies, and two amendments were requested in 2017 to adjust the experimental conditions. Sample size calculations per each study were performed using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) analyses and reported in the ethics forms. All participants were provided with a participant information sheet, where the experimental procedure, including a specific section with explanation and illustration of the fNIRS device, was described. It was also made clear that the study was deemed to be of minimal risk to participants and that the probability and magnitude of discomfort when using the fNIRS would be null or minimal, due to the brief time of recording (approximately 10 minutes). On the participant information sheet, it was also specified that participants would not receive any clinical interpretation of their performance, as the researcher is not a registered Clinical Practitioner in the UK, but that general findings of the studies would be available at request. Following the testing sessions, all participants were reimbursed with £5, £10 or £15 Tesco or Amazon vouchers, or, if younger, with up to 3 SONA points, depending on the experiment. Approval to use Tesco vouchers was obtained through the LJMU finance office and was justified by the fact that they were more suitable for older participants, than the more common Amazon vouchers. These vouchers were purchased by the researcher, whilst Amazon vouchers were purchased by a faculty technician. All expenses were covered by the researcher's bench fees.

3.3.1 Samples

Studies 1 (Chapter 4) and 6 (Chapter 9) were completed on a secondary dataset, provided by collaborators at the Wisconsin Alzheimer's Institute, as part of the Wisconsin Research for Alzheimer's Prevention study (WRAP). The WRAP is an ongoing longitudinal project that started in November 2001, which now counts nearly 2000 volunteers. Participants speak English, are free of dementia, but have familiar history of autopsy-confirmed or probable AD as defined by NINCDS-ADRDA research criteria (Mckhann et al., 1984) and are between 40 and 65 at their first visit. Follow-up visits are typically after two-to-four-years interval. Each participant completes an entry assessment that includes neuropsychological assessment with standardized and widely used clinical neuropsychological measures, APOE genotyping, laboratory tests (cholesterol, creatine, etc), clinical measurements (blood pressure, weight, height) and a health history form (Johnson et al., 2018; Sager, Hermann, & La Rue, 2005). Diagnoses at follow-up visits are reviewed at a consensus case conference and include: early-MCI (denominated Cognitively Unimpaired-Declining, or CUD, status in

Study 6), clinical MCI based on NIA-AA criteria (Albert, et al., 2011), dementia based on NINCDS-ADRDA criteria (Mckhann et al., 1984).

Studies 2 (Chapter 5), 3 (Chapter 6) and 4 (Chapter 7) were planned and conducted by the researcher. Recruitment for Study 5 (Chapter 8) was conducted by a volunteer, after undertaking training with the researcher. Younger and older populations were recruited in different ways. Younger participants were recruited by emailing LJMU students and ~100 were tested for the entire research project. The older adult participants pool, which currently includes nearly 120 volunteers, was created by the researcher by gaining access to the LJMU Psychology and Sports Science participants pools and to the Join Dementia Research national service after completing the required training. Moreover, older volunteers were found by approaching local branches of the University of Third Age, Dementia Action and by promoting the laboratory activities at events such as: Dementia friends info session as part of the Wellbeing Week (February 2017), the Alzheimer's Research UK North West Public Engagement event (May 2017), the Greater Manchester Dementia Consortium Showcase (May 2017), coping with dementia session as part of the dementia awareness week (May 2017), the Minerva Group event (July 2017) and the House of Memories Dementia awareness workshop (February 2019). Potential older participants were approached in person, through emails, letters of invitation or flyers uploaded on the Organizations' websites. Younger participants were aged between 18 and 35 years old, whereas older adults were recruited if aged 50 or 60 and above, according to the inclusion criteria applied in each study. Other inclusion criteria were: being fluent in English, having no history of diagnosed neurological disorders, having no currently diagnosed mental condition, and being right-handed when fNIRS recording was included.

3.3.2 Location

Studies 2, 3, 4 and 5 were conducted in one of the experiment boots located on the second floor of the Tom Reilly building, at the Byrom street - LJMU City campus. One-off visits of 30-minute, 1 hour or 1 hour and 30 minutes, depending on the study, were planned. A reminder was automatically sent to all participants a day before the visit. Younger participants, as already familiar with the campus, were instructed to meet the researcher in the specific laboratory room. Older adults were provided with information on how to reach the university main entrance, including a campus map with a highlighted meeting point. They were offered free car space at the campus if requested, tea and biscuits at arrival and the possibility to book consecutive visits with friends or partners who fulfilled the inclusion criteria and were interested in taking part in the study. At the experimental sessions the aim of the study and the experimental procedure were further described, before signing the consent form.

3.3.3 Instrumentation

The tests utilised during the sessions included standardized cognitive, neuropsychological and psychological tests commonly used in research and clinical practice. The tests were pencil-and-paper or computer-based (designed by the researcher) and one was administered as a semi-structured interview.

These tests mostly aimed to evaluate general cognitive functioning and other specific cognitive abilities that may interfere with episodic memory and, specifically, with temporal or spatial clustering. Memory performance and associative memory processes were investigated utilising a newly designed computer-based test called Spatio-Temporal (STeM) test. Covariates that may also affect memory performance were psychological traits, such as anxiety or depression, and cognitive reserve. These measures were assessed in Studies 2, 3, 5. All tests were obtained through the Research services of the faculty, if not freely available online. One test investigating general cognitive functioning and typically adopted with clinical populations (Repeated Battery for the Assessment of Neuropsychological Status, RBANS), was requested and purchased by the School of Psychology.

3.3.3.1 Assessment of psychological status

Although one of the studies' exclusion criteria was that participants had no current diagnosed mental conditions, clinical measures of psychological status were included in the experiments in order to investigate anxiety and depressive symptomatology or undiagnosed disorders. Trait anxiety was assessed, given that research has shown anxiety to have an impact on memory performance (Airaksinen, Larsson & Forsell, 2005; Beaudreau & OHara, 2008). Similarly, depression has been found to affect memory and cause memory impairment (Burt, Zembar, & Niederehe, 1995). In older adults, severe depression adversely impacts individuals' full cognitive processing (Baune et al., 2010) and might cause pseudodementia, whereby the effects of depression on cognitive functions generate symptoms similar to those of organic dementia (Sáez-Fonseca, Lee, & Walker, 2007). Anxiety was evaluated with the State-Trait Anxiety Inventory – form T (STAI-T; Spielberger et al., 1983), whereas mood levels were assessed with the Patient Health Questionnaire-9 (PHQ-9; Kroenke & Spitzer, 2002).

3.3.3.1.1 STAI-T

The STAI, although developed for younger samples, was chosen among other anxiety scales due to its reported reliability in older populations (Stanley, Beck & Zebb, 1996) and its relatively short administration time. The T-anxiety scale (trait anxiety) of the STAI was used in order to investigate undiagnosed anxiety. STAI-T is based on a 4-points Likert scale consisting of 20 questions on a self-report basis (examples of items reported in Table 3.1) and scores range from 20 to 80. Median scores indicate moderate anxiety, whilst high scores indicate severe anxiety. Worry, tension, apprehension and nervousness are evaluated.

Table 3.1 Examples of items from the State-Trait Anxiety Inventory

The T-Anxiety scale consists of twenty statements that evaluate how respondents feel "generally"	
1 = ALMOST NEVER 2 = SOMETIMES 3 = OFTEN 4 = ALMOST ALWAYS	
A. I am a steady person	1 2 3 4
B. I lack self-confidence	1 2 3 4
C. I make decisions easily	1 2 3 4

3.3.3.1.2 PHQ-9

The PHQ-9 is a 9-item depression module from the full 3-page PHQ (Spitzer et al., 1994). It is self-administered and has been validated in both adults (Arroll et al., 2010) and in the elderly (Frederick et al., 2010). It is half the length of other typically administered depression measures and, in contrast to other self-report instruments (i.e., Geriatric Depression Scale), each item reflects the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnostic criteria for depression, thus making it a provisional diagnostic tool for major and minor depression. It is based on a 4-points Likert scale and scores range from 0 to 27 (examples of items reported in Table 3.2).

Table 3.2 Examples of items from the Patient Health Questionnaire-9

Over the last 2 weeks, how often have you been bothered by any of the following problems?				
	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
9. Thought that you would be better off dead or of hurting yourself in some way	0	1	2	3

Major depression is diagnosed if five or more of the nine symptoms have been present at least “more than half the days” in the past 2 weeks, and one of the symptoms is depressed mood or anhedonia. One of the nine symptom criteria (“thoughts that you would be better off dead or of hurting yourself in some way”) counts if present at all, regardless of duration.

3.3.3.2 Assessment of cognitive reserve

Cognitive reserve was assessed in Studies 2 and 5 using the Cognitive Reserve Index – questionnaire (CRI-q; Nucci, Mapelli, & Mondini, 2012), which was administered as a semi-structured interview. The CRI-q includes some questions about demographic data and 20 items grouped in three sections investigating: education, working activity and leisure time. Following the Ethics Research Committee request, the initial part including demographic information was excluded from the questionnaire. CRI-Education includes two questions on total years of education and training courses; CRI-Working Activity investigates working activities undertaken during adulthood, divided in five levels (unskilled manual work, skilled manual work, skilled non-manual work, professional occupation, highly intellectual occupation); CRI-Leisure Time comprises questions about cognitively stimulating activities carried out during leisure time weekly, monthly, annually and at fixed term. These questions are divided for intellectual, social and physical activities. Scores are calculated automatically through an Excel file provided by the authors and range between low, medium-low, medium, medium-high and high cognitive reserve index.

3.3.3.3 Assessment of neuropsychological status

Cognitive functioning was assessed in Studies 2 to 5 using the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005), a 10-minute cognitive screening tool. The MOCA was administered on younger and older adults who claimed to be cognitively healthy and to have no diagnosis of dementia, in order to exclude any unreported cognitive decline. The test was chosen over the most common Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) or the Dementia Rating Scale (DRS; Mattis, 1988) due to reported difficulties of these instruments to detect early dementia in clinical practice (Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994; Tombaugh & McIntyre, 1992; Wind et al., 1997). In Study 3, where the degree of cognitive functioning was more relevant, the RBANS (Randolph, 1998) was administered to older participants. The RBANS is a screening battery that has been consistently validated in both cognitively intact older adults (Duff et al., 2003), in those with suspected AD (Duff et al., 2008) and it can be used up to moderately severe dementia (Randolph, Tierney, Mohr, & Chase, 1998). This battery is widely used in clinical settings and provides information on several aspects of cognitive functioning. This battery was also chosen given that the researcher received extensive training and practice on the RBANS administration, scoring and interpretation during a previous 6-month internship at the University of Western Australia.

3.3.3.3.1 MOCA

The MOCA is a one-page 30-point test that can be administered in 10 minutes. Tasks are grouped to investigate:

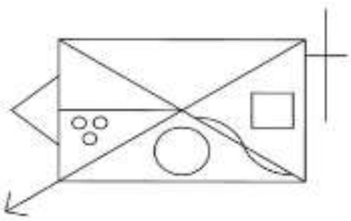
- Short-term and long-term memory, involving one immediate and one 5-minute delayed recall task;
- Visuospatial abilities, involving clock-drawing task and three-dimensional cube copy;
- Executive functions, with a short version of the Trail Making Test-B, phonemic fluency task, two-item verbal abstraction task;
- Attention, concentration and working memory are assessed through a sustained attention task, serial subtraction task, digit forward and backward;
- Language is evaluated with a three-items naming task, repetition of two synthetically complex sentences and the previously mentioned phonemic fluency task;
- Spatial and temporal orientation is assessed through questions regarding time and place of the visit.

Total scores are adjusted for low education (≤ 12) and their sum is a maximum of 30 points, with the cut-off score of ≥ 26 points. A copy of the MOCA is provided in Appendix 1.

3.3.3.3.2 RBANS

The RBANS is a 20-minute neuropsychological screening test. It includes 12 subtests (examples in Table 3.3) measuring attention (digit span, coding), language (picture naming, semantic fluency), visuospatial and constructional abilities (figure copy, line orientation), and immediate and delayed memory (list learning, recognition and recall, story memory, figure recall). Total score is calculated in the index score section and adjusted for age. Depending on the level of cognitive functioning, average scores range from 90 to 109 and index scores per each subtest can be plotted on a provided graph in order to observe differences between cognitive domains. Scores between 80 and 89 are considered low average cognitive performance, whereas scores ≤ 79 strongly suggest general cognitive impairment (Randolph, 1998).

Table 3.3 Examples of the subtests of the Repeated Battery for the Assessment of Neuropsychological Status.

10) List Recognition						3) Figure Copy
List	Circle		One	Circle	One	
1. **Apple**	Y	N	6. Sailor	Y	N	
2. Honey	Y	N	7. Velvet	Y	N	
3. **Market**	Y	N	8. **Carpet**	Y	N	

3.3.3.3.3 Trail Making Test

The Trail Making Test (TMT) version A and B (Reitan, 1958) was administered in Studies 2 and 3. The TMT measures executive functioning, such as attention, processing speed and mental flexibility (Tombaugh, 2004). This test was chosen among others due to the fact that it is a sensitive, brief and free of charge instrument to measure executive functioning and general cognitive level (Rasmusson, Zonderman, Kawas, & Resnick, 2003). The TMT-A consists of 24 circles on a sheet with the numbers 1-24 written in the circles in random locations on the paper. Participants are asked to draw a line from one circle to the next, following the numerical order and without lifting the pen from the paper, until they reach number 25. In the TMT-B, 25 circles contain numbers 1-12 and letters A-L. This time participants are requested to draw a line by following an ascending order, alternating numbers with letters (e.g., 1 – A – 2 – B – 3 – C). In the event of an error, participants are acknowledged and asked to start from the previous correct position. Test administration is discontinued after 5 minutes, if the participant is unable to complete the task. Time is taken during the task and is used for the scoring, which involves subtracting the time to complete TMT-B to TMT-A (Germano, Kinsella, Storey, Ong, & Ames, 2008; Ngandu et al., 2015).

3.3.3.3.4 Digit Symbol Substitution test

The DSS was used in Studies 2 and 3. It is a subtest of the Wechsler Adult Intelligence Test (WAIS; Wechsler, 1955) and investigates sustained attention, response speed, shifting and visuospatial skills. In the DSS, participants are presented with a page filled with rows of boxes with a number from 1 to 9 above each box (in a random sequence), and a blank space below each number. At the top of the page a key with a unique, simple, geometric shape beneath each of the numbers (1-9) is provided. Participants are asked to use the key to fill in the numbers corresponding to each shape, for as many boxes as they can complete, until the examiner stops them, after 90 seconds. A scoring template is provided in order to score each response, for a maximum of 89 points.

3.3.3.3.5 Stroop colour-word test

A modified version of the Stroop test was utilised in Study 3 (Chapter 6) in order to specifically evaluate selective attention and, primarily, inhibition abilities. In the Stroop test, participants are asked to identify the colour of a stimulus for congruent (e.g., the word RED presented in the colour red) and incongruent (e.g., the word RED presented in the colour blue) trials. Response latency for incongruent trials is generally longer than response latency for congruent trials and this is known as the Stroop effect. The Stroop test has been used in research to examine age-related decline in inhibitory control (West & Alain, 2000), given that the Stroop effect is typically greater in older adults (Langenecker, Nielson, & Rao, 2004).

The test utilised was designed using E-Prime 2.0 software (Psychology Software Tools, PA, USA) and included a practice phase of 10 stimuli and a testing phase of 30 stimuli. During the practice phase participants were given the following instructions: “In this experiment you will be given a series of words, for example ‘red’ or ‘blue’. Your task is to ignore what the word says and press the key corresponding to the colour of the word. You will undergo a short practice trial before starting the real experiment”. Before starting the practice phase, it was made clear that participants understood the task, then they were instructed to keep in position their fingers on the keys of the keyboard designated to the colours (S = Red, C = Blue, L = Green, M = Yellow). Per each answer, participants received written feedback from the computer acknowledging them of the correctness or incorrectness of their answer. Before initiating the testing phase, the following instructions appeared on the screen monitor: “The practice trial is completed. You will now undergo the experimental session. Please note that no feedback will be provided this time. Try to answer as fast and accurate as possible". Details on the Stroop test scoring procedure are provided in paragraph 3.3.5.2.

3.3.3.3.6 Digit Span Backward and Forward

The Digit Span was used in Studies 2 and 3. It is a working memory subtest of the Weschler Adult Intelligence Scale, first edition (WAIS; Wechsler, 1955) and it also measures attention, mental manipulation and auditory processing (Coalson, Raiford, Saklofske, & Weiss, 2010). It consists of presenting a string of digits at a constant presentation rate (1-second) and voice pitch, and asking participants to repeat them in the same order of presentation (forward) or in the reverse order (backward). After each correctly recalled string, the length of the following run of digits is increased by 1. Each of the 7 strings consists of two possible trials, starting with three digits and increasing until nine for the digit forward and from 2 to 8 for the digit backward. Each trial can be scored 1 if correct or 0 if incorrect, for a total possible score of 18. The test is interrupted if participants do not recall, or recall incorrectly, two consequent groups of digits.

3.3.3.3.7 Associative memory measure

The Spatio-Temporal Memory (STeM) test was designed by Drs. Davide Bruno and Dan Clark in order to investigate the preference in temporal versus spatial clustering in immediate free recall. The STeM is a ten minutes test including four picture naming tasks, each of them followed by immediate free recall. Given that past literature has suggested that individuals tend to make use of semantic associations even in unrelated, randomly chosen lists of words (Howard & Kahana, 2002b), and that older adults persistently use semantic clustering (Golomb et al., 2008), stimuli on the STeM were presented in lists of semantically related blocks (e.g., all stimuli refer to vegetables) in order to avoid unexpected semantic interference during the retrieval phases and thus interfering with the exclusive use of temporal or spatial clustering. However, in Study 5 stimuli were not organised in semantically related blocks in order to explore spontaneous associative processes and to ensure the previous results were not an artefact of semantic blocking. The 32 pictorial stimuli were selected from the Bank of Standardized Stimuli (BOSStimuli) database (Brodeur, Guérard, & Bouras, 2014) and were presented in colours on a white background, using E-Prime 2.0 software. In Studies 2 and 4 each task involved presentation of 8 stimuli belonging to the same category, for a total of: 8 images of fruits, 8 images of vegetables, 8 pictures of items of clothing and 8 images of animals. Each item from the same category appeared on the computer screen, positioned 30 cm from participants, for 3000 sec, with a 1000ms inter stimulus interval, in a circular array containing 7 black boxes and a target picture (see Figure 3.1). Items were displayed randomly, so that any picture could appear in any of the locations and in any temporal order.

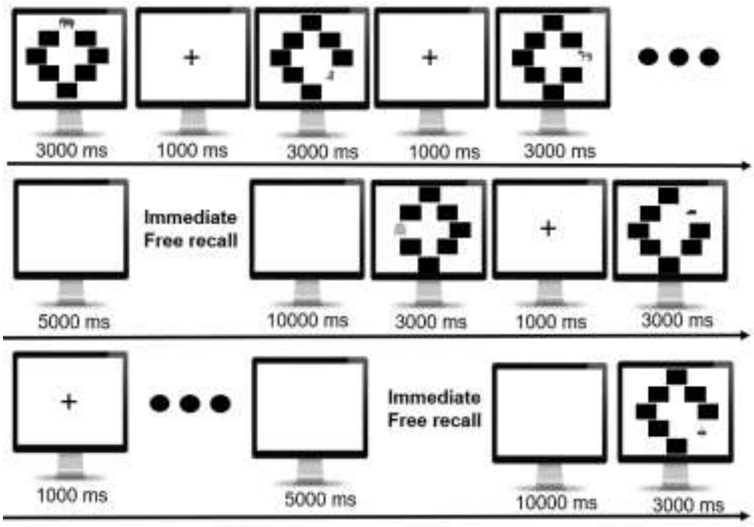


Figure 3.1 Example of the Spatio-Temporal Memory (STeM) test.

During the study phase participants were introduced to the memory task and instructed to name each image with the following instructions: “We are going to show you a series of boxes arranged around a circle. One of these boxes will be replaced by a picture of a well-known ‘category name’. Your task is to look at the picture and to name the item. The image will be displayed for 3 seconds and then the next image will load”. Naming the items ensured participants were attending to, and accurately perceiving, each stimulus. After each category was presented, participants were asked to freely and verbally recall the items presented, in any order. Participants were given as much time as needed to recall as many items as they could, before proceeding to the next sequence of images. Free recall typically was ~15 seconds.

In order to investigate the effect of divided attention and type of material on preferential memory associations, in Study 3, two of the four tasks of the STeM were substituted with verbal rather than pictorial stimuli, whilst a distractor task was introduced in one verbal and in one pictorial task. The distractor task involved the presentation of auditory stimuli (beeps), during the study phase. Participants were asked to count the beeps aloud while simultaneously naming the stimuli, then prompted to write on the computer keyboard the total number of tones, before proceeding to the retrieval phase.

In order to test if the categorical nature of the STeM test may facilitate retrieval and use of temporal versus spatial clustering, in Study 5 a list of unrelated pictures substituted the same-category tasks previously used in the STeM test. Therefore, thirty-two pictures were selected from the BOSStimuli database. Since previous studies have indicated that individuals remember better animate than inanimate targets (Nairne, VanArsdall, & Cogdill, 2017), only inanimate stimuli were included in the unrelated learning list. The test was administered matching previous experiments, with the exception that an unexpected delayed recall was introduced 15-minute after the test was completed. Taking advantage of an unrelated list, the delayed recall test was introduced to explore associative processes at delayed retrieval, given that older adults' memory deficits are maximised in this phase.

3.3.4 Neuroimaging instrumentation

Neurovascular activity was recorded in Study 4 in order to explore haemoglobin changes in the PFC of younger and older participants. Recording was performed using continuous-wave functional Near-Infrared Spectroscopy (fNIRS) OxyMon III system (Artinis Medical System TM, the Netherlands), a functional neuroimaging technology that detects hemodynamic changes in the human cortex, similar to the fMRI.

