The Neural Processes Underpinning Visual Associative Memory:

A Comparison of Young Grapheme-Colour Synaesthetes, Older Adults and Young Controls

Gaby Pfeifer

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Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to these or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed: Gaby Pfeifer

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Abstract

The traditional modular account of memory segregates visual associative memory and visual perception, with the former underpinned by the medial temporal lobes (MTL) and the latter by posterior visual regions. By contrast, the representational account of memory envisages visual associative memory as a perceptual-mnemonic continuum that can be traced from early visual cortex to anterior MTL structures. In this thesis, we tested these fundamentally different memory models by using a novel between-group design with young grapheme-colour synaesthetes, older adults and young controls, each of whom have their respective strengths and weaknesses in memory and perception. Specifically, grapheme-colour synaesthetes possess enhanced perceptual mechanisms, allowing them to experience black letters, words or digits as inherently coloured. They also show enhanced early visual cortex sensitivity in response to non-synaesthesia inducing stimuli (Barnett et al., 2008) as well as enhanced memory for verbal and visual stimuli. Using psychophysical techniques and functional magnetic resonance imaging (fMRI), we compared these three groups on a range of cognitive processes involved in visual associative memory: encoding, working memory, associative retrieval and recognition.

In the behavioural study, we tested the hypothesis that synaesthetes have a generic memory advantage for achromatic abstract pair-associates, which do not elicit synaesthesia. To test this prediction, we probed the memory of our 3 participant groups on fractal pair-associates. We found a learning and retrieval advantage of synaesthetes relative to older, but not to younger adults, suggesting a subtle generic memory advantage of synaesthetes, which was not detected between young and older adults. This study lends support to the enhanced processing hypothesis in synaesthetes, indicating that sensory-perceptual processing differences can translate into a generic associative memory advantage.

In a subsequent fMRI-study, we compared the 3 participant groups on a delayed pair-associate retrieval task, assessing associative retrieval, visual working memory (WM) and recognition. Whole-brain and region-of-interest analyses of brain activity at associative retrieval and recognition yielded significant group differences in occipito-temporal regions, but not in the MTL. This finding advances the representational account of memory by demonstrating the contributions of posterior visual processing regions to visual associative memory. Specifically, we observed inverted group effects between retrieval and recognition, indicating that reduced

sensitivity in visual cortex (as in aging) comes with an activation increase during top-down retrieval and an activation decrease during bottom-up recognition, whereas enhanced sensitivity (as in synaesthesia) showed the opposite pattern. The results provide novel evidence for the direct contribution of enhanced and reduced perceptual mechanisms in synaesthesia and aging respectively to visual associative memory.

The modular account of memory emphasises a role of the hippocampus in declarative memory. In Experiment 3, we tested the account by examining the effects of associative retrieval on hippocampal activation and neocortical connectivity in a group of young and older adults. Older but not young adults showed a significant hippocampal activation increase during dissimilar pair-retrieval, indicating age-related deficits in discriminating dissimilar stimuli among a set of familiar pair-associates. Moreover, we found hippocampal connectivity with specific networks that i) compensated for age-related perceptual deficits in the similar condition, and ii) modulated flexibly in young adults according to stimulus type (similar and dissimilar pair retrieval). Our results support a representational rather than a modular view of memory, suggesting a role of the hippocampus in memory and perception that was modulated by age and the perceptual similarity of our stimulus set.

Previous research has shown that visual WM and visual imagery facilitate long-term memory. Moreover, synaesthetes show enhanced visual working and long-term memory, and experience more vivid visual imagery than controls. We therefore compared the 3 groups on visual WM and subjective ratings of visual imagery to discern the influence of sensory-perceptual mechanisms and visual WM on visual associative memory. Results showed that while WM-maintenance *per se* was most efficient in synaesthetes (showing reduced activity in prefrontal cortex and visual regions relative to young and older adults), it was not predictive of faster or more accurate associative retrieval. Thus, WM made no direct contribution to associative memory. Subjective visual imagery correlated with visual regions during WM-maintenance as well as with retrieval accuracy in synaesthetes, but not in young and older adults. Our results further demonstrated the facilitating effect of synaesthetes' enhanced sensory-perceptual mechanisms on the neural efficiency in tasks requiring top-down support (i.e. WM and visual imagery) and on associative retrieval.

We discuss how our findings compare with the two diverging models of memory, and consider the implications for dementia and cognitive intervention programs.

Contents

Chapter 1: Introduction

1.1 General Introduction

Research into visual associative memory (VAM) has seen a revival in recent years in the human neuroimaging literature. Specifically, within the field of cognitive neuroscience, the study of VAM has often been exemplary in translating the mechanisms of associative memory known from non-human primate research (Osada et al., 2008; Sakai and Miyashita, 1991) to humans. How does the brain bind objects that are commonly seen together in the environment to become linked in our mind? Where are the multiple associative features and objects represented in the brain? And how do we retrieve visual associations to aid successful orientation and action within our environment? For instance, if one of two related objects gets lost (e.g. the charger of your mobile phone), retrieval and temporary imagination of the missing object's features such as its size, shape and colour enhance our perception during search and the speed of detection within the environment (Chaumon et al., 2008; Kosslyn and Sussman, 1994). As such, successful associative retrieval reaches beyond successful binding, drawing on multiple cognitive mechanisms that include bottom-up perception and top-down imagery (Albright, 2012), as well as attention (Ciaramelli et al., 2008) and working memory (Curtis and D'Esposito, 2003; Ranganath, 2006). The result of these mechanisms is an experience of declarative memory, i.e. the conscious recollection of associated stimuli or events that constitute our factual knowledge (semantic memory), or personal experiences (episodic memory). The quantity and quality of such declarative memories raise the following questions: 1) What are the neural correlates that underpin the respective cognitive mechanisms? And 2) How are these mechanisms integrated during the event of successful associative retrieval?

To address these questions, we used a combined approach of cognitive neuroscience and neuropsychology, querying the cognitive and neural mechanisms of visual associative learning, retrieval, recognition as well as working memory. For the cognitive neuroscience approach we used functional magnetic resonance imaging (fMRI), to identify the neural pathways during a delayed pair-associative (DPA) retrieval task and a delayed matching-to-sample (DMS) task. For the cognitive neuropsychology approach we used reverse engineering, looking at the cognitive and neural mechanisms of memory that decline in healthy aging (Park and

McDonough, 2013) and comparing these against healthy young adults. The novel contribution of this project was to also examine individuals at the high end of perception and associative memory ability. To this end, we investigated the cognitive and neural mechanisms of grapheme-colour synaesthetes. Grapheme-colour synaesthetes perceive black letters and digits as inherently coloured (Ward, 2013). The neural bases of perception and memory in grapheme-colour synaesthetes give rise to the unusual perceptual associations between letters and colours. Thus, comparing associative memory of synaesthetes against young and older adults allowed us to advance our knowledge of the influence of perception on memory and probe two influential memory models, the modular account of memory (Squire and Wixted, 2011) and the representational account of memory (Bussey and Saksida, 2007; Graham et al., 2010; Saksida and Bussey, 2010).

1.2 Associative memory in the theoretical context

1.2.1 The modular account of memory

The modular account of memory refers to a longstanding taxonomy, which segregates long-term memory into multiple systems of declarative and non-declarative memories, as illustrated in Figure 1 (Squire, 1994). The basic tenet of the modular memory account has largely remained invariant over the past two decades. In a recent review by proponents of the modular memory account (Squire and Wixted, 2011), declarative memories are defined as facts (semantic memory) or events (episodic memory) that are consciously recalled and that can be verbally expressed. Non-declarative memories refer to various forms of implicit memory, including priming, conditioning, perceptual learning, as well as skills and habits that have become automatic and cannot easily be expressed verbally (e.g. riding a bicycle; accurately writing on the keyboard without explicitly recalling each letter that is being typed). Within the context of the modular memory account, VAM can therefore be both, declarative (e.g. the conscious recall of an image of your spectacle case in which you have left your glasses) or non-declarative (relying on implicit associative knowledge, e.g. bananas are yellow).

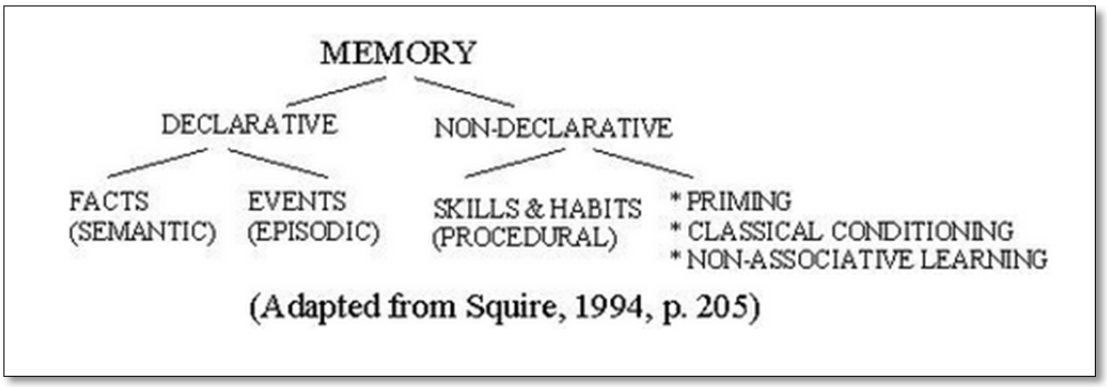


Figure 1. The modular account of memory.

The conceptual division of declarative and non-declarative memories is underpinned by a related anatomical division. While the domain of declarative memories is attributed to the medial temporal lobes (MTLs), which include the hippocampus proper, the entorhinal cortex (ERC), perirhinal cortex (PRC) and the parahippocampal cortex (PHC), non-declarative memories are formed in the sensory association cortices and are distributed across the neocortex. Thus, according to the modular memory account, the MTLs are exclusively dedicated to mnemonic functions and do not resolve any problems related to perception. Sensory association cortices on the other hand are purely perceptual (i.e. non-declarative). Although they are engaged in processing new information as part of perceptual encoding, they are not sufficient to establish durable traces of what is considered declarative memory [although sensory association cortices have storage function of sensory/associative memories after they have been detached from the MTL; see (Squire and Wixted, 2011), p. 273]. The anatomical distinction between memory and perception, a central point of divergence between the modular and the representational account of memory, is specified below.

With respect to its history, the modular account of memory is inspired by neuropsychological patients, first and foremost by the famous case of HM (Scoville and Milner, 1957). HM suffered anterograde amnesia after surgical removal of his bilateral hippocampi, including some of the neighbouring MTL areas. Given that HM could not form any new memories after his surgery, but was able to recall memories prior to the event, it was concluded that the hippocampus was not the storage site for long-term memories per se, but instead was necessary for learning and consolidating new material into long-term, declarative memory. Further work by Brenda Milner (Milner, 1970) showed that HM had spared learning abilities despite the removal of his hippocampus, which fell under the category of non-declarative memories. For example, when HM was asked to perform a visual recognition test of incomplete objects, he showed significant priming effects in naming the incomplete objects one hour later, although he had no conscious recollection of ever having seen the objects before. The priming effect was present even four months after the initial presentation, demonstrating that non-declarative forms of visual-perceptual learning are not reliant on the MTL system.

Another amnesic patient, Clive Wearing, is a professional musician who, at the age of 47, suffered a viral infection (Herpesviral encephalitis), which severely damaged his hippocampus [(Baddeley, 2002); Excerpt from BBC documentary: http://www.youtube.com/watch?v=Vwigmktix2Y]. He has since sustained very dense retrograde and anterograde amnesia. Remarkably however, this patient is still able to play the piano and can even acquire new musical sequences on the piano. As in the case of HM, Clive Wearing does not consciously recall any episodes of his learning or playing the piano, but nevertheless shows evidence of non-declarative procedural memory that is not reliant on the MTL system.

What are the anatomical underpinnings for establishing non-declarative memories? Several loops between the neocortex and the basal ganglia were shown to be implicated in non-declarative learning and memory in non-human primates (Alexander et al., 1986) and in the human brain (Foerde and Shohamy, 2011; Packard and Knowlton, 2002; Robinson et al., 2012; Urner et al., 2013). The basal ganglia comprise a core set of three bilateral subcortical nuclei, including the caudate nucleus and the putamen (which together form the striatum) and the globus pallidus. The cortico-striatal loops function via the input of sensory and/or motor information from the neocortex that sends signals to the striatum. The striatum further projects to the globus pallidus, which in turn sends signals to the thalamus. The final projection is from the thalamus back to domain-specific cortical regions that vary according to the respective motor, cognitive, or affective functions performed (Figure 2). For example, while it is known that motor planning and execution predominantly involve the putamen and its cortical connections to the supplementary motor area (SMA) and the motor cortex (Alexander and Crutcher, 1990; Marchand et al., 2008), the caudate, which has cortical connections to the prefrontal cortex [PFC; (Robinson et al., 2012)], is heavily involved in perceptual and cognitive functions. Thus, in humans, non-declarative procedural memories of, e.g. habitual, repetitive motor sequences are formed under the activation of the putamen and the motor cortex (Grafton et al., 1995). By contrast, non-declarative visual discrimination learning critically depends on the caudate nucleus, a finding that is consistent across non-human primates (Divac et al., 1967; Gaffan and Eacott, 1995; Gaffan and Harrison, 1987) and humans (Robinson et al., 2012).

In summary, the modular memory account makes a clear conceptual distinction between declarative and non-declarative memories. These different memory systems are underpinned by distinct neural pathways, with the former comprising a MTL system and the latter a cortical-basal ganglia system.

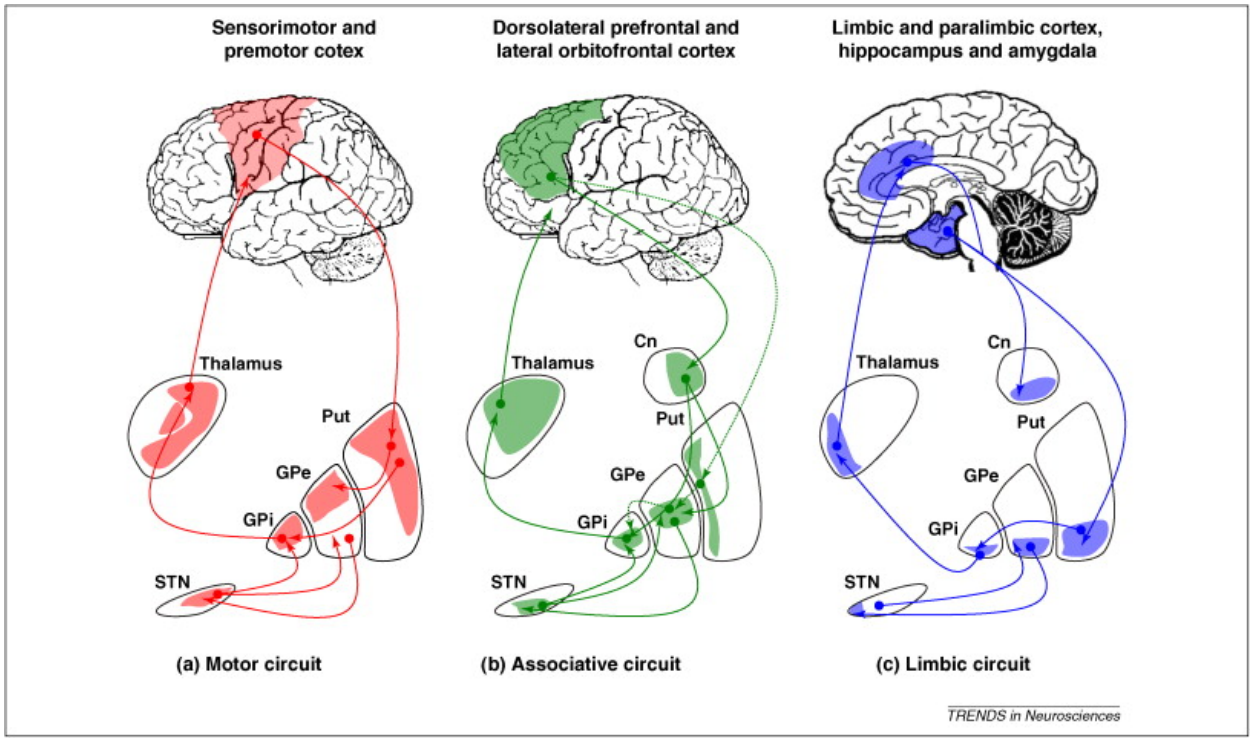


Figure 2. Three domain-specific cortico-basal ganglia loops. From left to right: motor, associative and limbic circuit. [Adapted from (Krack et al., 2010)].

1.2.2 The dual-process account of memory

While the modular memory account envisages memories as either declarative (and thus available to consciousness) or not, the dual-process account of memory acknowledges that declarative memories often vary themselves in quality. Accordingly, the dual-process account of memory further subdivides declarative memories into two distinct processes: recollection and familiarity (Montaldi and Mayes, 2010; Yonelinas et al., 2010). *Recollection* refers to the retrieval of stimuli or events that are enriched by contextual information of semantic or episodic nature. For instance, a stimulus (e.g. a person we meet on the street) might trigger semantic memory associations (e.g. the person's name and the relation to oneself), thus

referring to the recollection of declarative semantic memory. Likewise, a stimulus (e.g. your lost spectacles) might trigger an associated event (e.g. remembering that you last wore them whilst driving to work), thus referring to declarative episodic memory. *Familiarity*, on the other hand, can be understood as the feeling of knowing a particular stimulus or environmental cue. It is therefore considered in the realm of declarative memory. However, there is no recollection of the cue's context, or of any semantic associations, therefore lacking an important link to source memory. The qualitative differences between *recollection* and *familiarity* are thus treated as two distinct psychological processes by the dual-process account of memory. This is in contrast to the modular memory account, which envisages the two as a unitary process that simply varies according to memory strength [i.e. the more familiar something appears, the more it approaches the threshold of recollection; see (Smith et al., 2011)].

What are the neural underpinnings of recollection and familiarity? Given their declarative nature, both processes are mediated by the MTL system, yet with a division of labour in individual substructures. Guided by cytoarchitecture, dual process models of memory propose a unique role for the hippocampus in recollection, and a role for the PRC and PHC in familiarity (Diana et al., 2007; Montaldi and Mayes, 2010). The hippocampus belongs to the phylogenetically oldest parts of the archicortex, containing three-layered tissue. It distinguishes itself from neighbouring structures including PRC and PHC, which are part of the neocortex and contain six-layered tissue [although parts of the PRC have four-layered tissue; see (Suzuki, 2010)]. The cytoarchitectonic differences between the hippocampus and neighbouring MTL regions are likely to support fundamentally different algorithms for information processing. This is expressed, for example, by specific pattern separation mechanisms of the hippocampus (Montaldi and Mayes, 2010; Yassa and Stark, 2011). Pattern separation allows segregating highly processed object and spatial information from posterior regions, conferred by the PRC and PHC, respectively (Figure 3).

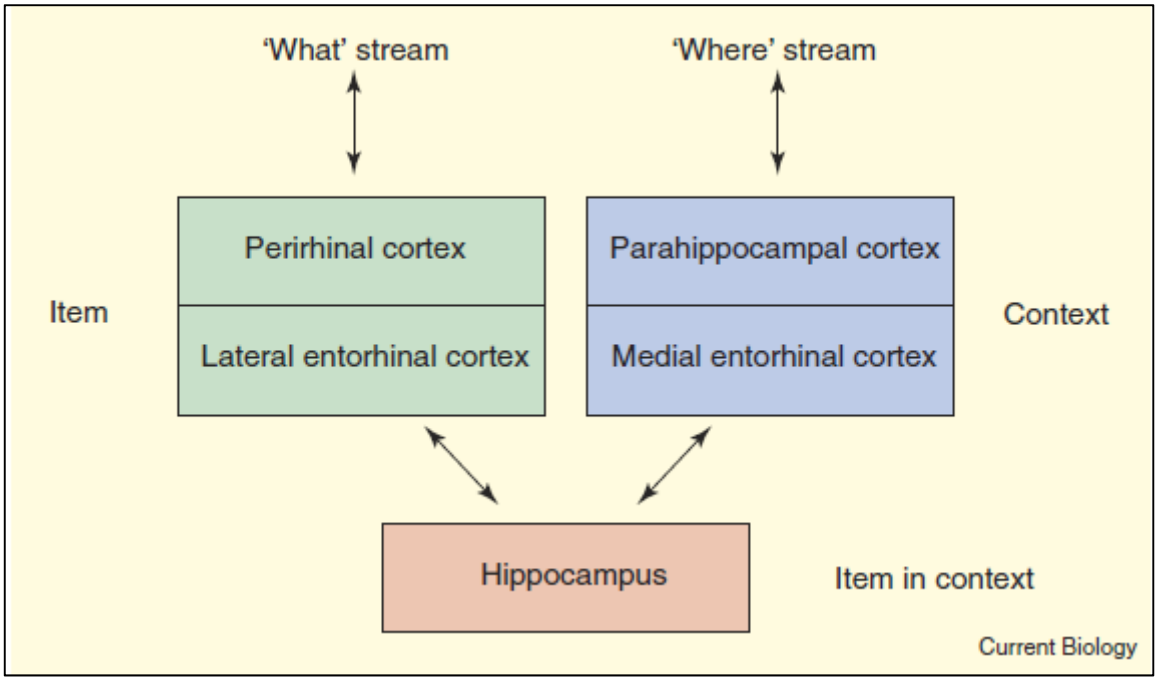


Figure 3. The functional organization of the medial temporal lobe memory system envisaged by the dual-process account of memory. [Figure taken from (Eichenbaum, 2006)].

For instance, the PRC receives its strongest input (~60%) from unimodal visual areas in the ventral visual ("What") stream (Suzuki and Amaral, 1994) and is therefore involved in processing item information. By contrast, the PHC receives input from posterior regions in the cingulate, retrosplenial and parietal cortex of the dorsal spatial ("Where") pathway (Suzuki and Amaral, 1994), conferring spatial information. The respective item and spatial information processed by these regions then converges on the hippocampus via the ERC (de Curtis and Pare, 2004; Suzuki, 2010), where associative recollection takes place [Figure 3; (Eichenbaum, 2006)].

In contrast to the recollection process subserved by the hippocampus, the PRC and PHC have a role in familiarity processing, making these brain regions suitable for stimulus recognition (old *vs.* new judgements). Indeed, familiarity processing has been inferred from recognition paradigms showing repetition suppression: single unit recordings in the macaque monkey have demonstrated reduced cell responses in the PRC after repeated presentation of visual stimuli (see review by (Brown and Aggleton, 2001). Similarly, human neuroimaging studies have

typically reported reduced perirhinal and parahippocampal activity following processing of old vs. new stimuli (Gonsalves et al., 2005; Henson et al., 2003), indicating a selective sensitivity to familiarity following repetition of visual stimulus exposure.

In summary, the dual-process account of memory is concerned with the MTL, which is envisaged as a declarative memory system, akin to the modular account of memory. Within the MTL-structures however, individual substructures perform two types of mnemonic processes: familiarity of item and spatial information is processed by the PRC and PHC respectively, while recollection of contextual details is subserved by the hippocampus.

1.2.3 The representational account of memory

Grounded in non-human primate research is the representational account of memory, a neuroanatomical model explaining stimulus representation and processing along the human ventral visual (VVS) perirhinal-hippocampal stream (Bussey and Saksida, 2007; Graham et al., 2010; Murray et al., 2007; Saksida and Bussey, 2010). The model envisages two basic principles. First, the location of stimulus processing critically depends on the stimulus type: simple features are processed in early, less selective primary visual regions and become further unitised and processed as complex features in rostral temporal regions, including the perirhinal cortex (PRC) and the hippocampus (Figure 4). Second, visual stimuli are represented as a perceptual-mnemonic continuum along the VVS. Accordingly, visual long term memory retrieval does not divide neatly into declarative and procedural knowledge subserved by separate MTL structures and sensory cortices. Instead, memory retrieval is envisaged as a stimulus-dependent hierarchical process that takes place in dedicated brain structures along the VVS. These principles are in opposition to modular views of memory that postulate a specific role for the hippocampus and neighbouring MTL structures in declarative memory, and a role for posterior ventral visual regions for visual perception and procedural knowledge (Bayley and Squire, 2003; Eichenbaum, 2000, 2013; Squire et al., 2004; Squire and Wixted, 2011; Yonelinas et al., 2010).

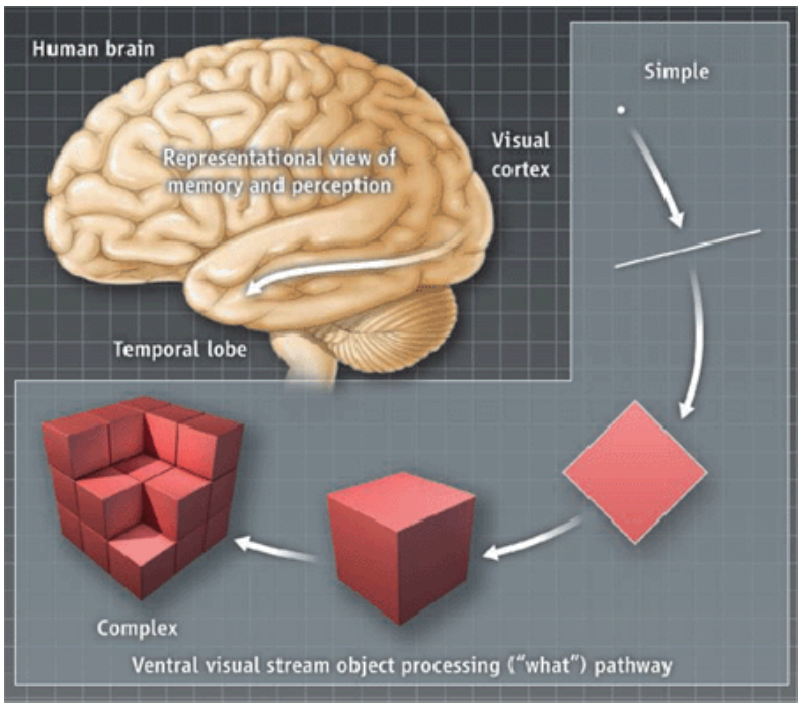


Figure 4. The representational account of memory [Figure taken from (Saksida, 2009)]

A key principle of the representational memory account is the idea that the *type of stimulus* is critical for effective computation in dedicated brain regions along the VVS. Simple features (e.g. colour, form) are processed individually and less selectively by early visual regions, and are progressively unitised in anterior regions of the VVS to represent global objects (Bussey and Saksida, 2007). The representational view is inspired by findings from the non-human primate literature. For instance, feature binding was observed in the macaque visual cortex, where V2 cells were responsive to more than one stimulus features, including colour and form, and colour and motion direction (Friedman et al., 2003; Gegenfurtner et al., 1996). More anteriorly, single cell recordings in monkey inferior temporal cortex (area 36) have demonstrated a tuning of specific 'associative' neurons to more complex visual patterns. Following learning of fractal pair-associates, associative neurons became selectively active in response to a newly learned target, even in the absence of its associated cue (Naya et al., 2003; Sakai and Miyashita, 1991). More recent research with macaques demonstrated hierarchical coding as a feed forward procedure, showing direct functional coupling of item-processing cells in TE with more complex pair-associative cells in TE that were selectively responsive to the item (Hirabayashi et al., 2013).

Interestingly, pair-associative coding has also been found more posteriorly, in neurons of the middle temporal (MT) cortex (Schlack and Albright, 2007). Given that the MT-cortex is selectively involved in motion processing (Albright, 1984), monkeys were trained on associating up- or downward moving dots with respective up- or downward pointing static arrows. Following associative learning, neural discharges were found in MT-cells upon presentation of the static arrows alone. Moreover, arrow-responsive cells were highly selective to the direction of the moving dots they had been paired with, suggesting associative learning had occurred in MT-cortex. Other research postulated that associative learning in IT-cortex was caused by feedback mechanisms of the MTL-system. For instance, Higuchi and Miyashita (1996) found no evidence of associative plasticity in inferior temporal (IT) cortex after lesioning the MTL, implying that the MTL-structures are critically and pervasively implicated in associative memory formation. However, findings such as those by (Schlack and Albright, 2007) refute this claim: associative tuning in MT-cortex could not have been caused by feedback mechanisms from the MTL-system, because the MT-cortex is not anatomically connected to the MTL-system (Suzuki and Amaral, 1994). Instead, the above findings demonstrate the distributed representations in cortical areas that code for specific classes of stimuli, which is in line with the stimulus-type principle of the representational memory account.

The second principle of the representational account suggests a perceptual-mnemonic continuum of stimulus processing along the VVS, with no clear anatomical division of brain areas involved in memory and perception. This principle has mainly been investigated in the PRC due to its location in antero-medial temporal cortex, just between the putative MTL memory system and the putative perceptual system of the VVS. In the traditional modular view of memory, the PRC is regarded a part of the MTL (Squire and Wixted, 2011) for two reasons: Firstly, the PRC contains four-layered tissue that resembles allocortical brain structures such as the three-layered hippocampus, while distinguishing itself from neighbouring neocortical temporal regions containing six-layered tissue (Suzuki, 2010). Secondly, tract tracing studies in macaque monkeys identified anatomical connections of PRC to visual area TE in lateral IT-cortex, to auditory regions in the anterior superior temporal sulcus (STS), as well as somatosensory regions in the insular cortex (Lavenex and Amaral, 2000; Suzuki and Amaral, 1994), making it a polymodal association area that is not simply a continuum of the unimodal visual areas in the VVS (Suzuki, 2010).

These patterns of cytoarchitecture and connectivity have led proponents of the modular view of memory to propose a role of the PRC in declarative memory that is akin to that of the hippocampus (Henson, 2005; Squire et al., 2004). However, although the PRC is a polymodal association area, its specific function is *the conjunction of features* individually processed in neighbouring visual areas (Bussey and Saksida, 2002), a crucial function both for memory and perception. Indeed, there is extensive support for the PRC and its role in feature conjunction from animal research, neuropsychological patients and fMRI studies using perceptual discrimination tasks [see (Saksida and Bussey, 2010) for review]. Using these tasks, monkeys with perirhinal lesions are typically impaired in discriminating ambiguous stimuli that share great feature overlap (Buckley et al., 2001; Bussey et al., 2002). Bussey and colleagues (Bussey et al., 2003) further showed that poor visual discrimination following PRC lesions was specifically related to perception and not memory: using a pair-associate visual discrimination paradigm, monkeys with and without PRC lesions required a comparable amount of learning trials to discriminate a designated S+ stimulus from an S- stimulus, when the two stimuli shared little feature overlap. By contrast, relative to control monkeys, monkeys with PRC lesions were significantly impaired in this task when feature overlap between S+ and S- was high (Figure 5). This indicated that PRC lesions did not impair memory *per se*, as the modular memory account would suggest, but instead indicated a role for the PRC in the perceptual discrimination of visually similar stimuli that prevented the lesioned monkeys to encode the relevant stimulus into memory.

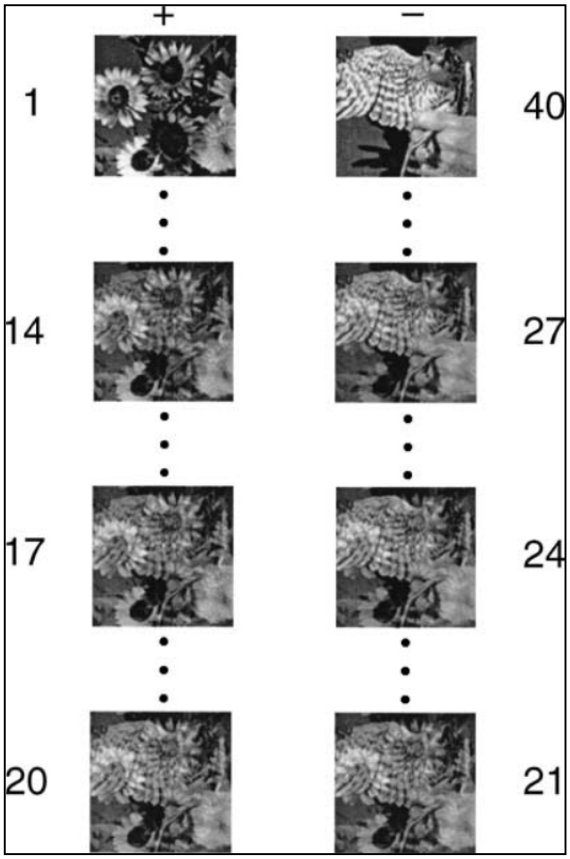


Figure 5. Stimulus set of the study by Bussey and colleagues (Bussey et al., 2003). Stimulus pairs were morphed from top to bottom to introduce increasingly greater feature ambiguity between S+ and S-.

Converging fMRI evidence from healthy young participants (Devlin and Price, 2007) has shown a specific increase in perirhinal activation for difficult object, but not difficult feature (e.g. colour, shape) discrimination, suggesting a role of the PRC in the representation of conjunctive objects. Since these tasks placed no demands on memory, the findings corroborate a role for the PRC in perceptual processing, in line with the perceptual-mnemonic view. Moreover, a neuropsychological study showed that patients with widespread MTL damage including PRC were significantly impaired in an oddity task relative to patients with specific hippocampal damage and healthy controls (Barense et al., 2007).

By contrast, the patients with specific hippocampal damage showed comparable performance to controls on this task, suggesting that the additional damage to the PRC in MTL patients contributed to problems in perceptual discrimination. More recently, Barense et al. (2012) have shown that poor perceptual discrimination in amnesic patients with widespread MTL damage including PRC led to interference effects in consecutive discrimination trials: ambiguous object pairs were discriminated significantly worse in successive presentations than in the first presentation. This effect was not found in the hippocampal patients, suggesting that poor functioning of the PRC in MTL patients caused problems in perception and memory alike, which is in line with the perceptual-mnemonic view.

Although the perceptual functions of MTL structures have largely been supported by testing the PRC, recent evidence also supports a role for the hippocampus in perception. Using an object-scene association paradigm, the hippocampus proper was repeatedly found to be responsive to global changes of object-scene relationships during incidental encoding (Howard et al., 2011; Kumaran and Maguire, 2006, 2007). A subsequent surprise memory test in Howard et al.'s (2011) study, assessing cued object recall of the objects-in-context, showed rather poor performance (5.9 %; SD = 3.54%), and the actual fMRI-activation pattern observed was unrelated to the participants' subjective scene familiarity and object recall. This suggests a role for the hippocampus in perceptual processing of object-scene relationships that are not always accompanied by associative memory formation, as the modular view of memory would suggest. Moreover, it is interesting to note that a perceptual role for the hippocampus was found for stimuli containing spatial elements, which is consistent with the notion that the hippocampus is responsive to more complex, spatial representations (Bussey and Saksida, 2007).

1.2.4 Extending the representational account of memory to the posterior ventral-visual stream

While the MTL structures have extensively been researched in the visual associative memory (VAM) literature, posterior brain regions in the VVS have (notoriously) received less attention. This is not surprising, given that modular views of memory have regarded posterior visual regions as part of an implicit, procedural memory system with a key role in perception (Squire and Wixted, 2011). Within the context of the representational memory account however, stimulus dependent representations are found along the VVS that serve both perceptual and mnemonic functions. The notion of hierarchical processing implies that posterior regions carry important fine-grained representations that make a significant contribution in the early processing, formation and retrieval of visual associations. In the following section, we review evidence from the developmental and aging literature, showing that the fine-tuning of the developing visuo-perceptual system and its age-related decline translate into overt changes in visual associative memory over the lifespan. We then review evidence from grapheme-colour synaesthesia, which further suggests that enhanced perceptual qualities arising from early posterior occipito-temporal cortex may contribute to enhanced memory performance, in line with the representational account of memory.

1.2.4.1 Early development and cortical plasticity

Developmental studies are well-suited to reveal the developmental trajectory of the fine-tuning of our visuo-perceptual system in higher-level visual association cortex. While the primary visual cortex is typically well-developed in early childhood, the structural grey matter integrity between the early visual system and posterior temporal association cortices continues to mature between the ages nine to around twenty (Gogtay et al., 2004; Zielinski et al., 2010). Resting state structural covariance measures further increase and expand from primary visual cortex along the inferior temporal and the dorsal parietal stream in middle childhood (ages 9 – 14), followed by significant pruning between the ages 14 – 18 (Zielinski et al., 2010). The age-related fine-tuning of the visuo-perceptual system is reflected in behavioural

performance. For instance, while children aged 6 – 11 years required up to 13 exposures to be able to discriminate ellipse-shaped scribbles from a memorised prototype, adults managed to discriminate the scribbles after just three exposures to the prototype, indicating enhanced visuo-perceptual learning mechanisms in adults (Gibson and Gibson, 1955). Converging neuroimaging evidence has demonstrated the direct relationship between the developmental maturation of the ventral visual pathway and increased visual recognition memory in adulthood (Grill-Spector et al., 2008). Specifically, selective regions in the fusiform face- and parahippocampal place area showed significant volume increases from childhood to adulthood, concomitant with performance gains in recognising faces and places respectively. Others have found improved VAM from childhood to young adulthood for complex everyday object-scene associations (Chai et al., 2010) as well as for item-colour associations (Ghetti et al., 2010). Using fMRI, these studies have demonstrated an age-related functional fine-tuning of the PHC: while a positive correlation was found between age and activation in the PHC during encoding of object-scene associations (Chai et al., 2010), a notable decrease was found during item-colour encoding from childhood to adulthood (Ghetti et al., 2010). This suggested that scene-selectivity in the PHC and related episodic memory improvements were only fully matured in young adulthood. These findings demonstrate that the visuo-perceptual system becomes increasingly more fractionated from childhood to adulthood in order to serve dedicated associative representations more effectively. Moreover, the findings underpin the notion of a perceptual-mnemonic continuum along the VVS from a developmental perspective and highlight the mnemonic contributions of the posterior visuo-perceptual system to VAM.