The use of fNIRS technology in older adults and in memory research will be addressed in Chapter 7. This technique was selected given its many advantages, especially in research with vulnerable populations (Arenth, Ricker, & Schultheis, 2007). Firstly, fNIRS is non-invasive, non-ionizing and safe to use on individuals with metallic implants, compared to other neuroimaging instruments, such as the fMRI or the PET. Secondly, it is less expensive when compared to the fMRI, which also requires a spacious physical dedicated space. Moreover, the relative lack of sensitivity to movements during data acquisition is one of the greatest advantages if compared to other methods, such as the electroencephalogram (EEG). fNIRS has a better spatial resolution than the EEG, and better temporal resolution than the fMRI (Scholkmann et al., 2014). Given the aforementioned advantages, fNIRS is a privileged instrument to explore neurovascular activation during cognitive tasks in healthy older adults and in adults at risk of or with dementia (Pinti et al., 2018).

The principle behind NIRS is that chromospheres such as oxygenated and deoxygenated haemoglobin (HbO, HHb) have characteristic optical properties that permit measurements of changes in HbO and HHb concentrations during neural firing, a process known as neurovascular coupling. Neurovascular coupling takes place as a consequence of neural activity. Specifically, in order to satisfy energy demands of neural tissues in an active brain region, local oxygen consumption increases, as well as cerebral blood flow. Increment in blood flow leads to changes in HbO and HHb concentrations (Obrig & Villringer, 2003). Light in the NIR spectral range, emitted by a source with different wavelengths (optimal wavelengths: ~650-950 nm), is able to penetrate different tissues (skull, cerebrospinal fluid) and to reach the upper layers of the brain (Mohammadi-Nejad et al., 2018). Light, inside the neural tissue, is absorbed by chromophores at different spectra, and scattered outside the brain by the non-absorbed components in a typical banana-shaped course (Herold et al., 2017), as shown in Figure 3.2.

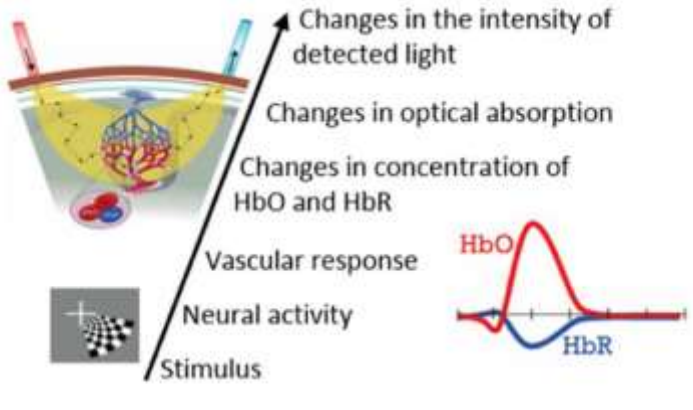


Figure 3.2 Schematic view of optical absorption of NIR light in human tissue, from Mohammadi-Nejad et al., 2018. HbO: Oxygenated haemoglobin. HbR: de-oxygenated haemoglobin

Given the different absorption spectra of the chromophores, and assumed constant light scattering, it is possible to quantify the activity-dependent concentration changes in HbO and HHb with the modified Beer-Lambert (Delpy et al., 1988) and use them as indicators of brain activity (Bunce, Izzetoglu, Izzetoglu, Onaral, & Pourrezaei, 2006).

Training on fNIRS equipment, data processing and analysis was gained through a one-off session with one of the LJMU staff members who originally purchased the system, through 2-weeks training at the Laboratoire d'Étude de la Santé Cognitive des Ainés (LESCA) in Montreal, 3-day fNRIS training course at the University College of London and through a newly established collaboration with the Artinis Medical System (The Netherlands).

3.3.4.1 fNIRS configuration

A 12-channels configuration, including 3 receivers and 8 transmitters (11 diodes), was selected from those provided by the Artinis Medical Systems, in order to permit 2.5 cm source-detector separation and 1.25 cm penetration depth. Data were sampled at 10 Hz, in accordance with previous studies on memory in older adults (Basso Moro, Cutini, Ursini, Ferrari, & Quaresima, 2013; Ferreri et al., 2014; Metzger, Schopp, Haeussinger, Dehnen, & Synofzik, 2016). The 12-channels template was in accordance with the international 10/20 system used in electroencephalography, and diodes were placed in order to cover the left and right PFC (Figure 3.3). Channels approximately covered Broadman’s areas 9, 10 and 46 of the PFC (more details in Chapter 7).

Figure 3.3 Montage of the 12-channels functional Near-Infrared Spectroscopy. Receivers are in blue, transmitters in yellow.

Baseline brain activity was recorded before the STeM test for 120 seconds. During this recording, participants were asked to relax whilst looking at images of landscapes on the computer screen and listening to relaxing music. After this, the STeM test was introduced and participants' PFC activity was recorded. Each encoding phase was followed by about 10-s interval during which participants were instructed to recall as many items as possible, in any order. The retrieval phase was followed by about 10-s interval during which participants were given instructions for the following task (Figure 3.4).

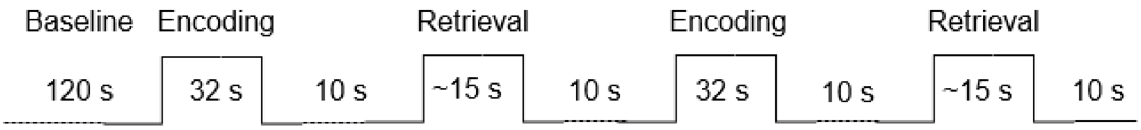


Figure 3.4 Representation of the fNIRS recording during the one task of the STeM test.

3.3.4.2 fNIRS limitations

As previously discussed, fNIRS technology has several advantages over other neuroimaging and electrophysiological techniques and it is especially useful in research with vulnerable populations (Arenth et al., 2007; Li et al., 2018).

However, there are limitations in fNIRS research that ought to be taken into account. Firstly, given that fNIRS light can detect neurovascular coupling up to few centimetres depth (Ferrari & Quaresima, 2012), it provides lower spatial resolution compared to fMRI, whereas temporal resolution is relatively poor when compared to EEG (Lloyd-Fox, Blasi, & Elwell, 2010), as shown in Figure 3.5. Secondly, fNIRS signals are particularly sensitive to systemic physiology, such as heart rate and respiration, which may contaminate measurements of haemodynamic response, leading to false positive (i.e., changes in HbO and HHb are wrongly assigned to cognitive activation) or false negative results (i.e., haemodynamic response related to functional brain activity is not detected due to systemic activity) (Fairclough, Burns, & Kreplin, 2018; Tachtsidis & Scholkmann, 2016). Moreover, fNIRS signals are also sensitive to specific skin pigmentations, hair colour and density (Strangman, Boas, & Sutton, 2002). Lastly, certain head movements and muscles contractions of the forehead may also create signal interference (Herold, Wiegel, Scholkmann, & Müller, 2018). Noise linked to motion artefacts and physiological oscillations can be however controlled for during signal recording and data processing.

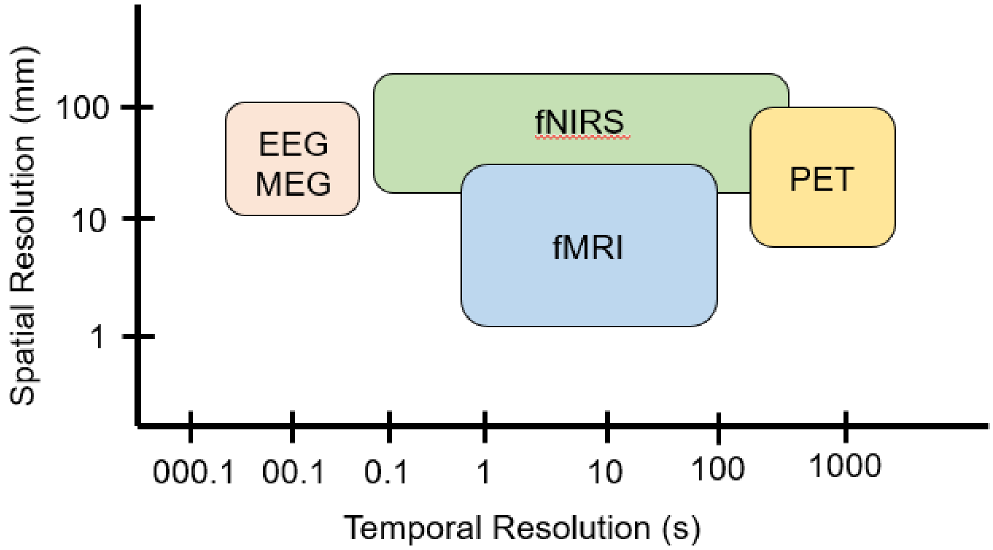


Figure 3.5 Spatial and temporal resolution of fNIRS compared with other neuroimaging and electrophysiological methods. Figure adapted from Takeda et al., 2015.

3.3.5 Data analysis and processing

Statistical analyses were mainly conducted using SPSS, Version 23 (IBM), for both cognitive and neuroimaging measures. In all studies all assumptions to run the performed analyses were met, unless otherwise stated. Normality of distributions were assessed by Shapiro-Wilk test for samples smaller than 50, and with Kolmogorov-Smirnov for samples bigger than 50 (p > .05). Independent sample t-tests or the Mann-Whitney test, depending on the normality of the sample, were used to determine any group differences on cognitive performances. Pearson's or Spearman's correlation analyses were also performed to observe statistical relationships between variables. Binomial logistic regressions were utilised in Studies 1 and 6 to explore the probability that delayed primacy and temporal contiguity predicted conversion from cognitively intact to early MCI (or CUD). Receiver Operating Characteristic (ROC) analysis was also performed in Study 1 to investigate the accuracy of this prediction. In Studies 2, 3, 4 and 5 mixed design ANOVAs were used to investigate the effects of age, experimental conditions and cortical differences on temporal and spatial clustering. The Greenhouse-Geisser correction was applied to ANOVAs when the assumption of sphericity was violated and post-hoc tests were Bonferroni corrected. False Discovery Rate correction was used in Study 1 to account for the Type 1 error inflation due to multiple tests. Measures of effect size, including Cohen's *d*, *r* and partial eta-squared (partial η^2) were included in each significant analysis. Statistics were reported following the American Psychological Association's guidelines (APA, 2010).

3.3.5.1 Temporal and spatial clustering

In each study investigating temporal and spatial clustering, the output order of recall was extracted from the STeM test in the same way. STeM clustering scores were calculated in MATLAB, Version 2018a (MathWorks) adopting the method developed by Polyn, Norman, and Kahana (2009) and using their provided MATLAB script. Specifically, the absolute value of the lag of each recall transition was ranked with the absolute values of the lags of all possible transitions. This provided a percentile score for each transition, which was then averaged with the other percentile scores of a subject's transitions, therefore providing a temporal factor score. The same analysis was run to compute spatial organization.

3.3.5.2 Stroop test

Response accuracy and reaction time were utilised to calculate a total score for the Stroop test. Following Stroop (1935), per each correct response, the average reaction time of congruent word/colour items was subtracted from the average reaction time of incongruent items. Although many other approaches have been proposed to score the Stroop test, the straightforward difference score was the most used (MacLeod, 1991).

3.3.5.3 Neuroimaging data

fNIRS raw data were pre-processed using the software provided by the Artinis Medical System (Oxysoft). Both baseline correction and averaging across channels and/or trials, after filtering, is typically recommended (Herold et al., 2018). Therefore, data were baseline-corrected using the mean average of baseline recording. Filtering of fNIRS signals was conducted using a 2-s moving-gaussian filter, among those available on Oxysoft. This filter was chosen following consultation with Artinis Medical System and excluded high frequency artefacts. Consequently, averaging of oxygenated and deoxygenated changes from baseline was conducted over the STeM recall epochs per each fNIRS channel. The mean average values of cortical activity (oxygenated and deoxygenated haemoglobin changes) were then exported in Excel format. Channels were averaged together in order to investigate cerebral areas of interest. Further information on channels averaging is reported in the methods section of Chapter 7. Lastly, the average among retrieval epochs per each participant was calculated in order to obtain a single value for retrieval. Averaging over channels and then over trials permitted to retain the variance over sessions (Spüler, 2019). Statistical analysis of fNIRS signal was conducted in SPSS through ANOVAs (Tak & Ye, 2014).

Chapter 4 Predicting early Mild Cognitive Impairment with free recall: the primacy of delayed primacy.

Study 1 was published in *Archives of Clinical Neuropsychology* (Talamonti et al., 2019). This study was presented at the British Neuropsychological Society spring 2017 meeting (London, UK), at the Alzheimer's Research UK North West 2017 meeting (Manchester, UK) and at the EPS Time Perception 2017 workshop (Liverpool, UK).

4.1 Introduction

Serial position effects occur in free recall when items presented early on a list (primacy) and items presented at the end of a list (recency) are remembered better than items in the middle (Murdock, 1962). This pattern of performance remains relatively stable during the aging process (Healey & Kahana, 2016; Ward & Maylor, 2005; Wright, 1982), although cognitively healthy older adults tend to forget a greater proportion of words from the middle and recency positions as compared to younger adults (Griffin et al., 2017). However, individuals with Alzheimer's Disease (AD) show reduced primacy recall relative to both healthy younger and older groups (Burkart, Heun, & Benkert, 1998; Moser et al., 2013), and sometimes show a paradoxical increment of recency recall (Bruno, Reichert, & Pomara, 2016b; Greenaway et al., 2006).

Poor primacy performance is also consistently reported (but see Bennett, Golob, Parker, & Starr, 2006) when comparing individuals with Mild Cognitive Impairment (MCI), which is considered a stepping stone to AD (Petersen, 2004), to healthy age-matched controls (Cunha et al., 2012; Howieson et al., 2017; Shankle et al., 2005); and lower primacy recall has been shown to differentiate between AD and MCI (Cunha et al., 2012). All in all, these findings suggest that performance in the primacy region of recall is more informative than performance in other serial positions, when studying the relationship between episodic memory and cognitive functioning in older adults.

Based on the above, and on their own findings showing that poor primacy performance in cognitively intact elderly predicted cognitive decline, Bruno, Reiss, Petkova, Sidtis and Pomara (2013) have suggested that primacy may also be a useful predictor of risk of conversion to MCI from a cognitively healthy baseline. Indirect evidence supporting this claim comes from studies showing that serial position effects predict conversion from MCI to AD (Egli et al., 2014). However, the way in which serial position is calculated may affect the aforementioned predictions. For instance, Cunha et al. (2012) used two distinct measures of serial position to determine which measure is the most sensitive to neurodegeneration: regional score and standard score. These scores were calculated by dividing the percentage of items recalled from each region by the sum of items presented over the three learning trials in that region (regional) or from the entire list (standard). In the longitudinal study, Cunha et al. (2012) investigated the capacity of initial primacy and recency scores to predict conversion to AD, in a group of 134 MCI patients. They first compared serial position effects between MCI-progressives and MCI-nonprogressives and found that both standard and regional recency scores significantly differentiated between the two groups. For comparison, when looking at primacy exclusively, only regional scores were able to statistically differentiate between those who progressed to dementia and those who did not.

Subsequently, a receiver operating characteristics (ROC) curve analysis was performed to measure the accuracy of the scoring systems in distinguishing between MCI-progressives and MCI-nonprogressives. The ROC curves showed that primacy was more sensitive than recency in predicting progression to AD when using regional scores, but recency was more sensitive than primacy with standard scores. However, as regional scores were overall more sensitive than standard scores in discriminating progression to AD, Cunha et al. concluded that primacy had potential clinical uses for early detection of AD.

An important consideration regards whether delaying recall increases the accuracy of serial position predictions. Bruno et al. (2013) noted that primacy performance after a delay (15-20 minutes) was a much stronger predictor than any performance measure taken from recall immediately after presentation in cognitively intact individuals, although they did not compare different ways of calculating serial position measures. This finding is consistent with the notion that long-term potentiation and synaptic consolidation require time, and therefore, testing memory after a delay may provide a more truthful assessment of memory ability. Indeed, decreased memory performance at delayed, rather than immediate, recall has been previously found to be predictive of AD (Gomar et al., 2011). Research has found delayed recall to depend mostly on long-term retention and synaptic consolidation, compared to immediate recall (Carlesimo et al., 1996; Dalezman, 1976). As AD pathology originates in the hippocampus (Raj et al., 2015), an area responsible for the storage and consolidation of information, it is plausible that any predictive value of primacy may be enhanced in delayed tasks.

In the current study, delayed primacy was compared to total and delayed recall and to three different serial position scoring methods in a sample of healthy older adults followed for a period of up to 13 years. The goal of the present study was to determine which measure best discriminated between individuals who eventually developed early symptoms of MCI, and those who maintained normal cognitive functioning. For the purposes of the present study individuals with more severe classifications (e.g., dementia) were excluded. However Johnson et al. (2018), using the Wisconsin Registry for Alzheimer's Prevention (WRAP) dataset, have shown that non-clinical individuals presenting early symptoms of MCI at baseline were associated with higher risk of progressing to MCI or dementia at their last visit compared to individuals who were cognitively intact, therefore suggesting the early MCI designation has predictive value (details on early MCI diagnosis in the Procedure section). It was hypothesised that delayed primacy performance would be the strongest measure for predicting those who exhibited early MCI at their last assessment among those who were unimpaired through all visits.

4.2 Methods

4.2.1 Participants

Participants were selected from the WRAP, an ongoing longitudinal cohort study examining cognitive trajectories and associated risk factors in a sample of older adults with or without family history of AD. The first follow-up occurs at least after 4 years, while all subsequent visits occur at 2-years intervals thereafter. Participants for this study were selected on the basis of having completed at least two visits, having received a diagnosis of normal cognitive functioning at baseline, and either being classified as still cognitively normal or with possible early MCI at their last visit (details on diagnoses in the Procedure section). Additionally, at baseline, selected participants were free of neurological diseases and psychiatric disorders, spoke English as their native language, and were 60 or older. From the total pool of 1551 volunteers, data from 191 participants who fulfilled the above inclusion criteria were analysed. Specifically, 46 participants completed five visits, 77 completed four visits, 48 came back for three visits and 20 came back for one follow-up. Of the 191 participants, 179 were classified as White/Caucasian, 10 were Black/African American, 1 was Spanish/Hispanic and 1 was Asian. All activities for this study were approved by the ethics committees of the authors' universities, and completed in accordance with the Helsinki Declaration.

4.2.2 Procedure

Each WRAP participant completed an entry assessment that included laboratory tests, clinical measurements, and a health history and lifestyle form assessing demographics, self-reported medical and psychiatric status and depressive symptoms (20-item Center for Epidemiologic Studies-Depression Scale [CES-D]). To classify cognitive status of participants WRAP includes two-tiered consensus conference method. First, a statistical algorithm is applied to identify cases of possible impairment; then a team of physicians, clinical neuropsychologists, and clinical nurse practitioners reviews those cases flagged by the algorithm, based on cognitive, medical history, lifestyle, subjective cognitive complaints, and informant data (Koscik et al., 2016). Specifically, reviews are carried if participants meet one or more of the following criteria: 1) performance of 1.5 SDs below the mean on factor scores or individual cognitive measures (Clark et al., 2016; Koscik et al., 2014); 2) cognitive performance on one or more tests fell below values used in other studies as cut-points for clinical MCI diagnoses; or 3) subjective cognitive or functional decline. The status of early MCI identifies individuals in the cohort whose objective performance is at least 1.5 SDs below expected in one or more cognitive domains relative to internal robust norms, but who do not demonstrate clinical levels of cognitive deficits nor have subjective reports of cognitive complaint, fundamental for MCI diagnosis (Albert et al., 2011). This category corresponds to clinical stage 2 in the 2018 diagnostic framework (Jack et al., 2018) and is believed to proceed a clinical diagnosis of MCI (see Appendix 2).

The neuropsychological battery comprised commonly used clinical tests (see Johnson et al., 2018; Sager, Hermann and La Rue, 2005 for a description of the baseline cognitive battery), including measures used as cognitive outcomes for this study: Trail Making Test A and B (Reitan, 1986) and Stroop Color Word Test (Stroop, 1935) for working memory and executive abilities; Wechsler Abbreviated Scale of Intelligence [WASI] Vocabulary and Similarities subtests (Wechsler, 1955), Boston Naming Test (BNT; Goodglass & Kaplan, 2000) and Wide Range Achievement Test [WRAT] Reading Test (Wilkinson & Robertson, 2006) for language and verbal skills; WASI Block Design subtest, WASI Matrix Reasoning and Judgment of Line Orientation (JLO; Benton, Hamsher, Varney, & Spreen, 1983) for visuospatial abilities; working memory subtests of the Wechsler Adult Intelligence Scale-III (WAIS; Wechsler, 1999) for working memory; and Rey Auditory Verbal Learning Test, (AVLT; Schmidt, 1996) for verbal and visual episodic memory.

In the AVLT, a list of 15 semantically unrelated words is orally presented to the participants in an initial trial, after which participants are required to freely recall the words. Subsequently, four more identical trials are performed, for a total of five learning trials (total recall). After these trials, a distractor list of 15 different and unrelated words is presented and subjects are asked to recall it. Finally, after a delay of approximately 20 minutes, participants are asked to freely recall items from the first presented list: this is referred to as the delayed recall.

To calculate the serial position scores, the 15-word list was divided as follows: primacy was characterised by the first 4 words of the list, whilst recency was composed of the last 4 (Foldi et al., 2003; Hermann et al., 1996; La Rue et al., 2008). Due to increasing evidence that primacy and recency, rather than middle-items, may be more influential in detecting cognitive decline, these two components were addressed in the present study. Primacy and recency scores were calculated in each learning trial, summed up and then divided by the total possible number of primacy and recency words recalled (20). In line with Cunha et al. (2012), primacy and recency regional and standard scores were derived from the five learning trials. Due to the fact that delayed recall consists of only one trial, it was not possible to use the same formulas for delayed primacy and recency. In line with the literature (Brueggen et al., 2016; Hermann et al., 1996; La Rue et al., 2008), delayed primacy and recency were defined as the proportion of correctly recalled primacy and recency items from the delayed trial. For instance, participant A recalled 6 words from trial 1, 9 from trial 2, 10 from trial 3, 9 from trial 4, 10 from trial 5, for a total of 44 words recalled. Of the 4 words that could be recalled from the primacy region at each of the 5 trials, participant A recalled 2 at trial 1, 2 at trial 2, 4 at trial 3, 3 at trial 4, 4 at trial 5. Regional primacy is calculated as:

$$\frac{2+2+4+3+4}{4 \times 5} = .70$$

Standard primacy is calculated as:

$$\frac{2+2+4+3+4}{44} = .34$$

Participant A also recalled 3 (out of 4) words from the primacy region at delayed recall, therefore delayed primacy is calculated as:

$$\frac{3}{4} = .75$$

Outcome measures were primacy and recency regional and standard scores, as well as delayed primacy and recency. In order to compare the initial level of cognitive functioning between participants who progressed to early MCI and those who did not, a composite score for a general cognitive ability variable was calculated as the average of four baseline cognitive factor z-scores: (1) Speed and Flexibility, obtained using the TMT-A and B and the Stroop Colour-Word test; (2) Verbal Abilities, obtained with the WASI vocabulary, WASI similarities, BNT and WRAT; (3) Visuospatial Abilities, using the WASI block design, matrix reasoning and the JLO; and (4) Working Memory, obtained using the digit span back and forward and the letter-number sequencing (details on the factor analyses can be found in: Dowling, Hermann, La Rue, & Sager, 2010; Koscik et al., 2014). Generally, the consensus diagnosis for early MCI included evaluation of two measures from AVLT test (excluding serial position data), as part of the 15 – 20 of the cognitive measures considered (e.g., executive function impairments or language impairments were also evaluated). Even though predictors and outcome cannot be thought of as being 100% "conceptually" independent, the level of circularity is therefore relatively low.

4.2.3 Statistical Analysis

All the analyses were performed using SPSS, Version 23 (IBM). Variables included in the main analysis were total and delayed recall and primacy and recency, calculated in standard, regional and delayed scores. As the serial position scores were not normally distributed, non-parametric analyses were utilised when these variables were included. Parametric analyses were used for normally distributed data.

First, each measurement of primacy and recency was correlated to general cognitive ability in both groups to assess their sensitivity to global cognition. Subsequently, Mann-Whitney tests and t-test were run to determine if there were differences in demographics, cognitive level and serial position performance between those who progressed to early MCI and those who did not. Therefore, the hypothesis that delayed primacy is a stronger measure in predicting progression to early MCI compared to clinically used measures of cognitive decline was tested through a binary logistic regression with delayed primacy as the predictor, and progression to early MCI or not as the binary outcome, whilst controlling for immediate and delayed total recall respectively. Since time between the first and last visit was not the same for each participant, time was also added as a control variable, together with age, gender, APOE4 status, and years of education. To avoid issues of multicollinearity, delayed primacy was regressed out of AVLT delayed recall, yielding standardized residuals; in turn, delayed primacy and the AVLT delayed recall standardized residuals were regressed out of AVLT total recall, generating also standardized residuals for AVLT total recall. A Spearman’s correlation analysis confirmed the independence of these measures.

Finally, Cunha et al.'s (2012) statistical method was followed and receiver-operating characteristic (ROC) curves were generated to check for specificity and sensitivity of delayed primacy, compared to regional and standard serial position calculations.

4.3 Results

Table 4.1 summarises the subjects' demographic characteristics and comparisons for cognitive and memory scores. One hundred fifty-eight (82.7%) of the 191 participants remained cognitively intact at the last visit, whereas thirty-three (17.3%) progressed to Early MCI. Of these, fourteen met psychometric amnestic MCI criteria and nine met non-amnestic MCI criteria (Koscik et al., 2014) at their last visit. 71% of the total sample was female, mean age at baseline was 62.29 (*SD* = 1.92) years, with 16.38 (*SD* = 2.99) total years of education. Correlation analyses between general cognitive abilities and serial position measures are shown in Table 4.2. General cognitive abilities were positively related to delayed primacy, $r_s(184) = .218$, $p = .003$ and recency scores, $r_s(184) = .196$, $p = .008$, and with primacy regional scores, $r_s(184) = .235$, $p = .001$.

Table 4.1 Demographics, cognitive level, and serial position performance between MCI-progressive and MCI-nonprogressive participants

	Early MCI-p (n = 33)	**Controls (n =158)**	***p***
Gender (females)	25 (76%)	111 (70%)	.526
APOE4 presence	7 (22%)	44 (28%)	.434
Age	62.58 ± 1.80	62.23 ± 1.95	.346
Years of education	16.59 ± 2.99	16.34 ± 3.00	.665
General cognitive abilities	-.40 ± .53	-.11 ± .60	.001
Time	7.97 ± 2.56	7.94 ± 2.10	.952
AVLT Total Recall	47 (35 - 60)	51.50 (35 - 68)	.001
AVLT Delayed Recall	10 (5 - 15)	11 (6 - 15)	.016
Serial position effect measures:			
Primacy			

Regional scores	.65(1 - .20)	.70(1 - .40)	.227
Standard scores	.29 (.49 - .20)	.29 (.42 - .14)	.690
Delayed scores	.75 (1 - 0)	.75 (1 - .25)	.003
Recency			
Regional scores	.15 (.20 - 0)	.15 (.20 - 0)	.186
Standard scores	.33 (.40 - .18)	.32 (.51 - .19)	.953
Delayed scores	.50 (0 - 0)	.50 (0 - 0)	.570

Note. Early MCI-p = mild cognitive impairment progressive; Controls = non progressive to early MCI; Time = time between first visit and last follow-up.

Table 4.2 Spearman correlation between cognitive performance and serial position measures

Measures	**Cognitive ability**
Regional primacy	.235*
Regional recency	.054
Standard primacy	.051
Standard recency	-.123
Delayed primacy	.218*
Delayed recency	.196*

Note. Regional scores = primacy/recency words recalled divided by total number of primacy/recency words presented; Standard scores = primacy/recency words recalled divided by total number of words recalled; Delayed scores = proportion of delayed words recalled for primacy and recency; * = correlation significant at p < .01.

As cognitive ability was normally distributed, an independent samples t-test was performed to compare the initial cognitive functioning of the two groups and results showed a statistically significant difference between MCI progressives and MCI-nonprogressives, $t(184) = 3.471$, $p = .001$, $d = .25$. As data were not normally distributed, Mann-Whitney tests were run to determine if there were differences between the two groups in memory measures, including immediate and delayed total recall and serial position effects measures. Statistically significant differences on memory measures were found for delayed primacy ($U = 1820.500$, $z = -2.933$, $p = .003$, $r = .21$) between MCI-progressive and MCI-nonprogressive participants. Significant differences were also found for immediate total recall ($U = 1617.500$, $z = -3.429$, $p = .001$, $r = .25$) between MCI-progressive and MCI-nonprogressive individuals. Lastly, delayed total recall was statistically lower in the MCI-progressive compared to the MCI-nonprogressive group (U = 1916.500, z = -2.408, p = .002, r = .17). Spearman's correlation was performed in order to guarantee that there was no correlation between delayed recall and total recall ($r_s(189) = -.004$, p = .953), between delayed recall and delayed primacy ($r_s(189) = .074$, p = .308), and between total recall and delayed primacy ($r_s(189) = .010$, p = .896). The logistic regression model was statistically significant, $\chi 2(8) = 16.951$, p = .031. The model explained 14% (Nagelkerke R2) of the variance in conversion to early MCI and correctly classified 84% of cases. Delayed primacy was the only statistically significant measure to predict progression to early MCI, compared to the other control variables, as shown in Table 4.3.

Table 4.3 Logistic regression predicting progression to early MCI based on delayed primacy performance at baseline

Measures	***B***	***SE***	***Wald***	***p***	***Exp(B)***
Delayed primacy	-3.452	1.044	10.925	.001	.496
AVLT Total Recall	-.093	.214	.191	.662	.911
AVLT Delayed Recall	-.314	.224	1.977	.160	.730
Time	.003	.002	3.170	.075	1.003
Age	.194	.204	.910	.340	1.106
Years of education	.250	.212	1.393	.238	1.086
Sex	.925	.525	3.107	.078	2.522
APOE4	-.479	.508	.887	.346	.620

Note. B = unstandardized regression coefficient; SE = standard error of the coefficient; Exp(B) = odds ratio; Time = time between first visit and last follow-up; AVLT Total and Delayed Recall = standardized residuals.

The ROC curves (Table 4.4) showed that, compared to the other serial position measures, delayed primacy was the only statistically significant measure able to discriminate between those who converted to early MCI, with 65% accuracy. Figure 4.1 shows areas under the ROC curves for delayed primacy, compared to regional and standard primacy.

Table 4.4 Areas under the ROC curve by serial position scoring measures in progressive MCI and controls.

Measures	Early MCI-p vs. Controls		
	AUC	***p***	***95% CI***
Regional primacy	.57	.230	[.45, .68]
Regional recency	.57	.215	[.46, .67]
Standard primacy	.48	.691	[.36, .60]
Standard recency	.50	.953	[.39, .61]
Delayed primacy	.65	.006	[.55, .75]
Delayed recency	.53	.587	[.43, .63]

Note. Early MCI-p = progressed to early mild cognitive impairment; controls = non progressive MCI. ROC = receiver-operating characteristic. AUC = area under the curve. CI = confidence interval.

Diagnostic concordance was also assessed using positive predictive values (PPV) and negative predictive values (NPV). With a cut-off of 1 out of 4 on delayed primacy, the PPV was 33% and the NPV was 83% (sensitivity 6%, specificity 97%), whilst a cut-off of 2 out of 4, produced a PPV of 30% and an NPV of 86% (sensitivity 36%, specificity 82%).

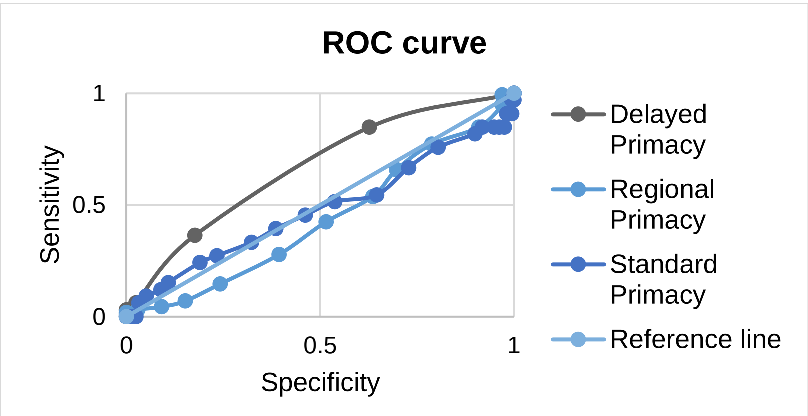


Figure 4.1 Receiver Operating Characteristic (ROC) curve of delayed, regional and standard primacy measures.

4.4 Discussion

The current study was the first, to the best of our knowledge, to compare several memory and serial position measures and their sensitivity in predicting progression to early MCI from a baseline of intact cognition. In the results, as per hypothesis, delayed primacy was the strongest memory measure in predicting conversion to early MCI from a cognitively intact baseline, when compared to established diagnostic memory methods, such as AVLT total and delayed recall. The ROC analysis showed that delayed primacy is still the only significant measure also when compared to other serial position calculations, although falling in the “poor” range. The general findings are consistent with Bruno et al.'s (2013) results, showing in a longitudinal study that delayed primacy recall was the most sensitive predictor of cognitive decline in cognitively intact older adults, when compared to total recall, middle and recency, and when evaluating both immediate memory (i.e., learning trials) and delayed performance.

None of the control variables was found to predict conversion to early MCI. This may be due to the sample being heterogeneous for age, years of education and sex. Moreover, APOE4 has been found to have limited value for predicting dementia in clinical practice (for a review, see Elias-Sonnenschein, Viechtbauer, Ramakers, Verhey, & Visser, 2011), therefore it is not surprising that significance was not reached in our model.

Lower delayed primacy performance is associated with an increased likelihood of conversion to early MCI. The low PPV values indicate that the conversion is not imperative (33% or 30%), however the relatively high rate of false positives shows that there is higher chance (83% or 86%) that the person with higher delayed primacy may not progress to early MCI. These findings also align with the sensitivity and specificity of the cut-off reported for delayed primacy. Therefore, high delayed primacy may play a protective factor for cognitive decline, thus suggesting potential implications for neuropsychological assessments. For instance, delayed primacy may be considered among other cognitive markers for the purposes of determining who is suitable (i.e., at greater risk of conversion) for inclusion in clinical trials for AD drugs.

Primacy effects have been characteristically linked to increased opportunities for rehearsal relative to other portions of the serial position curve (Rundus, 1971; Tan & Ward, 2000), although primacy effects have also been observed without rehearsal (Wright, 1994). Indeed, Bruno et al. (2015) have previously suggested that a mechanism involving opportunities to rehearse and later consolidate the information, relying on a pathway involving the prefrontal cortex and the hippocampus, may explain the predictive strength of delayed primacy recall – as also argued in the Introduction. However, Bruno et al. (2016) argued that delayed primacy recall could be parsed into two separate mechanisms. First, a tendency to begin recall by retrieving items from the beginning of the list – tendency that is emphasised in delayed trials, where short-term, recency-based effects dissipate. Second, the ability to use temporal context from retrieved items to cue the recall of temporally contiguous stimuli. While the latter appears to rely on hippocampal function, the former is more uniquely associated to primacy. Alternatively, it is also possible that primacy is a valuable predictor of cognitive decline, specifically at delayed recall, because it taps into the individual's ability to focus attention during learning (Sederberg et al., 2006). In this regard, it is to note also how APOE4 carries show attentional deficits in working memory tasks (Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002). Similarly, primacy may also be involved in processing novelty items (Davelaar, 2013) and/or changes in contextual information (Howard & Kahana, 2002a). More research is needed to address these questions.

The ROC analysis findings on standard and regional scores yielded lower diagnostic power compared to previous reports on clinical population (Cunha et al., 2012; Egli et al., 2014), where serial position measures were used to investigate conversion from MCI to AD. Specifically, Cuhna et al.'s ROC analysis showed an accuracy falling in the "fair" range for both regional primacy (70%) and standard recency (68%), compared to the "poor" range of delayed primacy (65%). The lower accuracy may be due to the fact that the current sample was composed of healthy participants who converted to a pre-clinical stage, whilst previous studies (Cunha et al., 2012; Egli et al., 2014) investigated an already clinical population who progressed to dementia. Furthermore, the size of the present sample was not equal across groups, with a larger proportion of controls compared to those who progressed to early MCI, which may reduce the comparability to studies with different samples. For instance, Cunha et al. (2012) reported that number of individuals with MCI who progressed to dementia was higher than the number of those who did not. This discrepancy is not surprising since it is more likely that individuals with MCI progress to any type of dementia, rather than healthy individuals develop MCI. Indeed, other studies investigating progression to early MCI reported similar conversion rates (14% in Bruno, Koscik, Woodard, Pomara, & Johnson, 2018; 15.2% in Johnson et al., 2018). Moreover, the years of education of individuals with AD and MCI in Cunha et al. (2012) was relatively low ($M = 5.20$, $SD = 3.97$ and $M = 6.78$, $SD = 4.32$) compared to the current sample ($M = 16.59$, $SD = 2.99$). Since education is an important protective factor for cognitive decline, the higher education of our participants may have contributed to the lower conversion to early MCI. Although Egli et al. (2015) and Howieson et al. (2017) considered delayed recall performance in comparing serial position measures, they did not specifically isolate either delayed primacy or delayed recency.

There are some limitations in the present study that may be taken into account for future directions. Firstly, the main analyses did not include information regarding sub-categories of MCI due to the fact that these diagnoses are based on performances on the AVLT, which would have brought circularity problems for the statistical design. Future studies may consider to include these classifications if possible. Secondly, not all participants with early MCI progress to clinical stages, therefore caution should be used in generalising the findings. Moreover, the algorithm used for the consensus conference process does not include any criteria for subjective self-report of memory problems. Therefore, the early MCI group may miss individuals who have subtle decline that is not detected by the flagging algorithm. Lastly, although delayed primacy was the only statistically significant serial position measure in the ROC analysis, it yielded low diagnostic power. However, it should be noted that prediction of conversion to early MCI was examined in this study, which is a preclinical classification. Therefore, further studies should consider investigating the appropriateness of delayed primacy, compared to other serial position measures, for prediction of clinical MCI from a healthy baseline.

So far, this is the first study to longitudinally investigate conversion to early MCI from a stage of intact cognitive functioning level and to compare the efficacy of several serial position measures. In line with previous research on healthy and declining populations, it was found that delayed primacy is the most accurate scoring measure in predicting progression to an early stage of MCI, even when considering memory measures broadly utilised for neuropsychological assessment, such as total and delayed recall. Since MCI is a crucial stage for dementia development, further research may focus on its early stage to improve early detection of cognitive impairment in clinical settings, and to allow early neuropsychological interventions. Being able to predict early MCI from a cognitive functioning stage may help prevent, or delay, its clinical appearance and, consequently, its progression to dementia.

Chapter 5 Age differences for spatial and temporal clustering in episodic memory

Study 2 was presented at the International Neuropsychological Society 2018 meeting (Prague, CR) and at the Liverpool Neuroscience day 2018 meeting (Liverpool, UK).

5.1 Introduction

In Study 1, the input order of free recall was investigated to predict progression to early MCI from a sample of cognitively intact older individuals. Delayed primacy was found to be a stronger predictor of cognitive impairment, compared to other serial position measures, thus confirming previous studies suggesting delayed primacy as a potential tool for early detection (Bruno et al., 2015, 2013). Given that few studies have so far examined the output order of free recall, which influences retrieval mechanisms and is as crucial as the input order in memory performance (Howard & Kahana, 1999), Study 2 focused on the output processes in free recall.

Over the years, research on human episodic memory has focused on understanding how new information is organised in the brain (Mandler, 1967; Tulving, 1962). When a memory task includes semantically related words, items are likely to be recalled together (semantic proximity principle; Bousfield & Cohen, 1953; Howard & Kahana, 2002). However, when the task excludes semantically related words, recall seems to be facilitated by the temporal contiguity effect, wherein items presented at nearby study positions are more likely to be recalled together (Kahana, 1996). Temporal clustering is remarkably consistent in free recall studies, so much so that researchers have suggested a fundamental nature of temporal contiguity in cognitive processes (Healey & Kahana, 2014; Lehman, Smith, & Karpicke, 2014). Whilst being very common in younger adults (Healey & Kahana, 2014) and believed to be a fundamental organizational factor in memory formation (Polyn & Cutler, 2017), temporal clustering appears to be particularly challenging for older adults (Kausler, 1994; Parkin et al., 1995). For instance, in Golomb, Peelle, Addis, Kahana and Wingfield (2008), younger and older adults were asked, after presentation, to freely recall a list of words. As older adults showed much weaker temporal clustering compared to the younger group, Golomb et al. (2008) suggested a specific age-related deficit for temporal clustering. Moreover, they also noted that, whilst temporal clustering was not employed efficiently, older adults tended to utilise persistently semantic associations, even when maladaptive for serial recall. Therefore, it may be that alternative strategies are engaged by older adults in order to overcome the age-related deficiency in temporal clustering and try to increase memory performance. For instance, when semantic organization is not attainable, but information about spatial context is provided, it is possible that material may be organised spatially rather than temporally in this population. In the domain of spatial memory, spatial proximity between items has been found to be a predictor of the order in which items are recalled later on in younger participants (Miller et al., 2013; Pacheco & Verschure, 2018).

Although age-related deficits for spatial memory have been previously reported (Old & Naveh-Benjamin, 2008), the current literature suggests that age-related declines become evident only in complex tasks (for a review see: Klencklen, Després, & Dufour, 2012). For instance, Pouliot and Gagnon (2005) found that, although significantly different, older participants showed only a minor decrease in recall for spatial locations compared to the younger group. Similarly, Olson et al. (2004) found that younger and older adults showed similar performance on the short-term spatial memory test and that both groups encoded locations relative to other locations. Taken together, these studies suggest that in older adults, a spatial rather than temporal organization may be preferred.

In the present study the dual contribution of temporal and spatial information and its relation to the ageing process was investigated. The experiment included two groups of participants (younger and older adults: aged 18 – 25 and 50 and older, respectively) who were asked to freely recall a list of stimuli presented randomly around a spatial array. This approach allowed to determine whether participants tended to use (spontaneously) either spatial or temporal clustering, which, for the nature of the experiment, were the only possible associations. It was hypothesised that: 1) younger adults would show greater temporal clustering, when compared to the older group; 2) a preference for spatial clustering would be shown by older, rather than younger adults, in order to compensate for a deficit in temporal clustering.

5.2 Method

5.2.1 Participants

A total of 50 younger participants, mainly LJMU students, and 45 older participants were recruited using emails, and advertisements on Liverpool John Moores University and on the University of Third Age websites. Older adults were selected if aged 50 or above, and older and younger participants had no history of major clinical conditions or psychiatric diseases. All participants were reimbursed for their time with a £10 voucher. The study was approved by the Liverpool John Moores University Research Ethics Committee (UREC).

5.2.2 Materials and procedure

The experiment was briefly described and informed consent was obtained from each participant. First, participants were asked to complete the MOCA (Nasreddine et al., 2005) for the evaluation of general cognitive ability. Second, mood (PHQ-9; Kroenke & Spitzer, 2002), anxiety (STAI-Y; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) and cognitive reserve (CRIq; Nucci, Mapelli, & Mondini, 2012) were assessed. Third, participants completed a computer-based task exploring memory performance (STeM test). All the tests were described in Chapter 3 (paragraph 3.3.3.) The STeM test included a picture naming task followed by immediate free recall of 32 stimuli divided in four categories (8 fruits, 8 vegetables, 8 items of clothing and 8 animals). Each item from the same category appeared on the computer screen in a circular array containing 7 black boxes and a target picture (see Figure 5.1). Items were displayed randomly, so that any picture could appear in any of the locations and in any temporal order.