1.2.4.2 Age-related decline of the visual-perceptual system and effects on memory retrieval

During old age, dedicated brain systems become increasingly less differentiated [de-differentiation hypothesis; (Goh, 2011; Park and McDonough, 2013)]. According to the de-differentiation hypothesis, brain systems that have become fine-tuned and specialised in young adulthood to perform task-specific requirements lose their specificity with age. Several studies have demonstrated the

neural dedifferentiation in older adults' occipito-temporal regions, showing that stimulus-selective regions in older adults' VVS (e.g. the fusiform face area) responded less selectively (e.g. to faces) than in young adults, but instead responded to broader classes of stimuli (Park et al., 2004; Park et al., 2012). Neural de-differentiation in older adults requires the support of additional brain areas to achieve comparable performance levels to young adults (Shing et al., 2010). For example, studies using fMRI have repeatedly shown an age-related increase in frontal brain activation at the expense of posterior brain activation across episodic memory and working memory tasks (Cabeza et al., 2004; Davis et al., 2008; Gutchess et al., 2005). This pattern of a posterior-to-anterior shift in age (PASA) is found during memory retrieval even after controlling for objective and subjective task difficulty (Davis et al., 2008), ruling out the possibility that increased age-related frontal activation is a mere confound of increased task demand posed to older adults. Rather, it has been interpreted as a functional reorganisation of brain systems to compensate the age-related degradation of visuo-perceptual mechanisms subserved by posterior regions within the ventral-visual pathway (Park and McDonough, 2013). The dedifferentiation account originated from behavioural findings showing that in older adults, tasks associated with fluid (perceptual speed, reasoning and memory) and crystallized intelligence (knowledge, verbal fluency), shared a significantly greater amount of total variance with sensory acuity (vision and hearing after correction) compared to a younger cohort [(Baltes and Lindenberger, 1997); see also (Lindenberger and Baltes, 1994)]. More recent fMRI research further confirmed that the neural specificity in older adults sensory visual regions predicted cognitive performance on tasks measuring fluid intelligence (Park et al., 2010). Together, these findings suggest that a well-differentiated sensory-perceptual system facilitates higher level cognitive functioning and leads to a more efficient functional network during task performance. Age-related decline in visual perception and memory can inform about changes in neural efficiency, showing that older adults increasingly rely on the PFC, while young adults show functional integrity of both, posterior perceptual- and frontal brain systems during memory retrieval (Shing et al., 2010).

1.2.4.3 Perception and memory in grapheme-colour synaesthesia

People with developmental grapheme-colour synaesthesia show enhanced perception and memory (Rothen et al., 2012) and therefore offer a novel way of examining the perceptual-mnemonic view envisaged by the representational account of memory. Developmental grapheme-colour synaesthesia (hereafter referred to as synaesthesia) is a stable perceptual phenomenon, found in about 1% of the population (Simner et al., 2006), whereby visual stimuli such as letters, words, or digits (graphemes) lead to a secondary experience of colour (e.g. the letter S may be perceived as green). Thus, synaesthetes form visual associations of two unrelated stimuli, shape and colour, even in the absence of an actual colour stimulus. These visual associations are automatic, obligatory and cannot be suppressed (Ward, 2013; Ward and Mattingley, 2006). The long-standing neurological explanation of this effect is a suggested increased connectivity between the visual word form area (VWFA) and the colour processing area V4, both located within the fusiform gyrus in the posterior VVS (Hubbard et al., 2011; Ramachandran and Hubbard, 2001). Some research suggests a genetic basis for synaesthesia (Asher et al., 2009; Ward and Simner, 2005), according to which gene mutations might afford local and global cortico-cortical connections, e.g. by means of insufficient pruning (Bargary and Mitchell, 2008). Indeed, several MRI-based studies found increases in grey-matter volume, cortical thickness and cortical surface area in synaesthetes that extended bilaterally from the calcarine cortex to the lingual- and fusiform gyri, supporting pruning deficiencies along the occipito-temporal pathway (Banissy et al., 2012; Jancke et al., 2009; Rouw et al., 2011; Weiss and Fink, 2009). However, the phenotypic expression of synaesthesia appears to be largely developmental in nature. Even in the case of monozygotic twins, one sibling can show strong synaesthetic digit-colour associations, while the other does not have these experiences (Smilek et al., 2002). Evidence of the developmental nature of synaesthesia comes from a synaesthete with no parental history of synaesthesia, in which the unusual letter-colour associations had been learned in childhood from a set of coloured refrigerator magnets (Witthoft and Winawer, 2006). Group studies further showed that the perceived colour saturation in response to letters positively correlates with letter frequency in print text (Beeli et al., 2007) as well as with the order of letters in the alphabet (Watson et al., 2012b). This suggests that letters

encountered more frequently or learned earlier in school show a developmental relationship with the perceived colour associations. Behaviourally, the grapheme-colour associations are so strong that the synaesthetes' perception modulates inhibitory control mechanisms, activating left dorsolateral prefrontal cortex to avoid interference with coloured letters that do not match their own synaesthetic colours (Weiss et al., 2005). The effect has classically been demonstrated by using a modified version of the Stroop task [see (Ward, 2013; Ward and Mattingley, 2006)]. This task employs coloured graphemes (e.g. letters, digits, words), which induce a synaesthetic colour that is incongruent with the graphemes' perceptual colour. Synaesthetes are required to respond to the graphemes' perceptual colour and ignore the concurrent synaesthetic experiences. The typical finding in this task is that the synaesthetes' secondary responses interfere with the graphemes' perceptual colour and compromise performance. What these findings show is that the visual associations formed in posterior letter-colour processing areas (Brang et al., 2010; Hubbard et al., 2005; Nunn et al., 2002) result in experiences that reach beyond a purely perceptual effect, revealing mnemonic interferences of learned shape-colour associations. This is in line with the notion of a perceptual-mnemonic continuum envisaged by the representational account.

Interestingly, the enhanced visual associations need not be unique to synaesthesia: accumulating evidence suggests that letter-colour associations can effectively be trained in adult non-synaesthetes to an extent that the trained participants show interference effects comparable to synaesthetes in Stroop tasks variants (Bor et al., 2014; Colizoli et al., 2012; Kusnir and Thut, 2012; Meier and Rothen, 2009). When considering the developmental nature of synaesthesia, such experience-dependent learning effects appear plausible in the general population. For example, Kusnir and Thut (2012) employed an implicit learning paradigm of letter-colour associations to simulate the implicit learning conditions typically found in established synaesthetes (Beeli et al., 2007; Watson et al., 2012b; Witthoft and Winawer, 2006). Specifically, non-synaesthetes were trained on a visual search task in which some target letters were more likely than others to appear in the same colour. Unaware of the study's aim, the non-synaesthetes showed a selective improvement in detecting the consistent letter-colour associations over time, concomitant with subsequent Stroop interference effects for these stimuli. The important message of such findings is that the seemingly different mechanisms between synaesthetes and non-synaesthetes,

presumably underpinned by occipital-temporal regions, may in fact be very similar. The qualitative differences in visual associative processing seen between the two groups are likely to be influenced and shaped by environmental factors. Thus, the conclusions drawn for the synaesthetic population concerning perceptual-mnemonic processes in the ventral visual pathway can be considered to apply to the general population, albeit perhaps in a less exaggerated form [cf. (Kusnir and Thut, 2012)].

1.2.4.4 Contributions of posterior VVS to declarative memory: Evidence from grapheme-colour synaesthesia

The underlying assumption of the representational memory account is that the posterior visual system outside the MTL contributes to declarative VAM by means of hierarchical stimulus processing. Simple features are progressively unitised further up-stream and consequently aid perceptual discrimination as well as mnemonic retrieval in selective regions that represent the stimulus associations (Bussey and Saksida, 2002, 2007).

Turning to the synaesthesia literature, recent findings show a direct link between the synaesthetes' enriched visuo-perceptual encoding mechanisms and enhanced VAM [see (Rothen et al., 2012) for a review] that support the notion of posterior VVS contributions to declarative memory. Several memory tests employing synaesthesia-inducing verbal material have found that synaesthetes outperform non-synaesthetic control participants at various stages of encoding, immediate and long-term recall (Gross et al., 2011; Rothen and Meier, 2010; Yaro and Ward, 2007). Given that synaesthetes show structural (Banissy et al., 2012; Jancke et al., 2009; Weiss and Fink, 2009) and functional (Brang et al., 2010; Hubbard et al., 2005; Nunn et al., 2002) differences compared to non-synaesthetes within the posterior VVS, the enriched visuo-perceptual experiences can be expected to translate into enhanced VAM. For instance, research has shown that synaesthetes tend to group colour-inducing stimuli according to emerging perceptual colour patterns, while control participants draw on more effortful processing of semantic patterns (Ramachandran and Hubbard, 2001). More recently, Watson et al. (2012c) found that synaesthetes are capable of applying perceptual grouping to perform significantly better than non-synaesthetes in learning a list of black grapheme pair-associates (e.g. GH; YK) that

elicit reliable colour patterns, but are meaningless to control participants. Importantly, synaesthetes were capable of transferring the colour rules to subsequently learn novel test stimuli significantly more accurately than non-synaesthetes. This suggests that enhanced visuo-perceptual mechanisms can serve categorical learning at a higher level of VAM, which is in line with a system that envisages visual memory as a perceptual-mnemonic continuum. Moreover, the effect shows, on the basis of synaesthesia, that the posterior regions in the VVS make a qualitative contribution to declarative associative memory of low-level features such as shape and colour.

It could be argued that the overtly reported perceptual colours in response to letter shapes naturally lead to declarative VAM advantages in synaesthetes, given their extensive experience with these stimuli (Banissy et al., 2009). However, two studies have recently been reported showing that the synaesthetes' memory advantage is not restricted to synaesthesia-inducing verbal material, but equally applies to visual memory for complex random shapes (Gross et al., 2011) and achromatic fractal images (Ward et al., 2013). Importantly, these abstract visual stimuli do not evoke any explicit colour perceptions in synaesthetes. How can this effect be explained? One neurological explanation is based on the cascaded feed-forward processing mechanism (Hubbard et al., 2011). According to this mechanism, the fine-grained features of random shapes, which are processed in early visual regions, share similarity with features that make up letters or digits. The shapes might therefore receive some colour input through the structural hyper-connectivity in the fusiform gyrus, and return an implicit colour-binding advantage in synaesthetes. This processing mechanism resembles the operations of a hierarchical feature unitisation from early posterior visual cortex to anterior MTL regions, according to which small features are progressively unitised further upstream (Bussey and Saksida, 2007; Staresina and Davachi, 2010).

In summary, synaesthesia research on perception and memory supports the principles proposed by the representational memory account [see (Rothen et al., 2012)] and further extends the envisaged mechanisms to posterior regions in the VVS. However, although the synaesthetes' declarative memory advantage appears to arise from the unusual processing mechanisms in posterior visual regions, the interaction with brain regions further up the VVS are not understood. In fact, no fMRI study to date has examined the relationship between synaesthesia and VAM. Neurological models explaining synaesthesia are currently based on neuroimaging

data obtained from examining purely perceptual processing mechanisms (Brang et al., 2010; Hubbard et al., 2005; Nunn et al., 2002). As such, the structural and functional differences in the synaesthetic brain have predominantly been investigated in posterior occipito-temporal-parietal areas that represent the synaesthetes' sensory-perceptual advantage. However, the differences found in posterior VVS may well give rise to structural alterations within the synaesthetes' global network (Hanggi et al., 2011) and contribute to higher-level processing differences in anterior regions of the VVS.

1.3 Experiment overview

The primary aim of this thesis is to advance the conceptual understanding of memory and perception, with an emphasis on establishing the neural correlates underpinning the cognitive processes involved in visual associative memory.

To advance our conceptual understanding of memory and perception we examined 3 different participant groups (young adults, young synaesthetes and older adults), each of which have their respective strengths and weaknesses in memory and perception, allowing us to test the modular account and the representational account of memory.

In examining the neural correlates of visual associative memory (VAM), we used psychophysical techniques and fMRI to assess four constituent cognitive processes involved in VAM: visual associative learning, retrieval, recognition and working memory.

In assessing these cognitive processes, we employed abstract, achromatic fractal stimuli that were manipulated in visual similarity. The motivation for choosing abstract fractal stimuli was to engage occipito-temporal regions (Martins et al., 2014) and examine their contributions to memory, as predicted by the representational account of memory. The fractals were chosen to be monochrome in order to avoid a colour-memory advantage for synaesthetes who are colour experts (Pritchard et al., 2013). Finally, in manipulating the visual similarity, we aimed at testing the role of the MTL and posterior regions of the VVS in memory and perception. Specifically, we increased feature overlap in the similar pair-associates that might engage the PRC, as has previously been found in perceptual discrimination tasks (Saksida and Bussey, 2010). By contrast, the hippocampus is involved in pattern separation (Yassa and Stark, 2011; Rolls, 2013) and in the recollection of stimuli from dissimilar domains (Mayes et al., 2007), suggesting that dissimilar pair-associates would tax the hippocampus.

We conducted the following 4 experiments:

Chapter 2: Associative memory advantage in grapheme-colour synaesthetes relative to older, but not young adults

Associative memory is one of the first faculties to decline in old age, which has led to the formulation of the associative deficit hypothesis (Naveh-Benjamin, 2000). The associative deficit hypothesis suggests that older adults are particularly impaired in associative memory, while memory for individual items is often indistinguishable from young adults (Naveh-Benjamin et al., 2009; Edmonds et al., 2012). By contrast, synaesthetes show a memory advantage relative to young adults (Rothen et al., 2012), and perform particularly well on visual associative memory (Rothen and Meier, 2010). In the present behavioural study, we aimed to synthesise aging and synaesthesia and examine how the disparate perceptual-mnemonic abilities between synaesthetes, young and older adults affect associative learning and retrieval. Moreover, the synaesthetes' memory advantage has often been demonstrated on verbal or colour stimuli, which either elicit synaesthetic colours or provide a direct perceptual advantage, respectively. The second aim of this study was therefore to investigate whether achromatic abstract pair-associates (that neither contain nor elicit colour perceptions) would show enhanced memory in synaesthetes relative to controls. A memory advantage for achromatic abstract pair-associates in synaesthetes would be indicative of enhanced sensory-perceptual mechanisms rather than synaesthesia-specific differences in letter-colour processing. Moreover, a generic memory advantage in synaesthetes would support the use of our abstract pair-associates in the subsequent fMRI studies, and allow making inferences about memory and perception in the general population.

Chapter 3: Representational account of memory: insights from aging and synaesthesia

In Chapter 3, we built on the design and stimuli of our behavioural study (following the finding of a generic memory advantage in synaesthetes) and tested the representational account of memory using fMRI. To this end, we mapped out the entire VVS and carried out region of interest (ROI) and whole brain analyses for two types of memory: associative retrieval and recognition. In line with the perceptual-mnemonic principle of the representational memory account, we predicted that the

synaesthetes' enhanced sensation and perception in response to visual stimuli was underpinned by neural substrates that boost visual memory as well. Specifically, we hypothesised that young synaesthetes would show the most differentiated neural network relative to young and older adults, while older adults would show enhanced activity in PFC to compensate neural dedifferentiation in occipito-temporal regions (Goh, 2011; Park et al., 2004; Park et al., 2012).

Chapter 4: Age-related changes in hippocampal-neocortical connectivity during successful associative retrieval

In Chapter 4, we tested the modular account of memory in its prediction that the hippocampus has a role in declarative memory (Squire and Wixted, 2011). To this end, we examined the effects of associative retrieval on hippocampal activation and neocortical connectivity in a group of young and older adults. Specifically, the hippocampus is involved in pattern separation, a mechanism that is impaired in older adults (Yassa et al., 2011). We therefore predicted to find group activation differences in response to similar and dissimilar pair retrieval that place different demands on pattern separation and discriminability within a set of highly familiar pair-associates. Alternatively, the hippocampus might show a stable activation pattern in response to similar and dissimilar pairs (given the invariance of the actual stimulus type that were all fractal images), but exhibit different functional coupling with neocortical regions to support associative retrieval of varying memory load. The former finding would be indicative of a mnemonic role of the hippocampus that is directly affected by associative retrieval. The latter finding would be indicative of a perceptual role of the hippocampus in response to fractals, where retrieval accuracy of varying memory load is mainly determined by the strength and the dynamics of hippocampal connectivity with other neocortical regions. We further expected age-related changes in memory and perception to modulate hippocampal activation and connectivity and help disclose the role of the hippocampus in associative retrieval.

Chapter 5: Neural correlates of visual working memory in grapheme-colour synaesthetes, young and older adults

Given that working memory (WM) and visual imagery play a role in long-term memory (Baddeley and Andrade, 2000), we examined the neural correlates of visual WM in our 3 groups in Chapter 5. While older adults show WM deficts (Dobbs and Rule, 1998), synaesthetes were found to perform better than controls in WM tasks (Terhune et al., 2013). However, the underlying neural mechanisms of WM are less well understood. Age-related WM deficits are typically attributed to a failure of top-down signalling from PFC that impairs neural specificity in ventral visual cortex (Gazzaley et al., 2005). But what are the neural mechanisms that support WM in synaesthetes? In the present study, we predicted that enhanced neural specificity in visual regions (as in synaesthesia) would result in a more efficient neural network to support WM maintenance. Moreover, previous studies have shown that synaesthetes reported more vivid visual imagery than controls (Barnett and Newell, 2008; Spiller et al., 2015), suggesting that the synaesthetes' efficient use of imagery might underpin visual WM. To examine this prediction with fMRI, we correlated participants' subjective visual imagery ratings with WM-maintenance. Finally, we related the WM and visual imagery results to associative retrieval performance in order to determine the mnemonic effects of the underlying group differences in memory and perception.

Chapter 2: Associative memory advantage in grapheme-colour synaesthetes relative to older, but not young adults*

*This chapter derives in part from: “Associative memory advantage in grapheme-colour synaesthetes relative to older, but not young adults”, Pfeifer, G., Rothen, N., Ward, J., Chan, D., Sigala, N. (2014). Frontiers in Psychology, 5:696. doi: 10.3389/fpsyg.2014.00696.

2.1 Abstract

People with grapheme-colour synaesthesia perceive enriched experiences of colours in response to graphemes (letters, digits). In this study, we examined whether these synaesthetes show a generic associative memory advantage for stimuli that do not elicit a synaesthetic colour. We used a novel between group design (14 young synaesthetes, 14 young and 14 older adults) with a self-paced visual associative learning paradigm and subsequent retrieval (immediate and delayed). Non-synaesthesia inducing, achromatic fractal pair-associates were manipulated in visual similarity (high and low) and corresponded to high and low memory load conditions. The main finding was a learning and retrieval advantage of synaesthetes relative to older, but not to younger, adults. Furthermore the significance testing was supported with effect size measures and power calculations. Differences between synaesthetes and older adults were found during dissimilar pair (high memory load) learning and retrieval at immediate and delayed stages. Moreover, we found a medium size difference between synaesthetes and young adults for similar pair (low memory load) learning. Differences between young and older adults were also observed during associative learning and retrieval, but were of medium effect size coupled with low power. The results show a subtle associative memory advantage in synaesthetes for non-synaesthesia inducing stimuli, which can be detected against older adults. They also indicate that perceptual mechanisms (enhanced in synaesthesia, declining as part of the aging process) can translate into a generic associative memory advantage, and may contribute to associative deficits associated with healthy aging.

2.2 Introduction

Synaesthesia is a stable perceptual phenomenon whereby one sensory stimulus (e.g. a visual word or auditory tone) leads to a secondary experience such as colours, tastes, smells, etc. Grapheme-colour synaesthesia in particular refers to the experience of seeing specific colours in response to particular letters, words, or digits (graphemes), e.g. 'five is blue'. Recent studies have shown that people with grapheme-colour synaesthesia (hereafter referred to as synaesthesia) have a memory advantage over control subjects matched for age, gender and education, especially for verbal stimuli that elicit a synaesthetic colour (Gross et al., 2011; Radvansky et al., 2011; Rothen and Meier, 2010; Yaro and Ward, 2007). The most prevalent and generic cognitive model to explain the synaesthetes' verbal memory advantage (see Rothen et al., 2012 for a review) is the dual-coding theory (Paivio, 1991). According to this theory, more efficient and durable memory traces are obtained when words are additionally associated with visual images. Dual-coding effects can be observed in the normal population when using memory strategies such as associating words with locations in space [Method of Loci, (Verhaeghen and Marcoen, 1996)] or using visual imagery, e.g. forming a mental picture of the words' meaning (Ishai and Sagi, 1997). Since synaesthetes automatically activate visual images in the form of colours in response to words, this may serve as an explicit verbal memory aid and can explain the memory advantage for verbal material.

However, the dual-coding theory falls short of explaining empirical evidence of enhanced memory performance in synaesthetes for visual stimuli that do not elicit a synaesthetic colour experience. Two types of stimuli, with and without colour, have been tested in synaesthetes. Regarding stimuli with colour, Yaro and Ward (2007) were the first to show that synaesthetes were significantly better than controls in memorising colours arranged in matrices. Two additional studies, probing visual associative memory (VAM) with colour stimuli further confirmed the selective colour memory advantage in synaesthetes relative to controls, which may not extend to other stimulus features, such as shape and location (Pritchard et al., 2013; Rothen and Meier, 2010). The memory advantage for colour may stem from the synaesthetes' frequent sensory experiences with colours following the secondary responses to words. These experiences in return sensitise colour-processing areas

in the brain and lead to enhanced colour perception (Banissy et al., 2009). The reliable colour memory advantage found in synaesthetes therefore suggests that synaesthetes might be 'colour experts' (Pritchard et al., 2013). Studies with stimuli that neither evoke a synaesthetic response, nor contain a perceptual colour, which would suggest a more general memory advantage in synaesthetes, have reported mixed results. An advantage for synaesthetes over controls has been reported with achromatic (black-and-white) abstract stimuli, (Rothen and Meier, 2010; Gross et al., 2011, Ward et al., 2013), although others have not found this effect (Yaro and Ward, 2007; Pritchard et al., 2013). Likewise, figural recognition memory is enhanced in synaesthetes (Rothen and Meier, 2010), while recognition memory for faces is not (Gross et al., 2011). Moreover, in assessing VAM, Gross et al. (2011) used achromatic abstract line-drawings paired with geometric shapes and found no significant retrieval difference between synaesthetes and controls. One possibility for Gross et al.'s findings might have been an underpowered design, in which four synaesthetes were tested, and all participants reached ceiling performance on the third trial, making it difficult to establish the potential memory advantages relative to controls. However, a second possibility is that the synaesthetes' memory advantage for non-synaesthesia-inducing stimuli is too subtle to be reliably detected against demographically matched control participants. It is worth noting that on average, the synaesthetes outperformed the controls in all of the above reviewed studies, even though the differences were not always statistically significant.

How can the potentially subtle, generic memory advantages in synaesthetes be explained? An alternative theory to dual coding and/or colour expertise posits that the superior performance of synaesthetes in declarative memory tasks stems from differences in their brain function or structure, e.g. increased white matter connectivity (Rouw and Scholte, 2007; (Whitaker et al., 2014), or functional connectivity (Dovern et al., 2012). Functional brain differences between synaesthetes and controls during perceptual processing of non-synaesthesia-inducing shapes have been examined with EEG (Barnett et al., 2008) and fMRI (Sinke et al., 2012). Both studies found these processing differences to occur as early as in cortical area V1. Interestingly, the study by Barnett et al. (2008) showed that stimulus features, such as spatial frequency and contrast, led to significantly different early visual evoked potentials in synaesthetes relative to controls. Specifically, high spatial-frequency Gabor-patches elicited an enhanced C1-component in synaesthetes,

which is generally attributed to processing in the primary visual cortex. Similarly, synaesthetes were significantly more sensitive to the varying luminance contrast of checkerboard stimuli, showing enhanced P1-components over occipital regions bilaterally. These findings demonstrate that sensory processing of non-synaesthesia-inducing stimuli occurs differently in the synaesthetic brain, and could be attributed to altered circuitry in occipital areas. This raises two questions: a) whether the sensory processing differences for non-synaesthesia-inducing stimuli translate into a memory advantage, and b) how the potentially subtle memory differences between synaesthetes and controls can best be detected at the behavioural level.

To investigate the first question we developed a VAM test with achromatic pair-associates that differed in visual similarity. This manipulation aimed to tease out potential contributions of the synaesthetes' early sensory and perceptual processing differences during associative learning and retrieval. To address the second question, we used a between-group design, comparing young synaesthetes with young control participants and a third group of older adults who show characteristic, age-related deficits in perceptual processing (Fjell and Walhovd, 2004; Riis et al., 2009) and associative memory (Naveh-Benjamin, 2000). Comparing cognitive performance amongst three participant groups is an approach frequently used in neuropsychology to detect subtle memory differences, for example between older adults with questionable onset of dementia, healthy age-matched control participants, and patients with Alzheimer's disease (Fowler et al., 2002). A similar rationale was used in the present study: We expected the associative memory differences between young synaesthetes and young controls to be too subtle to be detected for non-synaesthesia-inducing stimuli, given that these stimuli are not known to evoke a conscious colour experience in synaesthetes to provide an advantage in perceptual processing over young adults. Thus, the inclusion of a third group of older adults provided another benchmark against which the other two groups could be compared. Specifically, we reasoned that the difference between young and older adults, versus young synaesthetes and older adults could uncover the synaesthetes' subtle associative memory advantages. Intuitively, this would be similar to sampling from a larger range of points from the distribution of associative learning and memory ability, where synaesthetes might be on the right of the mean (represented by young matched controls), and older adults might be on the left of the mean.

Compared to the emerging memory research in the synaesthesia literature, VAM has been examined more extensively in older individuals. Age-related performance detriments are typically found during associative recognition (Cohn et al., 2008; Cowan et al., 2006; Edmonds et al., 2012; Naveh-Benjamin et al., 2007; Naveh-Benjamin et al., 2004; Naveh-Benjamin et al., 2009; Shing et al., 2008), as well as during encoding of visual pair-associates (Iidaka et al., 2001; Sperling et al., 2003). Associative memory deficits in older adults have been attributed to several neurological factors, such as white-matter hyper-intensities in memory-related fibre tracts (Lockhart et al., 2012), reduced gray-matter volume (Raz et al., 2005), and reduced activation in memory-related posterior parietal, inferior- and medial temporal lobe areas (Cabeza et al., 2004; Gutchess et al., 2005; Iidaka et al., 2001).

In the present study, we examined the effects of age and individual differences on associative encoding and associative retrieval. To this end, we employed a self-paced trial-and-error learning paradigm, in which participants were trained to performance criterion with a set of achromatic visual pair-associates (Learning phase). This learning paradigm was used to guarantee sufficient exposure to the pair-associates and satisfy subject-specific learning requirements. This allowed us to account for an age-related encoding deficit (Naveh-Benjamin, 2000; Shing et al., 2010) for review) and to assess associative retrieval (Retrieval phase) after participants had reached the same performance level. The stimuli were black-and-white fractal pair-associates. These stimuli were chosen to prevent any advantageous primary or secondary colour experiences for the synaesthetes, therefore allowing us to investigate any potential generic VAM advantages in this group. Moreover, previous studies found that older adults, although generally impaired in VAM, show specific deficits in memory for abstract pair-associates (Iidaka et al., 2001). We therefore assumed that achromatic abstract stimuli would be most promising to elicit the relevant age- and individual differences in our study.

To tax the differential qualities of perception and memory between synaesthetes and older adults, we further manipulated the ease with which the stimulus pairs could be associated during learning and discriminated from each other at retrieval. One effective way to manipulate associability/discriminability is by varying the picture similarity (Poirier et al., 2012; Yago and Ishai, 2006). Associative retrieval is less efficient if the visual similarity between cue and target decreases.

Specifically, low similarity not only reduces the diagnostic value of the cue to its veridical target, but also increases competition among a range of other familiar images presented during retrieval, making the discriminability between matching and non-matching pair-associates more difficult. To exploit the differential effects of similarity during visual associative learning and retrieval in the present study, we chose a set of visually similar pair-associates that were expected to facilitate associability during learning and require less discriminability at retrieval (low memory load), and a set of visually dissimilar pair-associates that impede associability during learning and require high discriminability at retrieval (high memory load).

For the learning phase we hypothesised that, if the synaesthetes' enhanced perceptual mechanisms for non-synaesthesia inducing stimuli translated into an early learning advantage, this would emerge during encoding of similar pair-associates, which afford advantageous perceptual processing during associative learning. We examined pair-associative retrieval at two stages: immediately after the learning phase, and following a 30 minute delay. At both retrieval stages, we derived signal detection measures of the Hit- and False alarm responses. We expected to find a memory advantage for similar over dissimilar pair-associates across groups and time of retrieval, due to their respective low and high demands of discriminability at test. Moreover, we hypothesised that if a retrieval advantage existed in synaesthetes, a significant effect would emerge in the dissimilar condition that had the highest demands on discriminability.

2.3 Learning phase: Methods

2.3.1 Participants

Fourteen young non-synaesthetes (8 female; age range = 19 – 29 years; M = 22.64), fourteen older non-synaesthetes (9 female; age range = 62 – 83 years; M = 68.79), and fourteen young grapheme-colour synaesthetes (9 female; age range = 19 – 31 years; M = 22.50) took part in the experiment and were compensated for their time. All participants were healthy individuals with no history of any psychiatric, ophthalmological or neurological diseases. Written informed consent was obtained from all participants. The study was approved by the BSMS Research Governance

and Ethics committee. All groups were matched on the number of years of formal education [Young adults, M = 15.43 years, SD = 0.515; Older adults, M = 15.00 years, SD = 3.08; Synaesthetes, M = 16.35 years, SD = 1.78], yielding no significant difference between groups, $F[2,39] = 1.558$, $p = .223$.

Synaesthetes were recruited from the University of Sussex and via the UK Synaesthesia association website www.uksynaesthesia.com. All synaesthetes reported seeing colours in response to letters or digits. To verify Synaesthesia, we used the 'Synesthesia battery' (Eagleman et al., 2007), available on www.synesthete.org, and the cut-off score of 1.43 (from Rothen et al., 2013). A mean consistency score of M = 0.84 (SD = 0.25) was obtained across the group of synaesthetes, which confirmed their synaesthesia.

We assessed all participants on three subtests of the object recognition test included in the Visual Object and Space Perception Battery [VOSP, (Warrington and James, 1991)]. A summary of the participants' scores is provided in Table 1. A one-way between-subject (young adults, older adults, synaesthetes) ANOVA on the averaged sum of the subtest scores revealed that there was no significant group difference in the performance of the object recognition test of the VOSP, $F[2,39] = 0.032$, $p = .968$, demonstrating that perceptual functions were comparable across groups.

Table 1. Performance on the Object recognition test of the Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991).

Object recognition	Young Adults (N=14)	Older Adults (N=14)	Synaesthetes (N=14)
Subtests	M (SD)	M (SD)	M (SD)
Silhouettes (object naming)[1]	21.64 (3.27)	20.14 (3.95)	20.71 (4.00)
Object decision[2]	18.57 (0.85)	17.50 (2.10)	17.64 (1.82)
Progressive Silhouettes[3]	7.79 (2.29)	10.71 (1.38)	9.75 (2.28)
Averaged Sum of subtest scores	**48.00 (4.27)**	**48.35 (5.40)**	**48.10 (4.63)**

[1] maximum possible score is 30
[2] maximum possible score is 20
[3] the lower the score, the better the performance

2.3.2 Stimuli

Eight pair-associates (black-and-white fractal images; Figure 1) were selected from a pool of 18 pair-associates that had been rated for visual similarity by an independent group of 19 participants. Based on the mean-ratings of these 18 pairs of stimuli, we selected the five most dissimilar and the three most similar pairs. This ratio was chosen to compensate for the difference in their learning- and retrieval difficulty and to ensure successful memory across pair-associates. Associative learning and retrieval effects of the selected similar and dissimilar pair-associates were subsequently verified on another group of 15 young adults in a prior pilot experiment.

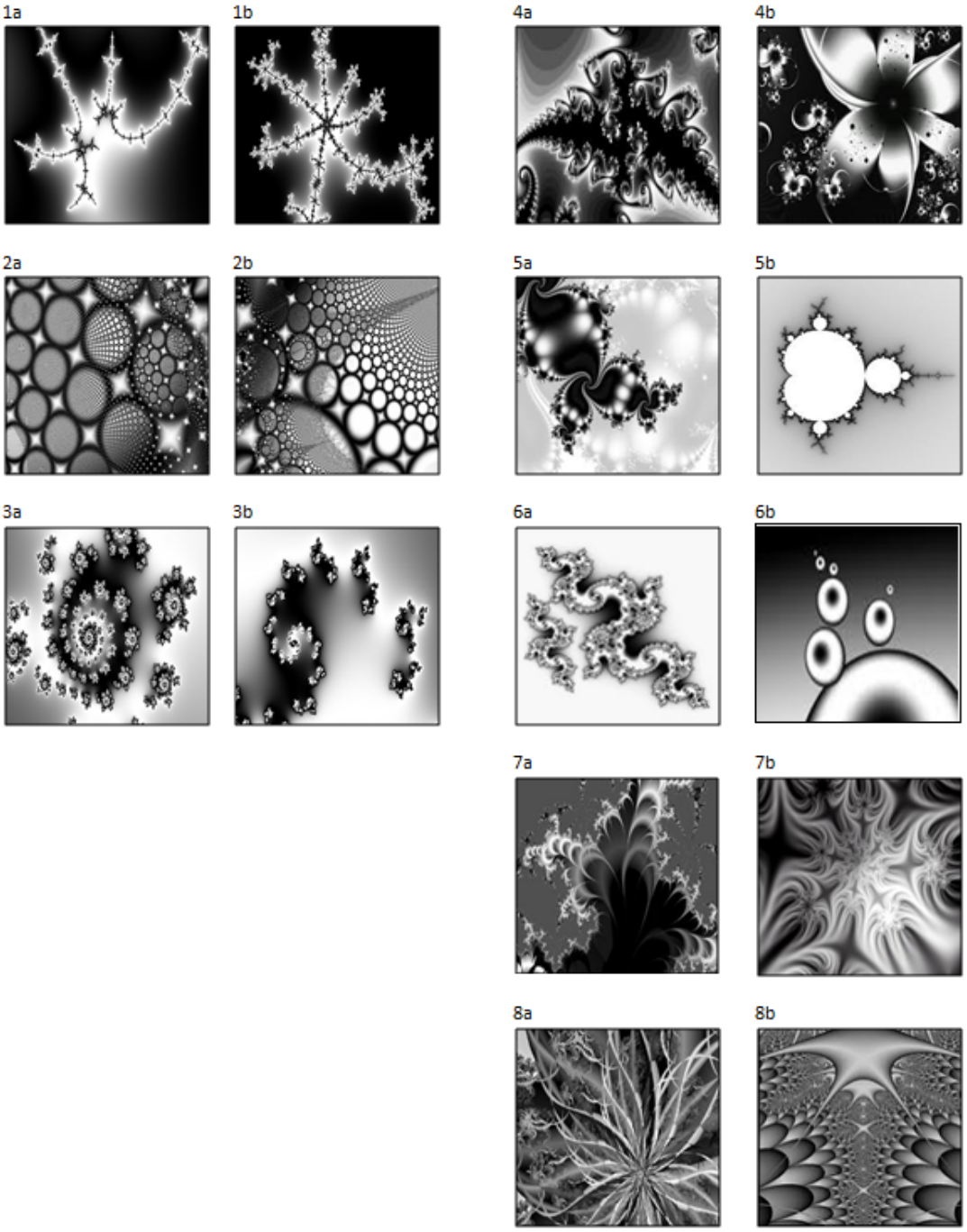


Figure 1. The three similar pairs (1-3) on the left, and five dissimilar pairs (4-8) on the right, rated by an independent group of 19 participants.

2.3.3 Procedure

A computer-based task was developed for pair-associative learning. Participants were seated in front of a 19 inch computer monitor, at a distance of 60 cm; the stimuli subtended approximately 3^0 of visual angle. Participants were asked to learn the correct combination of eight pair-associates via trial-and-error. They were instructed to memorise the pair-associates for a subsequent memory test. Each trial began with a fixation cross (2s), followed by a cue picture presented at the top of the screen and two possible matching target pictures below (Figure 2). The non-matching target was one from the set of pair-associates to be learned, rather than of a novel shape, to ensure equal picture familiarity. Participants were asked to indicate which of the two target pictures belonged with the cue, by pressing the left or right arrow key. The pictures stayed on screen until a response was recorded. Following the response, visual feedback appeared below the pictures (3s), indicating whether the matching target had been identified correctly or not (green tick or red cross respectively). Cue and target shapes of all pair-associates were presented interchangeably during learning: a stimulus that had been presented as the cue in one Run constituted the target in the following Run. A minimum of two Runs was required in the learning phase. Each Run contained eight trials and participants performed the test until they achieved a minimum of seven out of eight Hits on two successive Runs (learning criterion). Stimuli were delivered using Presentation® 14.9 (Neurobiobehavioral Systems, Inc.).

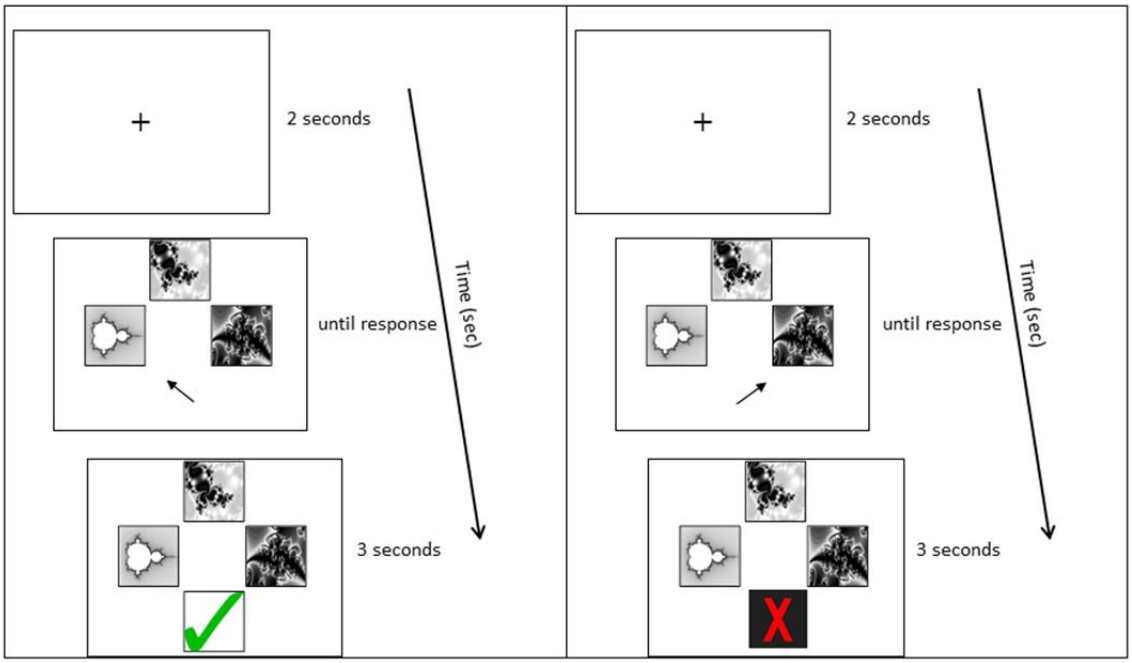


Figure 2. Example learning trial. Panels from top to bottom: Fixation cross; stimulus presentation; stimulus plus feedback. The left panel shows the feedback to a correct response; the right panel shows the feedback to an incorrect response.

2.3.4 Data analysis

Effect sizes. Cohen's d was used as an effect size measure for all pair-wise post hoc comparisons. The following formula was used for calculation: d = m1 - m2 / σ, where m1 = mean of group1, m2 = mean of group2, σ = the pooled standard deviation of the group means (Cohen, 1988). Cohen's d can be interpreted as: d = .20 (small effect); d = .50 (medium effect) and d =.80 (large effect; Cohen, 1992).
Partial eta squared (η_p^2) was used as an effect size measure in all analyses of variance (ANOVA) and in all analyses of covariance (ANCOVA). η_p^2 was calculated using the formula: $\eta_p^2 = SS_{effect} / SS_{effect} + SS_{residual}$, where SS_{effec} the sum of squares for the effect of interest and $SS_{residual}$ = the sum of squares of the error associated with the effect of interest. η_p^2 provides the effect of "the proportion of variance that a variable explains that is not explained by other variables in the analysis" (Field, 2009; p. 415) and can be interpreted as: η_p^2 = .01 (small effect); η_p^2 = .06 (medium effect) and η_p^2 = .14 (large effect; (Cohen, 1988).

Power analysis. Given the relatively small sample sizes in our three groups, we calculated the achieved power in all pair-wise post hoc comparisons to supplement our null hypothesis significance tests. The power calculations were performed using the G*Power calculator v. 3.1.6. Faul et al. (2009).

2.4 Results

2.4.1 Pair – associative learning

Number of Runs. Figure 3 illustrates the number of Runs required by each participant to learn the full set of eight pair-associates (similar and dissimilar pairs) to criterion. The average number of Runs was greatest for the older adults (*M* = 7.93; *SE* = 1.23), followed by young adults (*M* = 3.64; *SE* = 0.48) and fewest for the synaesthetes (*M* = 3.21; *SE* = 0.30). A one-way ANOVA, with group (young adults, older adults, synaesthetes) as the between-subject factor, yielded a significant effect on the number of Runs ($F[2,39] = 11.16$, $p < .001$).

Subsequent Tukey (HSD) post hoc comparisons revealed significant learning differences between synaesthetes and older adults ($p < .001$; d = 1.47; power = 0.58), young and older adults ($p = .001$; d = 1.28; power = 0.40), while there was no significant difference between synaesthetes and young adults ($p = .920$; d = 0.29; power = 0.94).

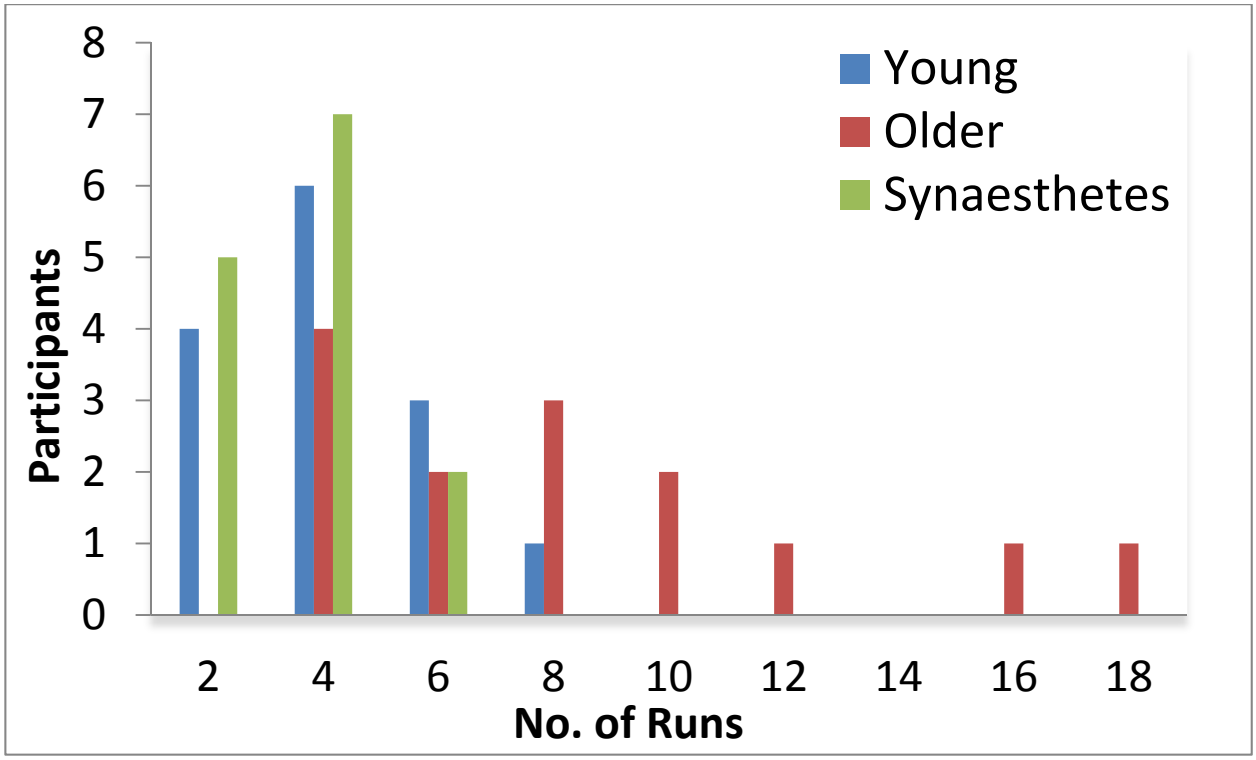


Figure 3. Number of Runs required by participants to learn the pair-associates to criterion. Average number of runs for the young (M = 3.64), for the synaesthetes (M = 3.21), and for the older adults (M = 9.93). The young adults and the synaesthetes learned significantly faster than the older adults.

Similarity effects on pair-associative learning. To examine the group differences in learning the similar and dissimilar pair-associates, two analyses of covariance (ANCOVA) were performed. For these analyses, each participant's trial-by-trial responses were averaged across the total number of Runs for each condition and were entered as the dependent variable. Group (young adults, older adults, synaesthetes) was included as the fixed effect and the total number of Runs was entered as the covariate.

Next, we examined whether there were any group differences in the successive learning rate of similar and dissimilar pair-associates over the first five Runs (the maximum number of Runs required by the synaesthetes). To this end, we performed five one-way ANOVA's per condition (similar, dissimilar), with group as the between-subject factor. In these analyses, we successively averaged the Hit-rate over an increasing number of Runs. In other words, we analysed the variance of the cumulative Hit-rates between groups over the first five Runs to examine if and when a significant group effect would emerge.

Similar pairs. Learning the similar pair-associates yielded high Hit-rates (averaged across all Runs) in all three groups [young (M = 96.87; SE = 1.40), older adults (M = 91.23; SE = 3.83) and synaesthetes (M = 98.93; SE = 0.73)]. The ANCOVA revealed that the covariate (number of Runs) did not significantly predict Hit-rate, F[1,38] = 2.473, p = .124, η_p^2= 0.061. Moreover, there was no significant group effect on the averaged Hit-rate, irrespective of whether the effect of the covariate was removed, F[2,38] = 0.530, p = .593, η_p^2 = 0.027, or not, F[2,39] = 2.78; p = .074; η_p^2 = 0.125.

As shown in Figure 4a, the two one-way ANOVA's of the first two Runs yielded no significant group effect on the cumulative Hit-rate (both $p > 0.05$). Starting on the third Run however, the group effect was significant (F[2,39] = 3.01, p = .043). Tukey (HSD) post hoc comparisons revealed that synaesthetes performed significantly better than older adults (p = .044), yielding a large effect size of d = 0.86 but insufficient power (0.57). No significant difference was found between young and older adults (p = .147; d = 0.63; power = 0.57) or between young adults and synaesthetes (p = .834; d = 0.43; power = 0.91).

Similarly, in Runs 4 and 5, we found a significant group effect on the cumulative Hit-rate (Run 4: F[2,39] = 4.04, p = .025; Run 5: F[2,39] = 4.05, p = .025). In both Runs, synaesthetes performed significantly better than older adults (Run 4: p = .027; Run 5: p = .028), yielding large effect sizes (Run 4: d = 0.92; Run 5: d = 0.9), but insufficient power (Run 4: power = 0.54; Run 5: power = 0.53). No significant difference was found between young and older adults (Run 4: p = .099; Run 5: p = .092), coupled with medium effect sizes (Run 4: d = 0.69; Run 5: d = 0.7) and insufficient power (Run 4: power = 0.55; Run 5: power = 0.55). The difference between young adults and synaesthetes was non-significant (Run 4: p = .830; Run 5: p = .854), however,

the effect size measures were medium (Run 4: d = 0.49; Run 5: d = 0.51) and the statistical power was high (Run 4: power = 0.93; Run 5: power = 0.93).

Dissimilar pairs. The averaged Hit-rate across all Runs in the dissimilar pair-learning condition was highest in the synaesthetes (*M* = 81.48; *SE* = 1.54), followed by young (*M* = 79.45; *SE* = 1.90) and older adults (*M* = 67.22; *SE* = 2.53). The ANCOVA revealed that the covariate (number of Runs) made a significant contribution to the Hit-rate, $F[1,38] = 16.869$, $p < .001$, $\eta_p^2 = 0.307$. With the effect of the number of Runs removed, there was a significant group effect on the averaged Hit-rate $F[2,38] = 3.419$, $p = .043$, $\eta_p^2 = 0.153$. Tukey post hoc comparisons revealed a significant difference between synaesthetes and older adults ($p = .015$, d = 1.89; power = 0.99), as well as between young and older adults ($p = .041$, d = 1.52; power = 0.97). The difference between synaesthetes and young adults was not significant ($p = 0.566$, d = 0.33; power = 0.69).

As shown in Figure 4b, the one-way ANOVA of the first Run in the dissimilar condition yielded no significant group effect on the cumulative Hit-rate ($F[2,39] = 1.12$, $p = .336$). Starting on the second Run however, there was a significant group effect on Hit-rate ($F[2,39] = 8.39$, $p = .001$). Tukey (HSD) post hoc comparisons showed a significantly greater Hit-rate for synaesthetes relative to older adults ($p = 0.001$, d = 1.58; power = 0.68) and for young adults relative to older adults ($p = 0.007$, d = 1.21; power = 0.61), while the difference between young adults and synaesthetes was not significant ($p = .829$, d = 0.23; power = 0.86). The significant group effect on the cumulative Hit-rate was maintained throughout Runs 3 to 5 (Run 3: $F[2,39] = 15.10$, $p < .001$; Run 4: $F[2,39] = 17.66$, $p < .001$; Run 5: $F[2,39] = 15.67$, $p < .001$). Specifically, for Runs 3 – 5, Tukey (HSD) post hoc comparisons revealed that both groups, synaesthetes and young adults, performed significantly better than older adults (both groups, Run 3 - 5: $p < 0.001$), while there was no significant difference between young adults and synaesthetes (Run 3 - 5: $p > 0.05$). Interestingly, although the effect sizes for the comparison of synaesthetes and older adults, and for young and older adults were large (Runs 3 - 5, d > 1.5), we only obtained sufficient power for the comparison of synaesthetes and older adults (Run 3: power = 0.91; Run 4: power = 0.95; Run 5: power = 0.91), while the comparison of young and older adults was underpowered (Run 3: power = 0.67; Run 4: power = 0.67; Run 5: power = 0.61). For the comparison of young adults and synaesthetes we

found a small effect size in Run 3 (d = 0.29), followed by a medium effect size in Runs 4 (d = 0.48) and 5 (d = 0.41). Sufficient power for these effects were obtained throughout Runs 3 – 5 (power > 0.80).

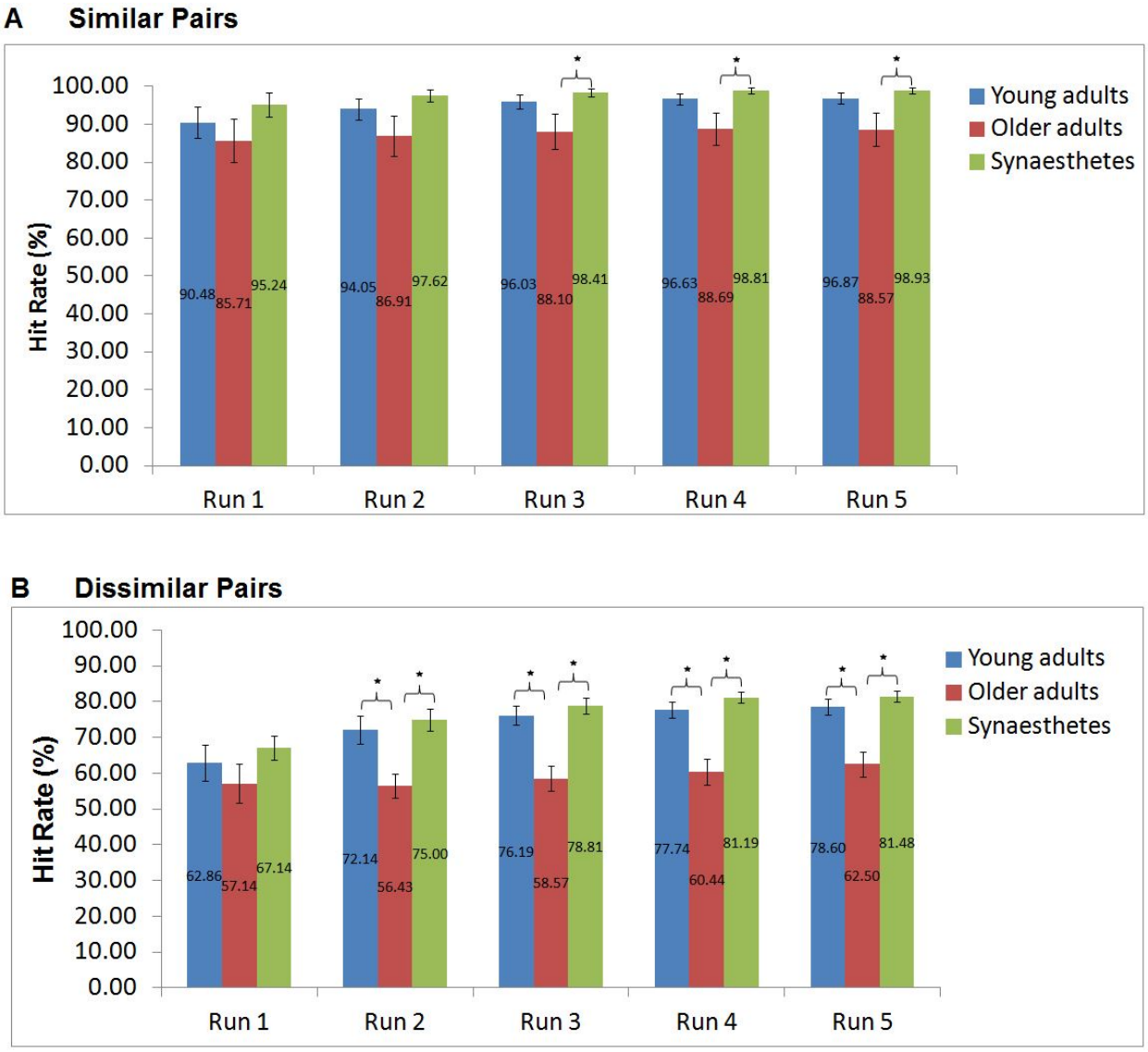


Figure 4. Percent Hit-rate during learning in young adults, older adults and synaesthetes. Learning of A) similar pair-associates, and B) dissimilar pair-associates illustrated on the first five Runs. Error bars: standard error of the mean.

2.5 Discussion

The results of the learning phase demonstrated two major points. First, interrogating different measures of associative learning (e.g. number of Runs vs. averaged Hit-rate vs. cumulative Hit-rate) is critical in establishing the precise group differences. Second, supplementing conventional null hypothesis significance testing with power analyses is crucial for small group sizes to be able to make inferences about the reliability of the obtained alpha-values and effect size measures.

The first point is illustrated by the analyses of the number of Runs (representing the crudest measure of group differences in associative learning) and of the averaged Hit-rate in the dissimilar condition. Both results suggest an effect of age on associative learning, with no effect of synaesthesia over and above age. Moreover, the averaged Hit-rate in the similar condition, which was high and comparable across groups, suggested a generic benefit of similarity in associative learning (Poirier et al., 2012), but no specific effect of synaesthesia.

The more interesting relationships could only be observed after interrogating cumulative Hit-rates. In the similar condition, the results of the null hypothesis significance tests were in line with our hypothesis, suggesting that synaesthetes showed an associative learning advantage, which could only be detected relative to older adults. The fact that the young adults showed no significant learning advantage relative to older adults rules out a mere age-effect for synaesthetes (who were age-matched to the young adults), and instead suggests an additive effect of synaesthesia and perceptual similarity on associative learning. The argument is strengthened by effect size measures, showing that the difference between young and older adults was medium, while for synaesthetes and older adults it was large. However, the results of the power analyses suggest that there is only a 50 - 60% chance of replicating the findings. Thus, the observed group differences in the similar condition, although detected in our present sample, cannot be extrapolated to the wider population. Interestingly, we also found a medium effect size between young adults and synaesthetes, despite the non-significant differences between these groups, indicating that there was a meaningful performance advantage of synaesthetes over young adults. Nevertheless, given that the achieved power in this comparison was above 90%, we are safe in retaining the null hypothesis to avoid

conducting a Type I error (Cohen, 1992). In summary, our sample of 14 synaesthetes demonstrated an enhanced sensitivity to perceptual similarity relative to the 14 older adults. Previous studies have shown the synaesthetes' differential processing mechanisms of non-synaesthesia-inducing stimuli at the perceptual level (Barnett et al., 2008; Sinke et al., 2012). Our results replicate and extend these findings, by showing a performance gain for synaesthetes during learning of similar pair-associates.

In the dissimilar condition, the results of the cumulative Hit-rate analysis showed a significant learning advantage for synaesthetes and young adults relative to older adults. However, although the effect size measures were large in both comparisons, only the comparison of synaesthetes and older adults yielded enough power (above 90%) for the findings to be reliable. Thus, the results suggest a reliable learning advantage in synaesthetes for non-synaesthesia inducing, dissimilar pair-associates, which could only be detected against older adults. The difference between synaesthetes and young adults was non-significant, however, the parametric increase in effect size measures (from small to medium) from Runs 2 - 4, demonstrates that the size of the difference between synaesthetes and young adults became increasingly larger over time.

2.6 Retrieval phase: Methods

2.6.1 Participants

We tested the same participants as in the learning phase.

2.6.2 Procedure

Participants remained seated in front of the computer monitor to take part in the immediate retrieval test. They were informed that they would be tested on the eight pair-associates acquired during the learning phase. Each trial began with a fixation cross (2s), followed by a cue picture presented at the centre of the screen

(1s). Participants were asked to use the cue to recall the matching pair-associate. Next, a blank white screen was shown for a variable delay of 2 - 4 seconds, during which participants had to hold the matching picture in mind. Then, a target appeared, which was either the matching stimulus to the cue, or another picture randomly chosen from the learned set of pair-associates (non-match). The target remained on screen until participants pressed a key, indicating whether it was a match or not. Figure 5 presents an example of such a trial. Participants' retrieval performance was assessed on two Runs. Each Run contained sixteen trials, including eight match trials and eight non-match trials that were randomly interleaved. The paired stimuli were presented interchangeably as cues or targets across the two Runs. No feedback was provided on the accuracy of the participants' responses. Following a 30 minute delay, during which participants carried out the object recognition test of the VOSP (Warrington and James, 1991), a surprise second retrieval test was administered. The procedure for this delayed retrieval test was identical to the immediate retrieval task described above. At the end of the experiment the synaesthetes were asked whether they had perceived colours in response to the visual pair-associates during the learning and/or retrieval phase. None of the synaesthetes reported any colour experiences.

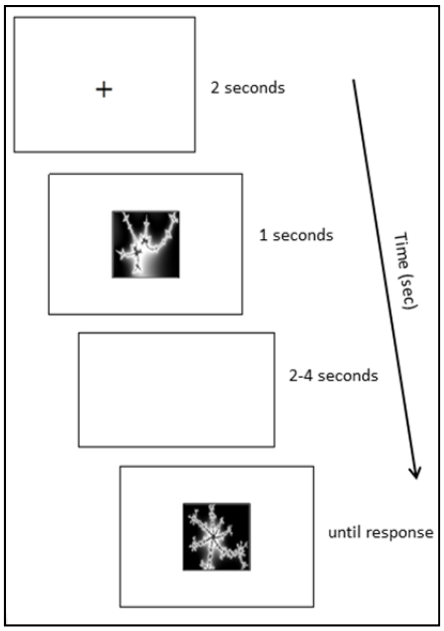


Figure 5. Example retrieval trial.

2.6.3 Data analysis

Signal detection. We carried out a signal detection analysis, deriving measures of d prime (d') and criterion C (Stanislaw and Todorov, 1999). Measures of d' represent a person's sensitivity in discriminating between signal trials (matching pair-associates) and noise trials (non-matching pair-associates). Thus, d' returns the difference between an individual's probability to give positive responses to matching pair-associates (Hits) and the probability of giving positive responses to non-matching pair-associates also (False alarms), providing a standardised estimate of effective memory retention (see e.g. Cowan et al., 2006; Cohn et al., 2008). Furthermore, we calculated the signal detection criterion C, which is a measure of response bias. A low subjective threshold for signal detection will lead to a bias towards 'yes' responses for matching and non-matching pair-associates, and is expressed by negative scores of C. Biased responses can mask participants' sensitivity in discriminating between signal and noise trials and lead to incorrect assumptions about their memory.

D prime and criterion C were calculated as follows: all probability scores of $Hits_{similar}$ and False $alarms_{similar}$ (respectively: $Hits_{dissimilar}$ and False $alarms_{dissimilar}$) were converted into *z* scores using the inverse phi function [Φ^{-1} (probability)] (Stanislaw and Todorov, 1999). To enable the conversion, all False alarm rates of 0 were raised to 0.01; all Hit-rates of 1 were lowered to 0.99 (Cowan et al., 2006). For d', the z scores of False alarms were subtracted from the z scores of Hits according to the following formulae:

$$\mathbf{d' = \Phi^{-1}(Hits_{similar}) - \Phi^{-1}(False\ alarms_{similar})}$$

$$\mathbf{d' = \Phi^{-1}(Hits_{dissimilar}) - \Phi^{-1}(False\ alarms_{dissimilar})}$$

Measures of criterion C were obtained using the following formulae:

$$C = -\mathbf{\Phi^{-1}(Hits_{similar}) + \Phi^{-1}(False\ alarms_{similar})/\ 2}$$

$$C = -\mathbf{\Phi^{-1}(Hits_{dissimilar}) + \Phi^{-1}(False\ alarms_{dissimilar})/\ 2}$$

2.7 Results

2.7.1 D prime

Figure 6 illustrates the mean d prime scores of sensitivity as a function of group, similarity of pair-associates and time of retrieval. A 3x2x2 mixed factorial ANOVA was conducted, with group (young adults, older adults, synaesthetes) as the between-subject factor, condition (similar, dissimilar) and time of retrieval (immediate, delayed) as within-subject factors. We found a significant main effect of group on sensitivity (across similar and dissimilar pair-associates), $F[2,39] = 9.088$, $p = .001$, $\eta_p^2 = 0.318$. Tukey (HSD) post hoc comparisons revealed that the difference in sensitivity was found between young and older adults, p = .008, d = 0.83; power = 0.27, between synaesthetes and older adults, p = .001, d = 1.12; power = 0.26, but not between young adults and synaesthetes, p = 0.679, d = 0.26; power = 0.74.

There was also a significant main effect of similarity on sensitivity, $F[1,39] = 106.725$, $p < .001$, $\eta_p^2 = 0.732$, suggesting that the d prime scores differed between the similar and dissimilar condition. The interaction between similarity and group was not significant, $F[2,39] = 0.541$, $p = .587$, $\eta_p^2 = 0.027$.

No significant main effect on sensitivity was found for time of retrieval, $F[1,39] = 1.740$, $p = .195$, $\eta_p^2 = 0.043$. However, there was a near-significant interaction between similarity and time of retrieval, $F[1,39] = 3.847$, $p = .057$, $\eta_p^2 = 0.090$, suggesting that although sensitivity was affected by the similarity of the pair-associates, this differed according to the time of retrieval. Figure 6 illustrates that while sensitivity in the similar condition was comparable across time, it was enhanced at delayed retrieval in the dissimilar condition. No interaction effect was found between time of retrieval and group, $F[2,39] = 0.143$, $p = .867$, $\eta_p^2 = 0.007$, or between condition, time of retrieval and group, $F[2,39] = 0.402$, $p = .672$, $\eta_p^2 = 0.020$.

In the following sections, we assessed the group effects on sensitivity further. To this end, we carried out four one-way ANOVA's, using group as the fixed effect, and the four respective conditions as the dependent variables ($Similar_{immediate}$; $Similar_{delayed}$; and $Dissimilar_{immediate}$; $Dissimilar_{delayed}$).

2.7.2 D prime of similar pair retrieval

Figure 6 shows the average d prime scores of sensitivity for immediate and delayed retrieval of similar pair-associates. The two one-way ANOVA's for the similar condition yielded a significant effect of group on sensitivity at both retrieval stages (immediate: $F[2,39] = 5.712$; $p = .007$; delayed: $F[2,39] = 4.394$; $p = .019$). Tukey (HSD) post hoc comparisons for immediate retrieval showed that while synaesthetes and young adults did not differ from each other ($p = 0.998$, d = 0.04, power = 0.99), synaesthetes and older adults did ($p = 0.014$, d= 1.02, power = 0.53), as did young and older adults ($p = 0.016$, d = 0.98, power = 0.52).

At delayed retrieval, there was no significant difference between synaesthetes and young adults ($p = 0.843$, d = 0.23, power = 0.87), and young and older adults ($p = 0.076$, d = 0.78, power = 0.59), while the synaesthetes maintained a significant retrieval advantage over older adults ($p = 0.021$, d = 1.01, power = 0.59).

2.7.3 D prime of dissimilar pair retrieval

Figure 6 shows the average d prime scores of sensitivity for immediate and delayed retrieval of dissimilar pair-associates. The one-way ANOVA at immediate retrieval yielded a near-significant effect of group on sensitivity ($F[2,39] = 3.19$; $p = 0.052$). Tukey (HSD) post hoc comparisons revealed that the effect was driven by the synaesthetes, whose d' scores were significantly above those of older adults (p = 0.048), yielding a large effect size of d = 1.08 and sufficient power (0.78), whereas we found no difference between young and older adults (p = 0.202), with a medium effect (d = 0.64) and insufficient power (0.65), or between synaesthetes and young adults (p = 0.758), showing a small effect of d = 0.27 and sufficient power (0.81).

Likewise, at delayed retrieval, we found a significant effect of group on sensitivity ($F[2,39] = 4.7$; $p = 0.014$). Tukey (HSD) post hoc comparisons again revealed a significant difference between synaesthetes and older adults ($p = 0.013$), with a

large effect size (d = 1.23), but with reduced power (0.72) relative to the immediate condition, while the difference between young and older adults was not significant (p = 0.083), albeit showing a large effect size of d = 0.87, but insufficient power (0.69). No significant difference was found between synaesthetes and young adults (p = 0.708, d = 0.3, power = 0.78). Thus, across two time points, we found evidence for a subtle memory advantage in synaesthetes for dissimilar pair-associates, which emerged in comparison to older adults.

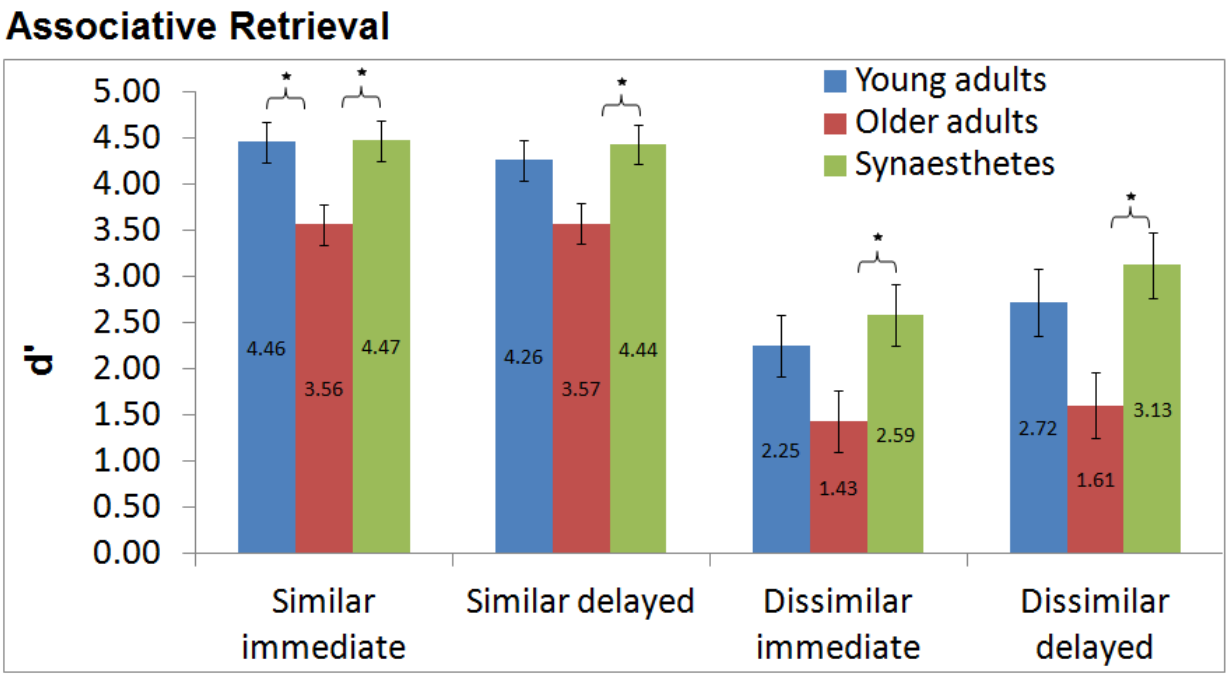


Figure 6. Mean d prime score of sensitivity as a function of group, condition and time of retrieval. Error bars: standard error of the mean. Higher d' scores represent greater sensitivity in discriminating between matching and non-matching pair-associates, indicating higher effective memory retention.

2.7.4 Criterion C

Figure 7 illustrates the mean scores of criterion C as a function of group, condition and time of retrieval. In the similar condition, older adults showed the largest negative scores across groups at immediate (*M* = -0.45; *SE* = 0.14) and delayed retrieval (*M* = -0.40; *SE* = 0.11), indicating a bias towards 'yes' responses. A negligible response bias towards yes responses was found for the young adults and the synaesthetes at immediate retrieval (both *M* = -0.01; *SE* = 0.07). At delayed retrieval, we found a decrease in the synaesthetes' criterion C (*M* = -0.11; *SE* = 0.074), with no change in the young adults (*M* = -0.01; *SE* = 0.10). In the dissimilar condition, we found a bias towards 'no' responses across groups at immediate retrieval, as indicated by positive values of C (young adults: *M* = 0.19; *SE* = 0.13; older adults: *M* = 0.11; *SE* = 0.15; synaesthetes: *M* = 0.15; *SE* = 0.12). At delayed retrieval, biased 'no' responses were found for young adults (*M* = 0.19; *SE* = 0.14) and synaesthetes (*M* = 0.08; *SE* = 0.12), while older adults tended to be biased towards giving 'yes' responses (*M* = -0.17; *SE* = 0.11).

A 3x2x2 mixed factorial ANOVA was performed, with group as the between-subject factor, condition (similar, dissimilar) and time of retrieval (immediate, delayed) as within-subject factors. We found a significant main effect of group on criterion bias, $F[2,39] = 5.590$, $p = .007$, $\eta_p^2 = 0.223$. Tukey (HSD) post hoc comparisons revealed that the difference in criterion bias was significant between young and older adults, $p = .009$, d = 0.75, power = 0.22, between synaesthetes and older adults, $p = .038$, d = 0.64, power = 0.33, but not between young adults and synaesthetes, $p = 0.823$, d = 0.16, power = 0.84.

There was also a significant main effect of similarity on criterion bias, $F[1,39] = 23.004$, $p < .001$, $\eta_p^2 = 0.371$, suggesting that the biased responses differed between the similar and dissimilar condition. As can be seen in Figure 7, participants tended to give more biased 'yes' responses in the similar condition, whilst providing more hesitant 'no' responses in the dissimilar condition. However the interaction between similarity and group was not significant, $F[2,39] = 1.657$, $p = .204$, $\eta_p^2 = 0.078$.

No significant main effect on criterion bias was found for time of retrieval, $F[1,39] = 0.991$, $p = .326$, $\eta^{p2} = 0.025$ and there was no interaction between time of retrieval and group, $F[2,39] = 0.231$, $p = .795$, $\eta_p^2 = 0.012$. Moreover, there was no significant interaction between similarity and time of retrieval, $F[1,39] = 0.850$, $p = .362$, $\eta_p^2 = 0.021$, or between similarity, time of retrieval and group, $F[2,39] = 1.060$, $p = .356$, $\eta_p^2 = 0.052$.

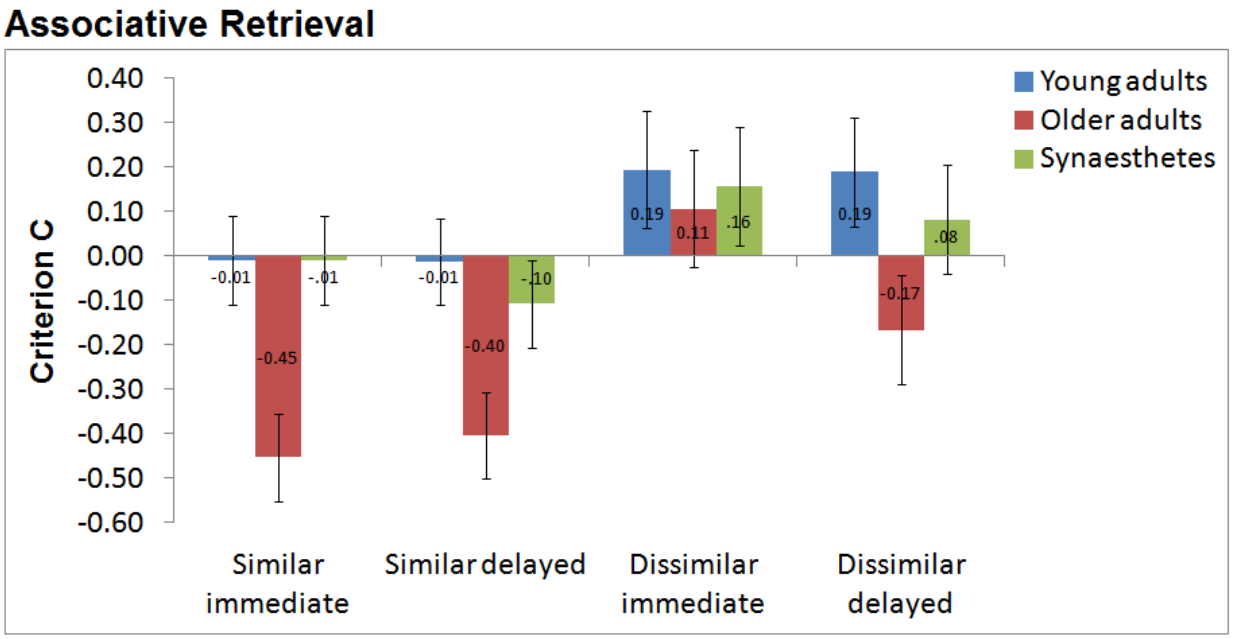


Figure 7. Mean criterion C scores as a function of group, condition and time of retrieval. Negative scores indicate a bias towards 'yes' responses for matching and non-matching pair-associates, while positive scores indicate a bias towards 'no' responses.

2.8 Discussion

In line with our first hypothesis, the retrieval results of the 3x2x2 ANOVA demonstrated that the stimulus similarity manipulation was effective at influencing associative retrieval, as shown by significantly higher d prime scores during retrieval of similar compared to dissimilar pair-associates. These results replicate previous findings by Poirier et al. (2012), suggesting that reduced similarity between a cue and a target increases the demands of discriminability, not only within, but also between pair-associates. Unlike perceptual tasks, where discrimination is challenging when two objects are similar, associative memory tasks increase the discrimination difficulty in the dissimilar condition. Specifically, in the dissimilar condition the cue is less diagnostic of the target and causes greater interference among a range of other familiar images (Poirier et al. 2012).Our d prime scores of dissimilar pairs were higher in the delayed than in the immediate condition, yielding a near-significant interaction between similarity and time of retrieval. One likely explanation for this result is an effect of practice.