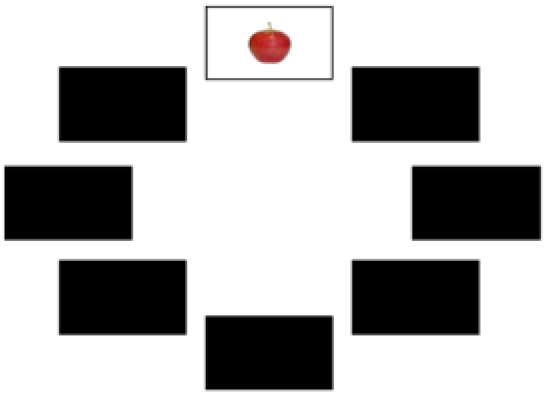


Figure 5.1 An example of the STeM test, wherein apple target is displayed in spatial location 1.

In the retrieval phase, participants were asked to freely recall items presented, in any order. In order to avoid semantic interference, retrieval was performed after each category was presented. The output order of recall was examined to calculate general memory performance (STeM total recall), spatial (STeM-S) and temporal (STeM-T) clustering.

Cognitive abilities were further assessed using the TMT (Reitan, 1986), Digit Span (Wechsler, 1955) and the DSS (Wechsler, 1955). The entire experiment took one hour to complete.

5.2.3 Data analysis

Five younger participants were excluded from the analyses, as they scored significantly low on the MOCA (< 25). Therefore, data analysis was performed on forty-five younger participants and forty-five older adults. All assumptions were met to perform the following analyses. Temporal and spatial contiguity scores were calculated as explained in Chapter 3 (paragraph 3.3.5.1). In addition to the main analysis, the procedure defined by Healey (2018) was followed. Since temporal and spatial scores may be confounded by several factors, values obtained from Polyn et al.'s (2009) procedure were corrected by chance. A permutation distribution was created by randomly shuffling the order of recall within the sequence 10,000 times and computing a temporal score for each shuffle. The actual temporal and spatial factor scores were then converted into z-scores by subtracting the permutation's mean and dividing by its standard deviation.

A two-way mixed ANOVA was conducted to determine whether there were differences between younger and older participants (group: between-subject variable) on temporal (STeM-T) and spatial (STeM-S) clustering (clustering: within-subject variable). The same analysis was performed on unadjusted temporal and spatial scores, in order to assess the accuracy of Polyn et al.'s (2009) method. Age-related differences in both demographics and cognitive performance were explored with t-tests for normally distributed data, and Mann-Whitney test for not normally distributed data. Finally, a Spearman's correlation was performed to investigate the relationship between contiguity effects and cognitive measures.

5.3 Results

Descriptive statistics with demographic data along with Mann-Whitney test are reported in Table 5.1. As expected (Jorm, 2000), younger adults showed higher levels of depression (Mdn = 4; U = 647.500, z = -3.334, p = .001, r = .35) and anxiety (Mdn = 38; U = 639, z = -3.394, p = .001, r = .36) when compared to older participants (Depression: Mdn = 2.00; Anxiety: Mdn = 31). Consistent with previous findings (Nucci et al., 2012; Opdebeeck, Martyr, & Clare, 2016), older adults reported significantly higher cognitive reserve (Mdn = 129) compared to younger participants (Mdn = 92), U = 49.500, z = 7.777, p < .001, r = .82. No statistically significant differences were observed between the two groups for general cognitive functioning with MOCA (U = 831, z = -1.485, p = .138) and for Digit Span (U = 929, z = -.683, p = .494). Performance in the TMT for the younger group (A: Mdn = 22; B: Mdn = 51) was significantly higher than for older adults (A: Mdn = 32; B: Mdn = 82), TMT-A: U = 515.500, z = -4.013, p < .001, r = .42, TMT-B: U = 419.500, z = -4.787, p < .001, r = .50. Additionally, DSS scores for younger participants (Mdn = 67) were statistically higher than for older adults (Mdn = 51),

U = 261, z = -6.067, p < .001, r = .64. Group differences on the TMT and the DSS were expected given the typical age-related decline of speed and flexibility.

Table 5.1 Demographics and comparisons of cognitive performance in younger and older participants

Measures	**Younger (n = 45)**	**Older (n = 45)**	***p***
	Mean (Standard Deviation)		
Age	21.64 ± 1.86	70 ± 7	
Gender (females)	31 (69%)	25 (56%)	.196
Years of education	16.44 ± 1.34	14.33 ± 3.30	.008
	Mean Rank (Sum of Ranks)		
MOCA	49.53 (2229.00)	41.47 (1866.00)	.138
PHQ-9	53.83 (2422.50)	37.17 (1672.50)	.001
STAI-Y	53.99 (2429.50)	37.01 (1665.50)	.001
CRIq	22.50 (990.00)	67.00 (3015.00)	<.001
TMT-A	34.46 (1550.50)	56.54 (2544.50)	<.001
TMT-B	32.32 (1454.50)	56.54 (2544.50)	<.001
Digit-Span Backward	43.36 (1964.00)	47.64 (2144.00)	.419
Digit-Span Forward	43.19 (1943.50)	47.81 (2151.50)	.372
Digit-Span Total	43.64 (1964.00)	47.36 (2131.00)	.494
DSS	62.20 (2799.00)	28.80 (1296.00)	<.001
STeM Total Recall	50.38 (2267.00)	40.62 (1828.00)	.072

Note. STeM = Spatio-Temporal Memory Test; MOCA = general cognitive assessment; PHQ-9 = Depression questionnaire; STAI-Y = Anxiety Scale; CRIq = Cognitive Reserve questionnaire; TMT = Trail Making Test; DSS = Digit Symbol Substitution test.

5.3.1 Memory performance

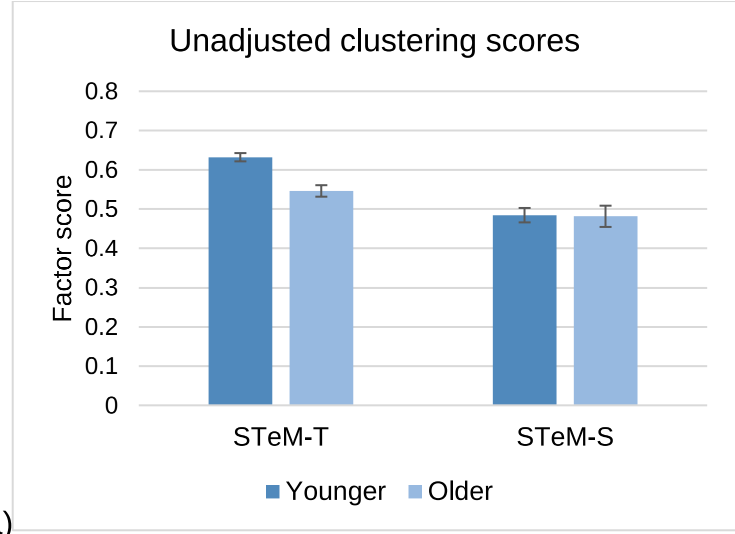
No statistically significant difference in free recall was found between young (*Mdn* = 28) and older (*Mdn* = 28) groups for the STeM total recall, U = 793.000, z = -1.801, p = .072.

However, results from the two-way ANOVA showed a significant interaction between type of clustering and group for both scores calculations (adjusted: $F(1, 88)$ = 14.049, *MSE* = 3.477, p < .001, *partial* η^2 = .138; unadjusted: $F(1, 88)$ = 14.049, *MSE* = .083, p < .001, *partial* η^2 = .138). Simple main effects were investigated. Mean STeM-T was significantly greater in the younger group (adjusted = .848; unadjusted = .632) compared to older participants (adjusted

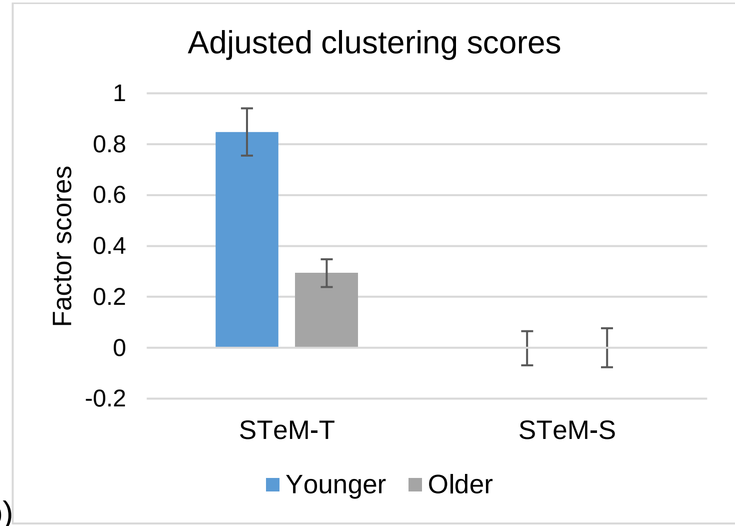
= .295; unadjusted = .546), adjusted: $F(1, 88) = 22.790$, $MSE = .302$, $p < .001$; unadjusted: $F(1, 88) = 22.790$, $MSE = .165$, $p < .001$, a mean difference of .554 (CI 95%, .323 to .784) for adjusted scores and .086 (CI 95%, .050 to .121) for unadjusted scores.

STeM-S was not significantly different between the two groups (adjusted: $F(1, 88) = .001$, $p = .980$; unadjusted: $F(1, 88) = .001$, $p = .980$). Moreover, both groups showed preference for STeM-T rather than STeM-S (adjusted: $F(1, 88) = 59.602$, $MSE = .284$, $p < .001$; unadjusted: $F(1, 88) = 59.602$, $MSE = .284$, $p < .001$), a mean difference of .573 (CI 95%, .425 to .720) for adjusted scores, and .089 (CI 95% .066 to .111) for adjusted scores. Figure 5.2 shows adjusted and unadjusted scores for temporal and spatial contiguity.

Since the older group included participants from a wide age range (50 – 88 years old), these analyses were repeated with a sample composed of 37 older adults aged at least 65 years old, in order to better explore potential age differences. Previous results were confirmed with a significant interaction between group and clustering (adjusted: $F(1, 80) = 13.019$, $MSE = 3.423$, $p = .001$, *partial* $\eta^2 = .140$, unadjusted: $F(1, 80) = 13.019$, $MSE = .082$, $p = .001$, *partial* $\eta^2 = .140$). Younger adults showed greater STeM-T compared to the older group (adjusted: $F(1, 80) = 23.734$, $MSE = .317$, $p < .001$; unadjusted: $F(1, 80) = 23.734$, $MSE = .180$, $p < .001$), a mean difference of .609 (95% CI, .360 to .857) for adjusted scores and .094 (CI 95%, .056 to .133) for unadjusted scores. No difference was found for STeM-S (adjusted: $F(1, 80) = .079$, $p = .780$; unadjusted: $F(1, 80) = .079$, $p = .780$).



a)



b)

Figure 5.2 Temporal (STeM-T) and spatial (STeM-S) factor scores of older and younger groups on the STeM test. Bars indicate standard error. (a) STeM-T and STeM-S calculated following Polyn et al.'s (2009) method; (b) STeM-T and STeM-S corrected with Healey's (2018).

Finally, a Spearman's rank-order correlation (Table 5.2) was conducted to assess the relationship between memory associations and cognitive performances in both groups separately. Results from adjusted scores are reported. In the younger group, there was a statistically significant negative relationship between STeM-T and TMT-B, $r_s(45) = -.380$, $p = .010$ and a positive relationship between STeM-T and DSS, $r_s(45) = .349$, $p = .019$. No statistically significant relationship was found in the older group, as reported in Table 5.2. The same results were obtained utilising unadjusted factor scores.

Table 5.2 Correlation between Cognitive performance and memory clustering

Measures	Younger		Older	
	STeM-T	***STeM-S***	***STeM-T***	***STeM-S***
TMT-A	-.257	-.085	-.188	-.085
TMT-B	-.380**	.039	-.115	-.228
Digit-Span Backward	-.034	.067	.154	.053
Digit-Span Forward	-.019	-.020	.275	-.031
Digit-Span Total	-.013	.015	.256	.029
DSS	.349*	.111	-.030	-.049

Note. ** = correlation significant at p < .01. * = correlation significant at p < .05.

5.4 Discussion

The aim of the present study was to investigate age effects on spatial and temporal associative memory in free recall. No differences were found in memory total recall between younger and older participants. However, differences in clustering styles were observed, as the younger group showed higher temporal contiguity compared to older adults, although in the latter group preference for temporal rather than spatial clustering was maintained.

Relevant age-related differences were also found on depression and anxiety symptoms, which younger adults showed more compared to older participants. This finding paralleled existing literature, where depression and anxiety have been consistently shown to decrease with aging (for a review: Jorm, 2000) as a consequence of the appearance of a positivity effect in emotional regulation in the elderly (Bruno, Brown, Kapucu, Marmar, & Pomara, 2014; Carstensen & Mikels, 2005). No differences were detected in cognitive general functioning (MOCA) between groups. This result was explained by the fact that the older sample was composed of cognitively intact individuals with no history of neurological disorders and with high level of education, which may have mitigated differences between the two groups. Differences between groups were however observed in some cognitive tests measuring frontal executive functions (TMT and DSS), wherein older participants performed more poorly than the younger group. These findings were consistent with age-related decline in tasks involving attention, processing speed, visual search and flexibility (Raz, 2000).

As aforementioned, performance on the STeM test also showed differences between groups. Specifically, the results revealed that younger participants tended to remember by prioritising use of temporal rather than spatial contiguity when compared to older adults, who showed less preference in clustering. Notably, this pattern was maintained when increasing the age floor to 65 years old for the older group.

The pattern shown by older adults was therefore analogous to what Kahana, Howard, Zaromb and Wingfield (2002) observed using immediate and delayed recall of lists of words to examine the contribution of recency and contiguity on memory retrieval. When prompted to recall items after a learning and a distractor phase, older adults were less likely to recall words from neighbouring input positions in succession, when compared to younger participants. The authors suggested that a temporal association deficit may contribute to age-related impairment in free recall. Similar findings were reported by Golomb et al. (2008), where older adults were unable to neutralise the previous used semantic strategy and showed difficulty maintaining temporal associations. Results from present study therefore confirmed the previous findings about temporal contiguity, whilst providing novel information regarding spatial contiguity in older adults and how these associative memories are employed in opposition. Although individuals have been found to increasingly rely on semantic, compared to temporal, memory associations as they age (Golomb et al., 2008), no studies had so far explored whether spatial clustering may be preferred over temporal contiguity. In the current study, contrary to the initial hypothesis, spatial contiguity was not preferred to temporal clustering in older adults to compensate for the age-related temporal clustering deficiency. These results may be due to the fact that, although older adults showed lower temporal contiguity than younger participants, their memory performance (i.e., total recall) was comparable to that of the younger group, thus suggesting a compensation mechanism was not needed.

The temporal associative deficit is also in line with the associative deficit hypothesis (Naveh-Benjamin, 2000) (Chapter 2, paragraph 2.3.5), where the ability to form and retrieve associations plays a role in age-related memory impairment. Specifically, Naveh-Benjamin (2000) found that memory performance was not affected by age when participants encoded unrelated items. However, older adults encountered a deficiency for associative processes, when they were requested to form and retrieve links between items of information. Study 2 findings suggested that this deficit was experienced also when the to-be-remembered information was spontaneously associated and it was specific to temporal organization. Similarly, Parkin et al. (1995) found that older adults experienced a marked decline in memory for temporal order (Exp. 1) compared to younger adults, although no age effect was detected for spatial order (Exp. 2), when a simple form of spatial discrimination was adopted in a simultaneous spatiotemporal memory experiment. In the present study a comparable pattern was found, despite the fact that temporal and spatial contiguity were investigated in the same experiment, and in opposition, rather than simultaneously. Although confirming the age-related deficit for temporal clustering, older adults' memory performance was not affected.

Temporal clustering has been linked to age-related episodic memory impairment (Bruno, Grothe, et al., 2016; Sumida et al., 2016), and suggested as a selective marker of Alzheimer's disease (Gillis et al., 2013). Accordingly, these findings showed that temporal clustering may be a valid marker for early diagnosis of cognitive decline not only in clinical population, but also in participants who do not show any memory impairment at total recall.

Moreover, these results were repeated by utilising the clustering score calculated with the method ideated by Polyn et al. (2009), thus confirming the accuracy of factor scores in detecting use of temporal and spatial clustering in different age groups.

The correlation analysis showed that temporal clustering in younger adults was positively associated to TMT-B and DSS, which reflects cognitive processes included in the domain of executive functions, such as attention, sequencing and shifting, speed processing and flexibility. It is therefore possible that temporal contiguity may be affected by tasks that interfere with full attention processes (i.e., divided attention) or when items' presentation involves greater cognitive processing during presentation (e.g., lexical vs. pictorial presentation). These hypotheses were explored in Study 3.

Chapter 6 Exploring the effects of divided attention and type of stimulus on associative memory in younger and older adults.

Study 3 was presented at the British Psychological Society – Cognitive section 2018 meeting (Liverpool, UK).

6.1 Introduction

6.1.1 Effects of Divided Attention tasks

The Divided Attention (DA) paradigm postulates that performing a secondary task while encoding new information has a deleterious effect on memory performance in both younger and older adults, compared to conditions where items are encoded at full attention (Anderson & Craik, 1974; Craik, Naveh-Benjamin, Govoni, & Anderson, 1996; Murdock, 1965; Naveh-Benjamin et al., 2005). Older adults also seem to be more affected than younger adults in high-demanding DA tasks, such as those involving conceptual processing (e.g., counting tasks), rather than in tasks requiring low-demand DA, such as perceptual-motor processing (e.g., pressing the keyboard when hearing a tone; Naveh-Benjamin et al., 2005). DA effects on memory performance have been explained by the fact that encoding requires frontal control and attention, therefore dividing attention between two tasks interferes with appropriate registration of new information (Naveh-Benjamin, Guez, Hara, Brubaker, & Lowenschuss-Erlich, 2014). The DA effect has been found in several experimental paradigms, including incidental and intentional tasks, free recall and recognition of verbal material (Naveh-Benjamin et al., 2014). Furthermore, previous findings showed that both memory for temporal order and spatial location may be affected by DA (Naveh-Benjamin, 1987, 1990). For instance, in one experiment with undergraduate students Naveh-Benjamin (1987) found that performing a secondary counting task while encoding spatial locations of objects negatively affected recall of spatial locations during the retrieval phase. Similarly, Naveh-Benjamin (1990) found equivalent results when testing memory for temporal order, which was affected by a secondary counting task at encoding. These findings suggest that DA at encoding may have detrimental effects also on contiguity effects, although no study has so far explored this hypothesis.

6.1.2 Effects of material

The Picture Superiority Effect (PSE), that is the tendency to recall pictures better than words, has been repeatedly found in both younger and older adults (Mintzer & Snodgrass, 1999; Park, Puglisi, & Sovacool, 1983) and in patients with Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) (Ally, Gold, & Budson, 2009). The PSE has been observed during tasks of free recall and recognition (Paivio, 1976; Paivio, Rogers, & Smythe, 1968), and of spatial memory, where participants remembered better spatial locations of pictures relative to words (Smith & Park, 1990). Since Study 2 of the present thesis used pictorial material for the STeM test, it is possible that temporal and spatial contiguity may have been influenced by the PSE. Although no study has specifically addressed the PSE on contiguity effects, previous research showed that temporal contiguity is found with both verbal and pictorial stimuli (Healey, Long, & Kahana, 2018), thus suggesting that type of material may not influence how events are organised in memory, although influencing general memory performance.

In the current study, the effect of material and DA at encoding on memory performance and on associative memory was investigated in younger and older adults. Specifically, it was hypothesised that: 1) Performing a secondary task during encoding would affect use of contiguity effects and total recall in all participants; 2) Type of material would not negatively affect use of contiguity in all participants; 3) Older adults, compared to younger adults, would show a deficit in temporal contiguity.

6.2 Method

6.2.1 Participants

The study was approved by the Liverpool John Moores University Research Ethics Committee (UREC). Thirty participants per group were recruited for the study. Younger participants (mean age 19.71 ± 2.22, 5 males) were students from LJMU. Older adults (mean age 67.70 ± 8.37, 7 males) were volunteers from the MeNu participants' pool or recruited from the University of Third Age. Inclusion criteria included being fluent in English, having no history of a major clinical condition or psychiatric disease, being at least 50 years old if older, and between 18 and 25 if younger.

6.2.2 Materials and procedure

The experiment was briefly described and formal consent was obtained from each participant. The entire experiment took one hour to complete and participants were reimbursed for their time with a £10 voucher or 3 university credits (the latter only applied to LJMU students). The same procedure of Study 2 was employed to examine cognitive abilities (i.e., MOCA, TMT, DSS, Digit span) and psychological status (i.e., PHQ-9, STAI) (see Chapter 5, paragraph 5.2.2). A computer-based Stroop test was added as a further measure of attention abilities (Stroop, 1935) (see Chapter 3, paragraph 3.3.3.3.5). The four tasks of the STeM test were modified in order to include two DA and two Full Attention (FA) conditions, each of which involving presentation of pictorial or verbal stimuli. In the DA conditions, participants were asked to simultaneously name items presented on the computer screen and to count distracting beeps, then they were prompted to type on the computer keyboard the total number of tones, before proceeding to the retrieval phase. Items were presented verbally in one condition and as images in the second condition. In the FA conditions, participants were required to name items appearing on the computer screen and to then freely recall them. In one FA condition images were used, whilst in the second FA condition words were used. Given that the STeM test included 4 different categories (fruit, animals, items of clothing and vegetables), the four conditions (FA-words, FA-images, DA-words, DA-images) were counterbalanced across participants in order to test each category at every possible condition. This resulted in 7 participants per group to be tested per each of the four STeM versions.

6.2.3 Data analysis

Due to technical problems with the STeM test during one experimental session and to the presence of outliers, two participants per group were excluded. The resulting twenty-eight participants per group were included in the statistical analyses. Temporal and spatial contiguity per each category, as well as the neuropsychological and psychological tests, were calculated as described in Chapter 3 (paragraph 3.3.5.1). To determine whether there were differences between younger and older participants in both demographics and cognitive performance, independent-sample t-tests and the Mann-Whitney U test were run for normally and not normally distributed data. Finally, mixed design ANOVAs were performed to explore differences amongst participants and conditions. Specifically, group (younger vs. older) was the between-subjects variable and type of material (words vs. pictures) and distractor condition (DA vs. FA) were the within-subjects variables when the dependent variable was general memory performance (2×2×2 mixed ANOVA). When spatial and temporal clustering were investigated, type of clustering was added to the design (2×2×2×2 mixed ANOVA).