We further predicted that if a retrieval advantage existed in synaesthetes, a significant effect would emerge in the dissimilar condition that had the highest demands on discriminability. This was supported by the results of the two one-way ANOVA's of the dissimilar condition, at immediate and delayed retrieval. Specifically, in these two ANOVA's, we found that synaesthetes performed significantly better than older adults, and the results were coupled with large effect sizes. More importantly, the results demonstrated sufficient power to be reliable, especially in the immediate retrieval condition. Thus, our retrieval results corroborate the notion of a memory advantage in synaesthetes for non-synaesthesia inducing stimuli, which emerged during dissimilar pair learning, and which could only be detected against older adults.

The fact that the comparisons between young and older adults in the two dissimilar conditions were non-significant but underpowered suggests that with increased sample sizes we might have observed a significant retrieval advantage of young relative to older adults. This may be particularly pertinent in the dissimilar delayed retrieval condition, where the alpha value between young and older adults reached 0.083, coupled with a large effect size. However, given the likely carry-over

effects from immediate retrieval (see interaction between similarity and time of retrieval), the results of the delayed retrieval condition may be confounded by these effects. We therefore argue that the results of the dissimilar immediate retrieval condition provide a more accurate measure of associative memory.

Indeed, the non-significant result between young and older adults in the dissimilar condition is rather atypical in the recognition memory literature, where poorer associative memory performance in older adults is the norm (Sperling et al., 2003; Naveh-Benjamin et al., 2004; Cohn et al., 2008; Naveh-Benjamin et al., 2009; Edmonds et al., 2012). We attribute this finding to the effects of the self-paced learning paradigm used in learning phase. These results are encouraging, as they suggest that when older adults are given sufficient time to learn visual pair-associates, their associative retrieval becomes non-significantly different from that of young adults. Implications of this finding are discussed further in the General Discussion.

With respect to the similar retrieval condition, significance testing suggested a subtle memory advantage for similar pair-associates in synaesthetes, which could only be detected against older adults (at delayed retrieval), and which was not found for the comparison of young and older adults. However, the power analyses revealed that both comparisons, that of synaesthetes and young adults relative to older adults, were not reliable, and that the only result showing high power was the non-significant comparison of young adults relative to synaesthetes. These findings demonstrate that the similar pair-associates were highly associable, which made it difficult to establish significant and reliable memory differences between groups, even with older adults.

While previous associative memory studies tended to investigate age-related changes in sensitivity (Naveh-Benjamin et al., 2009; Cohn et al., 2008; Cowan et al., 2006), few studies have measured participants' criterion bias (but see Cowan et al., 2006). Given the heterogeneous participant groups tested in the present study, it was deemed important to include measures of bias. Our findings showed that older adults were biased towards giving 'yes' responses throughout the similar and dissimilar conditions at delayed retrieval. One possibility for the biased responses might be the older adults' proclivity to rely on picture familiarity (Naveh-Benjamin et al., 2009, Edwards et al., 2012). Especially in the case of similar pair-retrieval, where familiarity

is easily established, this would trigger feelings of knowing the answer following the presentation of a cue, thus biasing older adults to provide positive responses irrespective of target-compatibility. The effect of increased familiarity was also evident in the dissimilar condition, where older adults were first biased towards giving 'no' responses at immediate retrieval, but were the only group to provide 'yes' responses at delayed retrieval, after the familiarity of the stimuli increased. Importantly, reliance on familiarity (rather than actual discriminability) has been explained by the reduced neural selectivity found in older adults' inferior temporal cortex, which alters perceptual sensitivity and spurs biased responses towards familiarity (Park et al., 2004). A similar explanation can account for the slight bias towards 'yes' responses in synaesthetes that we found in the similar condition at delayed retrieval. Synaesthetes were previously found to have enhanced neuronal excitability in the primary visual cortex, which lowered the signal-to-noise ratio of their conscious synaesthetic experiences (Terhune et al., 2011). These lower thresholds of cortical excitability in synaesthetes may have spurred biased responses towards relying on familiarity heuristics during retrieval of similar pair-associates over discrimination of the actual target.

2.9 General Discussion

In the present study we compared visual associative memory between synaesthetes and non-synaesthetes in two different age groups, using a novel between-group design. Synaesthetes were found to have an associative learning and retrieval advantage, even for stimuli that do not elicit a synaesthetic colour experience. Specifically, our findings yielded a significant difference between synaesthetes and older controls, but no differences between synaesthetes and younger adults or between younger and older adults. This suggests that there is a small difference between synaesthetes and younger adults that most experiments would be unable to detect without a highly impractical increase in subject numbers.

The results shed light on previous inconsistent findings of a memory advantage in synaesthetes for achromatic abstract stimuli (Gross et al., 2011;

Rothen and Meier, 2010), given that the memory advantage of young synaesthetes is too subtle to be reliably detected relative to age-matched controls, but emerges in comparison to older adults. Rothen et al. (2012) recently offered an explanation for the synaesthetes' memory advantage on the basis of the representational memory account. According to this account, visual stimuli are processed by the same neural substrates along the ventral visual stream as they are being retrieved from memory, suggesting a perceptual-mnemonic continuum of visual stimulus processing (Bussey and Saksida, 2007; Saksida and Bussey, 2010). The characteristics of grapheme-colour synaesthesia satisfy particularly well the stimulus-dependent processing operations suggested by the representational memory account. First, the synaesthetes' subjectively experienced colours in response to verbal stimuli encompass two features (colours, letters) that are both represented in the ventral visual stream. Second, the perceptual letter-to-colour associations lead to improved memory for verbal stimuli in synaesthetes (Yaro and Ward, 2007; Rothen and Meier, 2010; Radvansky et al., 2011), thus supporting the representational memory account of a perceptual-mnemonic continuum. Specifically, the verbal memory advantage supports the dual-coding theory, suggesting that when letters trigger colours, stronger memory representations are elicited in the same neural substrate. The representational account further supports the colour-expertise hypothesis (Pritchard et al., 2013): if there is a perceptual-mnemonic continuum, the synaesthetes enhanced colour perception (Banissy et al., 2009) should feed into enhanced colour memory. Thus, when colour is a constituent feature in abstract shapes, it is this feature for which synaesthetes show greatest associative memory, over shape or location (Pritchard et al., 2013).

Here, we have shown an associative memory advantage in synaesthetes over older adults for achromatic abstract stimuli, suggesting additional differences in the synaesthetic brain which facilitate memory functions. Indeed, the evidence suggests differences in the synaesthetes' anatomical and functional circuitry relative to controls that are often found along the ventral visual stream (see Rouw et al., 2011 for review). Processing of achromatic abstract shapes can be traced to even more posterior visual regions in the brain, as early as primary visual cortex. Given that synaesthetes were found to show perceptual processing differences for achromatic abstract stimuli in early visual cortex (Barnett et al.,

2008; Terhune et al., 2011), it is plausible, according to the representational memory account, that such early perceptual processing differences equally potentiate memory for these stimuli. This could explain the differences between synaesthetes and young adults found in the present study, which were too subtle to yield a significant memory advantage.

How can we explain the synaesthetes' memory advantage over older adults? One explanation is the altered white-matter microstructure in synaesthetes that has been observed in parietal, frontal and temporal areas (Rouw and Scholte, 2007; Whitaker et al., 2014), suggesting altered connectivity across the synaesthetic brain (see also Hanggi et al., 2011). By contrast, the brain of older adults is frequently characterised by white matter injury (Lockhart et al., 2012), or white matter atrophy (Vernooij et al., 2008), suggesting that the structural integrity, and thus, connectivity breaks down in old age. These anatomical differences are related to cognitive function and have shown, for instance, an age-related association between white matter integrity and enhanced perceptual discrimination of faces (Thomas et al., 2008), as well as an association between white matter injury in older adults and poorer visual associative memory (Lockhart et al., 2012). In synaesthetes, on the other hand, it has been shown that more diffuse white matter structure leads to cognitive advantages, such that those synaesthetes with more crossing fibres experienced greater subjective visual imagery (Whitaker et al., 2014). These findings suggest that the pervasive structural brain differences in synaesthetes and older adults may have brought about the behavioural associative memory differences, which were too subtle to detect against young adults.

We acknowledge that our interpretation is largely based on underlying neural differences between synaesthetes and older adults, bearing some limitations to the present study. Given that we recorded only behavioural measures, putative structural and functional group differences can merely be inferred from previous neuroimaging research. For instance, we suggested that the synaesthestes' enhanced sensitivity in visual cortex (Barnett et al., 2008) feeds into memory via the ventral visual stream (VVS; Bussey and Saksida, 2007). However, it is equally plausible that synaesthesia influences other cognitive processes, such as attention. Visual cortex is connected to the ventral and dorsal stream (Mishkin and Ungerleider, 1982; Goodale and Milner,

1992), with the latter projecting to the superior parietal lobe that supports visual attention (Corbetta et al., 2000). Interestingly, grapheme-colour synaesthetes, whose perceptual shape-colour associations are underpinned by the VVS, were found to have altered visual attention (Carriere et al., 2009; Smilek et al., 2008). For instance, in a free viewing task, Carriere et al. (2009) found that synaesthetes attended longer and more often to coloured letters that were congruent with the colour of their synaesthesia compared to incongruently coloured letters. Control participants did not show this attentional bias. In a subsequent visual search task, synaesthetes detected congruently coloured letters faster than incongruently coloured letters. Again, such a difference was not found for control participants.

Synaesthesia can further be interrupted by transcranial magnetic stimulation over the parietal cortex (Muggleton et al., 2007), suggesting a link between visual and attention-related processes in synaesthetes that are mediated by parietal cortex networks. Attention is also affected by age, and has been shown to significantly impair memory retrieval (Naveh-Benjamin et al., 2005). Consistent with the notion that parietal cortex is involved in attention (Corbetta et al., 2000), age-related attention deficits during an oddball task were localised over parietal cortex, showing reduced P3 amplitude and enhanced P3 latency in older relative to young adults (Fjell and Walhovd, 2004). Given the influence of attention and perception on memory, we aim to clarify group differences associated with learning and retrieval in a subsequent fMRI-study, with a specific focus on activation differences in the VVS.

A further limitation pertains to our claim of a ‘generic memory advantage’ in synaesthetes (by using achromatic abstract stimuli that did not elicit synaesthesia). Although the synaesthetes reported no colour perception in response to the fractal images, it cannot be ruled out that the enhanced memory effects were largely due to an entirely different network in synaesthetes that cannot easily be extrapolated to the general population. Enhanced intrinsic functional connectivity in synaesthetes relative to controls (Dovern et al., 2012) as well as different white-matter distributions across the synaesthetic brain (Whitaker et al., 2014) could have influenced the activation differences between young and older adults in such a way that they were not merely an effect of enhanced perceptual mechanisms in posterior visual regions, but supported by a wider network to assist in the mnemonic process. Our comparison of young

synaesthetes and older controls was primarily motivated by the idea that the two groups differ in memory and perception. However, other cognitive differences (e.g. attention, as discussed above) may also have influenced our findings. To account for any specific effects relating to synaesthesia and ageing, future research should use cross-sectional designs, comparing young and older synaesthetes in tests of attention, perception and memory. Moreover, longitudinal studies could examine the developmental trajectory of attention, perception and memory in synaesthetes over time.

With respect to aging, an interesting observation was the non-significant difference between young and older adults in the d prime scores of sensitivity, especially in the dissimilar retrieval condition that requires high levels of discriminability. Previous associative recognition tests have shown a significant memory reduction in older relative to young adults, characterised by older adults' frequent false alarm responses (Cohn et al., 2008; Shing et al., 2008; Naveh-Benjamin et al., 2004; Naveh-Benjamin et al., 2009; Edmonds et al., 2012). Specifically, these false alarm responses were attributed to age-related difficulties in discriminating match trials from non-match trials due to increased reliance on picture familiarity. In the present study, we have shown that this issue can be alleviated when the initial learning phase is self-paced, allowing sufficient time to encode the pair-associates. In practical terms, this suggests that age-related memory problems might be reduced by investing more time in associative learning.

Two limitations of the present study should be mentioned. First, the relatively small sample size of fourteen participants in each group has to some degree affected the generalizability of the data, as shown by our reported power calculations. Importantly however, the underpowered results were mostly found between young and older adults, suggesting that with increased sample sizes we would have been able to demonstrate a significant memory advantage in young vs. older adults, a finding that is not new. The more critical results however pertained to the differences found between synaesthetes and older adults, all of which demonstrated sufficient power in the dissimilar memory conditions. Second, it could be argued that our learning and retrieval paradigm might not be sensitive enough to detect the differential effects of aging and synaesthesia (e.g.

in the similar conditions). Ongoing work in our lab currently involves a four-alternative-forced-choice trial-and-error learning paradigm that might increase the sensitivity in detecting age and individual differences on the number of Runs required during pair-associative learning, as well as the effectiveness of this paradigm on subsequent retrieval.

In conclusion, this study shows that associative memory advantages are observed in synaesthetes even with achromatic abstract, non-synaesthesia-inducing stimuli. However, the advantages are subtle and can only be detected in comparison to older adults. Crucially, our results indicate that perceptual mechanisms (enhanced in synaesthesia, declining with aging) may contribute to a generic associative memory advantage, and may help explain the deficits in associative memory that occur with healthy aging.

Chapter 3: Representational account of memory: insights from aging and synaesthesia

3.1 Abstract

The representational account of memory envisages perception and memory to be on a continuum rather than in discretely divided brain systems (Bussey and Saksida, 2007). We tested this account using a novel between-group design with young grapheme-colour synaesthetes, older adults and young controls. We investigated how the disparate sensory-perceptual abilities between these groups translated into associative memory performance for visual stimuli that do not induce synaesthesia. At associative retrieval (when participants generated an associate in the absence of a visual stimulus), there was an effect of age in early visual cortex, with older adults showing enhanced activity relative to synaesthetes and young adults. At associative recognition (when participants decided whether a given visual stimulus was the associate), the group effect was reversed: synaesthetes showed significantly enhanced activity relative to young and older adults in early visual regions. ROI-analyses of the entire ventral visual stream further reflected that associative retrieval yielded significantly enhanced activity in young and older adults' visual regions relative to synaesthetes, while associative recognition was characterised by enhanced activity in synaesthetes' and young adults' visual regions relative to older adults. The inverted group effects observed between retrieval and recognition indicate that reduced sensitivity in visual cortex (as in aging) comes with increased activity during top-down retrieval and decreased activity during bottom-up recognition, whereas enhanced sensitivity (as in synaesthesia) shows the opposite pattern. Our results provide novel evidence for the direct contribution of perceptual mechanisms to visual associative memory based on the examples of synaesthesia and aging, as envisaged by the representational account of memory.

3.2 Introduction

The notion that perception and memory share similar neural representations is well established (Wheeler et al., 2000; Bussey and Saksida, 2007; Buchsbaum et al., 2012). In keeping with this principle, findings from the literature on normal aging show that reduced perception (McDonough et al., 2014) and declining sensory functions (Humes et al., 2013) are associated with poorer memory performance in older adults (Lindenberger and Baltes, 1994; McDonough et al., 2014). Age-related reductions in early visual cortex sensitivity (Wang et al., 2014) and a neural dedifferentiation in ventral visual cortex, leading to loss of neuronal sensitivity and specificity for visual stimuli (Park et al., 2012) can account for problems in visual perception and episodic retrieval (Goh, 2011; Park and McDonough, 2013). However, the causal influence of perception on memory is still unclear (St-Laurent et al., 2014). For instance, older adults typically compensate degraded sensory-perceptual functions with enhanced activity in prefrontal cortex (PFC), described as the posterior-to-anterior-shift in aging [PASA; (Davis et al., 2008)]. But do enhanced sensory-perceptual functions correlate with reduced PFC-activity and a more efficient retrieval network?

This can be addressed by studying grapheme-colour synaesthetes, whose enhanced perceptual mechanisms result in the perception of monochrome letters, words or digits as coloured, e.g. Ward (2013). They also show enhanced early visual cortex sensitivity to non-synaesthesia inducing stimuli (Barnett et al., 2008), and enhanced memory for verbal and visual stimuli (Rothen et al., 2012). Here, we investigated how the disparate sensory and perceptual abilities of three participant groups (young grapheme-colour synaesthetes, young and older adults) translate into visual associative memory for non-synaesthesia inducing, achromatic abstract pair-associates.

The scientific rationale for studying perception and memory in older adults and synaesthetes is based on the principles of the representational account of memory (Bussey and Saksida, 2007). According to this account, visual stimuli are represented as a perceptual-mnemonic continuum along the ventral-visual-stream (VVS). Memory retrieval is envisaged as a stimulus-dependent hierarchical process represented in functionally differentiated brain areas along the VVS. The model is

well-suited to explain the unusual colour perceptions in synaesthetes, which presumably emerge from a cross-wiring of the letter and colour area in posterior VVS (Ramachandran and Hubbard, 2001; Hubbard et al., 2011). This model proposes that the same neural substrates that underpin the synaesthetes' colour perceptions will give rise to a memory advantage for verbal and colour stimuli (Rothen et al., 2012). Likewise, the model predicts that synaesthetes will have a generic memory advantage for achromatic, non-synaesthesia inducing stimuli (Rothen and Meier, 2010; Gross et al., 2011; Pfeifer et al., 2014), as a result of enhanced sensory processing in early visual cortex (Barnett et al., 2008; Terhune et al., 2011). Taken together, the synaesthetes' enhanced sensation and perception in response to visual stimuli is underpinned by neural substrates that are likely to boost visual memory as well.

These predictions were put to the test in the present fMRI study. We employed a delayed pair-associative (DPA) retrieval task and conducted whole brain and region-of-interest (ROI) analyses for two types of memory: associative retrieval and recognition. We hypothesised that young synaesthetes would show the most differentiated neural network relative to young and older adults across these memory types, while older adults would show enhanced activity in PFC.

3.3 Materials and Methods

3.3.1 Participants

Nineteen young adults (8 female; age range = 21 – 32 years; M = 24.32), nineteen older adults (11 female; age range = 59 – 81 years; M = 66.21), and nineteen young grapheme-colour synaesthetes (15 female; age range = 19 – 33 years; M = 23.00) took part in the experiment after giving their informed, written consent. Some of these participants had already taken part in the behavioural study (Chapter 2), including 6 synaesthetes, 4 older adults and 1 young adult. To ensure that they did not have an advantage during associative learning and retrieval, we changed the entire stimulus set of the experimental and the control task (see section 3.3.2 Experimental design and Stimuli). The study was reviewed and approved by

the Brighton and Sussex Medical School Research Governance and Ethics Committee, which follows the guidelines of the World Medical Association Declaration of Helsinki. The participants had no history of psychiatric or neurological diseases. The average number of years of formal education for young adults was M = 16.95 (SD = 1.68), for older adults M = 13.95 (SD = 3.32), and for the synaesthetes M = 16.74 (SD = 2.11). The groups differed in the number of years of education $F[2,54] = 8.717$; $p = 0.001$. Tukey post hoc comparisons showed that the difference was significant between young and older adults ($p = 0.001$), between synaesthetes and older adults ($p = 0.003$), but not between young adults and synaesthetes ($p = 0.963$). Screening for cognitive impairment was carried out for all but 5 young adults, using the Mini Mental State Examination [MMSE; (Folstein et al., 1975)]. All participants performed comparably on the MMSE, $F[2,51] = 2.11$; $p = 0.131$, with high average scores across the 14 young adults (M = 28.93; SD = 0.93), 19 older adults (M = 28.15; SD = 1.46), and 19 synaesthetes (M = 28.89; SD = 1.37). Synaesthetes were recruited from the University of Sussex and via the UK Synaesthesia association website www.uksynaesthesia.com. All synaesthetes reported seeing colours in response to letters or digits. To verify Synaesthesia, we used the 'Synesthesia battery' (Eagleman et al., 2007), available on www.synesthete.org, and the adapted cut-off score of 1.43 (Rothen et al., 2013). Using this battery, a mean score of M = 0.81 (SD = 0.28; range = 0.38 – 1.39) was obtained across our group of synaesthetes, which is consistent with synaesthesia.

3.3.2 Experimental design and Stimuli

The fMRI protocol (Figure 1) consisted of a delayed pair-associative (DPA) task (experimental condition) and a delayed matching-to-sample (DMS) task (control condition). The DPA-task was always presented first in order to avoid retroactive interference effects on associative memory.

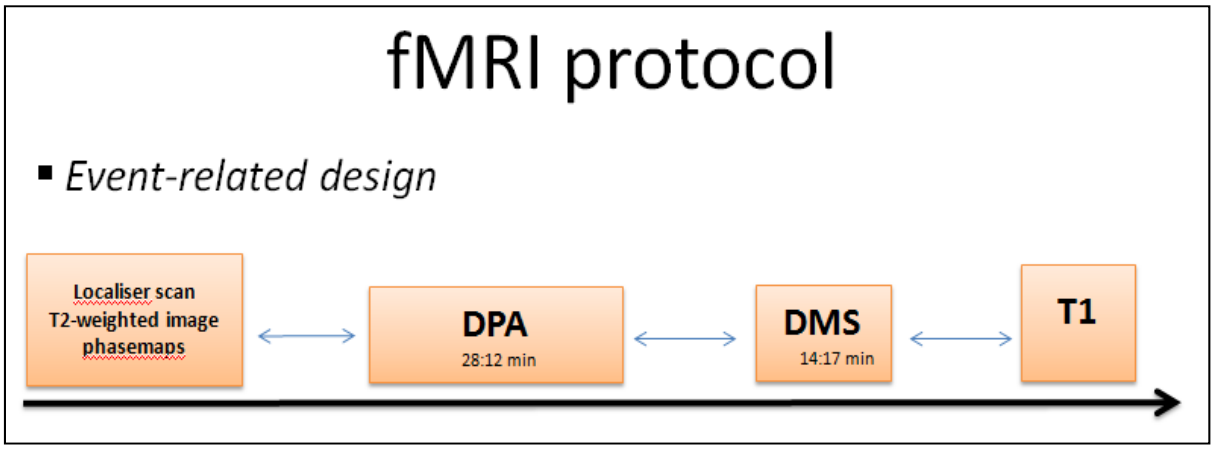


Figure 1. fMRI protocol.

DPA-task. For the DPA-task, we selected eight pair-associates (black-and-white fractal images) from a pool of 16 pairs that were rated for visual similarity an independent group of 20 participants. Participants gave their ratings on a 5-point Likert scale (Likert, 1932), where a rating of 1 indicated no visual similarity and a rating of 5 indicated high visual similarity between pairs. Based on the mean-ratings, we selected the 4 most dissimilar and the 4 most similar pairs respectively, representing high and low memory load conditions. A Wilcoxon signed-rank test demonstrated that the 4 selected similar pairs were rated significantly higher in visual similarity (M = 3.87; SD = 0.38) compared to the four selected dissimilar pairs (M = 1.31; SD = 0.20); significance Z = -2.521; p = 0.012 (two-tailed).

We used an event-related design, during which each of the selected pairs was randomly presented eight times, amounting to a total of 32 similar and 32 dissimilar pairs. The cue and target images were presented interchangeably throughout the task. On 62.5 % of the trials, the cue pictures were followed by a matching target, constituting 40 match-trials and 24 non-match trials. In this sense, lure stimuli were non-matching images from the same set of the 8 pair-associates rather than trial unique stimuli. Using recombinations of same-set stimuli constitutes a more powerful test of associative memory, requiring participants to retrieve the intact combination of pair-associates out of equally familiar stimuli rather than rejecting lures on the basis of their novelty (Mayes et al., 2007).

DMS-task. For the DMS-task, we chose an independent set of 8 individual black-and-white fractal images. We used an event-related design, consisting of a pseudo-random presentation of 32 individual fractal images, with each of the selected 8 images shown 4 times. On 62.5 % of the trials the cue pictures were followed by a matching target, constituting 20 match-trials and 12 non-match trials. Like in the DPA-task, lure stimuli were non-matching images from the same set of the 8 fractals rather than trial unique stimuli.

Across the DPA and DMS-task, the minimum trial distance between match and non-match trials was one (i.e. a match trial could immediately follow a non-match trial and vice versa), and the maximum trial distance was five (i.e. a non-match trial could follow four presentations of match-trials).

3.3.3 Training and scanning procedure

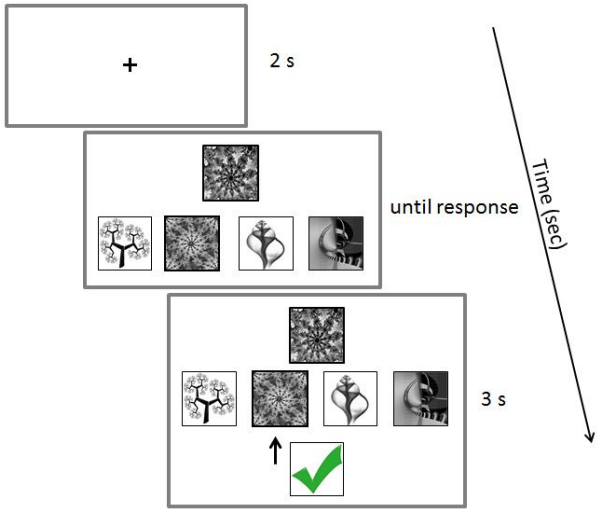
Associative learning task. Prior to scanning, participants were trained on the fractal pair-associates of the DPA-task. They were explicitly informed that they would be given a memory test on these stimuli during scanning. Each of the 8 pair-associates was randomly presented once at the centre of a computer screen for 4s and participants were instructed to remember the correct association of the pairs. The presentation was followed by a trial-and-error learning task. In this task, each trial began with a fixation cross presented for 2s, followed by a cue picture presented at the top of the screen and 4 possible matching target pictures below (Figure 2A). The targets were taken from the stimulus set of the 8 pair-associates and one target was always a match. Participants were asked to indicate which of the 4 targets belonged with the cue, by using different keyboard responses for each target. The pictures stayed on screen until a response was recorded. Following the response, visual feedback appeared below the pictures for 3s, indicating whether or not the matching target had been identified correctly (green tick or red cross respectively). Each Run contained 8 trials and participants performed the test until they achieved a minimum of 7 out of 8 Hits on 2 successive Runs (learning criterion). A minimum of 2 Runs was required in the learning phase. Cue and target shapes of all pair-associates were presented interchangeably during learning: a stimulus that had been

presented as the cue in one Run constituted the target in the following Run. Stimuli were delivered using Presentation® 14.9 (Neurobiobehavioral Systems, Inc., Berkeley, CA).

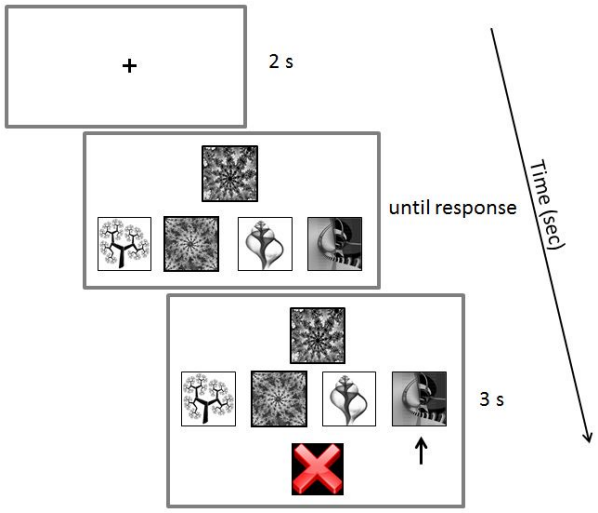
DPA and DMS-task. Following the associative learning task, participants were familiarised with the DPA and DMS-task prior to scanning. During scanning, an identical trial structure was used across the DPA and DMS-task (Figure 2B). During the cue-period (1s) of the DPA-task, participants were asked to use the cue to retrieve the matching target (*associative retrieval*). During the cue-period (1s) of the DMS-task, participants were asked to build up a mental image of the cue. During the delay period (8s), participants were required to either hold the retrieved picture in mind (DPA-task), or to hold the cue image in mind (DMS-task). The target presentation (1s) in the DPA-task comprised the *associative recognition* stage, where participants were asked to recognise the target as the matching or non-matching pair-associate. During the target presentation (1s) of the DMS-task, they were to judge whether the target was the identical image to the cue. Following target presentation in both tasks, a response window appeared and stayed on screen for 5 seconds, during which participants were asked to press 1 of 4 buttons, providing combined decisions about the target (match/non-match) and self-rated confidence (confident/not sure). The button-presses were followed by a variable intertrial interval (ITI) of 6 – 12 s before the next trial.

A. Prescan

Associative learning



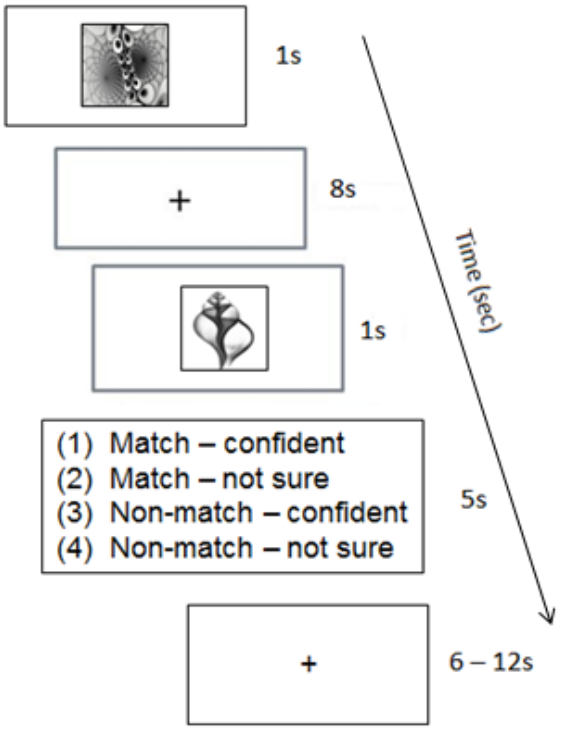
Example correct trial



Example incorrect trial

B. Scan

DPA trial



DMS trial

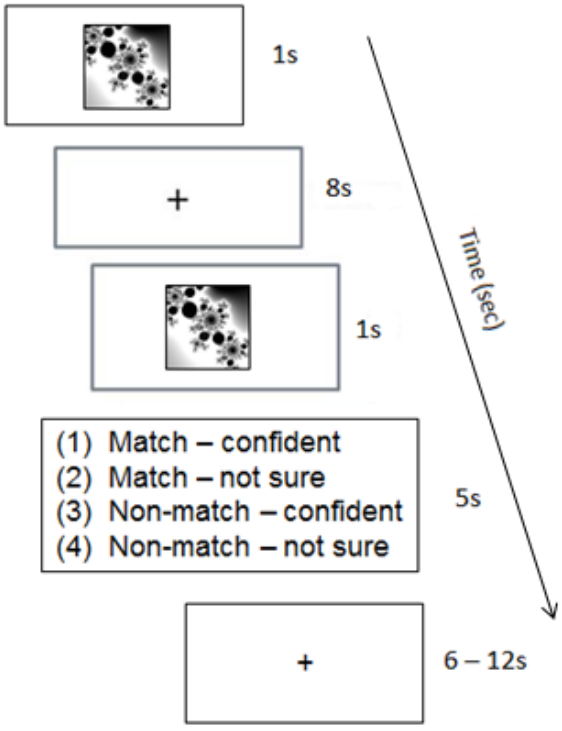


Figure 2. Experimental design. A) The prescan phase involved a four alternative forced-choice trial-and-error learning task of 8 pair-associates. Panels from top to bottom: Fixation cross; stimulus presentation during which participants were asked to select one of 4 possible pair-associates from the bottom of the screen to match the cue image at the top; stimulus presentation plus feedback. Example trials of a correct (left) and incorrect (right) response are shown. B) The scan phase involved two types of trials, DPA and DMS. DPA trials required participants to retrieve a cue's matching pair-associate and hold it in mind over an 8 second delay. DMS trials required participants to hold the cue in mind over an 8 second delay. Upon target presentation, participants were asked to decide whether the target was a match or non-match (in DPA and DMS trials) and give their responses within a 5 second time window (Prompt). ITI = Interstimulus interval; s = second.

3.3.4 fMRI data acquisition

Imaging data were collected using a 1.5 Tesla MRI scanner (Siemens Magnetom Avanto) with a 32-channel phased-array head coil, tuned to 66.6 MHz. Visual stimuli were presented on an in-bore rear projection screen, at a viewing distance of approximately 45 cm, subtending 5 degrees of visual angle. Stimuli were delivered using Cogent2000 v1.32 running under MATLAB R2006b (The MathWorks, Inc., Natick, MA). Time-course series of the two runs were acquired using a T2*-weighted echo planar imaging (EPI) sequence, obtaining 644 volumes during the DPA-task, and 324 volumes during the DMS-task. Each volume consisted of 35 axial slices oriented in parallel to the AC-PC line, and covering the whole brain. Slices were acquired bottom-up in the interleaved mode. The following functional imaging parameters were used: TR=2620ms, TE=42ms, flip angle 90˚, matrix= 64x64, FoV=192x192mm, slice thickness=3.0mm with a 20 % gap, resulting in 3.0mm isotropic voxels. To aid distortion correction, corresponding phase and magnitude field maps were acquired with a TR=513ms, TE1=5.78ms, TE2=10.54ms, flip angle 60˚. A whole-brain, high-resolution T1-weighted 3D structural image was obtained using a magnetisation-prepared gradient-echo sequence, consisting of 192 contiguous axial slices (TR=1160ms, TE=4.24ms, flip angle 15˚, matrix = 256x256, FoV= 230x230mm, 0.9mm isotropic voxel size). The T1-weighted image was used as an anatomical reference for each participant's functional data.

3.3.5 fMRI analyses

We used SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; www.fil.ion.ucl.ac.uk\spm) running under MATLAB R2013a for data preprocessing and statistical analyses. Preprocessing of functional images was carried out for each task separately, including slice-time correction to the middle slice in time, spatial realignment to the first image, and unwarping using the acquired field maps. The T1-weighted structural image was co-registered to the mean functional image and subsequently segmented to obtain normalisation parameters based on the standard MNI template. The segmentation parameters were used to transform each subject's functional images and the bias-corrected structural image into MNI space. Voxel sizes of the functional and structural images were retained during normalisation, and the normalised functional images were spatially smoothed using an 8mm Gaussian kernel (full-width-half-maximum). Statistical analyses were performed using the General Linear Model. At the single-subject analysis, the DPA-task and the DMS-task were entered as separate sessions into the model. For the DPA-task, we separated the similar and dissimilar trials and specified regressors associated with the cue and target-period for each condition. The target-period was further separated into match and non-match trials. This resulted in two regressors of interest relating to associative retrieval: similar_cue (sC), dissimilar_cue (dC); and four regressors of interest relating to associative recognition: similar_target_match (sTM), similar_target_non-match (sTNM), dissimilar_target_match (dTM), dissimilar_target_non-match (dTNM). (An additional task-related regressor was specified for the delay period, the results of which are not reported in the present study). Associative retrieval (cue period) was analysed by including only accurate and confident responses in the sC or dC regressors (collapsing across confident Hit- and correct rejection trials). Associative recognition (target-period) was analysed by including confident Hits in the sTM or dTM regressors, and confident correct rejections in the sTNM or dTNM regressors, respectively. For all target regressors, we used an equal number of match and non-match trials for each participant. Match and non-match trials were equated by randomly excluding surplus trials of either trial type.

Regressors of no interest included the prompt (containing participant's button presses), a nuisance regressor (containing all misses, false alarms, non-confident responses, non-responses) and six regressors representing motion-related variance. For the DMS-task, we used the identical regressor specification as for the DPA-task (modelling cue, delay and target-periods), with only one condition. The main regressor of interest was the DMS-related activity of the cue-period [DMS cue (DMSC)], containing accurate and confident responses (collapsed across confident Hit- and correct rejection trials). This regressor served as a control condition for DPA-related activity of the cue-period (sC, dC) to account for perceptual and working memory-related signals and retain activity related to associative retrieval (Ranganath et al., 2004). Regressors of no interest for the DMS-task included one prompt, one nuisance, and six motion regressors (as above). Modelling of regressors of interest was identical across the DPA and the DMS-task, given the identical trial structure: For each regressor representing a cue and target-period, activation was modelled using a boxcar function starting at onset and lasting for 1 second. All regressors were convolved with a canonical hemodynamic response function available in SPM8 (Friston et al., 1998). A high-pass filter was applied with a period of 128 seconds to remove low-frequency signals relating to scanner drift and/or physiological noise.

Grey matter volume analyses. Given that we compared a group of 19 older adults against 38 younger adults (19 synaesthetes and 19 controls) and had an unequal gender distribution across our 57 participants (male: N = 23; female: N = 34), we calculated each participants' total and regional grey (GM) matter volume (in ml), which was subsequently entered as a covariate in all second-level fMRI analyses to indirectly account for age- (Lemaitre et al., 2005; Raz et al., 2005) and gender-related (Luders et al., 2002) GM volume differences. Total GM volume was calculated from the subject-specific GM masks in native space, which were obtained following the segmentation of participants' high resolution structural T1 images. Participants' regional GM volume was extracted from 12 anatomically defined ROIs (see ROI-analyses) and served as ROI-specific covariates in our ROI analyses. Given that the masks of the anatomical ROIs were in standard (MNI) space, regional GM volume within these ROIs was extracted from participants' normalised brains. This involved the spatial normalisation of each participant's structural T1 image to MNI space using the preprocessing normalisation parameters. Total GM volume was segmented from these normalised structural T1 images. All segmented, normalised

GM images underwent a Jacobian modulation. No smoothing was applied for the purpose of avoiding GM overlap from neighbouring brain regions.

Second-level analyses. Results of the single-subject analyses were taken to group-level by computing several ANOVAs for the cue (associative retrieval) and target-period (associative recognition). For the cue-period, two independent one-way ANOVAs were computed with group (young adults, older adults, synaesthetes) as the between-subject factor, for which the respective contrast images of the similar and dissimilar condition relative the control task were used (sC > DMSC and dC > DMSC, respectively). We first computed the main effects of task from the contrasts (sC > DMSC) and (dC > DMSC) using a t-contrast across groups for each ANOVA. Exclusive masks of the task effects were saved for analysis of group effects. To demonstrate the direct task activation differences between the similar and dissimilar condition, we computed the task effects from two additional independent one-way ANOVAs using the contrast images (sC > dC) and (dC > sC). All parametric maps and masks derived from the above ANOVAs were thresholded at $p < 0.001$ (uncorrected), with an extent threshold of $k = 5$ voxels [following the significance levels set for experiments with comparably rigorous control tasks, e.g. (Ranganath et al., 2004; Schott et al., 2005; Staresina and Davachi, 2010)].

To investigate group differences, we computed two independent one-way ANOVAs by entering the beta images sC and dC. Using F-contrasts, the group effects of sC and dC were inclusively masked with the main task effects and suprathresholded at $p < 0.001$ (uncorrected), $k= 5$ voxels. Thus, the masking served three purposes: 1) it constrained the signal to areas for which the effects of the control task were subtracted, 2) it ensured that we reported group differences within task-related regions that show significant activations above zero, and 3) it increased the threshold of identified voxels, which had to survive the $p < 0.001$ (uncorrected), $k= 5$ voxels threshold of the task effect and the group effect (Daselaar et al., 2010).

For the target-period, the subject-specific beta images of similar and dissimilar match and non-match trials (sTM, dTM, sTNM and dTNM) were subjected to a 3x2x2 mixed ANOVA using the full factorial design specification in SPM8. Group (young adults, older adults, synaesthetes) was entered as the between-subject factor, and condition (similar and dissimilar pair-associates) and target-type (match and non-matches) as the within-subject factors. All main and interaction effects derived from

the ANOVA are reported at a threshold of $p < 0.05$ (FWE-corrected), with an extent threshold of $k = 5$ voxels.

ROI analyses. These were carried out for associative retrieval and recognition to specifically test the representational account of memory by mapping out the entire ventral visual stream. To this end, we specified 6 anatomical ROIs bilaterally: inferior occipital gyrus, posterior inferior temporal gyrus, anterior inferior temporal gyrus, fusiform gyrus, perirhinal cortex (PRC), and the hippocampus. The mask for the perirhinal cortex was taken from (Holdstock et al., 2009), available on http://www.neurolang.com/research/perirhinal-map/. The hippocampus was taken from the Anatomy toolbox v1.8, 2011 (Eickhoff et al., 2005), containing the substructures subiculum, cornu ammonis, dentate gyrus and the hippocampal-amygdala-transition-area. Since this mask extended into neighbouring regions including the entorhinal cortex, thalamus and the ventricles, we manually retraced it for both hemispheres to exclude these areas. For the drawing, the mask of the Anatomy toolbox was overlaid on the single-subject brain in MRIcron as a guide to ensure all relevant substructures were retained. All other masks were from the WFU PickAtlas v2.4 [(http://www.nitrc.org/projects/wfu_pickatlas/; (Maldjian et al., 2003)].

For the ROI analyses, we used non-smoothed images to reduce signal overlap from neighbouring brain areas. For simplicity, the beta images for the cue-period (associative retrieval) and target-period (associative recognition) were averaged across condition (similar, dissimilar) and target type (match, non-match). Separate one-way ANOVAs were computed for each ROI, with group (young adults, older adults, synaesthetes) as the between-subject factor and the respective beta images for the cue and target-period as the within-subject factor. Each ANOVA-model contained the participants' ROI-specific GM volume to account for age and individual differences. For each model, we computed the average signal in each ROI across groups (i.e. the task effect), and applied a threshold of $p < 0.005$ (uncorrected), $k = 0$ voxels. Using the rfx-plot toolbox (Gläscher, 2009) available in SPM8, we then extracted the percent signal change for each group for subsequent analyses on the percent signal change using SPSS.

3.4 Results

3.4.1 Behavioural results

Associative learning. The number of Runs to acquire the pair-associates (averaged across similar and dissimilar pair-associates) was highest for older adults (M = 5.47; SE = 0.69), followed by young adults (M = 3.68; SE = 0.59) and synaesthetes (M = 2.59; SE = 0.34). A one-way ANOVA revealed a significant main effect of group, F[2,54] = 5.518, p = 0.007. Tukey post hoc comparisons showed that synaesthetes required significantly fewer Runs than older adults (p = 0.006; d = 0.38; power = 1.11), while no difference was found between young and older adults (p = 0.072; d = 0.65; power = 0.56) and between young adults and synaesthetes (p = 0.585; d = 0.38; power = 0.78).

Similarity effects on associative learning. Table 1 shows the percent Hit-rate averaged across number of Runs for each group and condition. An ANCOVA with number of Runs as the covariate showed that the number of Runs predicted Hit-rate in the dissimilar condition, F[1,53] = 19.266, p < 0.001, η_p^2= 0.521, but not in the similar condition, F[1,53] = 0.986, p = 0.325, η_p^2= 0.018. With the number of Runs removed, there was no significant group effect in either condition, (both F's < 2.5; p > 0.05).

Table 1. Mean and standard error of the percent Hit-rate for learning the similar and dissimilar pairs (N = 19 in each group).

Hit-rate (Task)	**Young adults** Mean (SE)	**Older adults** Mean (SE)	**Synaesthetes** Mean (SE)
Hit-rate (Similar pairs)	98.00 (1.37)	100.00 (--)	100.00 (--)
Hit-rate (Dissimilar pairs)	78.54 (3.37)	64.75 (3.68)	83.04 (4.10)

However, averaging across the number of Runs might have masked a potential group difference in associative learning. We therefore conducted a cumulative Hit-rate analysis of the first seven Runs for the dissimilar condition (not for the similar condition, given the observed ceiling effects). All of the seven one-way ANOVAs yielded a significant group effect (Runs 1-7: F[2,54] > 3.71, p < 0.05).

Tukey post hoc comparisons of the first two Runs showed a significant learning effect for synaesthetes relative to older adults (Run1 : $p = 0.024$; Run2: $p = 0.005$), but no difference between young and older adults (Run1 : $p = 0.232$; Run2: $p = 0.085$) or between young adults and synaesthetes (Run1 : $p = 0.547$; Run2: $p = 0.500$). From Run 3, we found a significant effect of age and synaesthesia on associative learning, which was maintained throughout Run 7: young adults and synaesthetes performed significantly better than older adults (Runs 3-7, $p < 0.05$), while no difference was found between young adults and synaesthetes (Runs 3-7, $p < 0.05$).

Delayed pair-associative retrieval (DPA). To investigate participants' performance on the DPA-task during scanning, we separated all confident and accurate responses of similar and dissimilar pairs according to Hits and Correct rejections (match and non-match trials). This was done to examine whether non-match trials, which require a 'recall-to-reject' response (i.e. recollection of the cue), were more difficult to respond to than match trials that can be accepted on the basis of familiarity (Cohn et al., 2008). Figure 3 shows the average accuracy (Hits and Correct rejections) for each group. A 3x2x2 mixed ANOVA with factors group (young adults, older adults, synaesthetes), condition (similar, dissimilar) and target type (match, non-match) yielded no significant main effect of group $F[2,54] = 2.493$, $p = 0.092$, $\eta_p^2 = 0.085$. However, there was a significant main effect of condition, $F[1,54] = 27.307$, $p < 0.001$, $\eta_p^2 = 0.336$, and a significant interaction between group and condition $F[2,54] = 8.622$, $p = 0.001$, $\eta_p^2 = 0.242$. Estimated marginal means revealed that young adults showed comparable accuracy for similar and dissimilar pair retrieval (averaged across target type: young adults, similar: M = 93.61, SE = 1.44; dissimilar: M = 93.48, SE = 3.733), while the accuracy-rate of older adults and synaesthetes was higher for similar pairs (older adults: M = 96.80, SE = 1.43; synaesthetes: M = 96.59, SE = 1.46) than dissimilar pairs (older adults: M = 76.40, SE = 373; synaesthetes: M = 85.87, SE = 3.73). The main effect of target type was also significant, $F[1,54] = 12.002$, $p = 0.001$, $\eta_p^2 = 0.182$. However, contrary to our predictions, accuracy for non-match trials was higher than for match trials. A significant interaction between condition and target type, $F[1,54] = 14.258$, $p < 0.001$, $\eta_p^2 = 0.209$, further revealed that the difficulty in remembering target matches depended on similarity: estimated marginal means showed comparable mean

accuracy-rate in response to similar match (M = 95.79; SE = 0.79) and similar non-match trials (M = 95.55; SE = 1.13), while the mean accuracy-rate for dissimilar match trials (M = 79.91; SE = 3.12) was lower than for dissimilar non-match trials (M = 90.59; SE = 1.84). There was no significant interaction between group and target type, $F[2,54] = 1.358$, $p = 0.266$, $\eta_p^2 = 0.048$.

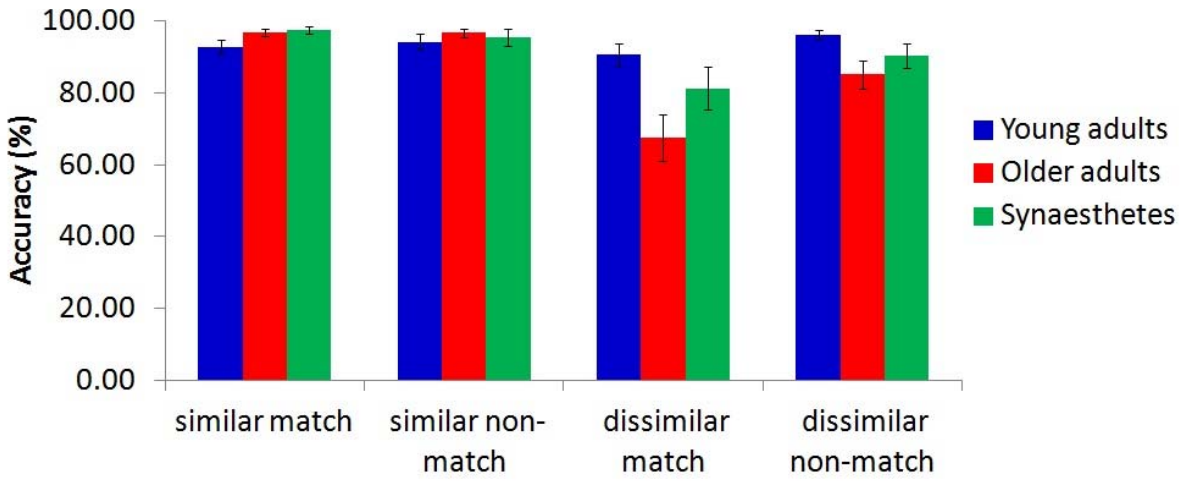


Figure 3. Mean Accuracy-rate of retrieved pair-associates (in-scanner) during the DPA-task. Error bars indicate the standard error of the mean.

Delayed matching-to-sample (DMS). For the DMS-task, accuracy was high and comparable across groups, [young adults: M = 96.22, SE = 1.21; older adults: M = 96.38, SE = 1.25; synaesthetes: M = 96.88, SE = 1.37]. A one-way ANOVA yielded no significant group effect, F[2,54] = 0.072, p = 0.931.

3.4.2 fMRI results

3.4.2.1 Associative retrieval: Cue-period

We compared the cue-period of the DPA-task against the cue-period of the DMS-task, contrasting across conditions (similar, dissimilar) and groups.

Task effects. Here, we tested the hypothesis that retrieval-specific activity (i.e. with perceptual and working memory effects accounted for) would engage a less extensive network for similar than for dissimilar pair-associates across groups. In line with our prediction, retrieval of similar pairs (contrast: sC > DMSC) yielded activity in 11 clusters, encompassing areas in the precuneus, bilateral angular gyrus, rectal gyrus, cuneus, bilateral middle temporal gyrus, left precentral gyrus, right superior frontal gyrus and the cerebellum. Retrieval of dissimilar pairs (contrast: dC > DMSC) yielded activity in 19 clusters, including bilateral occipital and inferior parietal regions, precuneus, bilateral frontal regions, left orbital gyrus, bilateral insula, left inferior temporal gyrus, bilateral hippocampus, caudate, thalamus and the cerebellum. Results of the direct comparison between the similar and dissimilar condition (sC > dC; dC > sC) are reported in Tables 2 and 3 respectively, and further confirm the wider activation network for the dissimilar than for the similar condition.

Table 2. Associative retrieval: Similar > Dissimilar, main effect of task (averaged across groups).

Brain region	MNI coordinates			T-value	Cluster size
	x	y	z		
Right SupraMarginal Gyrus	57	-25	25	T = 7.27	1403
Right Middle Temporal Gyrus	57	-55	7	T = 7.09	
Right Rolandic Operculum	45	-22	19	T = 4.44	
Right Inferior Frontal Gyrus (p. Opercularis)	54	11	16	T = 3.49	
Left Superior Frontal Gyrus	-12	50	22	T = 6.53	1295
Right Superior Medial Gyrus	6	59	13	T = 6.38	
Right Superior Frontal Gyrus	15	44	40	T = 6.02	
Left Rectal Gyrus	0	47	-17	T = 5.29	
Right Mid Orbital Gyrus	3	50	-14	T = 5.17	
Left Mid Orbital Gyrus	-9	56	-5	T = 4.93	
Right Middle Cingulate Cortex	9	-31	43	T = 7.03	786
Left Posterior Cingulate Cortex	-6	-49	31	T = 5.47	
Right Precuneus	9	-46	61	T = 5.21	
Right Superior Parietal Lobule	18	-46	64	T = 5.18	
Right Postcentral Gyrus	27	-37	67	T = 4.62	
Right SMA	3	-19	52	T = 4.37	
Left Middle Cingulate Cortex	0	-16	46	T = 4.36	
Left SMA	-9	-10	58	T = 3.55	
Left SupraMarginal Gyrus	-66	-28	25	T = 6.46	576
Left Heschls Gyrus	-45	-19	10	T = 4.54	
Left Insula Lobe	-39	-4	-5	T = 4.15	

Left Superior Temporal Gyrus	-54	-16	7	T = 4.12	
Left Rolandic Operculum	-51	-4	7	T = 4.10	
Left Postcentral Gyrus	-60	-16	40	T = 3.44	
Left Middle Temporal Gyrus	-51	-67	22	T = 5.52	301
Left Middle Occipital Gyrus	-48	-76	4	T = 3.31	
Right Middle Temporal Gyrus	63	-7	-20	T = 5.85	192
Right Superior Temporal Gyrus	48	-10	-14	T = 3.38	
Left Middle Temporal Gyrus	-63	-13	-17	T = 5.94	185
Left Medial Temporal Pole	-39	14	-32	T = 3.80	
Left Precuneus	-9	-49	61	T = 4.35	84
Left Superior Parietal Lobule	-18	-49	64	T = 4.27	
Left Postcentral Gyrus	-24	-43	58	T = 3.98	
Right Olfactory cortex	3	17	-11	T = 3.83	20
Left Olfactory cortex	0	14	-5	T = 3.57	
Left Middle Cingulate Cortex	-15	-34	43	T = 4.06	13
Right Inferior Frontal Gyrus (p. Triangularis)	48	38	-2	T = 4.04	13
Left Hippocampus	-27	-7	-20	T = 4.03	8

MNI coordinates represent the location of the peak voxels. The peak voxels of each cluster with the cluster size are followed by separate maxima (8mm apart) within the cluster. Results were thresholded at $p < 0.001$ (uncorrected) with a minimum cluster size of 5 voxels.

Table 3. Associative retrieval: Dissimilar > Similar, main effect of task (averaged across groups).

Brain region	MNI coordinates x	y	z	T-value	Cluster size
Left Inferior Parietal Lobule	-30	-64	40	T = 9.99	1687
Left Middle Occipital Gyrus	-33	-88	22	T = 8.49	
Left Precuneus	-12	-67	43	T = 7.67	
Left Superior Occipital Gyrus	-15	-67	28	T = 6.97	
Right Middle Occipital Gyrus	33	-67	34	T = 6.31	
Right Precuneus	18	-61	31	T = 6.22	
Right Angular Gyrus	33	-61	43	T = 5.44	
Left Inferior Frontal Gyrus (p. Triangularis)	-42	23	25	T = 9.99	1253
Left Insula Lobe	-30	26	1	T = 9.61	
Left Precentral Gyrus	-36	5	34	T = 7.74	
Left Inferior Frontal Gyrus (p. Triangularis)	-39	32	13	T = 6.87	
Left Middle Orbital Gyrus	-42	50	-2	T = 5.41	
Left Superior Orbital Gyrus	-24	53	-8	T = 3.60	
Left SMA	-3	17	46	T = 7.87	368
Right Middle Cingulate Cortex	9	29	37	T = 5.15	
Right Insula Lobe	36	23	-2	T = 7.09	205
Right Thalamus	6	-7	1	T = 5.28	198
Left Caudate Nucleus	-12	8	7	T = 4.62	
Right Caudate Nucleus	15	5	13	T = 4.61	
Left Putamen	-15	11	1	T = 4.40	

Left Thalamus	-12	-10	7	T = 4.30	
Left Inferior Temporal Gyrus	-45	-58	-11	T = 6.54	95
Right Cerebellum	36	-61	-29	T = 4.87	94
Left Calcarine Gyrus	-15	-76	7	T = 4.44	81
Right Middle Frontal Gyrus	48	32	22	T = 5.01	76
Right Cerebellum	12	-70	-26	T = 5.00	71
Right Fusiform Gyrus	30	-40	-20	T = 4.37	35
Right Parahippocampal Gyrus	39	-31	-14	T = 3.95	
Left Cerebellum	-39	-64	-26	T = 3.66	18
Right Superior Orbital Gyrus	24	56	-8	T = 3.82	12
Brainstem	-3	-22	-14	T = 3.93	12
Left Hippocampus	-24	-25	-8	T = 3.78	9
Right Hippocampus	33	-34	4	T = 3.60	7

MNI coordinates represent the location of the peak voxels. The peak voxels of each cluster with the cluster size are followed by separate maxima (8mm apart) within the cluster. Results were thresholded at $p < 0.001$ (uncorrected) with a minimum cluster size of 5 voxels.

Group effects. In examining group effects during associative retrieval, we tested the hypothesis that older adults would show a less differentiated network than young adults, while synaesthetes would show the most differentiated network across groups. The one-way ANOVA showed a significant main effect of group in the dissimilar condition within the left calcarine gyrus. Tukey post hoc tests on the percent signal change of the peak voxel [MNI: -6 -64 -19] revealed that the group effect was driven by young adults and synaesthetes, who both showed less percent signal change relative to older adults. Results approached significance for the difference between synaesthetes and older adults ($p = 0.069$) and young and older adults ($p = 0.065$), while no difference was found between synaesthetes and young adults ($p = 0.999$).

To evaluate the hypothesis that synaesthetes show the most differentiated and older adults the least differentiated network across groups, we performed post hoc tests for the dissimilar retrieval condition in SPM, using the contrasts old > young, old > synaesthetes, young > synaesthetes, and the reverse contrasts, respectively. All group comparisons were calculated by inclusively masking the dC images with the task effect dC > DMSC (see Second-level analyses). We found a significant effect for the two contrasts old > young and old > synaesthetes (Figure 4). Specifically, relative to young adults, older adults showed significantly greater activity in the cuneus and thalamus. Relative to synaesthetes however, older adults showed activity in a wider network, spanning the cuneus, cerebellum, thalamus, bilateral inferior parietal regions, as well as the left middle frontal and precentral gyrus. Thus, although there was no activation difference between young adults and synaesthetes, our data reveal that synaesthetes showed the most differentiated and efficient retrieval network, which could be detected against older adults. No group difference was found for the similar condition, suggesting comparable retrieval strategies across groups in the low memory load condition.

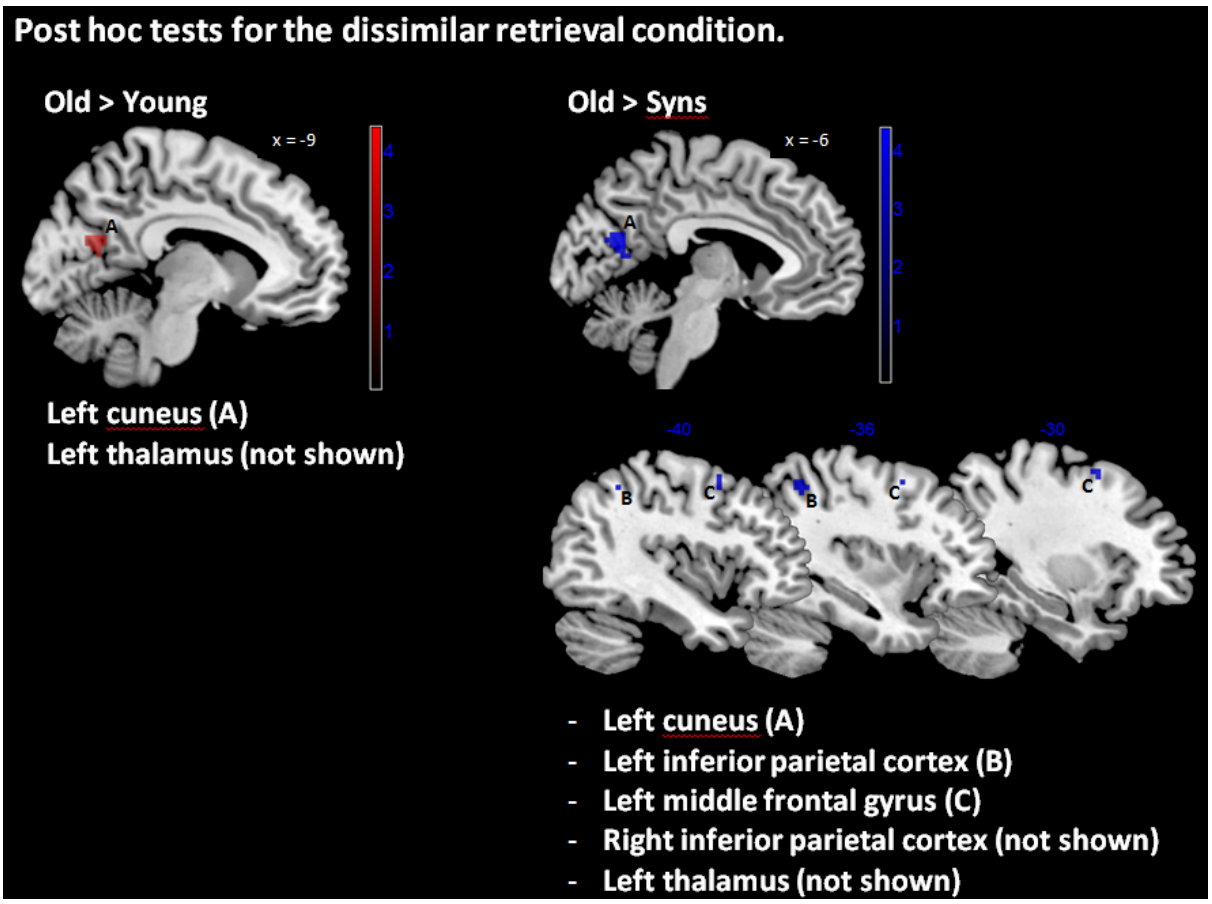


Figure 4. Post hoc results of associative retrieval. Regions exhibiting enhanced activation in older versus young adults (left) and older adults versus synaesthetes (right) during retrieval of dissimilar pair-associates at the cue-period. Group contrasts were masked with the task effect dC > DMSC and suprathresholded at $p<0.001$ (uncorrected), k = 5vox.

ROI results, retrieval. Next, we tested the hypothesis that the synaesthetes' enhanced sensitivity in early visual cortex is reflected by greater retrieval efficiency. We predicted that ROI-activity in synaesthetes would be reduced relative to non-synaesthetes, especially in posterior regions of the VVS. To this end, we computed a 3 x 6 mixed ANOVA, with group as the between-subject factor, and ROI (inferior occipital gyrus, posterior inferior temporal gyrus, fusiform gyrus, anterior inferior temporal gyrus, PRC, hippocampus) as the within-subject factor. Figure 5 illustrates the average percent signal change from posterior to anterior ROIs along the ventral visual stream. Throughout the ROI results (cue and target), we applied the Greenhouse Geisser correction (Greenhouse and Geisser, 1959) for non-sphericity of the within-subject variable where necessary, which is indicated by adjusted degrees of freedom. The ANOVA showed a significant main effect of group, $F[2,54] = 3.863$, $p = .027$, $\eta_p^2 = 0.125$, a significant main effect of ROI, $F[3.80, 205,176] = 13.24$, $p < .001$, $\eta_p^2 = 0.197$, but no significant interaction between group and ROI, $F[10,270] = 1.44$, $p = .161$, $\eta_p^2 = 0.051$. Tukey post-hoc tests on the group effect revealed lower activity (averaged across ROIs) in synaesthetes relative to older adults that was statistically significant ($p = 0.036$), and in synaesthetes relative to young adults that approached significance ($p = 0.074$). No activation difference was found between young and older adults ($p = 0.948$). Figure 5 further illustrates the significant differences between pairs of groups on individual ROIs (t-tests, reported at $p < 0.05$) that are marked with an asterisk. As can be seen, synaesthetes had consistently lower signal change relative to young and/or older adults in posterior ROIs (from the inferior occipital to the anterior inferior temporal gyrus), while activity was comparable between groups in anterior regions including the PRC and the hippocampus. This suggests more efficient processing strategies in synaesthetes' posterior visual areas and similar processing strategies to the other two groups in anterior-medial brain structures.

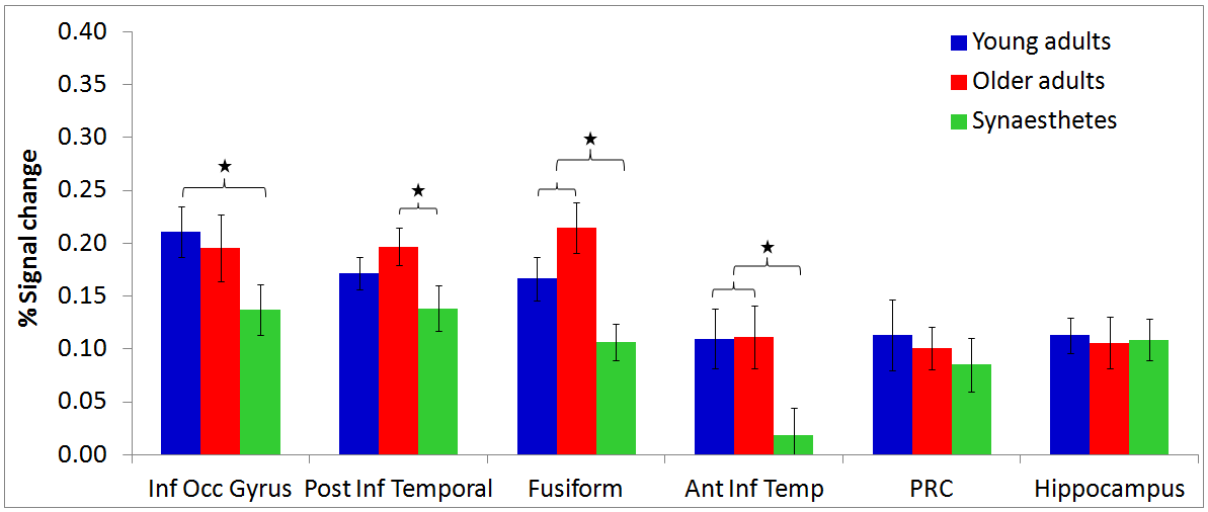


Figure 5. Percent signal change, showing 6 regions of interest plotted for young adults, older adults and synaesthetes during associative retrieval (cue-period), averaged across condition (similar, dissimilar). Asterisks indicate significant group differences derived from t-tests on the mean percent signal change for each ROI. Error bars indicate the standard error of the mean. Inf Occ Gyrus = Inferior Occipital Gyrus; Post Inf Temporal = Posterior Inferior Temporal Gyrus; Fusiform = Fusiform Gyrus; Ant Inf Temp = Anterior Inferior Temporal Gyrus; PRC = Perirhinal cortex.

To demonstrate that group differences were specific to associative retrieval and not affected by working memory demands, we further analysed the DMSC images, serving as a working memory control. Figure 6 illustrates the average percent signal change in all ROIs from posterior to anterior regions along the ventral visual stream. Activity in the anterior inferior temporal cortex was extracted from active voxels at a more lenient threshold of $p < 0.05$ (uncorrected). We computed a 3x6 mixed ANOVA, with group as the between-subject factor, and ROI (inferior occipital gyrus, posterior inferior temporal gyrus, fusiform gyrus, anterior inferior temporal gyrus, PRC, hippocampus) as the within-subject factor. The main effect of ROI was significant, $F[3.76, 202.95] = 16.01$, $p < 0.001$, $\eta_p^2 = 0.229$, but the main effect of group was not, $F[2,54] = 1.964$, $p = 0.150$, $\eta_p^2 = 0.068$, and there was no interaction between group and ROI, $F[10,270] = 1.301$, $p = 0.230$, $\eta_p^2 = 0.046$, indicating that the group effects in the DPA-task were specific to associative retrieval. Significant group differences were only found when conducting independent t-tests on individual ROIs, showing significantly lower percent signal change in young relative to older adults in the posterior inferior temporal gyrus and in synaesthetes relative to older adults in the fusiform gyrus ($p < 0.05$; Figure 6).

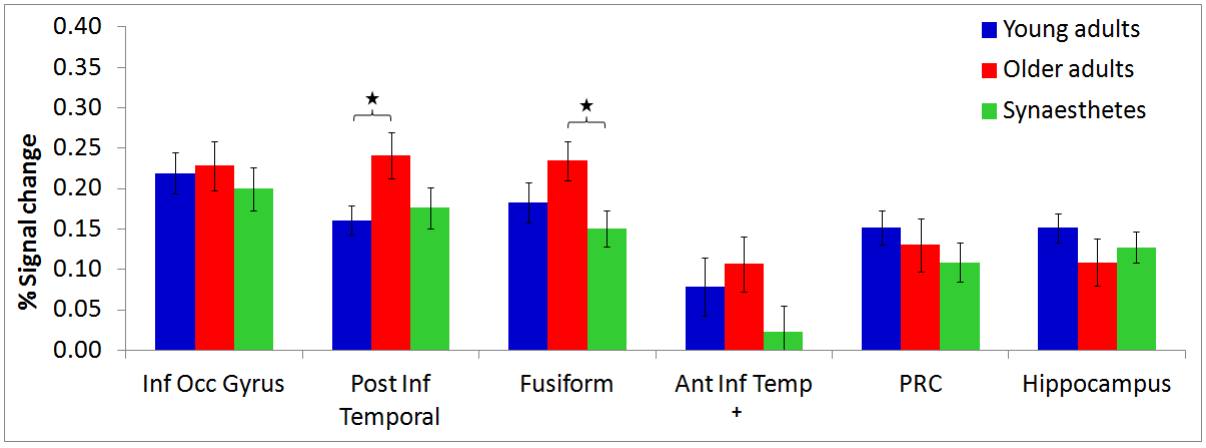


Figure 6. Percent signal change of 6 regions of interest plotted for young adults, older adults and synaesthetes during the cue-period of the DMS-task. For the anterior inferior temporal gyrus denoted with a + sign, we extracted the percent signal change from active voxels at a more lenient threshold of $p < 0.05$ (unc.). Error bars indicate the standard error of the mean. Asterisks indicate significant group differences derived from t-tests on the mean percent signal change for each ROI. Inf Occ Gyrus = Inferior Occipital Gyrus; Post Inf Temporal = Posterior Inferior Temporal Gyrus; Fusiform = Fusiform Gyrus; Ant Inf Temp = Anterior Inferior Temporal Gyrus; PRC = Perirhinal cortex.

3.4.2.2 Associative recognition: Target-period

To examine associative recognition, we compared activity pertaining to target type (match, non-match) and condition (similar, dissimilar) during the target-period of the DPA-task.

Task effects. We tested the hypothesis that target non-matches would be more difficult to recognise than target matches. Specifically, target non-matches require a 'recall-to-reject' response, while target matches can be accepted on the basis of familiarity to an expected target (Cohn et al., 2008). Thus, we predicted the target non-matches to yield increased activity in frontal and parietal regions across groups (Woolgar et al., 2011). We further expected a modulatory influence of similar and dissimilar pair-associates (effect of condition) on brain activity, as well as an interaction between condition and target type. Results of the 3 (group: young adults, older adults, synaesthetes) x2 (condition: similar, dissimilar) x2 (target-type: match, non-match) mixed ANOVA yielded a significant main effect of target type (F-test) in the left superior parietal lobe. In line with our predictions, the results of two subsequent t-contrasts (averaged across groups) revealed that the task effect was driven by non-match trials, yielding activity in the left superior and left inferior parietal lobe. By contrast, no significant effect was found for match trials. We did not observe a main effect of condition (F-test) and no significant interaction between condition and target type (F-test).

Group effects. We then tested the hypothesis that synaesthetes, who have enhanced sensitivity (Barnett et al., 2008) and excitability in primary visual cortex (Terhune et al., 2011), would show enhanced activity in early visual regions during the recognition phase relative to the other two groups (Rothen et al., 2012). Moreover, based on research showing that older adults demonstrate a posterior-to-anterior shift in brain activity (Davis et al., 2008), we expected enhanced visual cortex activity in young relative to older adults, and enhanced frontal activations in older adults during the recognition phase. The ANOVA yielded a significant main effect of group in posterior visual regions (Table 4) but no significant interaction between group and condition, between group and target type, or between group, condition and target type. To examine the group differences more closely, we computed Tukey post hoc tests for 3 cluster maxima: the left cuneus, and the left and right lingual gyrus. To

this end, we extracted the average percent signal change for each cluster and group and performed three 3x2x2 mixed ANOVAs with group, condition and target-type as factors. In line with our prediction, we found greater average percent signal change in each condition and target-type for synaesthetes than for young and older adults in the left cuneus and the left lingual gyrus (Figure 7). Tukey post hoc tests for the average signal across condition and target-type showed a significant difference between synaesthetes and young adults (both clusters, $p < 0.01$), synaesthetes and older adults (both clusters, $p < 0.01$), but not between young and older adults (both clusters, $p > 0.05$). In the right lingual gyrus, the average percent signal change was higher in young adults ($M = 0.59\%$; $SE = 0.08$) and synaesthetes ($M = 0.65\%$; $SE = 0.08$) relative to older adults ($M = 0.41\%$; $SE = 0.08$). The post hoc test yielded no significant difference between groups ($p > 0.05$), although the difference between synaesthetes and older adults approached significance ($p = 0.086$).

Table 4. Brain regions with a significant main effect of group at associative recognition.

Brain region	MNI coordinates			F-value	Cluster size (voxels)
	x	y	z		
Left Cuneus	0	-82	19	20.68	83
Left Calcarine Gyrus	-12	-85	13	19.28	
Right Calcarine Gyrus	18	-76	4	17.50	
Left Cerebellum	-42	-73	-23	35.69	42
Left Lingual Gyrus	-15	-70	1	20.79	17
Left Calcarine Gyrus	-24	-61	4	14.80	
Left Cerebellum	-15	-85	-23	20.29	12
Right Lingual Gyrus	39	-79	-17	17.76	8
Right Inferior Occipital Gyrus	36	-82	-11	14.83	

MNI coordinates represent the location of the peak voxels. The peak voxels of each cluster with the cluster size are followed by separate maxima (8mm apart) within the cluster. Results were thresholded at $p < 0.05$, FWE-corrected with a minimum cluster size of 5 voxels.

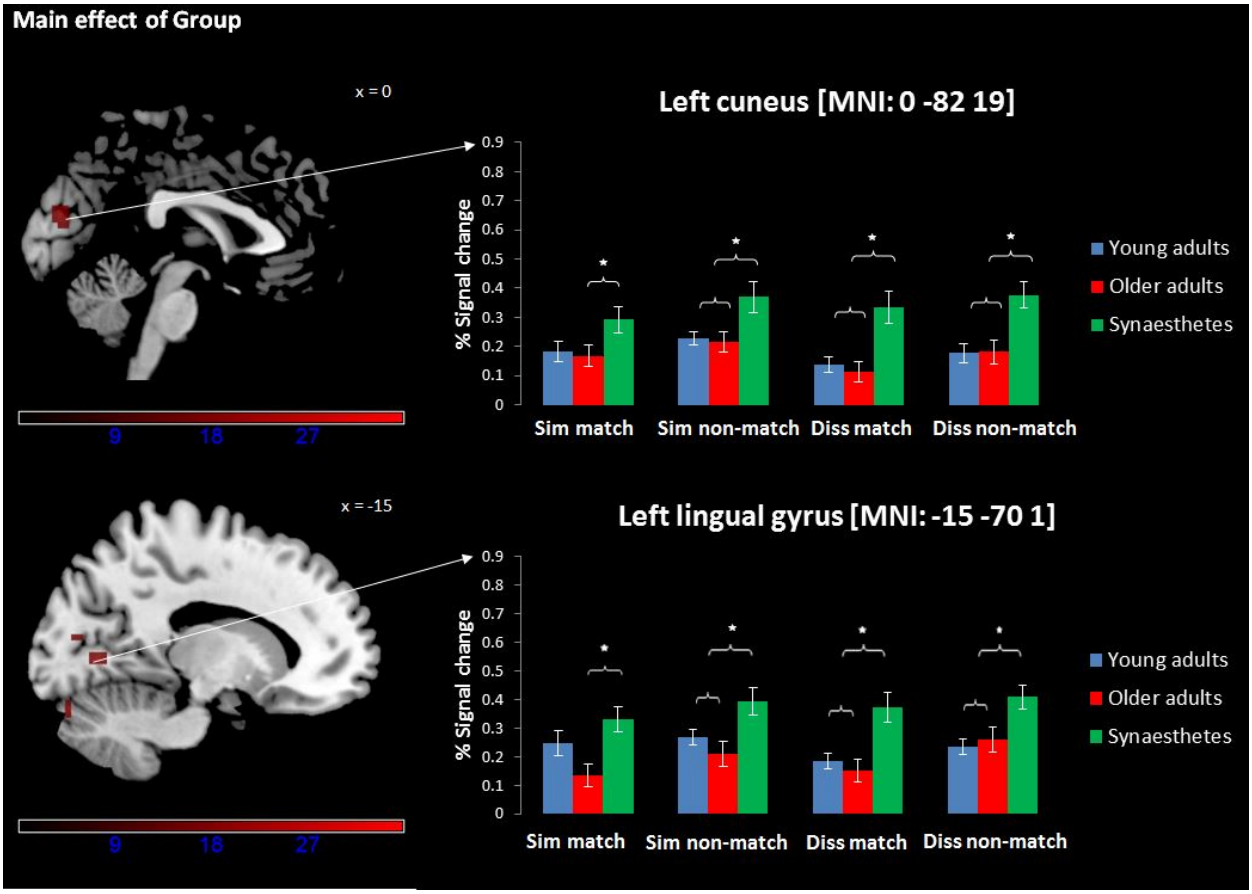


Figure 7. Main effect of group during associative recognition (target-period) shown in the cuneus (BA17; top) and the left lingual gyrus (BA17; bottom). Left panels (top and bottom) illustrate the main effects of group rendered on the individual subjects' brain available in MRIcron. Right panels show the percent signal change averaged across the cuneus (top) and the left lingual gyrus (bottom) for young adults, older adults and synaesthetes, in response to Sim match, Sim non-match, Diss match and Diss non-match trials. Error bars indicate the standard error of the mean. Asterisks indicate significant group differences derived from Tukey post hoc tests conducted for separate one-way ANOVAs for Sim match, Sim non-match, Diss match, Diss non-match.