6.3 Results

Descriptive statistics with demographic data along with Mann-Whitney tests are reported in Table 6.1. Similar to Study 1, younger adults showed higher levels of depression (*Mdn* = 6; $U = 120.500$, $z = -4.491$, $p < .001$, $r = .60$) when compared to older participants (*Mdn* = 2), although no differences were reported for anxiety levels, $U = 288.500$, $z = -1.698$, $p = .089$. No statistically significant differences were observed in the two groups for general cognitive functioning with the MOCA test ($U = 373$, $z = -.314$, $p = .753$) and the Digit Span ($U = 310$, $z = -1.174$, $p = .240$). Performance in the TMT for the younger group (A: *Mdn* = 22.5; B: *Mdn* = 52.5) was statistically significantly higher than for older adults (A: *Mdn* = 37; B: *Mdn* = 73.5), TMT-A: $U = 160.500$, $z = -3.798$, $p < .001$, $r = .51$, TMT-B: $U = 254.500$, $z = -2.254$, $p = .024$, $r = .30$. DSS scores for younger participants were statistically higher than for older adults, $t(54) = 4.414$, $p < .001$, $d = .59$. Moreover, performance in the Stroop test was significantly higher for the younger group compared to older adults, $t(54) = -2.125$, $p = .011$, $d = .28$.

Table 6.1 Demographics and comparisons of cognitive performance in younger and older participants

Measures	**Younger (n = 28)**	**Older (n = 28)**	***p***
	Mean (Standard Deviation)		
Age	19.71 ± 2.22	67.70 ± 8.37	-
Gender (females)	23 (82%)	21 (75%)	.524
Years of education	14.89 ± 2.22	14.36 ± 3.28	.477
Digit Symbol Substitution	64.29 ± 8.98	50.21 ± 14.27	<.001
Stroop test	61.03 ± 64.94	164.87 ± 250.31	.038
STeM Total Recall FA-W	6.31 ± .81	6.82 ± 1.19	-
STeM Total Recall DA-W	5.21 ± 1.37	5.43 ± 1.26	-
STeM Total Recall FA-I	6.78 ± .83	6.64 ± 1.13	-
STeM Total Recall DA-I	6.35 ± .78	6.54 ± .83	-
	Mean Rank (Sum of Ranks)		
MOCA	27.82 (779.00)	29.18 (817.00)	.753
PHQ-9	38.20 (1069.50)	18.80 (526.50)	<.001
STAI-Y	32.20 (901.50)	24.80 (694.50)	.089
TMT-A	20.25 (565.50)	36.09 (974.50)	<.001
TMT-B	22.59 (632.50)	33.61 (907.50)	.011
TMT (B-A)	25.55 (715.50)	30.50 (824.50)	.249
Digit Span - Forward	26.29 (736.00)	30.71 (860.00)	.287
Digit Span - Backward	26.21 (734.50)	30.79 (862.50)	.265
Digit Span Total	26.20 (733.00)	30.80 (862.00)	.277

Note. STeM = Spatio-Temporal Memory test with Words (W) or Images (I), at Full Attention (FA) or Divided Attention (DA); MOCA = general cognitive assessment; PHQ-9 = Depression questionnaire; STAI-Y = Anxiety Scale; CRIq = Cognitive Reserve questionnaire; TMT = Trail Making Test; DSS = Digit Symbol Substitution test.

6.3.1 Memory performance

The three-way mixed ANOVA on general memory performance found a significant interaction between material (words vs. pictures) and condition (DA vs. FA), $F(1, 54) = 37.633$, $MSE = .848$, $p < .001$, *partial* $\eta^2 = .411$, although no effect of age was reported, $F(1, 54) = .002$, $p = .962$. There was a statistically significant main effect of material, $F(1, 55) = 23.356$, $MSE = .976$, $p < .001$, *partial* $\eta^2 = .298$, and of condition, $F(1, 55) = 13.650$, $MSE = .977$, $p = .001$, *partial* $\eta^2 = .199$. Pairwise comparisons were performed for statistically significant simple main effects. Bonferroni corrected *p*-values are reported. Total recall at DA was higher for pictorial material than for verbal material, a mean difference of 1.393 (95% CI, 1.008 to 1.777), *p* < .001. Total recall of words was higher at the FA condition than during the DA task, a mean difference of 1.243 (95% CI, .834 to 1.652), *p* < .001. These results (Figure 6.1) confirmed the deleterious effect of DA and the PSE for words, which is evident during DA tasks.

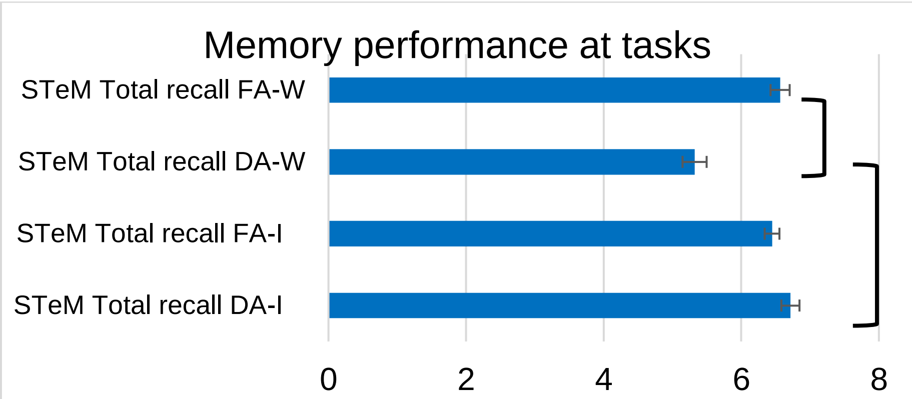


Figure 6.1 Chart shows means and standard deviations. FA-W = Full-Attention with Words condition; DA-W = Divided-Attention for words condition; FA-I = Full-Attention for Images condition; DA-I = Divided-Attention for Images condition. Bars indicate p value < .001.

The four-way mixed ANOVA showed no significant interactions. Specifically, there was no four-way interaction between type of clustering, group, material and condition, $F(1, 54) = 1.377$, $p = .246$. There was no significant three-way interaction between type of clustering, material and condition, $F(1, 54) = .927$, $p = .340$. There was no significant three-way interaction between type of clustering, group and condition, $F(1, 54) = .033$, $p = .857$. There was no significant two-way interaction between type of clustering and group, $F(1, 54) = 2.091$, $p = .154$. There was no significant two-way interaction between condition and group, $F(1, 54) = 1.070$, $p = .306$. There was no significant two-way interaction between material and group, $F(1, 54) = .807$, $p = .373$. There was no significant two-way interaction between condition and type of clustering, $F(1, 54) = .661$, $p = .420$. There was no significant main effect of condition, $F(1, 54) = 1.467$, $p = .231$. There was no significant main effect of material, $F(1, 54) = 1.720$, $p = .195$.

A significant main effect of type of clustering was found, $F(1, 54) = 37.818$, $MSE = .929$, $p < .001$, *partial* $\eta^2 = .412$. Specifically, temporal contiguity (.580 ± .013) was preferred to spatial contiguity (.489 ± .011) in all participants and conditions, a mean difference of .091 (95% CI, .061 to .121), $p < .001$ (Figure 6.2).

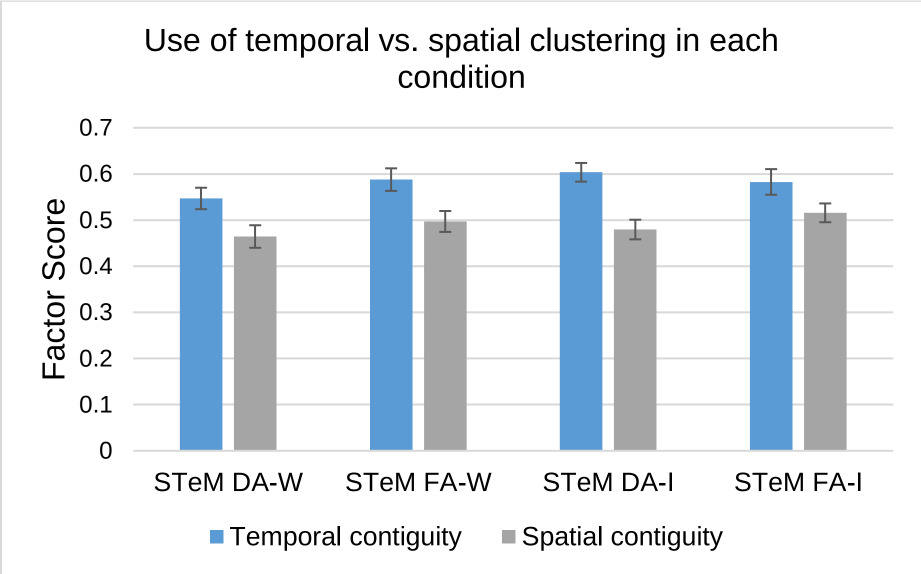


Figure 6.2 Temporal and spatial contiguity at divided attention (DA) and full attention (FA) for words (W) and images (I). Bars include standard errors.

6.4 Discussion

The current study investigated the influence of DA tasks and type of material on temporal and spatial contiguity, in different age groups. In line with previous research, the PSE was found to affect general memory performance positively during DA, whereas DA interfered with encoding of verbal material. Temporal and spatial contiguity did not differ across conditions, with temporal contiguity being preferred invariably. Age did not affect memory performance or use of associative processes. These results will be discussed in the next sections.

6.4.1 Memory performance

In line with the literature, DA affected memory performance, specifically when verbal stimuli were used. In conditions where pictorial stimuli were presented, participants showed minimal differences in performance between FA and DA condition. Whilst demonstrating the influential role of attention in memory encoding, these findings also confirmed PSE appears to be affected by attentional resources. This was, to the authors' knowledge, the first study to explore the effect of divided attention on PSE in episodic memory. Paivio (1991) suggested that pictures and words may be cognitively stored in two separates, but interconnected, systems, which utilise representations in image or verbal codes respectively. It is therefore possible that these systems require different level of processing that may or may not be disrupted by secondary competing tasks. According to the level of processing hypothesis (Craik & Lockhart, 1972), described in Chapter 1 (paragraph 1.1.1), it may be speculated that verbal material requires a deeper level of analysis than pictorial information. From a neuroscientific point of view, the fact that DA tasks influence encoding of lexical, but not pictorial, material may be due to the different neural pathways followed by these processes. Whilst DA and verbal encoding have been linked to activation of the left prefrontal cortex (PFC) (Iidaka et al., 2000), encoding of nonverbal material seems to activate both PFC hemispheres, as well as temporal areas (Grady, Mcintosh, Rajah, Beig, & Craik, 1999; Kelley et al., 2018).

6.4.2 Associative processes

Temporal contiguity was preferred to spatial contiguity in all conditions, independent of the age group. No differences were however reported in the amount of temporal associations during DA versus FA conditions and by utilising verbal versus pictorial material.

In line with the initial hypothesis, temporal contiguity was not affected by presentation modality, given that it did not increase when pictorial, rather than verbal, stimuli were presented. These findings were in line with previous research showing clear temporal contiguity effects when using simple or more complex pictures (Nguyen & McDaniel, 2015) and in recall of complex memories (Moreton & Ward, 2010).

However, the hypothesis that contiguity effects would be affected by DA tasks was not confirmed, as temporal contiguity did not differ between DA and FA conditions. Rather than an absence of relation between attentional processes and contiguity effects, these findings may suggest that contiguity effects are related to retrieval rather than encoding processes. Therefore, DA tasks may not have affected temporal contiguity because they were presented at encoding. Previous studies speculated that associations are formed at retrieval to perform better on memory tests (Kahana, 1996; Sederberg et al., 2010). However, no study had specifically investigated such assumptions. Future research may explore the effect of DA tasks on temporal contiguity at retrieval, in order to confirm this hypothesis.

Age was not found to affect memory performance and associations. Although it was previously shown that younger and cognitively highly performing older adults may perform alike at memory tests (Cabeza et al., 2002), age-related deficit in temporal clustering has been reported repeatedly (Wingfield & Kahana, 2002), including in Study 2 of this thesis (see Chapter 5), where the STeM test was utilised. Given that analyses were conducted for each trial (of 8 stimuli), rather than the averaged four trials used in Study 2 (8 stimuli × 4 trials), a lack of variance may be the most plausible explanation. In order to test this hypothesis, temporal and spatial contiguity were averaged amongst trials and a two-way ANOVA was performed with group as between-subject variable (younger vs. older) and type of clustering as within-subject variable (temporal vs. spatial). A significant interaction was found between the two variables, $F(1, 54) = 4.999$, $MSE = .028$, $p = .030$, *partial* $\eta^2 = .085$. Post-hoc analyses showed that use of temporal contiguity was greater in both younger (.608 ± .016) and older adults (.573 ± .016), compared to the use of spatial contiguity (younger: .475 ± .015; older: .504 ± .015), a mean difference of .133 (95% CI, .093 to .173) in younger adults, and .070 (95% CI, .030 to .110) in older adults. However, no differences between groups were found for temporal ($F(1,54) = 2.411$, $p = .126$) and spatial ($F(1,54) = 1.778$, $p = .188$) contiguity. These results showed that the absence of age-related effects on contiguity effects was not related to a lack of variance.

Study 3 results showed that, contrary to general memory performance, contiguity effects are not affected by lower attentional resources at encoding or type of material. For this reason, these findings implicitly show that temporal contiguity is involved in retrieval rather than encoding processes.

Chapter 7 Age-related prefrontal cortex activation in associative memory: an fNIRS study.

Study 4 was submitted for publication to *NeuroImage* in September 2019 and presented at the International Society for fNIRS 2018 Conference (Tokyo, Japan) and at the Liverpool Neuroscience Day 2019 meeting (Liverpool, UK).

7.1 Introduction

In Study 4, the neural substrates of contiguity effects were examined, in order to shed light on the age-related change in associative memory and its neural bases.

An unavoidable consequence of older adulthood is age-related brain decline, which manifests with gradual loss of hemispheric specialization (Cabeza et al., 1997), amongst other symptoms (Agbangla et al., 2017; Bertsch et al., 2009; Jernigan et al., 2001; Pakkenberg et al., 2003). The Hemispheric Asymmetry Reduction in Older adults (HAROLD) model (Cabeza, 2002) postulates that reduced lateralization, particularly in the prefrontal cortex (PFC), yields activation of bilateral or opposite areas to those typically utilised in younger adulthood, probably as an attempt to counteract age-associated neurocognitive decline (see Chapter 2, paragraph 2.3.6). Furthermore, the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) model (Reuter-Lorenz & Cappell, 2008) suggests that these compensatory mechanisms allow older adults to achieve an equal level of performance as their younger peers in low demanding tasks, but not in high demanding tasks, where the compensation strategy may fail to overcome the age-related brain decline (see Chapter 2, paragraph 2.3.7). A typical pattern shown in younger adults, for example, implicates activation of the left PFC during learning of new memories (encoding), whilst retrieval causes activation of the right PFC. These observations have been reported using both verbal and non-verbal information (Habib, Nyberg & Tulving, 2003) and are described in the Hemispheric Encoding/Retrieval Asymmetry (HERA) model (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994) (Chapter 1, paragraph 1.3.1.2). Older individuals, however, show opposite (Cabeza et al., 1997) or bilateral (Cabeza, Anderson, Locantore, & Mcintosh, 2002) patterns, whilst performing similarly to younger adults, consistent with the HAROLD and CRUNCH models. These age-related cerebral changes are related to deficits in a variety of cognitive functions, including episodic memory (Cabeza et al., 2017). However, in the domain of human memory, several phenomena have been explained from a cognitive approach, but still need neuroscientific corroboration.

An example of this issue is illustrated in our understanding of the associative deficit hypothesis (Chapter 2, paragraph 2.3.5). Cognitive studies on episodic memory suggest that age-related memory deficits may be the result of a decreased ability to form associations between items at recall, known as the associative-deficit hypothesis (Naveh-Benjamin, 2000). Temporal contiguity is a form of associative process that permits organization of memories following the temporal order in which events are perceived (Kahana, 1996). Evidence of temporal contiguity is consistently reported in laboratory tasks and is particularly evident in studies of younger adults (Healey & Kahana, 2014). Although some studies have investigated temporal contiguity in association with activity of the temporal lobe (Bruno, Grothe, et al., 2016; Manning, Polyn, Baltuch, Litt, & Kahana, 2011), activation of the PFC has been observed during recall of memory for temporal context (Amiez & Petrides, 2007; Jenkins & Ranganath, 2010) in younger individuals.

Memory for temporal order appears to be particularly challenging for older adults (Craik & Salthouse, 2016; Kausler, 1994; Parkin et al., 1995), and is impaired in individuals with Mild Cognitive Impairment (MCI) (Gillis et al., 2013). Golomb et al. (2008) also observed that, whilst temporal associations were not employed efficiently, older adults tended to retrieve items clustered by semantic category, even when maladaptive for serial recall. These findings suggest that older adults engage alternative associative processes in order to overcome the age-related deficiency in temporal clustering. Given that semantic contiguity has been found persistently in older adults (Healey & Kahana, 2016) and at the cost of efficient memory performance (Golomb et al., 2008), it is possible that other forms of memory organization may be preferred by older adults, as a compensatory cognitive strategy similar to what is suggested by CRUNCH. For instance, when spatial attributes are provided to younger adults, these attributes have been found to influence the output order of recall by increasing spatial contiguity (Miller et al., 2013). Involvement of the hippocampus and PFC have been reported during retrieval of spatial context in younger adults (Burgess et al., 2001; Hayes et al., 2004; Maguire, Frackowiak, & Frith, 1997), thus suggesting that similar areas may be activated during spatial clustering. Although age-related deficits for spatial memory have been previously reported (Old & Naveh-Benjamin, 2008), the current literature suggests that this age-related decline becomes evident only in complex tasks, most probably as consequence of attentional/executive deficits (for a review see: Klencklen, Després, & Dufour, 2012). For instance, Pouliot and Gagnon (2005) showed that, although significantly different, older participants experienced only a minor decrease on recall for spatial locations compared to the younger group. Similarly, Olson et al. (2004) found that younger and older adults showed similar performance on the short-term spatial memory test and that both groups encoded locations relative to other locations. Taken together, these studies suggest that in older adults experiencing deficits in temporal clustering, spatial contiguity may be an efficient alternative form of memory organization.

To the author's knowledge, no study has explored the brain areas specifically involved during spontaneous spatial versus temporal associations in different age groups. It is therefore critical to explore both neural and cognitive substrates of temporal and spatial contiguity in order to understand better how age and cognitive status affects these processes.

The present study was the first to investigate age-related changes in functional PFC patterns during associative processes and age-related differences in the use of temporal vs. spatial clustering in younger adults and in cognitively high- versus low-performing older participants. Moreover, this was the first study to explore these processes and patterns using functional Near-Infrared Spectroscopy (fNIRS) (see Chapter 3 paragraph 3.3.4 for more details on fNIRS technology).

fNIRS is a non-invasive functional neuroimaging technique that detects haemodynamic changes in the human cortex (for a review, see Ferrari & Quaresima, 2012), similar to the fMRI. Based on the optical absorption properties of blood haemoglobin, fNIRS enables calculation of changes in oxygenated haemoglobin (HbO) and deoxygenated haemoglobin (HHb), which are indicators of cortical activation (Jöbsis, 1977). Compared to the fMRI, fNIRS provides better temporal resolution, is relatively insensitive to motion artefacts, user-friendly and potentially portable. These advantages make fNIRS a particularly useful technique in studies with older adults and individuals with dementia (Arenth et al., 2007; Li et al., 2018).

Consistent with previous research presented above, it was hypothesised that: 1) following the HAROLD and CRUNCH models, younger adults would show greater PFC hemispheric specialization during associative memory, compared to the older groups, and 2) older individuals with lower cognitive functioning would employ greater spatial clustering, compared to younger adults, as an alternative to temporal clustering.

7.2 Methods

7.2.1 Participants

Thirty individuals were selected for the study. Ten participants were students recruited from Liverpool John Moores University (*M* = 28.60; *SD* = ± 3.24). Twenty individuals were from the University of Third Age, aged 60 or above (*M* = 69.55; *SD* = ± 5.11). Of these, ten were classified as cognitively high-performing and ten as cognitively low-performing on the basis of performance in the neuropsychological screening (details in the Procedure section). Participants were selected if they reported no current or past diagnoses of neurological diseases, psychiatric disorders and diagnosed neurodegenerative disorders. Participants were required to be fluent in English and right-handed. All participants were also gender-matched. The study was approved by the Liverpool John

Moores University Research Ethics Committee and completed in accordance with the Helsinki Declaration.

7.2.2 Procedure

All participants provided informed consent. Older adults firstly undertook the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), a 20-minute neuropsychological battery used in clinical practice to investigate their cognitive functioning (RBANS is fully described in Chapter 3, paragraph 3.3.3.3.2). Low-performing and high-performing individuals were identified based on a cut-off of 90, the lower average RBANS score. Although significantly different on the RBANS total score, the resulting two groups did not statistically differ in age or years of education (Table 7.1). General cognitive functioning in younger adults was assessed using the MOCA (Chapter 3, paragraph 3.3.3.3.1). Following the administration of these tests, participants completed the memory (STeM) test (see Chapter 3, paragraph 3.3.3.3.7 for details), simultaneously to fNIRS recording. Each older participant was reimbursed with a £15 voucher, whilst each younger participant was given £10 voucher as compensation.

7.2.3 fNIRS instrumentation

The STeM test was preceded by a 2-minute baseline of inactivity, during which participants were asked to relax while listening to music and looking at pictures of landscapes on the computer screen. The baseline recording period was used to calculate changes in the haemodynamic response (details in the following paragraph).