ROI-results, target. We further tested the sensitivity-hypothesis, which predicts that synaesthetes would show enhanced activity in early visual regions relative to non-synaesthetes during associative recognition. The percent signal change in response to target-images was extracted from 6 ROIs (inferior occipital gyrus, posterior inferior temporal gyrus, fusiform gyrus, anterior inferior temporal gyrus, PRC, hippocampus) and subjected to a 3x6 mixed ANOVA with group and ROI as factors. Although there was no main effect of group $F[2,54] = 2.395$, $p = 0.101$, $\eta_p^2 = 0.081$, the interaction between group and ROI was significant, $F[10,270] = 1.927$, $p = 0.042$, $\eta_p^2 = 0.067$. As can be seen in Figure 8, synaesthetes showed greater mean percent signal change relative to young and older adults in inferior occipital, fusiform, anterior inferior temporal gyrus and PRC, demonstrating enhanced sensitivity relative to the other two groups in response to target recognition. To demonstrate the group differences for each ROI, pair-wise group comparisons of the percent signal change were computed (t-tests, reported at $p < 0.05$; Figure 8). Synaesthetes showed significantly greater signal change relative to older adults in the inferior occipital gyrus, while synaesthetes and young adults showed significantly greater signal change relative to older adults in the fusiform gyrus.

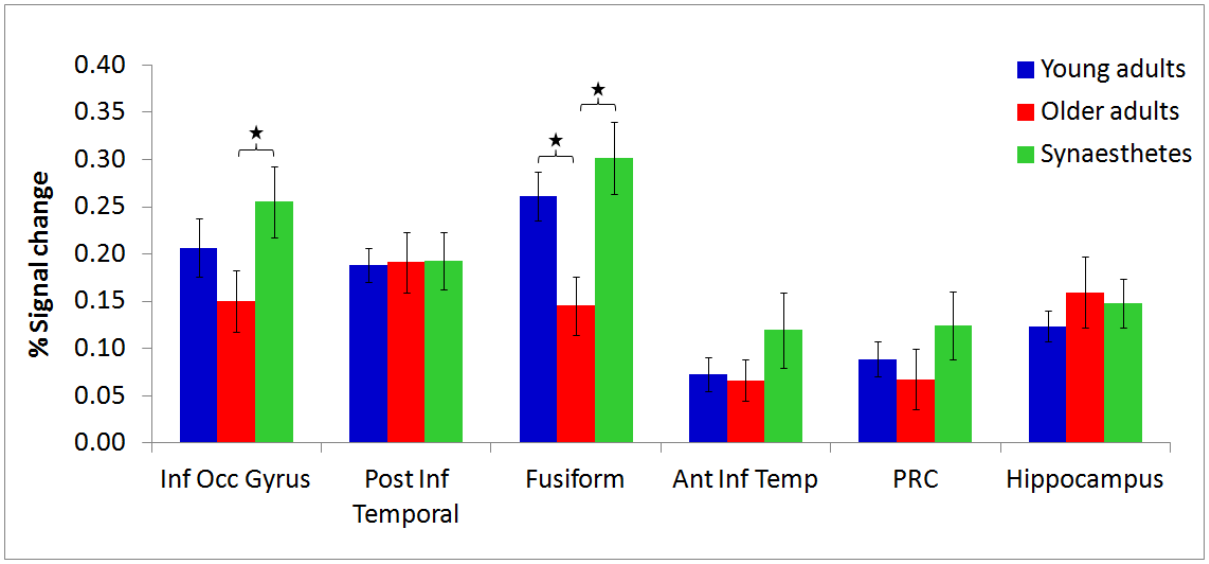


Figure 8. Percent signal change of 6 regions of interest plotted for young adults, older adults and synaesthetes during associative recognition (target-period). The percent signal change for each ROI was averaged across condition (similar, dissimilar) and target-type (match, non-match). Error bars indicate the standard error of the mean. Asterisks indicate significant group differences derived from t-tests on the mean percent signal change for each ROI. Inf Occ Gyrus = Inferior Occipital Gyrus; Post Inf Temporal = Posterior Inferior Temporal Gyrus; Fusiform = Fusiform Gyrus; Ant Inf Temp = Anterior Inferior Temporal Gyrus; PRC = Perirhinal cortex.

3.5 Discussion

Our study investigated whether differences in sensory-perceptual abilities, as observed in individuals with synaesthesia and older adults, translated into visual associative memory for non-synaesthesia inducing stimuli. We observed evidence of enhanced sensitivity in synaesthetes, which was manifest as i) a behavioural associative learning advantage, ii) a more differentiated network for associative retrieval, and iii) enhanced visual cortex activation for associative recognition.

Previous EEG studies have shown evidence of enhanced processing in the primary visual cortex in synaesthetes, indicative of increased sensitivity to visual stimuli (Barnett et al., 2008). The fMRI data acquired in this study, which demonstrate an effect of synaesthesia on activation in early visual regions, also suggest that sensory processing of non-synaesthesia-inducing stimuli differs in synaesthetes for both perceptual and memory tasks. These findings can be considered in light of the representational account of memory (Bussey and Saksida, 2007), which envisages the neural substrates of visual perception and memory to be on a continuum. According to this account, enhanced sensitivity to our fractal images at the point of perception would be predicted to translate into a learning and memory advantage. Indeed, the effects of synaesthesia were most evident when bottom-up perceptual cues were available (i.e. at associative learning and recognition). For instance, in the associative learning paradigm, stimuli were presented a priori and perceptually reinstated during the forced-choice task. While this guaranteed a high success rate across participants in the similar condition, it translated into a learning advantage in synaesthetes relative to older adults in the dissimilar condition. This effect was not seen in young relative to older adults, indicating that synaesthetes were most efficient in extracting bottom-up perceptual cues. Support for this claim comes from neurophysiological studies, showing that visual long-term memory is associated with long-term potentiation (LTP), which can be induced in primary visual cortex (Komatsu et al., 1981; Artola and Singer, 1987). Critical to the induction of LTP is the reduced GABAergic inhibition in visual cortex (Artola and Singer, 1987). Interestingly, synaesthetes were found to show hyper-excitability in primary visual cortex (Terhune et al., 2011), perhaps due to a facilitation of LTP induction following visual stimulation [but see (Terhune et al., 2014)]. Using magnetic resonance spectroscopy and

transcranial magnetic stimulation (TMS), another recent study (Terhune et al., in press) found a relationship between glutamate, but not GABA-levels, and phosphene perception in early visual cortex: across synaesthetes and controls, higher glutamate-levels were associated with lower thresholds of phosphene perception following TMS-application. Of the two groups, however, the synaesthetes' phosphene threshold was significantly lower than that of controls. Thus, neurochemical concentrations in synaesthetes' visual cortex could explain our synaesthetes' enhanced associative learning, where bottom-up perceptual cues were available. The fact that we did not find a behavioural retrieval advantage of synaesthetes in the dissimilar condition can be attributed to a speed-accuracy trade-off: the low number of Runs during associative learning, and thus, the reduced stimulus exposure, might have prevented the manifestation of a retrieval advantage for synaesthetes.

The fMRI results of our recognition phase extend Terhune et al.'s (2011) finding of enhanced cortical excitability in synaesthetes from the perceptual to the memory domain. We found a group effect in early visual regions, with synaesthetes showing significantly greater signal changes relative to the other two groups in the cuneus and left lingual gyrus. Our ROI-results further revealed significantly greater signal change in synaesthetes relative to non-synaesthetes in the inferior occipital gyrus. Notably, as in the associative learning task, our recognition task directed participants towards the visual properties of the targets to make a match or non-match decision. Thus, the synaesthetes' greater visual cortex activity in response to these stimuli suggests enhanced sensitivity during associative recognition.

Our whole brain analysis showed enhanced neural activity across groups in response to non-match relative to match trials during recognition. This finding was expected on the basis of previous research showing that target non-matches require a recall-to-reject response, while target-matches foster familiarity responses and may or may not trigger the re-instatement of the actual matching pair-associate (Cohn et al., 2008). Our DPA-paradigm might have further encouraged reliance on familiarity heuristics in the target-match condition, whereby participants awaited an expected target that had already been retrieved from memory and could thus be accepted on the basis of a familiar template.

In line with this argument, previous research has shown that older adults are particularly susceptible to making familiarity judgments in recognition paradigms,

which are typically reflected by high Hit-rates and high false-alarm rates (Naveh-Benjamin et al., 2009; Edmonds et al., 2012). These findings seemingly contradict our behavioural results: older adults showed a reduced Hit-rate in the dissimilar target-match condition, whilst showing comparable performance to synaesthetes and young adults in response to target non-matches (similar and dissimilar). One possibility for this finding is that the pair-associates used in the present study all shared high familiarity, given the relatively small stimulus set and the frequent stimulus exposure during the learning phase. Stimulus familiarity increases the demands of identifying true matching pair-associates, especially when pair-associates appear visually dissimilar and therefore not only compete within, but also between stimulus-pairings (Poirier et al., 2012). This might have encouraged retrieval strategies in which participants chose a recall-to-accept response in the dissimilar target-match condition in order to verify intact stimulus-pairings. The older adults' lower Hit-rate in the dissimilar target-match condition is thus a reflection of impaired recall in associative memory paradigms (Naveh-Benjamin et al., 2009; Edmonds et al., 2012). By contrast, a highly familiar stimulus set might simplify correct rejections when associative memory is weak: target non-matches can then be rejected on the basis of vague familiarity responses without explicit knowledge of what the actual target-match would have been. In line with this explanation, the correct rejection rate in our paradigm was high across all participant groups, suggesting lower cognitive demands in response to target non-matches relative to target-matches.

How can we reconcile the high correct rejection rate across groups on the one hand and the group differences during correct rejections in early visual regions on the other? One possible explanation is the differential neural selectivity in older adults' (Park et al., 2004; Goh, 2011; Park et al., 2012) and synaesthetes' (Ramachandran and Hubbard, 2001; Hubbard et al., 2011) ventral visual areas, which alters perceptual sensitivity. This was particularly evident in the ROI-results of the target-period: group differences were mainly found in posterior regions including the inferior occipital and fusiform gyrus, supporting the sensitivity hypothesis. Specifically, relative to older adults, synaesthetes and young adults showed increased signal change across non-match and match trials, reflecting the respective perceptual and memory demands. Non-match trials constitute an unexpected perceptual item that can result in increased signal change (Kok et al., 2012), while match-trials can trigger increased signal-change as a result of recall-to-accept responses (Ranganath et al.,

2004). The fact that older adults showed reduced signal change in inferior occipital and fusiform gyrus relative to the other two groups, may reflect impaired memory responses underpinned by impaired sensitivity.

A different pattern emerged from the group comparisons found at associative retrieval (cue presentation). Although we found a main effect of group in early visual cortex (as during recognition), the pattern of activation was reversed: synaesthetes, as well as young adults, showed lower calcarine gyrus activity relative to older adults at retrieval, and higher activity during recognition. This was supported by the ROI-results, showing reduced activity in occipital-temporal areas during retrieval, and enhanced activity during recognition in synaesthetes vs. older adults. We interpret this result as evidence for reduced sensitivity in older adults' primary visual cortex, in line with other studies (Ross et al., 1997; Levine et al., 2000; Justino et al., 2001; Peiffer et al., 2009). Although these studies typically found reduced visual cortex activity in older adults using bottom-up perceptual detection tasks, the enhanced activity found in our group of older adults during associative retrieval suggests that top-down memory processes require enhanced activity to compensate degraded sensory functions. In other words, the reversed group effect observed between associative retrieval and recognition indicates that reduced sensitivity in visual cortex (as in aging) comes with an activation decrease during bottom-up perceptual processing and an activation increase during top-down retrieval, whereas enhanced sensitivity (as in synaesthesia) shows the opposite pattern.

The results of our post hoc tests also revealed greater activity in older adults relative to synaesthetes in parietal and frontal regions, over and above the enhanced activity in the cuneus, an effect that was not found for the comparison of older vs. young adults. This demonstrates a subtle effect of synaesthesia and provides evidence for a more differentiated retrieval network that can only be detected against older adults. The fact that no differences were found between young adults and synaesthetes could be attributed to our non-synaesthesia inducing stimuli; the black-and-white fractal images were expected to trigger group effects related to differences in visual sensitivity, which differs most between synaesthetes (enhanced sensitivity; (Barnett et al., 2008) and older adults (reduced sensitivity; (Goh, 2011). These findings support the sensitivity hypothesis and are consistent with the representational account of memory: enhanced sensitivity in early visual cortex may

accentuate stimulus processing along the VVS in synaesthetes and reduce top-down control required from frontal and parietal regions. Future research should investigate whether differential processing functions in early visual cortex may have a pervasive effect on the entire retrieval network.

In conclusion, our results revealed a neural network of visual associative memory (retrieval and recognition) that reflects differences in visual perception and memory between synaesthetes, young and older adults. To our knowledge, this is the first fMRI study to investigate the neural correlates of memory in synaesthetes, allowing us to examine the influence of perception on memory. Our data suggest that the synaesthetes' memory advantage for non-synaesthesia inducing stimuli was driven by enhanced visual sensitivity. Behaviourally, this was demonstrated by faster learning of dissimilar pair-associates relative to older adults. In fMRI, group differences relating to associative retrieval and recognition were mainly found in early visual regions. Specifically, the synaesthetes' enhanced sensitivity in visual cortex gave rise to a more differentiated and efficient neural network during retrieval, when processing was directed to internal representations of associations. By contrast, during recognition, synaesthetes showed enhanced activity in early visual regions, reflecting enhanced sensitivity to external, behaviourally relevant stimuli. Our results support the notion that memory and perception are underpinned by a continuum of neural substrates in the ventral visual stream, as outlined in the representational account of memory (Bussey and Saksida, 2007).

Chapter 4: Age-related changes in hippocampal-neocortical connectivity during successful associative retrieval

4.1 Abstract

In the previous chapter, we demonstrated that differences in memory and perception were supported by ventral visual regions. Our findings extend previous reports that were largely concentrated on the PRC (Saksida and Bussey, 2010; Ryan et al., 2012; Barense et al., 2007; 2012) to posterior regions in the VVS. However, the most anterior region in the VVS, the hippocampus, has traditionally been assigned a role in declarative memory (Squire, 1986; Squire and Wixted, 2011). In the present fMRI study, we therefore probed hippocampal activation and connectivity in a group of young and older adults with different strengths in memory and perception. Moreover, whilst comparing young and older adults, we further sought to elucidate the network changes in response to visual stimuli that varied in perceptual similarity.

4.2 Introduction

4.2.1 Intrinsic functional connections with the hippocampus

Most memory models converge on the assumption that the hippocampus acts as a collector of information from the neocortex, making it suitable for the retrieval of visual (and other types of) associations (Diana et al., 2007; Montaldi and Mayes, 2010; Squire and Wixted, 2011); Bussey and Saksida, 2007). Consistent with this notion, findings from non-human primate research have revealed neuroanatomical connections within the medial temporal lobe (MTL) structures, and between MTL and neocortex that support an associative process: within the MTL, the hippocampus receives input from the perirhinal cortex (PRC) and the parahippocampal cortex (PHC), which project to the hippocampus via the entorhinal cortex (ERC; (de Curtis and Pare, 2004; Suzuki, 2010). Tract tracing studies with macaque monkeys further showed that the PRC and PHC each receive themselves afferent connections from two distinct cortical networks, allowing sensory information to be relayed to the hippocampus from across the brain (Lavenex and Amaral, 2000; Suzuki and Amaral, 1994). For instance, the PRC has anatomical connections with the anterior temporal cortex (including unimodal visual area TE in lateral inferior temporal cortex, the anterior superior temporal sulcus, and medial parahippocampal regions), as well as with the insular, orbitofrontal and anterior cingulate cortex. On the other hand, the PHC receives input from posterior temporal cortex (visual area V4 and the auditory cortex in the dorsal bank of the superior temporal sulcus), the dorsolateral and orbitofrontal cortex, as well as from posterior regions in the retrosplenial and parietal cortex (Suzuki and Amaral, 1994). Converging evidence for these two MTL cortical networks comes from the human neuroimaging literature. Using high-resolution fMRI, two studies found intrinsic functional coupling between the PRC and lateral anterior temporal and orbitofrontal cortex, while the PHC has intrinsic connections with posterior superior and medial temporal regions, the retrosplenial cortex, parietal-occipital regions (Kahn et al., 2008; Libby et al., 2012) and the orbitofrontal cortex (Kahn et al., 2008). Moreover, both studies showed a coupling of PRC and PHC with the hippocampus, with the former being connected to the head of the hippocampus and the later to its body and tail. These findings demonstrate the latent converging input of sensory information to the hippocampus via multiple anatomical connections

with the neocortex. However, no previous study has examined the modulatory influence of associative retrieval on the functional connectivity of a hippocampal-neocortical network, and how such coupling changes with age. Importantly, these task- and age-related changes in the functional coupling of a memory network can provide a window into the memory retrieval process itself (rather than merely identifying the brain regions involved), as well as into the retrieval deficits associated with healthy aging. In the present study, we addressed these two points by comparing the functional connectivity with the hippocampus between a group of young and older adults, using the visual associative retrieval paradigm described in the previous chapter.

4.2.2 Task-related modulations on hippocampal-neocortical connectivity

Accumulating evidence suggests that cognitive task performance modulates the intrinsic functional connectivity across a variety of networks. Shirer et al. (2012) found increased functional coupling between the MTL and retrosplenial cortex during retrieval of autobiographic memories versus rest, whilst finding increased functional connectivity between a frontal-parietal-basal ganglia network during a subtraction task relative to rest. Moreover, Andrews-Hanna et al. (2007) found increased functional coupling between the medial PFC and posterior midline regions during a semantic judgement task. Yet, there appears to be only one previous study (Ranganath et al., 2005), which directly examined the modulatory influence of a memory task (incidental encoding of visual memories) on hippocampal-neocortical coupling. The results of this study showed remarkable overlap with the two MTL networks reported in the above intrinsic connectivity studies (Kahn et al., 2008; Libby et al., 2012): the left hippocampus was coupled with anterior temporal lobe regions and the medial orbitofrontal cortex, suggesting functional coupling with a PRC network. Further hippocampal coupling was found with a PHC network, including the posterior cingulate and retrosplenial cortex, precuneus, superior temporal and inferior parietal cortex, as well as areas in early visual cortex. One possibility for this finding is that incidental picture encoding shows little modulatory influence on the intrinsic memory network. Indeed, Geerligs et al. (2014) demonstrated that the resting state frontal-parietal network in a group of young adults could only be modulated by a high-demanding 2-back working memory task, while no modulatory influence on the

resting state pattern was found for a low-demanding visual attention task. Thus, in the case of memory, the functional connectivity pattern of an intrinsic hippocampal-neocortical network (Kahn et al., 2008; Libby et al., 2012) was expected to be modulated by a more demanding associative retrieval task. To specifically examine the task-related trajectories of the hippocampal-neocortical network in the present study, we manipulated our associative retrieval paradigm with respect to memory load.

4.2.3 Aging, associative memory and the hippocampus

Given the specific associative deficits widely reported in older adults (Cohn et al., 2008; Cowan, 2006; Edmonds et al., 2012; Iidaka et al., 2001; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2007; Naveh-Benjamin et al., 2009; Shing et al., 2008), the role of the hippocampus, which precisely acts as an associative collector of visual information, is of particular interest. Univariate results from a wide range of memory tasks reveal an inconclusive pattern, with some studies reporting over-activation (Yassa et al., 2011) (Addis et al., 2014) and others reporting under-activation (Cabeza et al., 2004; Daselaar et al., 2003; Mitchell et al., 2000; Sperling et al., 2003) of the hippocampus in older relative to young adults. Moreover, differences in activation patterns are not predictive of task performance. For example, Cabeza et al. (2004) scanned a group of young and older adults during recognition of previously studied words. Although there was no significant difference in accuracy between the two groups, older adults showed lower hippocampal activity. Our own results, however, showed that relative to young adults, older adults had increased hippocampal activation during dissimilar pair-associative retrieval, although task performance was lower in older adults (see Chapter 3). In order to explain such activation differences, functional connectivity measures of the hippocampus with other cortical regions can provide valuable insights into the precise compensation mechanisms employed by older adults, which must be in place in order to achieve comparable task performance with young adults.

4.2.4 Age-related modulation of hippocampal-neocortical connectivity

In recent years, a growing number of studies have begun to investigate age-related differences in functional connectivity during cognitive task performance, (e.g. Andrews-Hanna et al., 2007; Geerligs et al., 2012; Grady et al., 2003; Grady et al., 2010; Kalkstein et al., 2011; Sambataro et al., 2010). The common finding from across these studies is an overall reduction in functional brain connectivity with age, which is found within task-related networks, as well as within the non-task-related, default mode network (DMN). The age-related reduction in connectivity *within* a particular network (e.g. the DMN), is often accompanied by enhanced functional coupling with brain regions *outside* of that network (Geerligs et al., 2012; Kalkstein et al., 2011), suggesting reduced functional specificity of dedicated brain systems with age. Moreover, when engaged in memory-related encoding processes (Grady et al., 2003; Grady et al., 2010), semantic judgement (Andrews-Hanna et al., 2007), or word recognition (Daselaar et al., 2006), critical brain regions such as the MTL or the ventral medial PFC are more strongly correlated with a frontal network in older adults, while young adults exhibit greater functional coupling with posterior regions such as the posterior cingulate, retrosplenial cortex and visual regions. This finding converges with the posterior-to-anterior shift in aging (PASA)-account (Davis et al., 2008), suggesting increased compensation by a frontal network in older adults, while younger adults rely on posterior brain regions that support memory, imagery and perception (Albright, 2012). An alternative account, which has been further advanced through recent functional connectivity studies, is the idea of deficient resource allocation with age (Geerligs et al., 2014; Sambataro et al., 2010). Deficient resource allocation is typically expressed by an altered flexibility in functional coupling, whereby older adults demonstrate changes in functional coupling following minimal changes in task demand [e.g. from baseline to a simple visual attention task (Geerligs et al., 2014)], but demonstrate limited flexibility in functional coupling when task demands exceed the available resources [e.g. from a 1-back to 2-back working memory task (Sambataro et al., 2010)].

Most age-related changes in the functional coupling of brain networks are associated with cognitive decline and ultimately lead to reduced task performance (Onoda et al., 2012). Reduced task performance in older adults was also found in the

behavioural results of our fMRI study (Chapter 3). Specifically, we found a significant interaction in associative retrieval between age and memory load: young and older adults showed a comparable number of retrieved similar pair-associates that were highly associable, but older adults retrieved significantly fewer trials of the dissimilar pair-associates than young adults. Thus, the question we asked in the present study was, how the hippocampus in young and older adults interacts with other cortical regions during successful retrieval and how this differs between two memory load conditions. In assessing the functional connectivity of the hippocampal-neocortical network in our two age groups, we expected to find differential hippocampal coupling between young and older adults in one of two ways: In line with the compensatory account, we hypothesised that older adults might show increased hippocampal coupling with frontal regions, specifically during the dissimilar condition, as a compensatory mechanism to successfully retrieve these pair-associates (albeit to a lesser extent than similar pair-associates). Alternatively, older adults may have reached a resource ceiling (Geerligs et al., 2014) in the functional coupling between hippocampal-neocortical regions during dissimilar pair retrieval. This might be expressed by a relatively undifferentiated coupling in older adults from the low to the high memory load condition and could equally explain the age-related retrieval deficit for dissimilar pair-associates.

4.3 Methods

4.3.1 Participants

The same participants as in Chapters 3 were tested in this study. Details can be found in Chapter 3, section 3.3.1 Participants.

4.3.2 Experimental design and Stimuli

The experimental design and stimuli were the same as described in Chapter 3, consisting of a delayed pair-associative (DPA) retrieval task and a delayed matching-to-sample (DMS) task. Details can be found in section 3.3.2 Experimental design and stimuli.

4.3.3 fMRI data acquisition

Details of the fMRI data acquisition are described in Chapter 3, section 3.3.4.

4.3.4 fMRI analyses

Preprocessing steps and first-level analyses are identical to those described in Chapter 3. Specific to the present study is that our ROI and functional connectivity analyses are based on brain activity during associative retrieval (cue-period) as detailed in section 3.3.5. This resulted in two regressors of interest, pertaining to the similar and dissimilar retrieval condition (Sim_cue; Diss_cue). Details of the functional connectivity analysis and the use of these regressors are described in section 4.3.7.

4.3.5 Defining Regions of Interest

The left hippocampus was selected as a seed ROI for the functional connectivity analysis. This choice was guided by the univariate results of the DPA-task, which showed hippocampal involvement during the initial cue period as a result of successful associative retrieval. Specifically, we carried out a conjunction analysis to identify the hemisphere(s) in which the hippocampus was commonly activated across groups (young and older adults) and conditions (similar and dissimilar pair-associates). The contrast image derived from the conjunction analysis was thresholded at $p < 0.001$ (uncorrected), with an extent threshold of k = 5 voxels. Using this threshold, we found a peak in the left, but not right hippocampus, at MNI coordinates (-24, -34, -2). Thus, our initial hippocampal seed region was defined around this peak using the small volume correction available in SPM8, with a 3mm radius, containing a total of 6 voxels. The average time-course of this ROI was subsequently used for a seed-to-voxel based functional connectivity analysis (using the procedure specified the section *Functional connectivity analysis*). However, the results of this analysis did not yield any between-group differences in hippocampal-neocortical connectivity with a threshold of $p < 0.001$, k = 5 voxels. For the within-group analysis, only local correlations with voxels adjacent to the hippocampal seed region were found, likely reflecting autocorrelations with the seed ROI (see e.g. (Kahn et al., 2008)). When the threshold was lowered to $p < 0.005$; k = 5 voxels, a speckle pattern was found for the within and between-group analyses of our young and older adults. Overall, this suggested that the small seed region of 6 voxels provided insufficient power for our seed-to-voxel analysis. In order to increase the power, we used an anatomically defined ROI of the entire left hippocampus (including the subiculum, cornu ammonis, dentate gyrus and the hippocampal-amygdala-transition-area), using the Anatomy toolbox v1.8, 2011 (http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html); (Eickhoff et al., 2005)).

All results are reported from data of this anatomically defined ROI of the left hippocampus.

Four additional anatomical ROIs were created as control regions to investigate whether the expected age-related changes in functional connectivity were ubiquitous across the brain, or could more specifically be attributed to the hippocampal-neocortical network. To this end, we performed pair-wise regressions between bilateral sensory visual and motor areas, comprising the lateral premotor cortex (BA6) and secondary visual cortex (BA18) bilaterally, which are commonly involved in visual associative retrieval tasks (Neuner et al., 2007; Ranganath et al., 2004). Despite the evidence that functional connectivity decreases in healthy aging (e.g. Andrews-Hanna et al., 2007; Geerligs et al., 2014; Grady et al., 2010; Kalkstein et al., 2011), the interhemispheric connectivity of sensory visual areas seems to remain intact in older adults (Andrews-Hanna et al., 2007). Thus, in line with the study by Andrews-Hanna et al., 2007, we selected BA18 of the right and left hemisphere as our first pair of control ROIs.

The second set of control areas was selected in the lateral premotor cortex (left and right BA6). These areas were chosen as they were previously shown to exhibit the strongest anatomical interhemispheric connections among a number of other motor regions in non-human primates (Dancause et al., 2007), which receive most of their input via the corpus callosum (Boussaoud et al., 2005). Thus, the lateral premotor cortex is a candidate control region to assess interhemispheric functional connectivity on the basis of its anatomical connections. Specifically, with respect to aging, previous studies have often demonstrated an age-related atrophy in the corpus callosum (see review by (Fling et al., 2011). Interestingly, such callosal degeneration has been associated with *increased* interhemispheric resting state connectivity in motor regions in older relative to young adults (Langan et al., 2010; Solesio-Jofre et al., 2014), contrary to the finding that older adults typically show *reduced* functional connectivity in other networks. Increased resting state connectivity between motor regions has been explained by an age-related reduction in functional hemispheric asymmetry, which in young adults is characterised by strong contralateral engagement of motor regions in unimanual tasks (Fling et al., 2011). In older adults however, unimanual task performance is associated with greater ipsilateral recruitment of motor regions (Langan et al., 2010). In other words, while young adults activate the hemisphere contralateral to their dominant hand, older adults instead show activation of the same hemisphere, over and above the contralateral hemisphere. Such age-related hemispheric asymmetry has originally

been documented for a number of cognitive tasks (Cabeza, 2002), showing similar findings of greater bilateral cortical recruitment in older adults, while young adults typically activate dedicated unilateral regions. A finding of increased functional coupling between the lateral premotor cortices in older relative to younger adults would be indicative of a pervasive change in functional connectivity across the brain that reaches beyond the age-related changes attributable to the hippocampal-neocortical network. We created two ROIs of the lateral BA6 using the WFU-Pickatlas v2.4 (http://www.nitrc.org/projects/wfu_pickatlas/; (Maldjian et al., 2003) and two ROIs of BA18 using the Anatomy toolbox v1.8. These four ROIs were carried forward to assess interhemispheric functional coupling between each seed ROI (left BA18; left lateral BA6) and its associated target ROI (right BA18; right lateral BA6).

4.3.6 ROI analysis of the left Hippocampus

Using the left hippocampal map of the Anatomy toolbox, we performed a second-level ROI-analysis prior to the connectivity analysis in order to examine the group differences in response to similar and dissimilar pair retrieval. Specifically, this was done to interrogate the activation strength within the left (L) hippocampus between groups and conditions and refer this back to our behavioural results. Unsmoothed contrast images (Young, Sim; Young, Diss and Old, Sim; Old, Diss) were used for the ROI-analysis to restrict the BOLD signal to the chosen anatomical ROI. The ROI-analyses were performed by masking the images inclusively with the image of the L hippocampus and setting a threshold of $p < 0.005$ (uncorrected), k = 0 voxels. Using the rfxplot toolbox (Gläscher, 2009) available in SPM8, extraction of percent signal change was limited to voxels surviving the above threshold and was calculated for each group (Young, Old) and each condition (Sim, Diss).
The percent signal change refers to the effect size of the evoked BOLD-response, which has been rescaled to a voxel-wise baseline by dividing the beta values of the effect of interest by the beta constant (Gläscher, 2009).

4.3.7 Functional connectivity analysis

Two types of functional connectivity analyses were performed: 1) the main seed-to-voxel analyses, in which we assessed the hippocampal-neocortical network within and between subjects and 2) the pair-wise regression analyses between the left and right BA18 and the left and right BA6, serving as control regions to examine any between-group differences in interhemispheric connectivity. The CONN fMRI connectivity toolbox in SPM8 (v13o, 2011, http://www.nitrc.org/projects/conn; (Whitfield-Gabrieli and Nieto-Castanon, 2012) was used for to perform these analyses.

Preprocessing. To minimise spurious functional correlations in the BOLD time-series pertaining to physiological noise, motion and task effects, additional temporal preprocessing steps were performed on all of the functional images that had initially been preprocessed in SPM8. Physiological noise relating to BOLD signal from white matter and cerebrospinal fluid was removed by including the segmented white matter and cerebrospinal fluid masks of each individual subject as regions of no interest. An anatomical computational correction strategy, implemented by the toolbox, was used to identify noise signals within these ROIs using principal component analyses, which were subsequently regressed from the BOLD time-series at each voxel. Next, temporal confounds due to motion were accounted for by including the subject-specific estimated motion parameters, as well as their first temporal derivatives. Finally, to remove any confounding variance from the BOLD time-series related to task performance, all task regressors, including their first temporal derivative, were entered as covariates of no interest in the preprocessing step. Following preprocessing, the residual BOLD time-series was band-pass filtered using a filter that retained frequency components between < 0.008Hz and < 0.09Hz.

First-level analyses. Using the residual BOLD signal after temporal preprocessing, we explicitly tested for the task-related modulations in the functional connectivity between our seed ROI (the left hippocampus) and all other voxels in the brain. Specifically, we were interested in the modulatory influence of confident Hit- and Correct rejection trials of the similar and dissimilar condition during the initial cue period, at which associative retrieval occurred. To this end, the average time series across all voxels within the left hippocampus was computed for each subject, for the

similar and dissimilar pair-associates separately (conditions Sim_cue; Diss_cue). Next, subject-specific, whole brain exploratory analyses were performed by computing the linear relationship of the extracted time course of the left hippocampus with that of all other voxels in the brain, using bivariate regression analysis. The resulting regression coefficients (beta-values) for each subject were saved as connectivity maps to be used for the second-level group analyses.

In order to perform the connectivity analyses for our four control ROIs, pairs of the right and left Brodmann area (BA) 18 and the right and left BA6 were entered into a separate model. First-level analyses involved extracting the subject-specific time courses of each of these ROIs for confident Hit- and Correct rejection trials of the similar and dissimilar condition (as above) and creating the respective ROI-to-ROI connectivity matrices.

Second-level analyses. The calculated seed-to-voxel connectivity maps of each subject were taken to group level to first investigate hippocampal-neocortical coupling within groups. To this end, positive and negative contrasts were computed, which examined the modulatory influence of DPA (collapsed across Sim and Diss) on the functional connectivity of young adults and older adults separately, resulting in four regression maps (Young_DPA_positive, Young_DPA_negative; Old_DPA_positive, Old_DPA_negative). The contrast images derived from the within-group analyses were thresholded at $p < 0.001$ (uncorrected), with an extent threshold of 5 voxels.

Next, we investigated the between-group differences of the hippocampal-neocortical network. Specifically, we were interested in examining how changes in memory load would differentially modulate hippocampal coupling with other brain regions between young and older adults, thus assessing group-specific resource allocation to varying task demands. Four contrasts were specified, examining the connectivity pattern between young and older participants during the similar and dissimilar condition (Young>Old, Sim; Young>Old, Diss; Old>Young, Sim; Old>Young, Diss). The contrast images derived from the between-group analyses were thresholded at $p < 0.005$ (uncorrected), with an extent threshold of 5 voxels.

For the control ROIs, we calculated the regression coefficients between seed and target regions in the visual and motor areas using bivariate regression analyses. Four between-source contrasts were specified to investigate whether the

interhemispheric connectivity between L BA18 and right (R) BA18, as well as between L lateral BA6 and R lateral BA6, were significant in each group (Young: L_BA18 > R_BA_18; Old: L_BA18 > R_BA_18; Young: L_lateral_BA_6 > R_lateral_BA_6; Old: L_lateral_BA_6 > R_lateral_BA_6). Next, independent t-tests were computed to examine whether interhemispheric connectivity in visual and motor regions differed significantly between young and older adults [Young > Old: L_BA18 > R_BA_18; Young > Old: L_BA6 > R_BA_6 (note that the between-group contrasts are relative contrasts, thus the opposite between-group contrasts yield the inverse regression coefficients]. The resulting regression coefficients represent the percent signal changes in BOLD activity at the target ROI associated with a 1 percent signal change of BOLD activity at the seed ROI (Whitfield-Gabrieli and Nieto-Castanon, 2012), and were calculated for the DPA condition (averaged across Sim and Diss). All ROI-to-ROI regression analyses were performed using a threshold of $p < 0.001$ (uncorrected).

4.4 Results

4.4.1 ROI results of the left Hippocampus

Mixed effects. To examine the effects of group and similarity on percent signal change, we carried out a 2 x 2 mixed ANOVA, entering group (young, old) as the between-subject factor and condition (similar, dissimilar) as the within-subject factor. Descriptive results are presented in Figure 1, showing the average percent signal change for each group and condition. We found a significant main effect of condition, $F[1,36] = 10.28$, $p = .003$, $\eta_p^2 = 0.222$, with percent signal change being higher during retrieval of dissimilar than similar pair-associates. However, there was no significant main effect of group, $F[1,36] = .185$, $p = .670$, $\eta_p^2 = 0.005$ and no significant interaction between group and condition, $F[1,36] = 2.024$, $p = .163$, $\eta_p^2 = 0.053$.

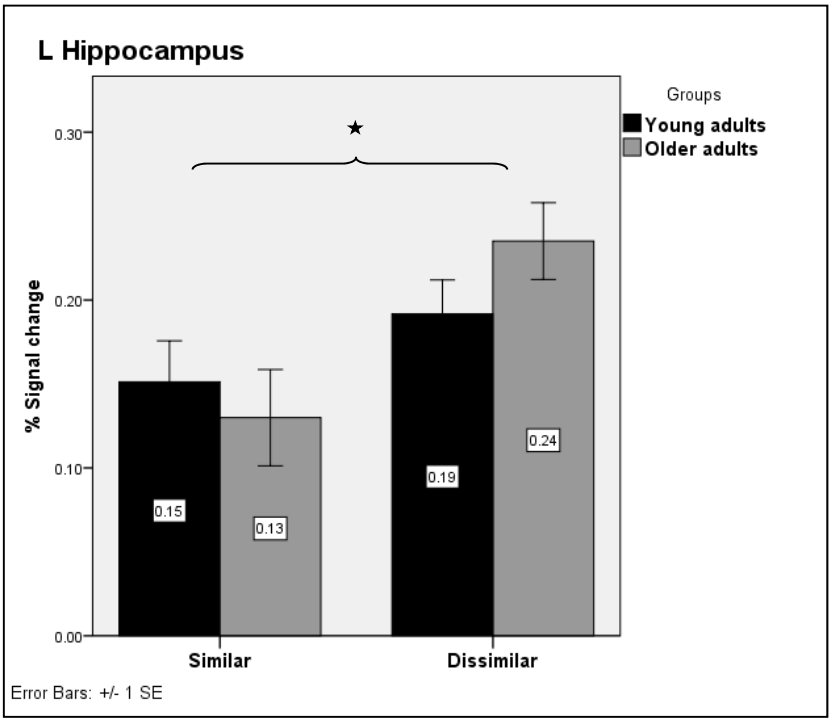


Figure 1. Percent signal change in the left hippocampus during retrieval of similar and dissimilar pair-associates, plotted for young and older adults. Error bars indicate the standard error of the mean.

Random effects. Next, we examined the condition effects on the activity in the left hippocampus within each group separately. To this end, two paired-samples t-tests were carried out, comparing the percent signal change between the similar and dissimilar condition in young and older adults. Descriptive results of the two t-tests are presented in Figure 2a and Figure 2b, respectively. The t-test for the young adults revealed that there was no significant difference in percent signal change between the similar and dissimilar condition, $t(18) = 1.433$, $p = .169$ (two-tailed). By contrast, older adults showed significantly greater percent signal change in the dissimilar condition, $t(18) = 2.957$, $p = .008$.

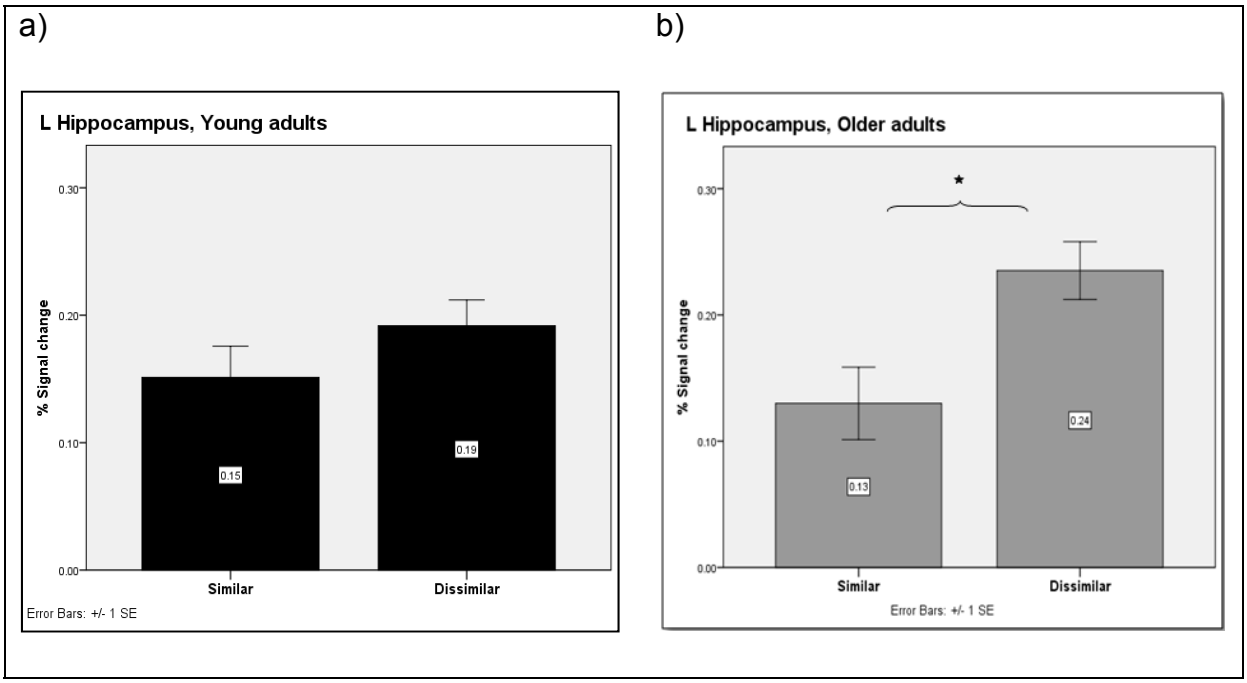


Figure 2. Percent signal change in the left hippocampus during retrieval of similar and dissimilar pair-associates shown in a) for young adults and in b) for older adults. Error bars indicate the standard error of the mean.

4.4.2 Functional connectivity: Results and Discussion

Random effects, positive contrast. Figures 3a and 3b illustrate the brain regions exhibiting significant positive functional coupling with the left hippocampus during the DPA-task, in young and older adults, respectively. Both groups revealed a hippocampal-neocortical network that closely resembled that of previous functional connectivity studies (Kahn et al., 2008; Libby et al., 2012; Ranganath et al., 2005). Large bilateral clusters were found in the anterior and middle temporal cortex (highlighted in dark red), as the areas exhibiting strongest coupling with the left hippocampus. Both groups showed hippocampal coupling with frontal regions including the orbitofrontal cortex and the left superior frontal gyrus. In addition, older adults showed positive hippocampal connectivity with the left superior medial frontal gyrus, while young adults showed hippocampal connectivity with the right premotor cortex (cf. Table 1 and 2). Connectivity with posterior brain regions was found in both groups between the left hippocampus and the left posterior angular gyrus, bordering the middle occipital cortex. Older adults further showed significant positive hippocampal coupling with posterior superior and middle temporal regions. Finally, hippocampal coupling with visual regions included the fusiform gyrus bilaterally, the left parahippocampal gyrus and the right inferior temporal cortex in older adults, while young adults showed hippocampal coupling with visual regions restricted to the left parahippocampal/lingual gyrus and the left inferior temporal cortex.

As can be visually appreciated from Figure 3, the older adults' connectivity pattern encompassed a smaller extent compared to young adults, which is in line with several studies investigating task-related functional connectivity in older adults (Andrews-Hanna et al., 2007; Geerligs et al., 2014; Grady et al., 2003; 2010; Kalkstein et al., 2011; Sambataro et al., 2010). For instance, as can be taken from Table 1, the first cluster in young adults encompassed a large extent of 4782 voxels, spanning medial temporal lobe regions, the lingual gyrus, the thalamus and the precuneus. By contrast, the extent of the first cluster in older adults only contained 1647 voxels, merely spanning the medial temporal lobe regions, the fusiform and lingual gyrus (Table 2).

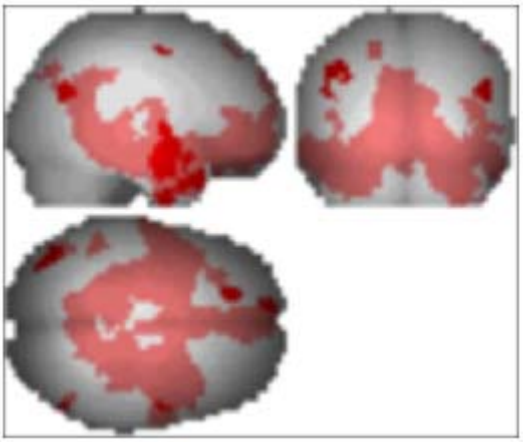
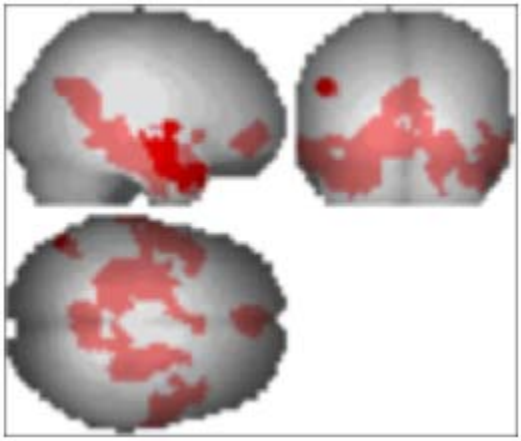
a) Young adults	b) Older adults
	

Figure 3. Positive retrieval-related connectivity with the left hippocampus in a) young and b) older adults. All images are shown at a height threshold of T > 3.61; *p* = 0.001 (uncorrected), with an extent threshold of 5 voxels.

Table 1. Young adults DPA, positive contrast

Brain region	MNI coordinates			*T-value*	Cluster size (voxels)
	x	*y*	*z*		
Left Hippocampus	-18	-19	-17	18.89	4782
Left Lingual Gyrus	-12	-31	-5	15.16	
Left ParaHippocampal Gyrus	-27	-34	-14	14.30	
Right Hippocampus	21	-25	-11	13.26	
Left Thalamus	-15	-34	4	12.99	
Left Precuneus	-15	-43	1	12.37	
Left Angular Gyrus	-36	-85	34	4.85	45
Left Middle Occipital Gyrus	-39	-82	31	4.24	
Left Middle Temporal Gyrus	-45	-64	22	4.14	
Right Middle Occipital Gyrus	54	-70	25	5.77	33
Left Inferior Temporal Gyrus	-54	-46	-11	4.72	23
Left Superior Frontal Gyrus	-18	41	49	4.52	16
RightPrecentral Gyrus	54	-4	49	4.08	5
Cerebellar Vermis	0	-37	-20	4.20	5

Results were masked with the left hippocampus and thresholded at p<0.001 (uncorrected), k = 5vox.

Table 2. Older adults DPA, positive contrast

Brain region	MNI coordinates			*T-value*	Cluster size (voxels)
	x	*y*	*z*		
Left ParaHippocampal Gyrus	-27	-31	-17	15.69	1647
Left Hippocampus	-21	-10	-17	14.98	
Left Fusiform Gyrus	-36	-31	-17	10.20	
Brainstem	-12	-31	-11	9.31	
Left Lingual Gyrus	-12	-34	-2	8.97	
Right ParaHippocampal Gyrus	27	-22	-17	8.69	
Right Temporal Pole	39	20	-32	6.34	299
Right Middle Temporal Gyrus	54	-7	-20	5.85	
Right Superior Temporal Gyrus	54	-1	-11	5.50	
Right Medial Temporal Pole	48	8	-26	5.17	
Right Amygdala	36	2	-23	4.69	
Right Rolandic Operculum	51	-1	1	4.46	
Right Mid Orbital Gyrus	6	53	-11	6.24	157
Left Mid Orbital Gyrus	0	50	-5	5.73	
Left Angular Gyrus	-51	-70	25	6.01	51
Left Middle Temporal Gyrus	-60	-25	1	4.85	17
Left Superior Frontal Gyrus	-18	35	55	5.70	15
Left Superior Medial Gyrus	-6	59	34	4.61	13

Table 2. continued	MNI coordinates				
Brain region	*x*	*y*	*z*	*T-value*	Cluster size (voxels)
Right Fusiform Gyrus	30	2	-41	4.13	13
Right Inferior Temporal Gyrus	36	2	-41	4.04	
Right Superior Temporal Gyrus	63	-19	10	4.57	11
Brainstem	0	-22	-17	4.77	10
Left Cerebellum	-9	-55	-8	4.04	6
Left Rectal Gyrus	-12	20	-14	5.77	5
Results were masked with the left hippocampus and thresholded at p<0.001 (uncorrected), k = 5vox.					

Random effects, negative contrast. Figures 4a and 4b illustrate the brain regions exhibiting significant negative functional coupling with the left hippocampus during the DPA-task, in young and older adults, respectively. In older adults, the strongest negative hippocampal coupling was found with the bilateral inferior and superior parietal cortex (first two clusters in Table 4). Although these regions were also negatively coupled with the left hippocampus in young adults (Table 3), they only emerged as the second and fourth cluster and contained fewer voxels than in the older adults. The young adults revealed additional negative coupling with the left and right precuneus as well as with the right middle cingulate cortex, which was not found for the older adults. Instead, older adults exhibited negative hippocampal coupling with early visual areas, in the left and right cuneus and calcarine gyrus.

The strongest negative hippocampal coupling in young adults was found with frontal regions (first cluster in Table 3), including the right inferior, middle and superior frontal gyrus, which contained 862 voxels. Older adults revealed negative hippocampal coupling with the right inferior and middle frontal gyrus only as their third cluster (430 voxels). This was followed by cluster five, which included the middle and superior frontal gyrus (58 voxels) and cluster six including the superior frontal gyrus (44 voxels).

Overall, our results for the negative contrast revealed a reduced hippocampal-neocortical connectivity pattern in older compared to young adults (Geerligs et al., 2012), which was expressed by a smaller voxel extent specifically within frontal brain regions. Moreover, reduced functional specificity in older adults was evident by a failure of negative coupling with several regions that were functionally coupled with the left hippocampus in young adults, including the precuneus, middle cingulate and precentral gyrus (Geerligs et al., 2012; 2014). Instead, older adults exhibited negative hippocampal coupling with early visual cortex that was not found in young adults (cf. Figure 4 and Table 4).

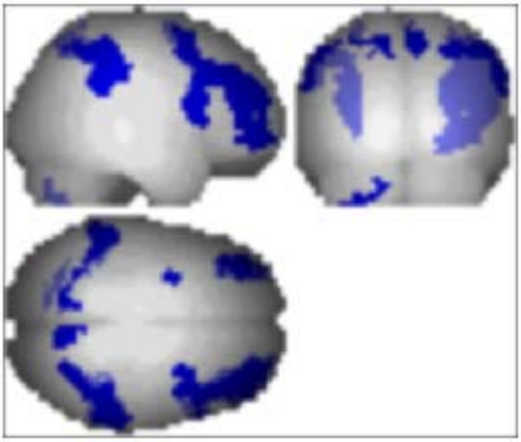
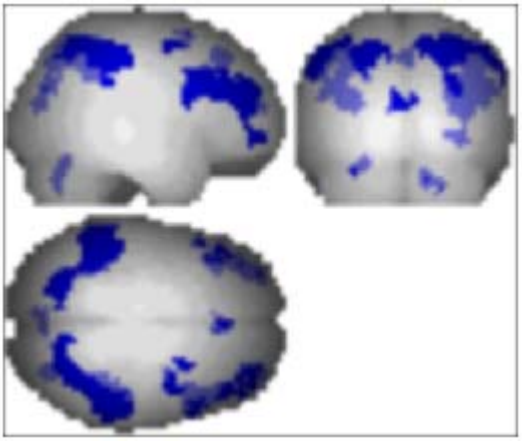
a) Young adults	b) Older adults
	

Figure 4. Negative retrieval-related connectivity with the left hippocampus in a) young and b) older adults. All images are shown at a height threshold of T > 3.61; *p* = 0.001 (uncorrected), with an extent threshold of 5 voxels.

Table 3. Young adults DPA, negative contrast

Brain region	MNI coordinates			*T-value*	Cluster size (voxels)
	x	*y*	*z*		
Right Inferior Frontal Gyrus (p. Opercularis)	45	14	10	6.98	862
Right Middle Frontal Gyrus	42	38	28	6.76	
Right Superior Frontal Gyrus	30	56	16	6.45	
Right Middle Orbital Gyrus	27	53	-11	6.42	
Right Inferior Parietal Lobule	51	-37	49	7.09	409
Right SupraMarginal Gyrus	57	-43	34	6.57	
Right Angular Gyrus	30	-64	49	5.57	
Left Middle Frontal Gyrus	-36	47	19	7.39	245
Left Middle Frontal Gyrus	-33	29	37	4.21	
Left SupraMarginal Gyrus	-54	-46	34	6.12	188
Left Inferior Parietal Lobule	-51	-40	49	5.96	
Right Precuneus	6	-67	58	5.33	50
Left Cerebellum	-12	-79	-38	5.35	43
Left Superior Parietal Lobule	-21	-64	55	5.32	37
Left Precuneus	-12	-58	58	4.62	
Left Middle Frontal Gyrus	-27	2	64	4.89	31
Left Precentral Gyrus	-27	-1	58	4.68	

Table 3. continued	MNI coordinates				
Brain region	*x*	*y*	*z*	*T-value*	Cluster size (voxels)
Left Cerebellum	-39	-58	-38	4.88	25
Right Middle Cingulate Cortex	12	-25	40	5.54	13
Results were masked with the left hippocampus and thresholded at p<0.001 (uncorrected), k = 5vox.					

Table 4. Older adults DPA, negative contrast

Brain region	MNI coordinates			*T-value*	Cluster size (voxels)
	x	*y*	*z*		
Right Inferior Parietal Lobule	39	-46	43	6.04	466
Right Angular Gyrus	36	-64	49	6.02	
Right Precuneus	18	-73	49	5.74	
Right Superior Parietal Lobule	15	-70	52	5.34	
Right Postcentral Gyrus	48	-28	40	4.96	
Left Inferior Parietal Lobule	-39	-49	46	7.29	454
Left Postcentral Gyrus	-48	-34	52	7.05	
Left Superior Parietal Lobule	-27	-67	49	6.71	
Left Inferior Parietal Lobule	-33	-43	49	5.96	
Left Superior Occipital Gyrus	-24	-70	31	4.07	
Right Middle Frontal Gyrus	30	50	25	7.02	430
Right Inferior Frontal Gyrus (p. Triangularis)	48	26	22	6.77	
Right Inferior Frontal Gyrus (p. Opercularis)	45	17	31	6.15	
Right Middle Orbital Gyrus	36	56	-5	5.23	
Left Middle Frontal Gyrus	-27	56	16	7.05	183
Left Inferior Frontal Gyrus (p. Opercularis)	-51	17	22	4.75	
Left Inferior Frontal Gyrus (p. Triangularis)	-45	32	25	4.57	
Right Middle Frontal Gyrus	42	-1	55	6.75	58
Right Superior Frontal Gyrus	27	8	58	5.65	

Table 4. continued Brain region	MNI coordinates *x*	 *y*	 *z*	 *T-value*	 Cluster size (voxels)
Right Superior Frontal Gyrus	6	32	46	6.46	44
Left Superior Frontal Gyrus	-6	26	46	4.67	
Left Cuneus	-6	-85	16	5.50	36
Right Cuneus	6	-82	19	4.07	
Right Calcarine Gyrus	9	-79	16	3.76	
Right Cerebellum	15	-70	-32	5.31	32
Right Middle Occipital Gyrus	30	-79	28	6.01	28
Left Cerebellum	-24	-67	-20	5.65	27
Left Middle Frontal Gyrus	-27	-4	52	5.39	10
Left Middle Frontal Gyrus	-24	14	49	4.80	7
Left Superior Frontal Gyrus	-21	17	52	4.53	
Right Calcarine Gyrus	18	-64	4	4.31	7
Left Precentral Gyrus	-45	-1	46	4.40	5
Left Cerebellum	-6	-79	-32	4.16	5

Results were masked with the left hippocampus and thresholded at p<0.001 (uncorrected), k = 5vox.

Mixed effects, similar pair retrieval. Figure 5 illustrates the results of group-specific hippocampal coupling during similar pair retrieval (the low memory load condition). For the contrast Young > Old, similar, we found hippocampal coupling with subcortical structures including the left putamen and the thalamus. The only frontal region coupled with the left hippocampus was located posteriorly, in the right lateral precentral gyrus. Additionally, young adults showed significantly greater hippocampal coupling than older adults with the left postcentral gyrus and the right cerebellum. Three clusters were found to be coupled with visual regions including the left cuneus, as well as the right parahippocampal and lingual gyrus (see Table 5).

The connectivity pattern for the between-group contrast Old > Young, similar, revealed significantly greater hippocampal coupling with the parietal and frontal cortex including the right supramarginal gyrus and right middle frontal gyrus, respectively. Moreover, older adults showed significantly greater hippocampal coupling than young adults with the left cerebellum. Although the number of clusters showing hippocampal coupling in the contrast Old > Young, similar, was smaller (i.e. four; Table 6) than that in the contrast Young > Old, similar (i.e. eight; Table 5), the frontal and parietal clusters found in older adults each contained more than twice as many voxels than any of the clusters found for the young adults. Thus, although the overall hippocampal-neocortical network might be reduced in older adults (see also the within-group comparisons for the DPA-task), the between-group contrasts revealed that relative to young adults, the older adults had a greater connectivity extent in the low memory load condition, specifically with the frontal and parietal regions.

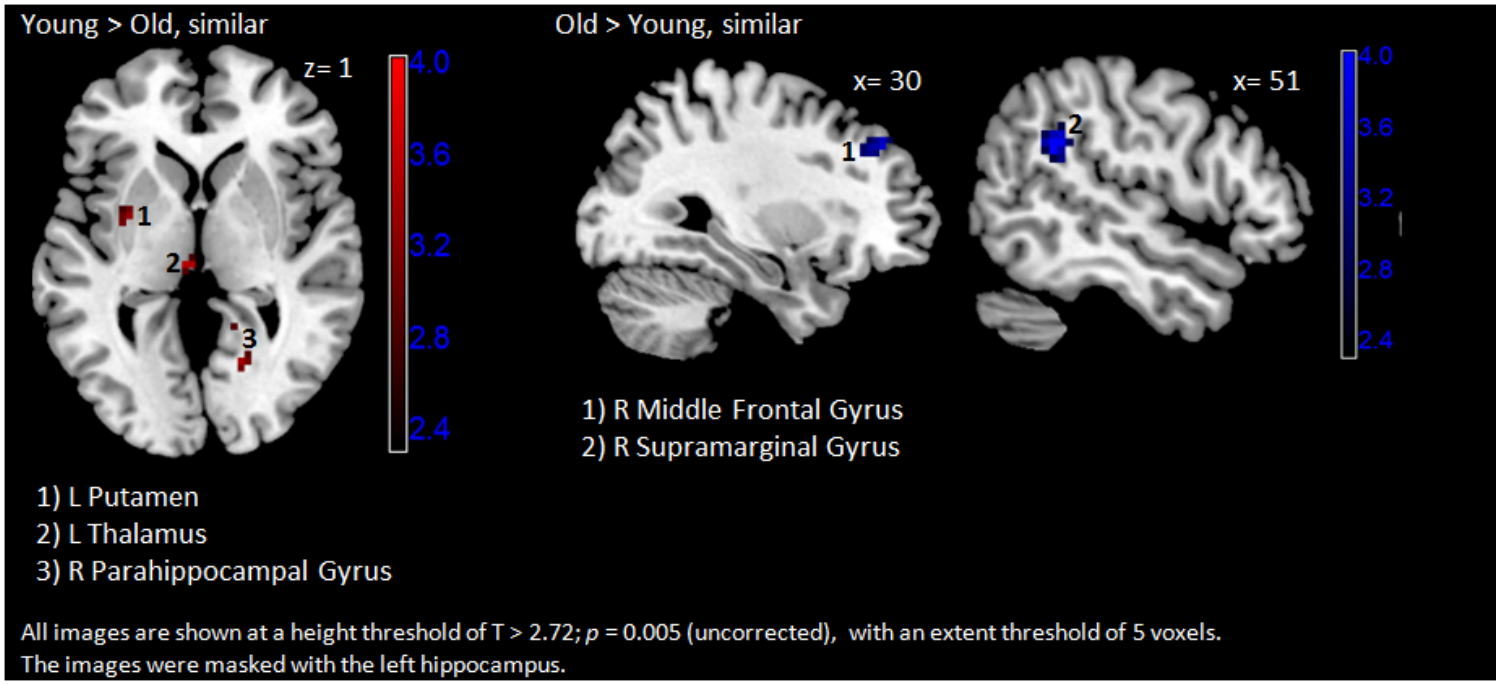


Figure 5. Regions exhibiting enhanced hippocampal coupling in young versus older adults (left) and in older versus young adults (right) during retrieval of similar pair-associates. Images are rendered on the individual subjects' brain available in MRIcron.

Table 5. Young > Old, Similar pair retrieval

Brain region	MNI coordinates			*T-value*	Cluster size (voxels)
	x	*y*	*z*		
Left Putamen	-33	-1	-2	3.49	16
Right Cerebellum	15	-73	-29	3.72	14
RightPrecentral Gyrus	54	-4	43	3.43	11
Left Cuneus	-6	-85	22	3.45	10
Right ParaHippocampal Gyrus	21	-43	-5	3.16	10
Right Lingual Gyrus	15	-49	1	2.82	
Left Postcentral Gyrus	-45	-13	49	3.32	8
Left Thalamus	-6	-22	1	3.51	8
Right Lingual Gyrus	18	-64	1	3.42	7
Results were masked with the left hippocampus and thresholded at p<0.001 (uncorrected), k = 5vox.					

Table 6. Old > Young, Similar pair retrieval

Brain region	MNI coordinates			*T-value*	Cluster size (voxels)
	x	*y*	*z*		
Right SupraMarginal Gyrus	51	-46	25	4.06	34
Right Middle Frontal Gyrus	30	41	37	3.67	39
Left Cerebellum	-12	-49	-50	3.32	11
Left Cerebellum	-42	-61	-32	3.40	10
Results were masked with the left hippocampus and thresholded at p<0.001 (uncorrected), k = 5vox.					

Mixed effects, dissimilar pair retrieval. Figure 6 illustrates the results of group-specific hippocampal coupling during the retrieval of dissimilar pairs (the high memory load condition). For the contrast Young > Old, dissimilar, we found five clusters within early visual areas, including the lingual, calcarine and fusiform gyrus, to be coupled with the left hippocampus. Notably, the right lingual and calcarine gyrus showed the greatest extent (55 voxels, cluster 1) of brain regions, in which hippocampal coupling was significantly enhanced in young relative to older adults (Table 7). We further found significantly greater hippocampal coupling in young relative to older adults with the left inferior parietal cortex, as well as with frontal regions including the middle orbital, superior medial and precentral gyrus.

Interestingly, the contrast Old > Young, dissimilar, revealed a hippocampal-neocortical network that was comparable to that of the contrast Old > Young, similar, involving significantly greater hippocampal coupling in older adults with a frontal-parietal network, including the right inferior parietal lobe and the right inferior and superior frontal gyrus. Moreover, older adults showed significantly greater connectivity than young adults between the left hippocampus and the right middle and left superior temporal lobes. Overall, the contrast Old > Young, dissimilar, revealed a smaller number of clusters as well as a smaller voxel extent of brain regions compared to the contrast Young > Old, dissimilar (cf. Tables 8 and 7). This result might in part reflect the reduced functional connectivity in older adults, as was found in the within-group comparisons of the present study [cf. also Andrews-Hanna et al., 2007; Geerligs et al., 2014; Grady et al., 2003; Kalkstein et al., 2011; Sambataro et al., 2010]. However, the between-group results of the similar condition showed that older adults did in fact exhibit greater hippocampal coupling relative to young adults, in particular with frontal-parietal regions, suggesting that older adults started to recruit a frontal-parietal network at lower task demands. Importantly, the finding of a hippocampal-frontal-parietal network in older adults, which was found across both retrieval conditions, supports our second hypothesis, suggesting that aging is associated with a deficient resource allocation, according to which the functional integration of associative retrieval remains largely invariant to changing memory load.

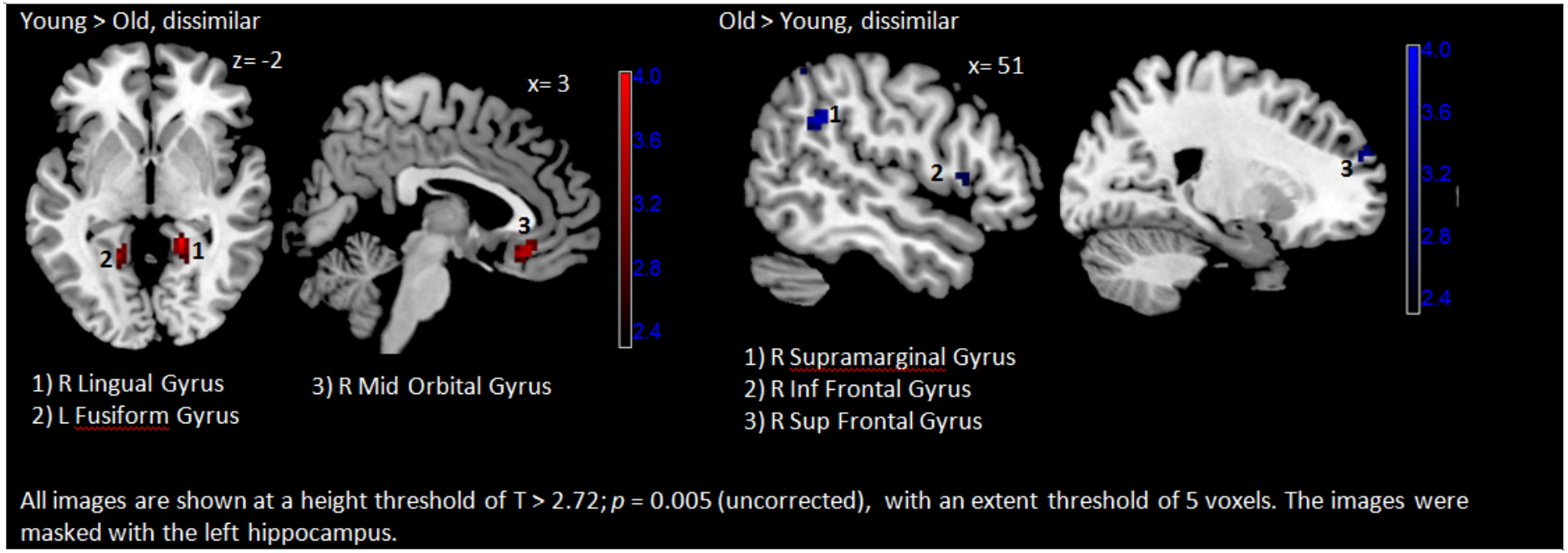


Figure 6. Regions exhibiting enhanced hippocampal coupling in young versus older adults (left) and in older versus young adults (right) during retrieval of dissimilar pair-associates. Images are rendered on the individual subjects' brain available in MRIcron.

Table 7. Young > Old, Dissimilar pair retrieval

Brain region	MNI coordinates			*T-value*	Cluster size (voxels)
	x	*y*	*z*		
Right Lingual Gyrus	18	-43	-2	3.99	55
Right Calcarine Gyrus	21	-58	4	3.90	
Left Cerebellum	-24	-43	-20	4.30	36
Left Fusiform Gyrus	-27	-49	-14	3.46	
Right Mid Orbital Gyrus	3	29	-14	3.55	26
Left Lingual Gyrus	-18	-52	-2	3.48	22
Left Inferior Parietal Lobule	-33	-73	40	3.79	19
Right Precentral Gyrus	45	-16	40	3.68	7
Right Lingual Gyrus	12	-70	-11	3.05	6
Left Superior Medial Gyrus	-9	65	10	3.48	5

Results were masked with the left hippocampus and thresholded at p<0.001 (uncorrected), k = 5vox.

Table 8. Old > Young, Dissimilar pair retrieval

Brain region	MNI coordinates			*T-value*	Cluster size (voxels)
	x	*y*	*z*		
Right SupraMarginal Gyrus	54	-46	31	3.67	18
Left Cerebellum	-45	-61	-44	3.09	12
Right Superior Frontal Gyrus	21	59	25	3.33	9
Right Middle Temporal Gyrus	60	-49	7	3.05	9
Brainstem	3	-22	-38	3.41	9
Right Inferior Parietal Lobule	48	-52	55	3.09	8
Right Inferior Frontal Gyrus (p. Opercularis)	48	20	10	3.18	8
Left Superior Temporal Gyrus	-45	-28	7	3.37	5
Results were masked with the left hippocampus and thresholded at p<0.001 (uncorrected), k = 5vox.					

4.4.3 Control ROIs

Since the results of our within-group comparisons suggest an age-related reduction in the functional connectivity with the left hippocampus, we investigated the interhemispheric connectivity between two pairs of control ROIs in the visual and motor cortex under the modulatory influence of the DPA-task (averaged across similar and dissimilar pair retrieval), in order to assess whether older adults show an overall reduced functional connectivity across cortical regions.

Random effects. With respect to the visual cortex, young adults showed a significant positive retrieval-related connectivity between the left BA 18 and the right BA 18, β = 0.64; $t(18)$=16.73, p < 0.001. A significant positive retrieval-related connectivity between these two visual regions was also found in older adults, β = 0.34; $t(18)$=6.47, p < 0.001. Likewise, for the motor cortex, we found a significant positive retrieval-related connectivity between the left BA6 and the right BA6 in young adults, β = 0.51; $t(18)$=13.85, p < 0.001 as well as in older adults, β = 0.44; $t(18)$=10.56, p < 0.001. These findings suggest interhemispheric connectivity in visual and motor regions during successful retrieval, which was found in young and older adults alike.

Mixed effects, visual cortex. Further between-group analyses yielded a significant group difference in the retrieval-related connectivity for the visual cortex, but not for the motor cortex. Specifically, for the visual cortex we found that the contrast Young > Old, DPA, revealed significantly greater connectivity between left and right BA 18, β = 0.30; $t(36)$=4.65, p = 0.0256, suggesting stronger interhemispheric connectivity of visual regions in young relative to older adults during associative retrieval (illustrated in Figure 7). However, no significant group difference in connectivity was found between left and right BA 6, β = 0.07; $t(36)$=1.31, p = 0.197. This result demonstrates that our group of older adults did not reveal generic functional connectivity changes in the brain. Instead, the reduced connectivity identified in our exploratory seed-to-voxel analyses can be more specifically attributed to a memory-related network.

Control Region of Interest

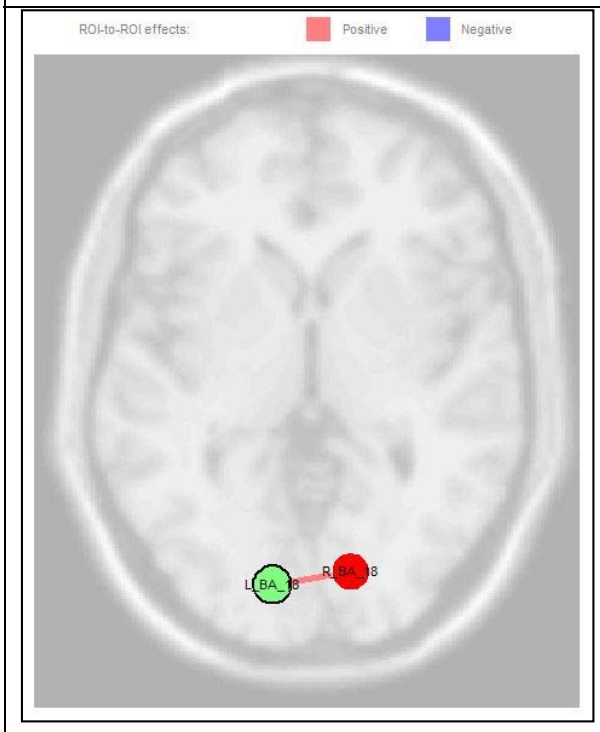


Figure 7. Between-group result for the contrast Young > Old, DPA, showing the significantly greater positive interhemispheric connectivity in young relative to older adults (indicated by the red line) between regions in the left (green) and right (red) Brodmann area 18. L = left; R = right; BA = Brodmann area.

4.5 Discussion

The present study examined the effects of age and memory load on hippocampal activation and connectivity with other cortical regions. Three findings are reported: First, we show age-related reductions in the functional connectivity and specificity of memory-related networks. Second, we confirm age-related deficient resource allocations that were previously found during attention and working memory tasks (Geerligs et al., 2014; Sambataro et al., 2010) and extend the effect to associative retrieval. And third, we report changes in hippocampal activation and connectivity that cannot be explained by memory processes alone, but which were susceptible to our perceptual similarity manipulation of pair-associates as well as to age-related changes in perception and memory. Consistent with previous research (Andrews-Hanna et al., 2007; Geerligs et al., 2012; 2014; Grady et al., 2003; 2010; Kalkstein et al., 2011; Sambataro et al., 2010), we found age-related reductions in hippocampal-neocortical connectivity that manifested with a reduced voxel extent of brain regions connected to the hippocampus. Moreover, older adults exhibited reduced specificity of a memory-related network, showing hippocampal coupling with a larger number of brain regions (more clusters) than young adults. Results of our random effects analyses further demonstrated age-related changes in brain regions that were positively and negatively correlated with hippocampal activity: Young, but not older adults, showed negative hippocampal coupling with regions in the default mode network, including the precuneus and middle cingulate gyrus (Raichle et al., 2001). We attribute this effect to deficient de-activations of the default mode network during memory tasks that has previously been reported in older adults (Miller et al., 2008). By contrast, older, but not young adults, showed positive hippocampal coupling with the right middle temporal gyrus and superior medial PFC, suggesting that the lack of hippocampal anticorrelation in posterior midline regions might have been compensated by hippocampal correlations with frontal and temporal regions (cf. Miller et al., 2008).

Our between-group comparisons revealed age-related changes in the functional specificity of ventral visual regions involved in retrieval (Ranganath et al., 2005; Daselaar et al., 2006) that are consistent with a neural dedifferentiation in older adults' VVS (Park et al., 2004; 2012; Goh, 2011). Our group of young adults showed

enhanced hippocampal coupling with posterior visual and parahippocampal regions in the VVS relative to older adults. This was particularly prominent in the dissimilar condition (contrast Young > Old, dissimilar) in which inferior occipito-temporal areas (lingual, calcarine and fusiform gyrus) emerged as the first two clusters to be coupled with the hippocampus. This finding supports the role of the hippocampus as associative collector of visual information from posterior visual regions (Mayes et al., 2007; Montaldi and Mayes, 2010). In keeping with non-human primate research, dissimilar pair-associates might have been represented by associative neurons in inferior temporal cortex (Sakai and Miyashita, 1991), and were processed forward to the hippocampus (Naya et al., 2003; Hirabayashi et al., 2013) to assist associative retrieval in young adults [see also (Staresina et al., 2013) for human fMRI support]. By contrast, the older adults' hippocampus showed stronger coupling with middle and superior temporal regions. The middle temporal gyrus is a multimodal integration zone located at the interface of auditory and visuo-spatial processing streams (Kaas and Hackett, 2000), and the superior temporal gyrus in the auditory cortex has intrinsic functional connections to the hippocampus via a PHC-network (Kahn et al., 2008). Thus, the increased age-related hippocampal connectivity with these regions suggests that older adults used less optimal retrieval strategies to compensate the reduced functional connections between hippocampus and memory-specific processing regions in ventral visual cortex.