During the STeM test, changes in HbO and HHb were monitored using a 12-channel continuous wave fNIRS device (OxyMon MK III, Artinis Medical System TM, The Netherlands). In all STeM tasks, an event-related design was used and the inter-trial interval was of 10s prior and after the recall of blocks. The short delay was included in order to ensure that participants' acute haemodynamic response had dissipated before the next task started. Sample frequency was set at 10Hz (Basso Moro et al., 2013; Ferreri et al., 2014; Metzger et al., 2016). Changes in light attenuation were measured at two wavelengths (765 and 855 nm) and using the modified Beer-Lambert law. As part of this calculation, the age-dependent differential path-length factor (DPF) was given by the formula: $4.99 + .067 \times (\text{Age}^{.814})$ in young adults (Duncan et al., 1996). Data on variation of DPF in adults aged 50 or above is not currently available, thus, DPF in the older group was set to 6.61 corresponding to age 50, in accordance with previous literature (Claassen, Colier, & Jansen, 2006; Vermeij, Beek, Rikkert, Claassen, & Kessels, 2012).

Three sources and eight detectors were positioned symmetrically over the bilateral PFC, according to the international EEG 10-20 system (Electrode Position Nomenclature Committee, 1994) (see Figure 7.1). The source-detector separation of 2.5 cm allowed for 1.25cm penetration depth (Haeussinger et al., 2011). The investigated cerebral areas were therefore: dorsolateral PFC, anterior PFC and medial PFC, corresponding to Brodmann areas (BAs) 46, 10 and 9.

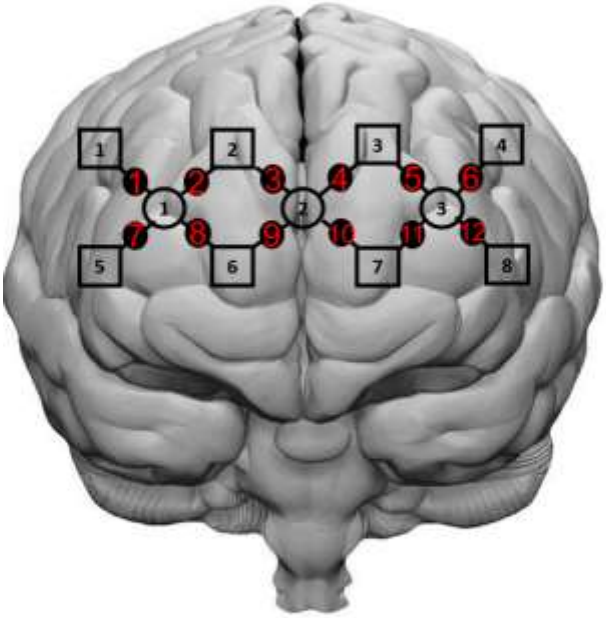


Figure 7.1 12-channels configuration of the fNIRS. Channels are in red. Numbers in squares are transmitters. Numbers in circles are receivers.

7.2.4 fNIRS signal processing

Prior to and during data collection, changes in HbO, HHb and total haemoglobin (tHb) were displayed in real time and signal quality was verified. Data were pre-processed according to the modified Beer–Lambert law logarithm in the OxySoft software (Artinis Medical System TM, the Netherlands). Data were visually inspected. A 2-s moving-gaussian filter was applied to attenuate the noise due to respiration and heart beat frequency. All measurements were relative changes in concentration of HbO and HHb, compared to baseline, since continuous-wave NIRS devices do not allow to determine absolute concentration of HbO and HHb. Specifically, to determine the changes in the haemodynamic response during associative processes, data were baseline-corrected using the mean value of the baseline period. Then, channels were grouped together for analysis, for comparison of regions of the PFC. Channels 1 and 7 were grouped together as the right DLPFC region (BA46). Channels 6 and 12 were grouped together as the left dorsolateral prefrontal cortical (DLPFC) region, corresponding to BA46. 2 and 3, and 4 and 5 corresponded to the right and left medial PFC (BA9), respectively. Channels 8 and 9, and 10 and 11 corresponded to the right and left anterior PFC region (BA10). Finally, HbO and HHb changes from baseline were averaged over the four SteM recall epochs. Following this procedure, which included averaging the haemodynamic response over channels and consequentially over trials, allowed to maintain the variance over sessions (Spüler, 2019).

7.2.5 Statistical analysis

Statistical analyses were performed using SPSS, Version 23 (IBM) and all assumptions were met to perform the following analyses. For behavioural results, an independent-samples t-test was run to identify older adults who were high and low performing, given the RBANS total score. A univariate ANOVA was conducted to analyse group differences on STeM total recall. STeM clustering scores were calculated adopting the method developed by Polyn, Norman and Kahana (2009) (see Chapter 3, paragraph 3.3.5.1). The same analysis was run to compute the spatial clustering score. Therefore, a two-way mixed ANOVA was used to test significant age-related differences in use of temporal or spatial clustering.

For fNIRS data, group differences in HbO and HHb concentrations were analysed using two mixed ANOVA with 2 (location: left, right hemisphere) x 3 (group: younger, low-performers, high-performers) x 3 (BA: 46, 10, 9) factors.

7.3 Results

7.3.1 Behavioural data

Descriptive statistics for demographic data of all groups are reported in Table 7.1, along with t-tests, where differences on general cognitive functioning between low- and high-performing older adults are reported. Data are mean ± standard error, unless otherwise stated.

Table 7.1 Demographics and comparisons of cognitive level in younger adults and in low-/high-performing older participants

Measures	Younger (n=10)	High-performing (n = 10)	Low-performing (n = 10)	*p*
Age	28.60 ± 3.24	68.10 ± 5.59	71 ± 4.40	.213
Females (%)	50%	50%	50%	-
Years of education	20.3 ± 2.00	14.15 ± 2.98	13.1 ± 2.28	.388
RBANS	-	101 ± 2.21	86 ± 2.98	<.001
MOCA	27.20 ± 1.75	-	-	-
STeM Total score	28.1 ± 2.06	28.3 ± 2.06	27.6 ± .69	.322
STeM temporal contiguity	.56 ± .07	.58 ± .09	.53 ± .09	-
STeM spatial contiguity	.50 ± .09	.49 ± .09	.48 ± .09	-

Note. Data are mean ± standard error; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; MOCA = Montreal Cognitive Assessment; p = group differences between cognitively high-performing and low-performing older adults.

A one-way ANOVA was conducted to investigate differences between groups on the STeM total recall. This was non-significant $F(1, 27) = .225$, $p = .800$, suggesting no overall difference in recall across the groups. Moreover, a two-way mixed ANOVA revealed no statistically significant interaction between group and clustering, $F(1, 27) = .174$, $p = .841$. However, the main effect of clustering (Figure 7.2) showed a statistically significant difference, $F(1, 27) = 6.495$, $MSE = 2.544$, $p = .02$, $r = .19$, and revealed general greater preference for temporal clustering compared to spatial clustering, a mean difference of .41 (95% CI, .80 to .74).

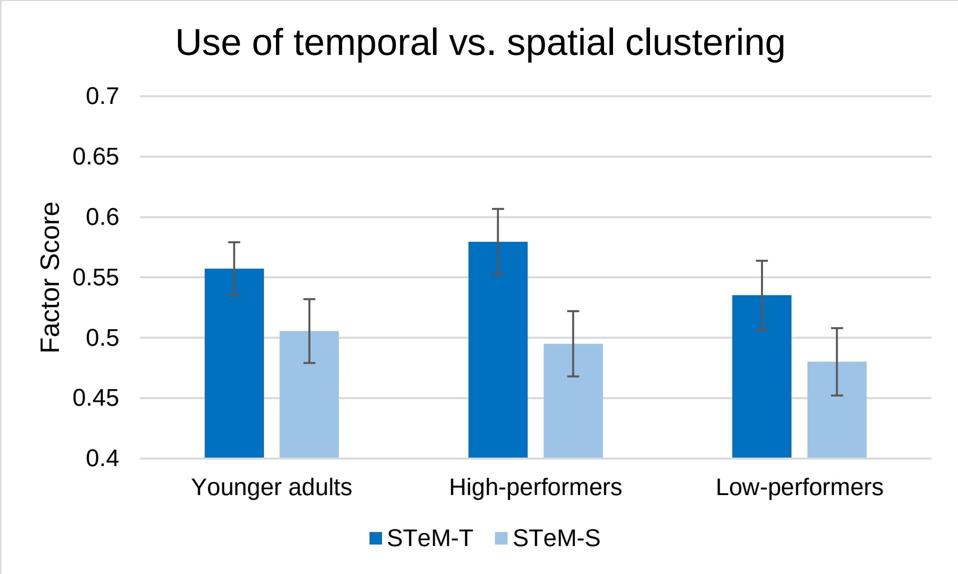


Figure 7.2 Temporal (STeM-T) and spatial (STeM-S) factor scores of older and younger groups on the STeM test. Bars indicate standard error.

7.3.2 fNIRS data

A three-way mixed ANOVA was performed in order to explore PFC HbO and HHb changes during the retrieval phase of STeM. Contrasts were used to investigate the interactions. There was a significant three-way interaction effect between BA (46, 10, 9), location (right and left hemisphere) and group (younger vs. low-performers vs. high-performers) (HbO: $F(4, 54) = 11.561$, $MSE = 5.540$, $p < .001$, *partial* $\eta^2 = .461$; HHb: $F(4, 54) = 3.215$, $MSE = 1.709$, $p = .019$, *partial* $\eta^2 = .192$). The first two contrasts revealed no significant group differences when comparing changes in right and left oxygenation in BA46 (HbO: $F(2, 27) = 1.352$, $p = .276$; HHb: $F(2, 27) = 1.388$, $p = .267$) and BA9 (HbO: $F(2, 27) = 1.059$, $p = .361$; HHb: $F(2, 27) = .545$, $p = .586$).

The third contrast investigated group differences when comparing right and left oxygenation changes in BA10 (Figure 7.3). These were significant for right BA10 (HbO: $F(2, 27) = 10.559$, $MSE = 5.515$, $p < .001$, *partial* $\eta^2 = .439$; HHb, $F(2, 27) = 6.700$, $MSE = 3.703$, $p = .004$, *partial* $\eta^2 = .332$) and left BA10 (HbO:

$F(2, 27) = 12.854$, $MSE = 6.308$, $p < .001$, *partial* $\eta^2 = .488$; HHb, $F(2, 27) = 2.120$, $p = .140$). Bonferroni corrections were applied for between-subject comparisons and adjusted p-values are reported. HbO changes were higher for right BA10 in younger adults (.788 ± .23) compared to the high-performing older group (-.687 ± .23), a mean difference of 1.475 (95% CI, .659 to 2.3), $p < .001$, and compared to the low-performing older group (-.102 ± .23), a mean difference of .890 (95% CI, .065 to 1.714), $p = .031$. HHb changes were greater for right BA10 in high-performing older adults (.582 ± .23) compared to younger participants (- .629 ± .23), a mean difference of 1.211 (95% CI, .362 to 2.059), $p = .003$.

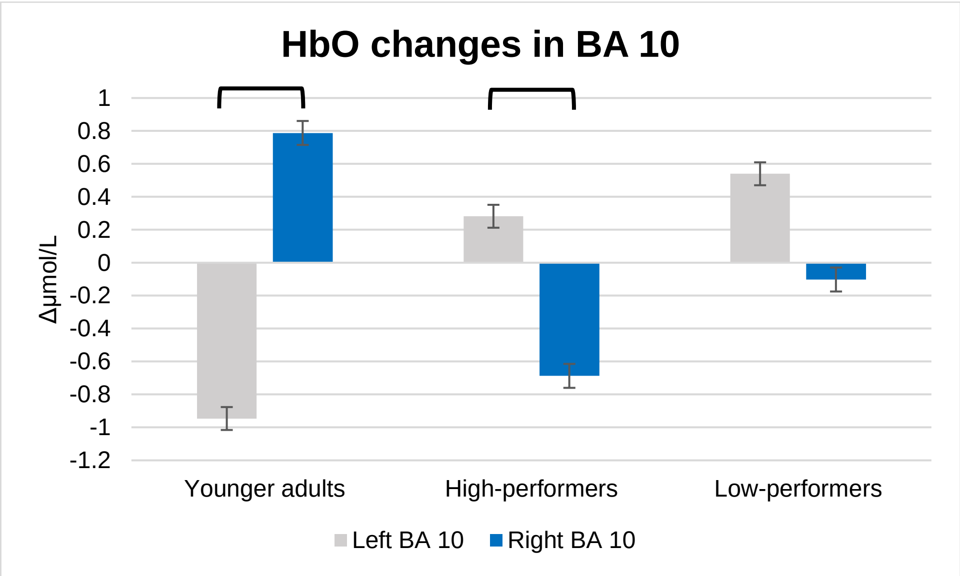


Figure 7.3 Changes in oxygenated haemoglobin in the anterior prefrontal cortex (Brodmann's areas 10) in younger adults, in cognitively high and low performing older adults. Bars indicate standard error.

Left BA10 showed greater HbO changes in the high-performers (.282 ± .22) and low-performers (.540 ± .22) than in younger participants (-.946 ± .22), a mean difference for high-performers of 1.229 (95% CI, .429 to 2.028), $p = .002$, and a mean difference for low-performers of 1.486 (95% CI, .687 to 2.286), $p < .001$. The final contrast explored within-group differences when comparing right and left HbO and HHb changes of BA10. This was significant in younger participants, (HbO: $F(1, 27) = 31.037$, $p < .001$, *partial* $\eta^2 = .535$, HHb: $F(1, 27) = 4.506$, $p = .043$, *partial* $\eta^2 = .143$) and in high-performing older adults for HbO, $F(1, 27) = 9.709$, $p = .004$, *partial* $\eta^2 = .264$ (HHb: $F(1, 27) = 2.125$, $p = .073$), but not in the low performing older group, (HbO: $F(1, 27) = 4.253$, $p = .049$, HHb: $F(1, 27) = 1.607$, $p = .056$). Specifically, younger participants showed greater HbO changes in the right BA10 (.788 ± .23) compared to the left (-.946 ± .22), a mean difference of 1.734 (95% CI, 1.095 to 2.372), $p < .001$. Younger participants also showed greater HHb changes in the left BA10 (.122 ± .27) compared to the right (-.629 ± .23), a mean difference of .750 (95% CI, .025 to 1.475), $p = .043$. High-performing older adults showed greater HbO changes of the left BA10 (.282 ± .22) than the right (-.687 ± .23), a mean difference of .970 (95% CI, .331 to 1.608), $p = .004$.

7.4 Discussion

The present study explored the neural substrates of associative processes in memory as a consequence of age and the use of temporal versus spatial clustering, within these associative processes. Our results revealed overall preference for temporal over spatial clustering in younger adults and in low-/high-performing older individuals. Although performing alike, each group exhibited differential cortical haemodynamic in the PFC, thus suggesting an effect of age on neurocognitive circuits involved in temporal contiguity. Specifically, older adults recruited opposite (i.e., left) or both hemispheres during memory retrieval of temporal associations.

7.4.1 PFC haemodynamic response

The fNIRS analysis revealed that: 1) younger adults showed an increase of HbO and decrease of HHb in the right PFC, corresponding to BA10, during retrieval; 2) high-performing older participants showed greater changes in HbO in left BA10; and 3) low-performing older individuals showed no hemispheric preference. The results of the younger group were in line with previous literature on memory retrieval, such as the HERA model (Tulving et al., 1994), on verbal and non-verbal material (Habib et al., 2003). Similarly, Okamoto et al. (2011) found greater right PFC blood oxygenation change during memory retrieval of taste information in younger adults using fNIRS technology. Results from the current study were also consistent with neuroimaging research on memory for temporal context. For instance, Cabeza et al. (1997) investigated age-related differences in PFC activity during temporal context retrieval and found that the right PFC was more active during retrieval of temporal-order information in younger adults, whereas older adults did not show any hemispheric specialization.

Previous fNIRS and fMRI studies on older adults suggested aging-related decline in prefrontal activity during cognitive performance (Kwee & Nakada, 2003; Vermeij et al., 2012) and found different PFC activation between age groups (Rajah, Languay, & Valiquette, 2010). This pattern was found in the present study and agrees with the HAROLD model (Cabeza, 2002), where, compared to younger adults, older adults activate bilateral or opposite areas in order to compensate for age-related brain changes. Given that right PFC is usually employed during memory retrieval (Habib et al., 2003), increased activation of left, rather than right, PFC in high-performing older adults suggests that some kind of hemispheric specialization in this group is still present, although through engagement of opposite neural pathways. Low-performing older individuals showed a different pattern, as they employed both hemispheres to achieve memory performance comparable to the other groups, thus suggesting that they may work harder to achieve a performance comparable to their high-performing peers.

These results were in agreement with other fNIRS and MRI studies on individuals with neurodegenerative diseases. Fallgatter et al. (1997) and Grady et al. (2003) reported that older adults with AD showed bilateral PFC activation as an attempt to compensate for losses attributable to neurodegeneration. The findings were also in line with CRUNCH, which suggests that age-related decline causes older adults' brains to recruit more neural circuits in order to achieve performance that is equivalent to that of younger brains, at low levels of task demands. Given that the STeM test requires encoding and free recall of 8 items per task, it can be considered a low-demand memory task.

7.4.2 Behavioural performance

The behavioural results showed that younger and high-performing older adults achieved comparable performance on the memory test, including memory total recall and preferential use of temporal clustering. Although unexpected, this was not surprising, as previous research has shown that older adults can perform as well as younger adults, by compensating with alternative neurocognitive networks (Cabeza, Anderson, Locantore, & Mcintosh, 2002). The low-performing group showed no significant difference in memory performance, either on total recall or temporal contiguity, compared to younger and high-performing older participants. The hypothesis that low-performers would use spatial clustering as an alternative to temporal clustering deficit was therefore rejected, as temporal clustering was consistently preferred throughout memory retrieval.

These comparable results may be caused by several factors. For instance, low-performers were individuals who scored under the average of the average functioning population, but had no diagnoses of neurodegenerative disorders. Therefore, it could be that their memory abilities were intact at the time of the visit. Alternatively, given that memory performance at delayed recall is considered a stronger predictor than immediate recall of conversion to AD (Gillis et al., 2013; Gomar et al., 2011), it is possible that the fact that the STeM test exclusively used short delays (immediate recall) limited the detection of group differences in associative memory. Third, the absence of group differences may be due to a lack of power, as groups of 30 participants were utilised in Gillis et al.'s (2013) cognitive study, where temporal context memory was found to be affected by cognitive decline. However, the current sample was appropriate for the main purpose of this study, which was to investigate the neural substrates of temporal contiguity, given a statistical power of .90, given an effect size of .25 (Faul et al., 2007).

To the best of the author’s knowledge, this was the first study to have used fNIRS to investigate neural substrates of temporal clustering during ageing. In sum, this investigation suggests that prefrontal areas are involved differentially in temporal clustering during the lifespan. Whilst temporal contiguity seems to be interlinked with right PFC activity in healthy brains, older individuals may recruit alternative networks that permit successful use of temporal associations and therefore efficient memory performance.

Chapter 8 Age-related differences for associative memory processes at immediate and delayed recall

Study 5 and 2 (Chapter 5) will be submitted for publication as one journal article to *Quarterly Journal of Experimental Psychology* in September 2019.

8.1 Introduction

Evidence from the literature on associative memory shows that both younger and older adults tend to cluster items semantically when categorizable lists are used (Wingfield et al., 1998). In older adults this pattern was hypothesised to be a consequence of the fact that semantic memory is relatively spared in older age, compared to other types of memory, and can therefore act as a compensatory mechanism. Golomb, Peelle, Addis, Kahana and Wingfield (2008) showed that in older adulthood, semantic binding becomes the preferred clustering strategy, even when maladaptive for recall. In spite of these observations, studies previously published on temporal contiguity in older adulthood have used semantically related lists (Golomb et al., 2008; Healey & Kahana, 2016; Wingfield & Kahana, 2002). In order to overcome this limitation, in the SteM test unexpected semantic clustering was controlled in Study 2, 3 and 4 by presenting items already clustered in distinct categories and by requiring participants to recall items after each presented block. By presenting stimuli in random spatial locations, spatial information was also provided as an alternative, forced associative process.

The main hypothesis was that the age-related deficit of temporal contiguity may than be compensated by use of spatial clustering. This hypothesis was not confirmed, given that older adults showed stronger preference for temporal over spatial clustering in disparate experimental conditions (Study 2, 3, and 4). These results may drive the conclusion that in absence of semantic information, temporal contiguity is the strongest associative process and that spatial clustering is not used as an alternative strategy. However, the lack of age-related differences at total recall in all the studies using the SteM test (2, 3, and 4) may be due to a ceiling effect and suggests that, although decreased, use of temporal contiguity in older adults was sufficient to obtain a memory performance comparable to that of younger participants. It could be then that total recall was facilitated by the use of categorical lists.

Older adults tend to perform more poorly than younger participants at recall of unrelated words, which are also typically applied in clinical practice (Park, Smith, Dudley, & Lafronza, 1989; Salthouse, Rogan, & Prill, 1984). Therefore, a more distinct age effect should be found if unrelated lists of items were used. This way, a spatial rather than temporal organization may become more influential. The aim of the present study was to investigate the applicability of unrelated lists to examine the temporal contiguity effect and to test the use of spatial clustering as an alternative associative strategy in healthy older adults.

Taking advantage of the unrelatedness of the task, temporal contiguity at delayed recall was also explored. To the best of the author's knowledge, no study has so far investigated temporal contiguity at delayed recall. Given that memory performance at delayed recall is particularly challenging for older adults, and more diagnostic for subsequent cognitive decline (Bruno et al., 2013; Gomar et al., 2011) it is probable that temporal contiguity, which is associated with memory performance, may be reduced accordingly.

In the present study, it was hypothesised that: 1) younger adults would show greater use of temporal clustering, compared to older adults; 2) older adults would exhibit greater spatial clustering, compared to younger adults; 3) temporal contiguity would be greater at immediate than at delayed recall.

8.2 Methods

8.2.1 Participants

A total of fifteen younger participants (27.22 ± 3.4, 11 females), all LJMU students, and fifteen older adults (71.77 ± 4.58, 9 females), all from the MeNu lab's database, were recruited. Older adults were selected if aged 60 or above, and no participants had a history of a major clinical conditions or psychiatric diseases. All participants were reimbursed for their time with a £5 voucher. The study was approved by the Liverpool John Moores University Research Ethics Committee (UREC).

8.2.2 Materials and procedures

The experiment took forty minutes to complete. After briefly describing the procedure, informed consent was obtained from each participant. First, general cognitive abilities were assessed on all participants using the MOCA (Nasreddine et al., 2005). Second, memory performance and contiguity effects were investigated using a modified version of the STeM test. Third, cognitive reserve was assessed with the CRIq (Nucci, Mapelli, & Mondini, 2012). Finally, participants were asked to freely recall any item from the memory test. The recalled items constituted the delayed recall task test, which occurred fifteen minutes after the immediate recall. The STeM test used in this study was a modified version of the original STeM (see Chapter 3, paragraph 3.3.3.3.7).

Specifically, rather than presenting items divided by categories, each of the four trials consisted of unrelated and uncategorizable stimuli selected from the same database (BOSStimuli).

8.2.3 Statistical analysis

Data were normally distributed. T-tests were performed to explore age-related differences in demographics, cognitive performance and memory performance. Temporal and spatial contiguity scores were calculated as explained in Chapter 3 (paragraph 3.3.5.1). A mixed model 2×2 ANOVA with age-group as a between-group variable (younger vs. older adults) and type of clustering (SteM-T vs. SteM-S) as a within-group variable was used to determine clustering preferences and age-related differences in clustering type. Given the nature of the STeM test, spatial clustering could not be extracted at delayed recall (i.e., spatial clustering can only be estimated after each trial). Therefore, a second two-way mixed ANOVA was performed to investigate the effect of age (between-subjects variable: younger vs. older adults) on temporal contiguity at immediate versus delayed recall (within-subjects variable).

8.3 Results

Descriptive statistics for demographic data of all groups are reported in Table 8.1, along with t-tests, where group differences on sex, years of education, cognitive reserve, general cognitive functioning and memory measures were investigated. Data are mean ± standard deviations unless otherwise stated. Groups did not differ for general cognitive functioning, $t(28) = 1.809$, $p = .081$, $d = .330$. Older adults showed greater cognitive reserve compared to the younger group, $t(28) = -5.474$, $p < .001$, $d = .999$. Older adults also had significantly fewer years of education compared to younger adults, $t(28) = 4.593$, $p < .001$, $d = .838$.

Table 6.1 Demographics and comparisons of cognitive and memory performance in younger and older participants

Measures	Younger (n = 15)	Older (n = 15)	
	Mean (Standard Deviation)		***P***
Age	27.20 ± 3.4	71.77 ± 4.58	-
Sex (females)	11 (73.3%)	9 (60%)	.456
Years of education	20.07 ± 2.37	15.47 ± 3.07	< .001
CRIq	100.53 ± 5.54	125.87 ± 17.04	< .001
MOCA	28.27 ± 1.87	27.00 ± 1.96	.081
STeM Total Recall	25.07 ± 1.94	21.47 ± 3.23	.001
STeM Delayed Recall	15.14 ± 3.64	11.80 ± 3.99	.023
Associative memory:			
STeM-T	.65 ± .13	.51 ± .06	-
STeM-S	.46 ± .11	.43 ± .17	-

Note. CRIq = Cognitive Reserve Index questionnaire; MOCA = Montral Cognitive Assessment; SteM = Spatio-Temporal Memory test; SteM-T = temporal contiguity; STeM-S = spatial contiguity.

8.3.1 Memory performance

T-test analysis showed that younger participants remembered a greater amount of items at both immediate and delayed recall, compared to older adults, immediate recall: $t(28) = 3.706$, $p = .001$, $d = .676$; delayed recall: $t(28) = 2.398$, $p = .023$, $d = .437$.

The two-way mixed ANOVA was run to understand the effects of age on contiguity effects and to investigate preferences on type of clustering. The Levene's test indicated that the assumption of homogeneity of variances was violated for STeM-T ($p = .037$). Given that the groups' sample sizes were equal and that multilevel mixed ANOVAs are quite robust to heterogeneity of variance (Box, 1953), data were not transformed. There was no statistically significant interaction between clustering type and group, $F(1, 28) = 1.481$, $p = .234$.

However, the main effect of clustering showed a statistically significant difference, $F(1, 28) = 17.868$, $MSE = .278$, $p < .001$, *partial* $\eta^2 = .390$. The main effect of group also showed a statistically significant difference in clustering between groups, $F(1, 28) = 6.675$, $MSE = .105$, $p = .015$, *partial* $\eta^2 = .193$. Specifically, younger participants showed an overall greater use of clustering compared to older adults, a mean difference of .084 (95% CI, .017 to .150). Temporal clustering was overall preferred to spatial clustering in all participants, a mean difference of .136 (95% CI, .070 to .202). Visual inspection (Figure 8.1) suggested a possible difference between older and younger adults in temporal contiguity, albeit not significantly identified by the interaction.

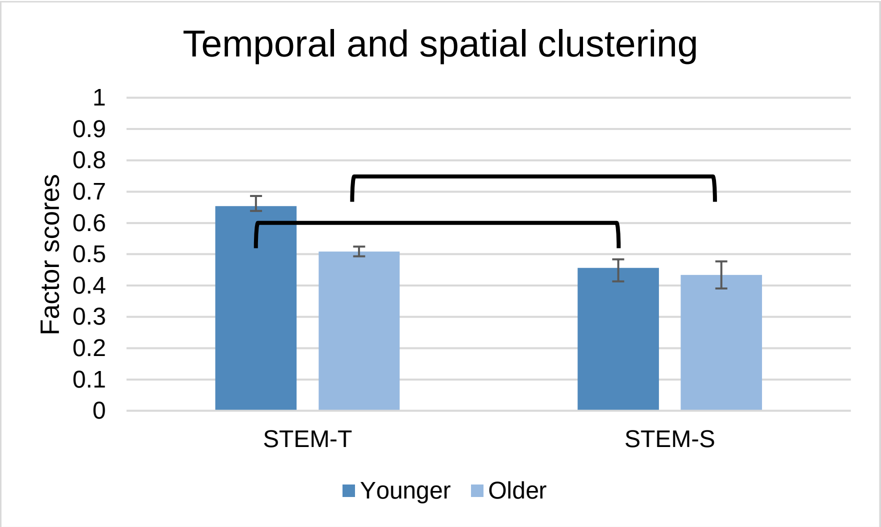


Figure 8.1 Mean Temporal (STeM-T) and spatial (STeM-S) clustering in older and younger groups on the Spatio-Temporal Memory (STeM) test. Bars indicate standard error.

A second two-way mixed ANOVA was run to explore the effect of age on temporal clustering at immediate versus delayed recall (Figure 8.2). A statistically significant interaction was found between recall time and group, $F(1, 28) = 16.422$, $MSE = .114$, $p < .001$, *partial* $\eta^2 = .370$. After applying a Bonferroni correction, a statistically significant difference was found in younger participants between the recall times, $F(1, 28) = 17.462$, $p < .001$, *partial* $\eta^2 = .384$. Temporal clustering in younger adults was greater at immediate recall than at delayed recall, a mean difference of .127 (95% CI, .065 to .190), $F(1,28) = 17.462$, $p < .001$, *partial* $\eta^2 = .384$. Older adults did not show a significant difference in temporal clustering at immediate and delayed recall, $F(1,28) = 2.409$, $p = .132$. Group differences were found on temporal contiguity at immediate recall, $F(1, 28) = 15.263$, $MSE = .158$, $p = .001$, *partial* $\eta^2 = .353$, but not at delayed recall, $F(1, 28) = 1.630$, $p = .212$. Specifically, at immediate recall temporal contiguity was greater in younger adults than in older adults, a mean difference of .145 (95% CI, .069 to .221). These results therefore confirmed what was suggested by the previous figure, that younger and older adults use temporal contiguity differently.

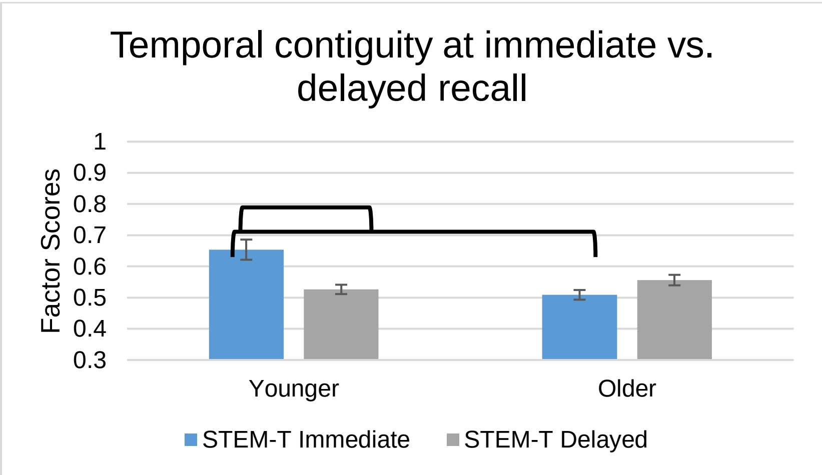


Figure 8.2 Mean Temporal (STeM-T) clustering at immediate and delayed recall in younger and older adults. Bars indicate standard error.

8.4 Discussion

In the current study the use of unrelated lists was investigated to examine recall patterns in free recall in different age groups. The temporal contiguity effect was found to be the preferred type of memory organization, compared to spatial clustering, in both younger and older adults, although less so in the older group. These findings replicated the results from Studies 2, 3 and 4, wherein, regardless of different experimental conditions, spatial clustering was not a preferred alternative strategy when compared to temporal clustering. The use of unrelated lists also emphasised age-related differences for both total recall and temporal contiguity. These results are in line with recent studies investigating the contiguity effect in younger adults using different lists (McCluey, Burke, & Polyn, 2018; Miller et al., 2013). For instance, Miller et al. (2013) showed that when items were drawn from same category lists, a spatial contiguity effect, although observed, was reduced compared to when different category lists were used. Similarly, McCluey et al. (2018) used categorised and uncategorised lists of words to examine differences in use of temporal clustering in younger adults and found that the category structure of a list negatively affected temporal contiguity. The present study showed that this pattern is emphasised in older adulthood, thus suggesting that unrelated lists may be a more sensitive measure of age-related deficit of temporal contiguity.

When temporal contiguity was compared between immediate and delayed recall, younger adults showed a relevant decrement in use of temporal associations, thus confirming the assumption that temporal contiguity was affected by the passing of time. Older adults showed no significant difference between the two recall times, but this finding may be due to the fact that temporal contiguity was already deficient at immediate recall in this population.

Taken together, Study 5’s results showed that unrelated lists are a more sensitive tool for the study of temporal contiguity impairment in older adults, both at immediate and delayed recall, by requiring fewer participants than previous studies presented in this thesis. It follows that temporal contiguity from uncategorised lists may be potentially used to detect cognitive decline, thus advancing the neuropsychological assessment in clinical settings. This hypothesis was explored in the following study.

Chapter 9 Memory organization and ageing: predicting cognitive decline with temporal contiguity

Study 6 was submitted for publication to *Alzheimer's & Dementia* in August 2019. This study was presented at the Alzheimer's Association International Conference (Los Angeles, USA) in July 2019 and at the Public Health International Conference (Liverpool, UK) in July 2019.

9.1 Introduction

Memories of events are typically recalled following the temporal order in which they have been perceived. This temporal contiguity effect is seen in laboratory settings, when participants recall lists of items in a similar order to how they were presented during the learning phase (Kahana, 1996). Over the years, several studies have found temporal contiguity to be remarkably consistent across individuals and experimental conditions, including in immediate and delayed memory (for a review, see Healey, Long, & Kahana, 2018). Temporal contiguity has been related to general memory performance and intellectual abilities, meaning that greater temporal contiguity tends to be positively related to better total recall in memory tasks and to greater IQ in younger participants (Healey, Crutchley, & Kahana, 2014; Sederberg, Miller, Howard, & Kahana, 2010). However, temporal contiguity decreases in older adulthood (Howard et al., 2006; Kahana et al., 2002). For instance, Wahlheim and Huff (2015) tested temporal organization in 24 younger and 24 older adults during dual-list free recall tasks. Albeit maintaining a temporal contiguity effect, older adults exhibited lower temporal contiguity compared to younger adults, thus suggesting an age-related deficit in temporal association. Older adults' impairment in temporal contiguity has been proposed previously (Golomb et al., 2008; Wingfield & Kahana, 2002) and its relation to poorer memory performance has been suggested (Bruno, Grothe, et al., 2016; Sederberg et al., 2010). Failure to cluster items according to their temporal context was reported by Golomb et al. (2008), who explored age differences in temporal and semantic associations in free and serial recall. Golomb et al. (2008) found that older adults exhibited a deficit in forming temporal associations compared to younger controls, whilst maladaptively compensating with semantic associations. Given Golomb et al.’s (2009) findings, it is plausible that temporal contiguity in older adults may predict cognitive decline over time. Implicit evidence of this assumption also comes from one study on temporal order memory (Gillis et al., 2013, discussed below). Similar to temporal contiguity, which examines the spontaneous order of responses during memory retrieval, temporal order memory explores the ability to voluntarily remember the temporal order of events.

Memory for temporal order is also affected by old age (Naveh-Benjamin, 1990) and appears to be significantly impaired in individuals with Mild Cognitive Impairment (MCI), the clinical precursor of Alzheimer’s Disease (AD). Gillis et al. (2013) investigated younger and older controls, and patients with MCI on temporal order memory at immediate and delayed recall, by using lists of different span lengths. They found that at delayed recall individuals with MCI performed significantly more poorly than their healthy peers, who in turn performed more poorly compared to younger participants. However, at immediate recall, age differences were detected only in the longest span. Although investigating intentional clustering (i.e., memory for temporal order), Gillis et al.’s (2013) findings suggest that analyses of spontaneous recall patterns at delayed rather than immediate memory may be a more sensitive measure of cognitive decline. Consistently, the accuracy of delayed recall in predicting cognitive decline has been reported previously in studies of input order of recall (Bruno et al., 2013; Talamonti et al., 2019). However, no research has so far examined the output order of recall, specifically the temporal contiguity effect, as potential marker of longitudinal cognitive decline.

In the present study, temporal contiguity at delayed memory was investigated as a predictor of progression to Cognitively Unimpaired-Declining (CUD) status (details on CUD classification in the "Cognitive status" section) from a healthy baseline of older adults, whilst controlling for established clinical measures. Given previous findings, it was expected that: 1) older adults who progressed to CUD status would exhibit poorer temporal contiguity, compared to those who remained stable across time, and that 2) lower temporal contiguity would be a significant predictor of conversion to CUD status.

9.2 Methods

9.2.1 Participants

Data from 419 individuals, who volunteer in the Wisconsin Registry for Alzheimer's Prevention (WRAP; Johnson et al., 2018; Sager et al., 2005), were extracted from a pool of over 1500 participants. WRAP is an ongoing longitudinal study of middle-aged individuals, who complete visits, typically every two years. Participants for this study were selected on the basis of having completed at least four visits, having received a diagnosis of cognitively unimpaired-stable (CUS) at baseline, and either being classified as still cognitively normal or with CUD status at visit 4 (Jack et al., 2018) (details on diagnoses in the Procedure section).

Additionally, at baseline, selected participants were free of neurological diseases and psychiatric disorders, spoke English as their native language, and were 50 or older (age range: 50-68). The follow-up times ranged from 7 years to 13 years, with a mean of 9 years (SD: 1.76). The study was approved by the ethics committees of the authors' universities, and completed in accordance with the Helsinki Declaration.

9.2.2 Procedure

Each WRAP visit includes administration of a neuropsychological battery of tests, clinical measures and laboratory tests (for a detailed description of the WRAP procedure see: Johnson et al., 2018; Sager et al., 2005). Tests used for the current study and to calculate the composite score for general cognitive functioning are listed and explained in the Procedure section of Chapter 4 (Study 1), paragraph 4.2.2.

To calculate temporal contiguity, the method adopted by Polyn, Norman, and Kahana (2009) was used on the AVLT delayed recall (see Chapter 3, paragraph 3.3.5.1). APOE-ε4 genotyping information was obtained via blood analysis (Engelman et al., 2013).

9.2.3 Cognitive status

WRAP utilises a two-tiered consensus conference method to identify participants' cognitive status. If cognitive abnormalities are detected by algorithm on neuropsychological tests, in depth review of data from participant visits is undertaken by a consensus review committee consisting of dementia specialists. Detailed criteria for the CUD classification, previously named early-MCI, can be found in the Procedure section of Chapter 4 (Study 1), paragraph 4.2.2. In summary, this diagnosis is assigned if there is lower-than-expected objective performance on commonly used clinical tests (typically > 1.5 SD below internal robust norms), but few or no subjective cognitive complaints or clinically significant deficit. The CUD classification represents consensus conference confirmed pre-MCI cognitive decline analogous to transitional cognitive decline in the 2018 diagnostic framework (Jack et al., 2018; Johnson et al., 2018) (see Appendix 2). For the purpose of the current study, only individuals categorised as either CUS or with CUD at visit 4 were included in the analysis. Participants with more severe classifications (e.g., clinical MCI, dementia) were excluded in this study, in order to specifically investigate the sensitiveness of temporal contiguity to subclinical cognitive decline.

9.2.4 Statistical Analysis

First, temporal contiguity was correlated with general cognitive ability and AVLT measures in the CUS and CUD groups combined to assess its sensitivity to global cognition and memory performance. Secondly, t-test comparisons were run to determine if there were differences in demographics, memory measures and temporal contiguity between those who progressed to CUD status and those who did not. Group differences for general cognitive abilities were explored through the Mann-Whitney test, given that data were not normally distributed. Finally, to test the hypothesis that temporal contiguity predicted conversion to CUD from a healthy baseline, a binary logistic regression was performed with temporal contiguity as the predictor and progression to CUD status or not as the binary outcome, whilst controlling for AVLT immediate and delayed total recall. Since time between first and last visit was not the same for each participant, time was included as a covariate, together with age, gender, APOE-ε4 status, and years of education. To avoid issues of multicollinearity, temporal contiguity was regressed out of AVLT total and delayed recall. Firstly, temporal contiguity was regressed out of AVLT total recall, yielding standardized residuals. Secondly, temporal contiguity and the regressed AVLT total recall were regressed out of AVLT delayed recall, also generating standardized residuals for AVLT delayed recall. A Pearson's correlation analysis confirmed the independence of these measures. Sensitivity analysis was also investigated using temporal contiguity as the only predictor, in order to explore the independent impact of this variable on the model's outcome.

Furthermore, to test whether immediate temporal contiguity may be a predictor of progression to CUD, the binary logistic regression was re-run with temporal contiguity averaged across the five learning trials, as the main predictor. The standardized residuals from the first analysis were replaced by standardized residuals of AVLT total and delayed recall regressed out of immediate temporal contiguity. Standardized residuals of delayed temporal contiguity were calculated from immediate temporal contiguity and the regressed AVLT total and delayed recall.

9.3 Results

Data on demographic variables and comparisons for cognitive and memory scores are reported in Table 9.1. Data are mean ± standard deviation, unless otherwise stated. Of the 419 cognitively intact participants at baseline, 61 (14.6%) met CUD criteria at visit 4, whereas 358 (85.4%) remained cognitively intact. 69.2% of the total sample was female, mean age at baseline was 56.65 (± 4.38), with 16.70 (± 2.93) total years of education.

Table 9.1 Demographics, cognitive level, and temporal contiguity between CUD and CUS participants

Measures	**CUD (n = 61)**	**CUS (n =358)**	**p**
Gender (females)	37 (60.7%)	253 (70.7%)	.118
APOE4 presence	21 (34.4%)	128 (35.8%)	.842
Age at baseline	57.08 ± 4.33	56.57 ± 4.38	.401
Years of education	16.70 ± 3.21	16.70 ± 2.88	.982
Ethnicity (White/Caucasian)	60 (98.4%)	351 (98%)	.868
General cognitive abilities	-.16 ± .57	.22 ± .63	< .001
Time between visits	9.16 ± 1.00	9.04 ± .97	.364
AVLT Total Recall	46.72 ± 6.25	53.41 ± 6.81	< .001
AVLT Delayed Recall	9.15 ± 2.31	11.06 ± 2.49	< .001
Immediate Temporal contiguity	.64 ± .07	.67 ± .07	.030
Delayed Temporal contiguity	.60 ± .16	.69 ± .13	< .001

Note. CUD = Cognitively Unimpaired Declining; CUS = Cognitively Unimpaired Stable; Time = time between first visit and last follow-up.

Correlation analyses between general cognitive abilities, memory performance and temporal contiguity are shown in Table 9.2. As cognitive ability was not normally distributed, Spearman correlation was run for this variable, whereas Pearson correlation was performed for AVLT total and delayed recall. Temporal contiguity was positively related to general cognitive abilities, $r_S(418) = .211$, $p = .004$, and both AVLT Total Recall, $r(418) = .155$, $p = .001$ and with AVLT Delayed Recall, $r(418) = .385$, $p < .001$.

Table 9.2 Pearson and Spearman correlations between cognitive and memory performance, and temporal contiguity.

	1	2	3	4	5
1. Immediate temporal contiguity	-				
2. Delayed temporal contiguity	.450*	-			
3. General cognitive functioning	.194*	.211*	-		
4. AVLT total recall	.327*	.155*	.340*	-	
5. AVLT delayed recall	.318*	.385*	.275*	.735*	-

Note. * = correlation significant at p < .01.

A Mann-Whitney test was performed to compare baseline cognitive functioning of the two groups and results showed a statistically significant difference between CUD (median = -.21, range = -1.34 – .90, mean rank = 147.95) and CUS (median = .24, range = -1.76 – 1.73, mean rank = 220.57), $U = 7134$, $z = -4.329$, $p < .001$, $r = .21$. As data were normally distributed, independent samples t-tests were run to determine if there were differences between the two groups in memory measures, including immediate and delayed total recall and temporal contiguity. Statistically significant differences on memory measures were found for immediate total recall ($t(417) = 7.169$, $p < .001$, $d = .35$) between CUD and CUS participants. Significant differences were also found for delayed total recall ($t(417) = 5.908$, $p < .001$, $d = .29$) between CUD and CUS individuals. Lastly, temporal contiguity was statistically lower in the CUD compared to the CUS group ($t(417) = 4.718$, $p < .001$, $d = .23$).

Pearson's correlation was performed in order to guarantee that there was no correlation between temporal contiguity and regressed AVLT Total Recall ($r(418) = -.008$, $p = .866$) and regressed AVLT Delayed Recall ($r(418) = .021$, $p = .664$).

The logistic regression model was statistically significant, $\chi^2(7) = 41.560$, $p < .001$. The model explained 17% (Nagelkerke R^2) of the variance in conversion to CUD and correctly classified 85.4% of cases. The analysis yielded two significant predictors: AVLT total recall ($\chi^2 = 33.334$, $p < .001$), and delayed temporal contiguity ($\chi^2 = 9.024$, $p = .003$). Other not significant variables are shown in Table 9.3. To note, the regression model remained statistically significant when the regressed AVLT measures were excluded from the analysis, $\chi 2(6) = 13.246$, $p = .039$.

Table 9.3 Logistic regression predicting progression to CUD based on delayed temporal contiguity at baseline

Measures	***B(SE)***	***Wald***	***p***	***Exp(B)***	***95% CI***
Delayed Temporal contiguity	-3.586(1.194)	9.024	.003	.028	[.003-.288]
AVLT Total Recall (residuals)	-1.035(.179)	33.334	<.001	.355	[.250-.505]
AVLT Delayed Recall (residuals)	-.075(.151)	.248	.618	.928	[.691-1.246]
Age	.012(.035)	.115	.735	1.012	[.945-1.083]
Years of education	.034(.049)	.480	.488	1.035	[.939-1.140]
Sex	.419(.343)	1.499	.221	1.521	[.777-2.976]
APOE4	-.016(.320)	.002	.961	.985	[.526-1.843]
TIME	-.009(.016)	.332	.565	.991	[.961-1.022]

Note. CUD = cognitively unimpaired-declining; B = unstandardized regression coefficient; SE = standard error of the coefficient; Exp(B) = odds ratio; 95% CI = 95% confidence interval; AVLT Delayed Recall = standardized residuals regressed out from temporal contiguity; AVLT Total recall = standardized residuals regressed out from temporal contiguity and AVLT delayed recall.

For the second binary logistic regression model, Pearson's correlation confirmed the independence between immediate temporal contiguity and the regressed AVLT total recall ($r(418) = .014$, $p = .784$), AVLT delayed recall ($r(418) = .011$, $p = .820$) and delayed temporal contiguity ($r(418) = .000$, $p = .996$). The regression model was statistically significant, $\chi 2(8) = 51.116$, $p < .001$. The model explained 20% (Nagelkerke R^2) of the variance in conversion to CUD and correctly classified 85.4% of cases. The results (Table 9.4) showed that immediate temporal contiguity was also predictive of CUD conversion ($\chi 2 = 6.510$, $p = .011$), although delayed temporal contiguity remained a stronger predictor ($\chi 2 = 7.279$, $p = .007$). Specifically, greater use of temporal contiguity at delayed recall was associated with a greater reduction in the likelihood of converting to CUD, compared to both AVLT total recall and temporal contiguity at immediate recall. Moreover, the regression model did not remain statistically significant when the regressed AVLT measures and delayed temporal contiguity were excluded, $\chi 2(6) = 9.564$, $p = .144$.

Table 9.4 Logistic regression predicting progression to CUD based on immediate temporal contiguity at baseline

Measures	***B(SE)***	***Wald***	***p***	***Exp(B)***	***95% CI***
Immediate Temporal contiguity	-5.504(2.157)	6.510	.011	.004	[.000-.279]
Delayed Temporal contiguity (residuals)	-.408(151)	7.279	.007	.665	[.494-.894]
AVLT Total Recall (residuals)	-1.039(.183)	32.276	<.001	.354	[.247-.506]
AVLT Delayed Recall (residuals)	-.067(.148)	.206	.650	.935	[.700-1.250]
Age	.012(.035)	.123	.726	1.012	[.946-1.084]
Years of education	.036(.050)	.522	.470	1.037	[.940-1.143]
Sex	.412(.343)	1.445	.229	1.510	[.771-2.957]
APOE4	-.020(.321)	.004	.950	.980	[.522-1.839]
TIME	.193(.159)	1.470	.225	1.212	[.888-1.655]

Note. AVLT Delayed Recall = standardized residuals regressed out from immediate temporal contiguity; AVLT Total recall = standardized residuals regressed out from immediate temporal contiguity and AVLT delayed recall; Delayed Temporal contiguity = standardized residuals regressed out from immediate temporal contiguity, and standardized AVLT Total and delayed recall.

9.4 Discussion

The current study was the first, to the best of the authors' knowledge, to investigate temporal contiguity longitudinally in subclinical cognitive decline. The binary regression analysis revealed that temporal organization in memory was associated with cognitive decline. Specifically, differences in temporal contiguity at baseline predicted increased risk of progression to CUD status, after approximately 9 years, and after adjusting for established diagnostic measures, such as AVLT total and delayed recall and APOE-ε4 genotype. To note, the CUD status describes cognitive decline that is not sufficiently severe for a diagnosis of MCI, but that increases conversion to a clinical status (Johnson et al., 2018). Therefore, these results suggested the potential applicability of temporal contiguity in clinical settings.

The main findings were in line with the Associative Deficit Hypothesis (ADH; Naveh-Benjamin, 2000), wherein age-related decline in episodic memory performance was explained by an inability to form associations. In a series of four experiments, Naveh-Benjamin (2000) compared memory for items and memory for associative relationships between items in younger vs. older participants and found that older adults exhibited, other than lower performance in all tasks, a specific and relevant deficit in memory for associative relationships. In subsequent works, the suggested ADH was tested on different types of associations, and a deficit specifically for temporal order was reported in healthy old age (Old & Naveh-Benjamin, 2008). In the present study, greater difficulty in temporally binding items was found in individuals who received a subsequent CUD diagnosis compared to those who remained cognitively stable across time, thus indicating that the associative deficit increases relative to the older person's cognitive status.

Following these findings, in the present study temporal contiguity was analysed at delayed recall, which occurred 20-min after the last immediate free recall trial. Delayed memory performance has been shown to be a sensitive predictor of cognitive decline (Bruno et al., 2013; Talamonti et al., 2019) and Bruno et al. (2016) reported that measures of output order taken at delayed performance, including information on the temporal order of free recall, were linked to general cognitive functioning (as measured by the MMSE), and to hippocampal volume in healthy older adults. The relationship between temporal contiguity at delayed recall and general cognitive functioning was confirmed in the present study through partial correlation analysis. The interlink between temporal contiguity and memory ability at immediate and delayed recall was also reported, thus confirming previous studies showing the contiguity effect to be positively associated with recall accuracy (Healey et al., 2014; Healey et al., 2018; Sederberg et al., 2010).

These results suggest that temporal contiguity at immediate recall may also be a predictor of progression to CUD. To confirm this point, the same binary regression was re-run by adding temporal contiguity, averaged across the five learning trials, as the main predictor. The results showed that immediate temporal contiguity was also predictive of CUD conversion. However, the following sensitivity analysis showed that the regression model was not significant when the controlling variables were excluded, thus confirming delayed temporal contiguity as a better predictor.

Although our results did not show temporal contiguity to be a better predictor than traditional memory measures (i.e., AVLT total recall), we show that temporal contiguity contributes in predicting cognitive decline above and beyond these variables, such as genetic risk (i.e., APOE-ε4). Therefore, temporal contiguity may be considered as one of the cognitive markers in the research of neurodegeneration. For instance, temporal contiguity may be considered in association with biomarker variables in studies of early detection, in order to enhance early diagnosis of dementia-related pathologies. These results also demonstrated that temporal contiguity at delayed recall was related to memory performance and cognitive functioning in healthy older adults.

In summary, the present study investigated whether temporal contiguity predicted progression to CUD status, a diagnosis linked to increased risk of MCI (Johnson et al., 2018), and demonstrated that temporal contiguity is significantly lower in this group. Moreover, the predictive value of temporal contiguity, taken at delayed recall, was maintained when variables commonly used in clinical practice were considered. Future research may explore temporal contiguity as a predictor of conversion to clinical diagnoses, such as MCI or AD, in order to investigate its potential for early detection.

Chapter 10 General discussion

The aim of this thesis was to spread awareness on the mechanisms underlying free recall patterns (e.g., serial position and contiguity effects) in episodic memory, and how they change with age. By analysing free recall patterns in episodic memory, it was possible to explore the cognitive and neural mechanisms of memory organization (studies 2, 3, 4, 5) and to explore the potential use of serial position and contiguity effects for the early detection of cognitive decline (studies 1 and 6).

Serial position effects refer to effects rising from the order in which information is learned (i.e., input order), and are observed when items from the beginning (i.e., primacy) and the end (i.e., recency) of a list are recalled better than items presented in the middle. Contiguity effects are observed when information is retrieved following patterns that were present at encoding, such as temporal context, indicating that contextual information is utilised at retrieval (i.e., output order) to trigger recall. For instance, temporal contiguity is shown when the temporal distance between events is used to facilitate and guide retrieval, whereas spatial contiguity occurs when associations are made relative to spatial information.

Throughout a series of experiments that used neuropsychological, cognitive and neuroimaging methods, this thesis: 1) provides evidence of the universality of temporal contiguity in adulthood and older age; 2) supports the notion that contiguity effects occur specifically at retrieval, rather than encoding processes; 3) shows that temporal contiguity is linked to PFC activity; and 4) underlines the potential use of input and output order in free recall as cognitive markers of cognitive decline.

Study 1 (Chapter 4) tested whether free recall patterns are cognitive markers of cognitive decline. Specifically, it was investigated which measure of serial position is the most accurate in predicting conversion to early MCI from a baseline of healthy older adults. This was achieved by examining various scoring methods of primacy and recency effects at immediate and delayed recall. Results showed that delayed primacy was the most sensitive measure to predict progression to early MCI, thus supporting previous studies on healthy individuals (Bruno et al., 2013), where delayed primacy was hypothesised as a potential cognitive marker of early detection of neurodegeneration.

Given the considerable amount of existing research on serial position effects, Studies 2 (Chapter 5), 3 (Chapter 6), 4 (Chapter 7), and 5 (Chapter 8) focused on exploring the cognitive and neural substrates of contiguity effects, for which literature is still scarce.

In **Study 2** (Chapter 5), contiguity effects were investigated through the STeM test, where four memory tasks were designed in order to permit retrieval throughout temporal or spatial contiguity (but not both simultaneously). Use of semantic clustering was controlled by providing same-category stimuli per each task and by asking participants to recall items immediately after each task, rather than at the end of the memory test. Study 2 results showed that younger adults used temporal clustering more compared to the older group, although performing alike on general memory performance (i.e., total recall). The results supported the previously proposed hypothesis that temporal organization in memory is affected by ageing (Golomb et al., 2008; Wingfield & Kahana, 2002). Moreover, both groups demonstrated a preference for temporal rather than spatial clustering, therefore showing that temporal contiguity, although deficient in older adults, remained the preferred associative method for memory performance, in the absence of semantic clustering.

Interestingly, Study 2 also showed a positive relationship between temporal contiguity and tests investigating executive functions. To further investigate such relationship, in **Study 3** (Chapter 6), it was explored whether temporal contiguity is affected by tasks interfering with processes involving executive functions. Specifically, the role of attentional processes and type of material on contiguity effects were examined. This was achieved by introducing a distractor (Divided-Attention) task during the STeM test (encoding phase) and by utilising verbal vs. pictorial material. Results showed that attention and material did not affect use of contiguity effects in either younger or older adults, although affecting their general performance. These findings provided evidence that temporal contiguity is more likely to be related to retrieval, rather than encoding, memory processes, thus in line with previous assumptions (Polyn & Cutler, 2017b; Wingfield & Kahana, 2002).

Given this assumption, in **Study 4** (Chapter 7), the neural substrates of temporal contiguity were investigated at retrieval. The original STeM test was utilised to examine the neural substrates of contiguity effects, via fNIRS, in younger, and in cognitively high- and low-performing older adults. The results showed clear PFC in younger and cognitively high-performing older adults with opposite lateralization patterns, whereas low-performers showed no clear hemispheric specialization. These findings were in line with influential models of neurocognitive ageing (i.e., the HAROLD and CRUNCH models) that posit a loss of hemispheric specialization in older adulthood, compensated by activation of alternative neural pathways. Moreover, temporal contiguity was preferred over spatial contiguity in all groups, thus repeating findings from Study 2 and 3. However, like in Study 3, age did not affect use of temporal contiguity. This discrepancy of results was ascribed to the considerable difference in sample sizes between the two studies (ten vs. forty-five participants per group), or to a ceiling effect caused by the use of categorized lists of items.

To address this last point, in **Study 5** (Chapter 8), age differences on contiguity effects were investigated by means of unrelated lists of items. Moreover, temporal contiguity was also examined at delayed recall. Results showed that using unrelated lists of items significantly reduced the ceiling effect found in Study 3 and 4, where no age-related differences were reported. Older adults performed more poorly than younger adults at both general memory performance (i.e., total and delayed recall), and experienced an age-related temporal contiguity deficit at both immediate and delayed recall. To note, this effect was observed by using groups of fifteen participants as opposed to Study 3, where groups of twenty-eight participants were used. These findings suggest that unrelated lists may be more powerful measures of age-related changes of temporal associative processes, compared to categorical lists, given the absence of categorical cues in unrelated lists.

Therefore, **Study 6** (Chapter 9) tested whether temporal contiguity at delayed recall of unrelated lists predicts cognitive decline (CUD status) in older adults. Results showed that lower temporal contiguity predicted conversion to CUD, after accounting for variables typically used in clinical practice, such as APOE genotype status and general memory performance, thus supporting the hypothesis that temporal organization in memory is affected by cognitive decline and suggesting that temporal contiguity may be used for early detection.

10.1 Methodological limitations

Other than limitations highlighted in each study, the following methodological aspects may be taken into consideration when interpreting this thesis' results. First, the STeM test used in Study 2 (Chapter 4), 3 (Chapter 5) and 4 (Chapter 7), from which contiguity effects were extracted, included one trial constituted of pictures of animals. Recent research has suggested that *living things* are remembered better than *nonliving things* (Nairne et al., 2017). Therefore, it may be that including the "animals" category in the STeM test influenced the contiguity effects. However, preliminary analyses to test this claim show that temporal contiguity, although greater for animated compared to unanimated items in all age-groups, is still significantly reduced in older adults when the animated list is removed.

Second, the time of day at which the STeM test was performed was not taken into consideration. Maylor and Badham (2018) recently showed that associative recognition memory is especially affected by time of testing, with both younger and older participants showing better performance when they are tested at their preferred time of day. Therefore, it is possible that contiguity effects in memory may also be influenced by this variable.

Finally, the STeM test comprised lists of eight items, each of which was recalled right after presentation (i.e., one learning trial). Although similar list-lengths have been used previously to investigate temporal contiguity in younger and older adults (Golomb et al., 2008; Sederberg et al., 2010), contiguity effects in those studies were calculated from the final total recall, which occurred after several learning trials of identical lists. It is thus possible that using more trials and more overall items (Wingfield et al., 1998) may accentuate age-related differences in the use of contiguity effects.

In Study 4 (Chapter 7), haemodynamic response was investigated in the PFC in different age groups. The neuroimaging instrument utilised, fNIRS, is well-known to lack anatomical information (Tak & Ye, 2014). Therefore, the localization of the areas of interest for Study 4 may have been slightly different amongst participants.

Finally, in Study 5 (Chapter 8) and 6 (Chapter 9) delayed recall was investigated. Although unrelated stimuli were utilised within each task at immediate recall, it could be that at delayed recall participants may have used unexpected semantic cues between items from different trials to guide retrieval. These cross-trial associations may have affected the amount of temporal contiguity shown, which was indeed lower than at immediate recall. This point may be considered for future studies, although it is arduous to have lists completely unrelated, as individuals typically tend to create some sort of associations in order to facilitate recall.

10.2 Future directions

Using a variety of experimental conditions, this thesis makes the argument that input and output order in free recall are markers of cognitive decline and may be considered as potential tools in research and clinical settings for early detection of neurodegeneration. In order to confirm their potentiality in these fields, future research should investigate cognitive and neural free recall patterns (i.e., delayed primacy and temporal contiguity) in individuals with dementia-related pathologies. Furthermore, current views of early detection highlight the importance of integrating cognitive and biological measures (e.g., tau and β-amyloid markers) to improve early diagnosis (Albert, 2019). Thus, input and output order of free recall should also be included in studies that use biomarkers for early detection of neurodegenerative disorders.

In Study 3 (Chapter 6), temporal contiguity was suggested to be related to retrieval processes, as DA at encoding did not affect this type of associative process. In future studies, temporal contiguity and DA tasks at retrieval may be examined to confirm this study's findings.

In Study 4 (Chapter 7), the PFC was found to be activated during temporal contiguity. Given that temporal contiguity was also related to electrophysiological activation of the temporal lobe in younger participants (Manning et al., 2011), future studies may consider investigating these areas in older adulthood.

Finally, the majority of experiments conducted in this thesis utilised the STeM test. This test consisted of four categorised lists of eight items each presented in a circular array that participants were asked to verbally identify during encoding and to freely recall after each list presentation. The within-category recall was chosen as an attempt to control for unexpected semantic clustering, which is extremely common, and maladaptive, in older adults (Golomb et al., 2008). Moreover, previous studies examining contiguity effects in older adults utilised categorizable lists of items (Golomb et al., 2008; Wingfield & Kahana, 2002; Wingfield et al., 1998). However, results from Study 5 and 6, wherein non-categorised lists were used, suggest that unrelated lists may be more sensitive instruments to investigate temporal contiguity. This may be considered for future directions.

10.3 Conclusion

In this thesis, a range of experiments were conducted in order to advance knowledge on the cognitive and neural substrates of input and output order in free recall and their potential applicability for early detection of cognitive decline. It has been found that both younger and older adults use temporal contiguity to guide retrieval, although older adults experience a decrease of this effect. Furthermore, temporal contiguity was found not to be affected by the type of material used during presentation. However, we now know that using categorised lists may mask the age-related decline of temporal contiguity, whereas unrelated lists may be more sensitive in this regard. Importantly, this thesis demonstrated that temporal contiguity is related to different patterns of PFC activation at different stages of age and cognitive functioning. Finally, we now know that both delayed primacy and temporal contiguity may be valuable instruments for early detection of cognitive decline.

In summary, the data reported in this thesis spread awareness on the mechanisms underlying the pattern of free recall and suggest that the analysis of input and output order may be a sensitive cognitive tool that should be considered for integration with the typical instruments currently used in clinical practice and in research.

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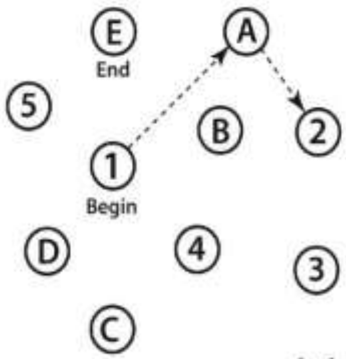
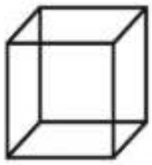
Appendix 1

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

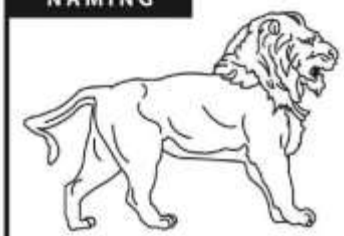
NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE			POINTS
[ ]	Copy cube [ ]	Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands	__/5





NAMING



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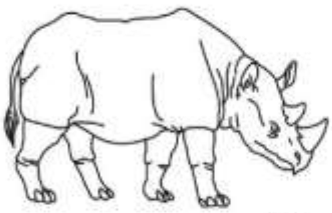

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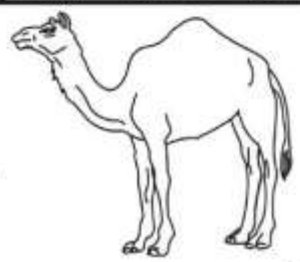

[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED	
1st trial						No points
2nd trial						

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] FBACMNAAJKLBAFAKDEAAAJAMOFAAB __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	__/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

 www.mocatest.org Normal ≥26 / 30 TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: ____________________

Appendix 2

2018 diagnostic framework (Jack et a., 2010)

Stage 1

Performance within expected range on objective cognitive tests. Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (the choice of the investigators) for age, sex, education, etc.*

Does not report recent decline in cognition or new onset of neurobehavioral symptoms of concern.

No evidence of recent cognitive decline or new neurobehavioral symptoms by report of an observer (e.g., study partner) or by longitudinal cognitive testing if available.

Stage 2

Normal performance within expected range on objective cognitive tests.

Transitional cognitive decline: Decline in previous level of cognitive function, which may involve any cognitive domain(s) (i.e., not exclusively memory).

- May be documented through subjective report of cognitive decline that is of concern to the participant.
  - Represents a change from individual baseline within past 1–3 years, and persistent for at least 6 months.
  - May be corroborated by informant but not required.
- Or may be documented by evidence of subtle decline on longitudinal cognitive testing but not required.
- Or may be documented by both subjective report of decline and objective evidence on longitudinal testing.

Although cognition is the core feature, mild neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist. In some individuals, the primary compliant may be neurobehavioral rather than cognitive. Neurobehavioral symptoms should have a clearly defined recent onset, which persists and cannot be explained by life events.**

No functional impact on daily life activities

Stage 3

Performance in the impaired/abnormal range on objective cognitive tests.

Evidence of decline from baseline, documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioural assessments.

May be characterised by cognitive presentations that are not primarily amnestic.***

Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, that is, may take more time or be less efficient but still can complete, either self-reported or corroborated by a study partner.

Stage 4

Mild dementia

Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing. Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities.
Stage 5
Moderate dementia Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.
Stage 6 Severe dementia Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible. Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.
*For stages 1–6: Cognitive test performance may be compared to normative data of the investigators' choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
**For stages 2–6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
***For stages 3–6: Cognitive impairment may be characterised by presentations that are not primarily amnestic.