4.5.1 Hippocampal activation and connectivity is related to perceptual analysis of familiar pair-associates.

The results of our ROI-analysis on hippocampal activity showed no significant activation difference between similar and dissimilar pair retrieval in young adults. Likewise, the young adults' behavioural performance was not significantly different between similar and dissimilar pair retrieval (Chapter 2), suggesting that the hippocampus was not involved in the extra retrieval effort imposed by dissimilar pairs. Instead, the young adults' hippocampal activation might have been driven by a bottom-up perceptual analysis of cued pair-associates. This interpretation is supported by the fact that all participants were well trained on the stimuli; hence, if

hippocampal responses to familiar similar and dissimilar pairs are perceptual in nature, they should be comparable in signal change, as was found in young adults. By contrast, older adults showed enhanced hippocampal activity in the dissimilar relative to the similar condition, concomitant with significantly poorer retrieval accuracy of dissimilar pairs. One interpretation of this finding is that older adults invested more effort than young adults in retrieving dissimilar pairs that constituted high memory load. However, older adults are not only impaired in associative memory (Naveh-Benjamin, 2000) but also show deficits in perceptual discrimination (Ryan et al., 2012). The dissimilar pair-associates used in our paradigm may have posed a particular challenge to perceptual discrimination. Specifically, they increased the competition between a set of familiar images to be retrieved, therefore enhancing the effort in discriminating between possible matching pair-associates (Poirier et al., 2012). We interpret the age-related deficit in dissimilar pair-retrieval as a deficit in hippocampal pattern separation, as discussed in the next section.

4.5.2 Pattern separation in the hippocampus and its relationship to visual associative memory.

Hippocampal pattern separation is a computational mechanism to discriminate similar but not identical stimuli, and thus avoid perceptual interference during encoding of new material (Yassa and Stark, 2011; Rolls, 2013). Pattern separation is supported by the granule cells of the dentate gyrus (DG), specifically through their sparse firing input to region III (CA3). The sparse representations of visual stimuli in the DG help dissociate overlapping sensory input in CA3 and thus facilitate pattern separation (Norman and O'Reilly, 2003). CA3 itself has frequently been associated with pattern completion, a process that is thought to occur when CA3 receives direct input from the ERC that bypasses the DG. Within CA3, a large number of cells possess recurrent axon collaterals, whereby axons project back to the dendrites of CA3 pyramidal cells. In other words, CA3 forms a small auto-associative network with recurrent feedback loops, making it capable of pattern completion (Rolls, 2013). Behaviourally, pattern separation and completion are well documented in the rodent literature (Gilbert et al., 1998; Leutgeb et al., 2007), human fMRI (Bakker et al., 2008; Paleja et al., 2014), and have been demonstrated in studies showing age-related

pattern separation deficits (Yassa et al. 2011; Holden et al., 2013; Toner et al., 2009). Typical 'pattern separation tasks' consist of continuous recognition paradigms, in which human participants are asked to judge visually displayed stimuli as 'old' (i.e. previously seen), 'new', or 'similar', but not identical, to a prototypical stimulus. Likewise, in rodent research, spatial environments are often created to be similar, but not identical, to previously experienced layouts (e.g. Leutgeb et al., 2007). In both cases, the 'similar' conditions tax the pattern separation system, requiring fine-grained discrimination between prototypical and similar to prototypical stimuli. The typical observation is that similar stimuli are more difficult to discriminate from their prototypes than dissimilar stimuli, especially when the hippocampal system is lesioned (Gilbert et al., 1998), or in old age (Toner et al., 2009; Yassa et al., 2011; Holden et al., 2013). This effect is found for various classes of stimuli. For instance, pattern separation has often been studied using 'hippocampal stimuli' (spatial environments, scenes) in order to tax place and spatial view cells that are prominent within the hippocampus (Leutgeb et al., 2007; Gilbert et al., 1998; Paleja et al., 2014; Rolls, 2013). However, numerous studies found identical effects when using other types of stimuli, including faces (Edmonds et al., 2012; Yago and Ishai, 2006), objects (Toner et al., 2009; Yassa et al., 2011; Holden et al., 2013) and abstract paintings (Yago and Ishai, 2006). These findings have led some researchers to postulate that the hippocampus is more domain agnostic than other structures engaged in pattern separation/completion, such as the PRC, the amygdala or the piriform cortex (Yassa and Stark, 2011; see also Bird et al., 2008).

In the present study, we found that the concept of pattern separation and completion was reversed from the conventional usage described above: in the context of associative retrieval, dissimilar pairs required pattern separation, while similar pairs afforded pattern completion. For instance, we found that similar pairs were retrieved more accurately than dissimilar pairs, while in conventional pattern separation tasks similar pairs often yielded reduced discrimination accuracy. There are several reasons for this finding: first, unlike similar stimuli in conventional pattern separation tasks, our similar pair-associates did not have to be discriminated from each other, but rather had to be identified as matching pairs. The similar pairs were therefore well-suited for pattern completion rather than requiring separation. Second, our group of older adults was particularly effective in the completion of similar patterns: mean accuracy scores were higher, and hippocampal activation was

comparable to young adults. A plausible explanation for this finding is that age-related pattern separation deficits manifest as improved pattern completion (Yassa et al., 2011). For older adults, this suggests that the improved completion mechanisms, coupled with similar visual stimuli, were particularly beneficial during associative retrieval.

In the dissimilar condition, older adults performed worse than in the similar condition (while young adults showed no difference between conditions). Again, this finding contradicts with the pattern separation literature, where higher levels of dissimilarity facilitated older adults' discrimination (Yassa et al., 2011; Edmonds et al., 2012). However, our visual associative memory task might have engendered the opposite effect. As demonstrated by Poirier et al., (2012), a retrieval cue is less diagnostic of a matching target when pair-associates are dissimilar (thereby hampering pattern completion). Additionally, a familiar set of dissimilar pair-associates increases the competition between images to be retrieved, therefore increasing the effort in discriminating between possible matching targets (and challenging the pattern separation system). Older adults were therefore negatively affected in two ways: their tendency for pattern completion made them more susceptible to misidentifying non-matching pairs as intact. Additionally, their deficit in pattern separation impaired the discrimination between available dissimilar targets.

Together, our data suggest that the dissimilar condition taxed the pattern separation system to avoid interference from non-matching pair-associates. Although this appears counterintuitive to the conventional pattern separation perspective, our findings stem from the context of associative retrieval rather than perceptual discrimination, which likely resulted in different cognitive demands. Retrieving visual stimuli in the mind's eye (i.e. from memory) might be much less sensitive to discriminating the fine-grained patterns that the visual system is able to encode during the perceptual discrimination of two simultaneously presented stimuli. In a cued retrieval paradigm, a visual stimulus is therefore easily recognised as an image that exists twice when it has a similar pair-associate and does not demand further coding of exact visual differences. Instead, pattern separation might occur at a much coarser level, discriminating dissimilar stimuli that come from the same visual category, in order to avoid interference. If viewed in this sense, pattern separation in our paradigm was not too different from its conventional usage, given that the

dissimilar pairs all came from the same stimulus category (achromatic fractal pairs) and therefore shared some basic similarity. Presumably, pattern separation would be more effective if retrieval was required of two entirely unrelated items (e.g. a fractal image paired with an unrelated concrete object; see e.g. Iidaka et al., 2001). To further investigate pattern separation in the context of associative memory, an interesting future experiment could employ a retrieval paradigm in which participants are explicitly instructed to retrieve the fine-grained details of highly similar pair-associates. Not only might such a task elicit BOLD-activation patterns akin to the ones typically found in perceptual discrimination tasks, but could further elucidate pattern separation mechanisms between brain structures (Hippocampus and PRC).

Our suggested role for the hippocampus in perception is incompatible with modular views of memory, which strictly emphasise a role for the hippocampus in declarative memory (Squire & Wixted, 2011; Henson, 2005). However, recent evidence has started to question the view that the hippocampus is selectively involved in declarative (conscious) memory. Two studies found increased hippocampal activity in response to previously studied pair-associates, even in the absence of conscious recollection (Hannula and Ranganath, 2009; Howard et al., 2011). This finding supports a role for the hippocampus that is more consistent with a perceptual-mnemonic view of stimulus representations (Bussey and Saksida, 2007). Moreover, two recent studies reported hippocampal activity in successful associative retrieval, but found no interaction between retrieval success and the type of information to be retrieved (Hannula et al., 2013; King et al., 2015).

This is consistent with a perceptual analysis of cued stimuli, according to which the hippocampus is responsive to learned pair-associates (Hannula and Ranganath, 2009), but is unaffected by the type of pair-associates to be retrieved (as in our case similar and dissimilar pairs). Indeed, recent findings have demonstrated that not hippocampal activity *per se*, but the strength and the dynamics of its connectivity with other neocortical regions determined retrieval accuracy (King et al., 2015; Hannula and Ranganath, 2009). Across 3 associative memory experiments, King et al. (2015) showed that retrieval accuracy was positively correlated with connectivity strength between the hippocampus and areas comprising the 'core recollection network' (left angular gyrus, medial PFC, posterior cingulate cortex, and left middle temporal gyrus). Moreover, across experiments, connectivity strength was associated with different members of the 'core recollection network' as well as other fronto-parietal and visual regions, suggesting task-related modulations on hippocampal-neocortical connectivity. These findings converge with our data. Although hippocampal activation in young adults did not significantly differ between similar and dissimilar pair retrieval, the hippocampus was connected to distinct networks for each condition. Specifically, during retrieval of dissimilar pair-associates, we found functional coupling between the hippocampus, orbitofrontal cortex, inferior parietal lobe and several posterior visual regions, consistent with the 'core recollection network' (King et al., 2015). During retrieval of similar pairs however, the hippocampus was connected with visual and motor regions, as well as to subcortical structures, including the thalamus and the putamen. Our findings suggest stimulus-dependent hippocampal–neocortical connectivity, whereby the hippocampus is involved in the perceptual analysis of familiar pair-associates, and its cortical connections assist with associative retrieval. Notably, the suggested role of the hippocampus in perception does not refute its traditional role in memory. It is entirely plausible that enhanced hippocampal activity in response to high memory load (de Rover et al., 2011; Hales and Brewer, 2010) reflects memory-related processes. However, for highly familiar pair-associates, perceptual processing might suffice and consequently determine neocortical connections to achieve retrieval accuracy, as demonstrated by the present study and by previous findings (Hannula and Ranganath, 2009; King et al., 2015).

Interestingly, retrieval of similar pair-associates, which afforded high associability and constituted low memory load, was subserved by a hippocampal-basal ganglia loop that resembles the procedural memory system envisaged by the modular account of memory (Squire, 1994). Specifically, within this system, the putamen and its cortical connections to motor areas (Alexander & Crutchar, 1990; Marchand et al., 2008) are involved in the planning and execution of motor actions. Given that similar pair-associates posed a high perceptual, but low memory load, it can be assumed that similar pair retrieval was similar to a habitual process that demanded little cognitive effort. Young adults might have relied on perceptual processing (shown by hippocampal connectivity with the cuneus, PHC and lingual gyrus) and repetitive motor planning in awaiting a matching target picture, consistent with a procedural memory process (Squire, 1994). By contrast, older adults showed hippocampal coupling with frontal-parietal regions at similar and dissimilar retrieval. This supports previous findings of a deficient resource allocation with age (Geerligs et al., 2014; Sambataro et al., 2010), showing an early resource ceiling with a frontal-parietal control network (Spreng et al., 2013) that remained invariant at changing memory load. Instead, age-related memory load effects were observed in the hippocampus: older adults compensated the greater interference effects of dissimilar pair-associates with enhanced hippocampal activation. The fact that accuracy was nevertheless significantly poorer in the dissimilar relative to the similar condition might be attributed to the early resource ceiling effect in hippocampal-neocortical coupling.

In conclusion, our results revealed age-related changes in hippocampal activation and connectivity during associative retrieval of familiar pair-associates that varied in perceptual similarity. We found age-related reductions in the functional connectivity and specificity that extend previous findings (e.g. Andrews-Hanna et al., 2007) to memory-related brain regions. The hippocampus was involved in the perceptual analysis of pair-associate images and showed age-related deficits in discriminating familiar dissimilar stimuli. During associative retrieval in young adults, the hippocampus was flexibly coupled with networks supporting low and high memory load of similar and dissimilar pair-associates, respectively.

By contrast, the hippocampal-neocortical network in older adults reached a resource ceiling at low memory load, consistent with the age-related deficient resource allocation hypothesis (Geerligs et al., 2014; Sambataro et al., 2010). Our findings show functional connectivity of the hippocampus with specific networks that a) compensated for the behavioural performance of older adults during low memory load, and b) modulated appropriately in young adults in changing memory load conditions.

Chapter 5: Neural correlates of visual working memory in grapheme-colour synaesthetes, young and older adults

5.1 Abstract

The sensory recruitment model envisages visual working memory (WM) as an emergent property that is encoded and maintained in sensory (visual) regions and facilitated by top-down control from prefrontal cortex [PFC; (Serences et al., 2009)]. The model implies that enhanced sensory-perceptual functions (as in synaesthesia) would entail an efficient WM-network, showing reduced activity in visual and PFC, while a sensory-perceptual decline (as in old age) would show the opposite effect. We tested this model using a novel between-group design (young grapheme-colour synaesthetes, older adults and young controls), and achromatic fractal stimuli that do not induce synaesthesia. We investigated how the disparate sensory-perceptual abilities between these groups would i) modulate activity in visual and frontal regions during visual WM, and ii) govern the use of visual imagery as a WM-strategy. Synaesthetes showed no behavioural advantage (accuracy, response times) relative to young and older adults in a standard (delayed matching-to-sample) and memory-related WM-task (delayed pair-associative retrieval). However, whole-brain and region-of-interest-analyses yielded significantly lower activity in synaesthetes' middle frontal gyrus and visual regions (cuneus, inferior temporal cortex) respectively, suggesting greater neural efficiency relative to young and older adults in both tasks. Subjective visual imagery correlated with visual regions during WM-maintenance and with retrieval accuracy in synaesthetes, but not in young and older adults. Our results advance the sensory recruitment model, suggesting that enhanced sensory-perceptual functions (as in synaesthesia) facilitated a number of cognitive mechanisms, including WM, visual imagery and associative retrieval.

5.2 Introduction

Visual working memory (WM) refers to the transient mental rehearsal of visual stimuli that have been perceptually cued or retrieved from long-term memory, but are no longer present in the environment. Visual WM is supported by a distributed network, involving lateral regions of the prefrontal cortex (PFC), as well as parietal and occipital-temporal areas (Curtis and D'Esposito, 2003; D'Esposito, 2007; Postle, 2006; Ranganath, 2006). However, the precise role of these brain regions has only been researched more recently. For instance, a WM model dubbed the 'sensory recruitment model' (Serences et al., 2009) envisages WM as an emergent property of functional interactions between sensory areas as early as V1 and higher-level control sites such as the PFC. Within this model, the PFC – rather than acting as a specialised storage site of information content [e.g. (Baddeley and Hitch, 1974; Goldman-Rakic, 1990)] – is thought to exert top-down control over posterior sensory regions, selectively facilitating attention to relevant stimuli and inhibition of distractors, and thus enabling sustained online WM representations (Postle, 2006). Key support for the model comes from recent research using multi voxel pattern analysis that could discern the representational content in relevant frontal and occipito-temporal regions. Two studies (Christophel et al., 2012; Riggall and Postle, 2012) showed that although there was a sustained BOLD-response in frontal regions throughout the delay-period of a visual WM task, decoding accuracy of the stimulus content was at chance-level. By contrast, no sustained BOLD-response could be detected within lateral occipito-temporal (Riggall and Postle, 2012) and early visual regions (Christophel et al., 2012), but decoding performance of the sub-threshold activity in these regions was significantly above chance-level. These and other studies (Albers et al., 2013; Han et al., 2013; Ranganath et al., 2004) suggest that content-specific information of visual WM is represented in occipito-temporal cortex, while the PFC appears to be involved in top-down signalling without coding for specific content. There are two corollaries of these findings: first, impaired or under-developed PFC-signalling should lead to significant interruptions of WM and second, enhanced neural sensitivity in occipito-temporal cortex should be advantageous to visual WM and/or exhibit greater neural efficiency across the brain during WM performance.

Support for the first idea comes from developmental cognitive neuroscience, showing that children (aged 10–15), whose PFC is still not fully developed (Casey et al., 2005), failed to activate a fronto-parietal network during a visual WM task, which consequently resulted in significant performance detriments compared to young adults (Crone et al., 2006). At the other end of the developmental lifespan, similar detriments are found in older adults performing WM tasks (Dobbs and Rule, 1989; Hasher and Zacks, 1988; Myerson et al., 2003). Specifically, and in line with the sensory recruitment model, age-related WM-deficits resulted from diminished top-down control from PFC to posterior inferior temporal regions (Gazzaley et al., 2008; Gazzaley et al., 2005; Kalkstein et al., 2011). Diminished top-down control can impair the neural specificity in ventral visual areas whilst coding for selective features (Kalkstein et al., 2011), and might contribute to poorer recognition at the point of target presentation (Gazzaley et al., 2005; 2008). Taken together, developmental studies support the role of the PFC in top-down signalling during WM, as proposed by the sensory recruitment model (Serences et al., 2009).

Given that WM performance has classically been associated with the PFC (Curtis and D'Esposito, 2003; Goldman-Rakic, 1990), evidence for the second hypothesis, that enhanced neural sensitivity in occipito-temporal cortex is advantageous to visual WM, is much more limited. Two studies have shown that the application of TMS over early visual cortex (V1 and V2) facilitated performance accuracy (Soto et al., 2012) and reduced response times [RT; (Cattaneo et al., 2009)] during visual WM tasks. These findings suggest that increased cortical excitability of visual regions, as induced via TMS-stimulation, can boost visual WM. Here, we further tested this hypothesis by examining young grapheme-colour synaesthetes who show enhanced cortical excitability (Terhune et al., 2011) as well as enhanced sensitivity in early visual regions (Barnett et al., 2008), concomitant with superior performance on a range of cognitive abilities including WM (Rothen et al., 2012; Terhune et al., 2013). Grapheme-colour synaesthesia (in the following referred to as synaesthesia) is a stable perceptual phenomenon, found in about 1% of the population (Simner et al., 2006), whereby black letters, words, or digits (graphemes) are experienced as inherently coloured (e.g. the letter S may be perceived as green). Synaesthesia has a neurological basis, showing increased white matter connectivity in inferior temporal gyrus and superior parietal lobe (Rouw and Scholte, 2007), as well as increased grey-matter volume along the calcarine, lingual- and inferior

temporal gyrus relative to controls (Banissy et al., 2012; Jancke et al., 2009; Rouw et al., 2011; Weiss and Fink, 2009). These anatomical differences are paralleled by functional differences in the same posterior brain regions and provide evidence of enhanced neural sensitivity in synaesthetes. For instance, some studies were able to show activation in colour area V4 whilst synaesthetes processed black letters [(Brang et al., 2010; Hubbard et al., 2005; van Leeuwen et al., 2011); but see (Hupe et al., 2011)]. When testing higher-level cognitive functions such as WM (Terhune et al., 2013) or episodic memory (Pritchard et al., 2013; Rothen and Meier, 2010; Rothen et al., 2012; Yaro and Ward, 2007), synaesthetes show a performance advantage over controls for colour stimuli, suggesting enhanced neural sensitivity in colour areas *per se*. Indeed, the synaesthetes' frequent sensory experiences with colours following the secondary responses to words may sensitise colour areas in the brain and lead to enhanced colour processing (Banissy et al., 2009). However, the synaesthetes' enhanced neural sensitivity goes beyond colour processing and is even found for stimuli that neither evoke a synaesthetic response, nor contain a perceptual colour. For example, perceptual processing of pseudo-letters yielded activity in the left inferior parietal lobe (IPL) that was not seen in controls (Sinke et al., 2012). Likewise, abstract patterns of high spatial frequency and varying luminance contrast yielded enhanced early visually evoked potentials that were attributed to processing differences in primary visual cortex (Barnett et al., 2008). Although behavioural evidence for the enhanced processing account for non-synaesthesia inducing stimuli is mixed, a number of studies have shown an advantage of synaesthetes relative to controls in drawing abstract stimuli from memory [(Gross et al., 2011; Rothen and Meier, 2010); but see (Yaro and Ward, 2007)], and in recognising achromatic fractal images (Pfeifer et al., 2014; Ward et al., 2013). Several behavioural studies have incorporated WM-tests as part of studying cognitive abilities in synaesthetes, again revealing mixed results. For instance, Rothen and Meier (2009) tested synaesthetes and controls on memory for matrices of incongruently coloured and black digits. Synaesthetes showed no evidence of a retrieval advantage immediately after learning (as a proxy for short-term memory[1]), suggesting that short-term memory was

[1] Although short-term memory and WM are related, they differ from each other in that the former refers to the retention, and the later refers to retention plus manipulation of information over a short delay [Aben, B., Stapert, S., Blokland, A., 2012. About the distinction between working memory and short-term memory. Frontiers in Psychology 3:301. doi 10.3389/Fpsyg.2012.00301].

not better than in controls, even when stimuli elicited a synaesthetic colour. However, in a later study, Rothen and Meier (2010) found a significant performance advantage of synaesthetes relative to a normative reference sample on WM and short-term memory tests, including visual memory span backwards (tapping out increasingly longer sequences on a board following an experimenter's illustration), immediate recall of logical memories (story recall), immediate recall of visual and verbal pair-associates, and immediate reproduction of abstract figures. Finally, a study by (Gross et al., 2011) employed WM and short-term memory tests similar to the ones utilised by (Rothen and Meier, 2010). In this study however, the synaesthetes only showed a performance advantage over controls in the visual reproduction of abstract figures (at initial copying and immediate recall) and on recall of verbal pair-associates in the first trial of a learning task, but not on the digit and spatial span tests. The inconsistent findings in the above studies demonstrate that the enhanced visual processing mechanisms found in synaesthetes (Barnett et al., 2008) may have a subtle effect on higher level cognitive functions, especially when these are probed with non-synaesthesia inducing stimuli. For example, our own behavioural findings (Pfeifer et al., 2014) showed a significant retrieval advantage for achromatic abstract fractal pair-associates in synaesthetes that could only be detected in comparison to older adults. In this study, three groups of 14 young synaesthetes, 14 young and 14 older adults were trained to performance criterion on eight pair-associates that were manipulated in visual similarity. The results showed that retrieval of similar pair-associates (low memory load) was significantly better in synaesthetes and young adults relative to older adults. However, retrieval of dissimilar pair-associates (high memory load) only showed significantly better performance of synaesthetes relative to older adults, and was not found for the comparison of young and older adults. In other words, only by including a third group of older adults did the synaesthetes' subtle associative memory advantages for abstract stimuli emerge. In the present study, we used the same between-group design and functional Magnetic Resonance Imaging (fMRI) to compare young synaesthetes, young and older adults on two WM-tasks. The two tasks consisted of a delayed pair-associative (DPA) retrieval task and a delayed matching-to-sample (DMS) task. While the DPA-task required the maintenance of retrieved pair-associates from memory (high WM-load) over a delay-period, the DMS-task constituted a pure WM condition, simply requiring participants to hold a cued image in mind (low WM-load). The stimuli consisted of achromatic abstract fractal images, allowing us to test the enhanced processing hypothesis in

synaesthetes for non-synaesthesia inducing stimuli [e.g. (Barnett et al., 2008; Rothen et al., 2012; Terhune et al., 2011; Yaro and Ward, 2007) and its relationship to visual WM. Insofar as synaesthetes show enhanced neural sensitivity in feature-selective and non-selective regions in occipito-temporal cortex (Barnett et al., 2008; Brang et al., 2010; Hubbard et al., 2005), we predicted to find activation differences in these regions relative to young and older adults during visual WM maintenance. Specifically, older adults might show greater activity than synaesthetes in inferior temporal regions as a result of age-related neural broadening (Park et al., 2012). Neural broadening opposes the neural specificity found in synaesthetes (Brang et al., 2010; Hubbard et al., 2005; van Leeuwen et al., 2011) in that feature-selective neurons lose their selectivity (e.g. the fusiform face area in response to faces) and code for a variety of other visual stimuli. Consequently, age-related neural broadening in inferior temporal cortex would yield increased BOLD-responses in fMRI relative to synaesthetes (and perhaps young adults). Second, if group differences were to be found in *early* visual regions, we might expect reduced activity in synaesthetes, who were found to show greater excitability (Terhune et al., 2011) and enhanced sensitivity (Barnett et al., 2008) in primary visual cortex relative to controls. Specifically, our previous findings (Chapter 3) showed reduced activity in synaesthetes' early visual cortex relative to young and older adults during associative retrieval, when thought processes were internally directed. Reduced activity in synaesthetes was therefore also predicted during the maintenance of visual images. A third possibility was that our whole-brain analyses might not detect a group difference in occipito-temporal regions, given that the content-specificity of maintained stimuli in posterior visual areas is often not accompanied by a sustained BOLD-response (Christophel et al., 2012; Riggall and Postle, 2012). Specific predictions were formulated regarding group differences in PFC: based on the sensory recruitment model (Serences et al., 2009), enhanced neural sensitivity in posterior visual regions (as in synaesthesia) should facilitate stimulus-representations during visual WM and render overall greater neural efficiency during WM performance. Hence, we expected the synaesthetes to require less top-down activity from PFC compared to the other two groups. By contrast, older adults, who showed diminished top-down control during WM-tasks (Gazzaley et al., 2008; Gazzaley et al., 2005; Kalkstein et al., 2011), were expected to show enhanced activity in PFC. Finally, the group differences were expected to be modulated by task difficulty.

A second aim of the present study was to investigate how brain activity during performance of the two visual WM-tasks was related to subjective visual imagery [measured using the Vividness of Visual Imagery Questionnaire; [VVIQ; (Marks, 1973)]. The rationale was that the delay period of our DPA and DMS-task required participants to hold images in mind, which can be taken as a proxy for visual imagery. Previous research has shown that the type of strategy used to maintain visual stimuli determines the neural pathway of the cognitive task at hand [(Hales and Brewer, 2012; Rothmayr et al., 2007)]. For instance, Rothmayr et al. (2007) asked participants to maintain Gabor patterns in WM that were tilted in different angles to the left or right. In condition A, they were instructed to use a verbal strategy to maintain the cue, whilst in condition B they were instructed to use a visual strategy. The visual strategy showed greater activity in superior frontal and right inferior/middle frontal regions, while the verbal strategy showed greater activity in Wernicke's area, encompassing superior temporal regions. Given the impact of strategy-use on the neural pathways of WM, we investigated whether our three groups differed in the subjective vividness of visual imagery, a criterion that might in turn influence the use of imagery as a strategy during WM maintenance. This was principally motivated by the fact that synaesthetes have previously reported better visual imagery than controls in self-report measures such as the VVIQ (Barnett and Newell, 2008; Meier and Rothen, 2013; Simner, 2013; Spiller et al., 2015). Moreover, synaesthetes appear to show a preference for using visual over semantic strategies: (Radvansky et al., 2011) found that during a verbal memory test, synaesthetes relied more on surface features of words (true or synaesthesia-induced colours) than on semantic features (accessing the meaning of words). Specifically, they did not show enhanced memory for single, isolated words that were semantically unrelated to colour (e.g. the word 'hour' among a list of words such as 'emerald', 'ruby'), a manipulation that typically boosts memory in the neurotypical population. Thus, synaesthetes appear to rely more on visual-perceptual processing of stimuli rather than semantic, memory-related strategies. In light of these findings, we expected the synaesthetes to use a visual strategy for holding images in mind, while young and older adults might rely more on a memory-related, semantic strategy. We predicted that synaesthetes would show a correlation between subjective imagery ratings (VVIQ-scores) and posterior visual brain regions during the DPA and DMS-task. By contrast, the young and older adults' imagery ratings were expected to correlate with visual and memory-related brain regions that are typically recruited in visual imagery and visual working memory

tasks, including the hippocampus (Ranganath et al., 2004), parietal cortex (Huijbers et al., 2011), precuneus (Cavanna and Trimble, 2006; Fletcher et al., 1995) and PFC (Amedi et al., 2005; Daselaar et al., 2010; Kalkstein et al., 2011).

5.3 Materials and Methods

5.3.1 Participants

The same participants as in Chapters 3 and 4 were tested in this study. Details can be found in Chapter 3, section 3.3.1 Participants.

5.3.2 Experimental design and Stimuli

The experimental design and stimuli were the same as described in Chapter 3, consisting of a delayed pair-associative (DPA) retrieval task and a delayed matching-to-sample (DMS) task. Details can be found in section 3.3.2 Experimental design and stimuli.

Vividness of Visual Imagery Questionnaire (VVIQ). After scanning, the VVIQ (Marks, 1973) was administered to examine participants' subjective vividness of visual imagery, and investigate how it related to the delay period activity of the DPA and DMS-task. The VVIQ is a 16-item questionnaire, which asks respondents to create mental images of verbally described scenes (e.g. 'visualise the sun rising above the horizon into a hazy sky') and rate the vividness of imagery they experience on a 5-point Likert scale (Likert, 1932). We reversed the scores of the original version of the VVIQ, so that a rating of 1 indicated "no image at all, you only 'know' that you are thinking of an object", and a rating of 5 designated "perfectly clear and as vivid as normal vision". Previous test-retest reliability measures of the VVIQ yielded a high correlation co-efficient of r = 0.74, and a split-half reliability coefficient of r = 0.85 (Marks, 1973). Moreover, an fMRI-study by Cui et al. (2007) demonstrated that subjective visual imagery, measured using the VVIQ, highly correlated with activation in the primary visual cortex when participants engaged in a visual imagery task (i.e. participants were asked to "visualize themselves or another person either bench pressing or stair climbing"; p. 475). Thus, there is evidence to suggest that participants' subjective visual imagery ratings can be measured objectively using fMRI.

5.3.3 Procedure

Prior to scanning, participants were trained on the fractal pair-associates of the DPA-task using a computer-based trial-and-error learning task. The learning task has been described in detail in a previous study (Chapter 3) and will be summarised here shortly. The task began with the sequential presentation of eight pair-associates at the centre of a computer screen for 4s, and participants were explicitly instructed

to remember the correct association of the pairs for a subsequent memory test. The presentation was followed by a four alternative forced-choice task, in which participants had to choose one of four possible target pictures from the bottom of the screen to match the cue picture at the top of the screen. Each response was followed by visual feedback, indicating whether or not the matching target had been identified correctly (green tick or red cross respectively). Participants performed the task until they reached an 87.5% learning criterion.

DPA and DMS-task. Following the associative learning task, participants were familiarised with the DPA and DMS-task prior to scanning. During scanning, an identical trial structure was used across the DPA and DMS-task (Figure 1). During the cue-period (1s) of the DPA-task, participants were asked to use the cue to retrieve the matching target (*associative retrieval*). During the cue-period (1s) of the DMS-task, participants were asked to build up a mental image of the cue. During the delay period (8s), participants were required to either hold the retrieved picture in mind (DPA-task), or to hold the cue image in mind (DMS-task). The target presentation (1s) in the DPA-task comprised the *associative recognition* stage, where participants were asked to recognise the target as the matching or non-matching pair-associate. During the target presentation (1s) of the DMS-task, they were to judge whether the target was the identical image to the cue. Following target presentation in both tasks, a response window appeared and stayed on screen for 5 seconds, during which participants were asked to press 1 of 4 buttons, providing combined decisions about the target (match/non-match) and self-rated confidence (confident/not sure). The button-presses were followed by a variable intertrial interval (ITI) of 6 – 12 s before the next trial.

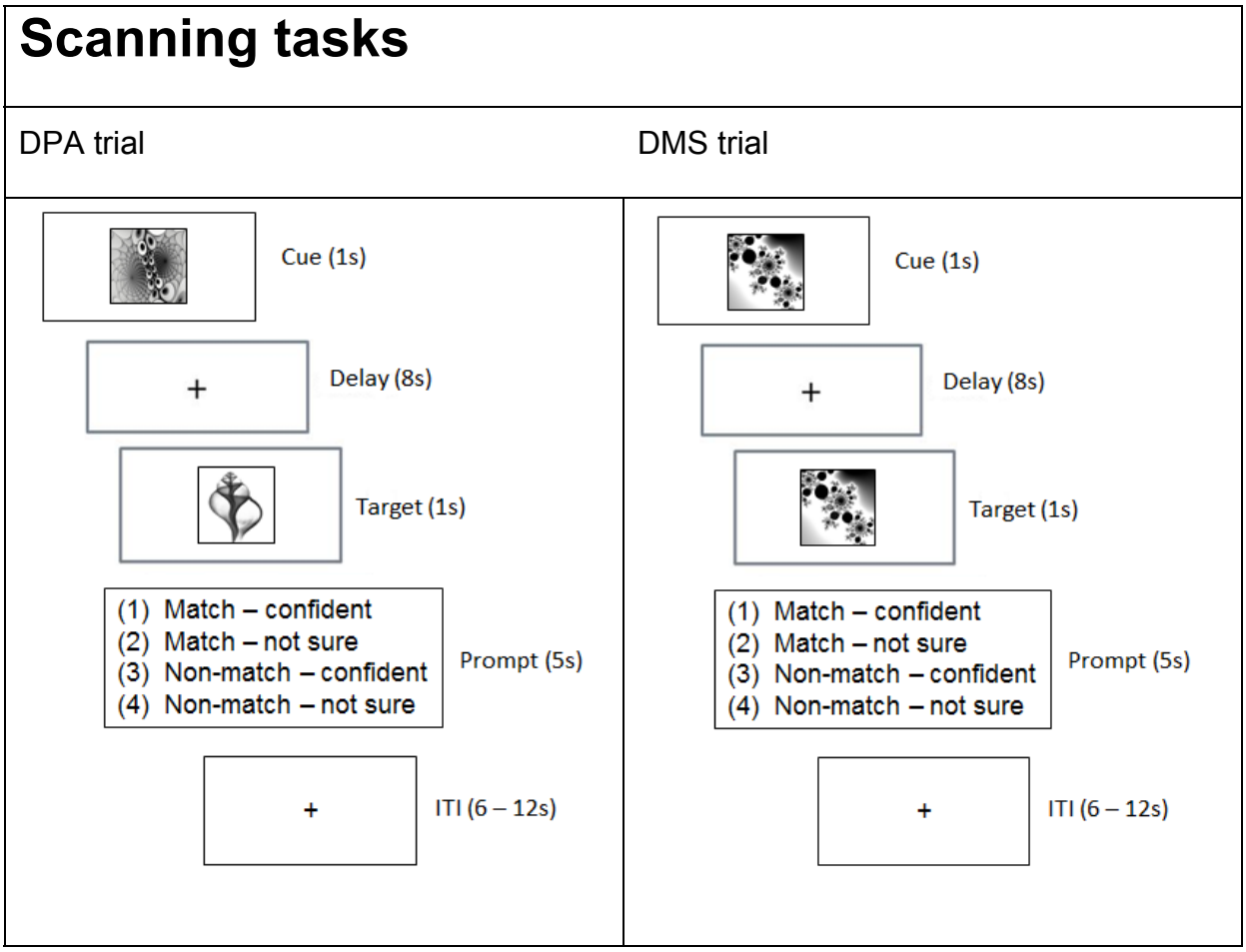


Figure 1. Experimental design. The scanning tasks involved two types of trials, DPA and DMS. DPA trials required participants to retrieve a cue's matching pair-associate and hold it in mind over an 8 second delay. DMS trials required participants to hold the cue in mind over an 8 second delay. Upon target presentation, participants were asked to decide whether the target was a match or non-match (in DPA and DMS trials) and give their responses within a 5 second time window (Prompt). ITI = Interstimulus interval; s = second.

5.3.4 fMRI data acquisition

Details of the fMRI data acquisition are described in Chapter 3, section 3.3.4.

5.3.5 fMRI analyses

We used SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; www.fil.ion.ucl.ac.uk\spm) running under MATLAB R2013a for data preprocessing and statistical analyses. Preprocessing of functional images was carried out for each task separately, including slice-time correction to the middle slice, spatial realignment to the first image, and unwarping using the acquired field maps. The T1-weighted structural image was co-registered to the mean functional image and subsequently segmented to obtain normalisation parameters based on the standard MNI template. The segmentation parameters were used to transform each subject's functional images and the bias-corrected structural image into MNI space. Voxel sizes of the functional and structural images were retained during normalisation, and the normalised functional images were spatially smoothed using an 8mm Gaussian kernel (full-width-half-maximum). Statistical analyses were performed using the General Linear Model. For the single subject analysis, the DPA and DMS-task were entered as separate sessions into the model. Across tasks, we specified regressors associated with the cue, delay, target and baseline (ITI) period. All regressors of interest contained only accurate and confident responses. Modelling of regressors was identical across the DPA and DMS-task, given the identical trial structure: For each regressor representing a cue and target-period, activation was modelled using a boxcar function, starting at onset and lasting for 1 second. Regressors representing a delay-period were modelled to start 3 seconds after delay-onset and lasted for 5 seconds until the end of the delay-period. This was done to avoid capturing any residual activity pertaining to the cue-period, but instead explaining a largely unique source of variance pertaining to delay-period activity (Rissman et al., 2004). Baseline regressors were modelled to start 1s after prompt-offset and lasted for 5 seconds. The baseline duration was chosen to match the duration of the delay-period to serve as a contrast for delay-period activity. Regressors of no interest included the prompt (containing participant's button presses), a nuisance regressor (containing all misses,

false alarms, non-confident responses, non-responses) and six regressors representing motion-related variance. All regressors were convolved with a canonical hemodynamic response function available in SPM8 (Friston et al., 1998). A high-pass filter was applied with a period of 128 seconds to remove low-frequency signals relating to scanner drift and/or physiological noise. Two t-contrasts were computed, in which we compared the two types of WM against Baseline using the contrasts DPA Delay > DPA Baseline (DPAd > DPAb) and DMS Delay > DMS Baseline (DMSd > DMSb). DPA-related contrast images only included trials of the high memory load condition (i.e. dissimilar pair-associates) for the strongest comparison of WM for retrieved pair-associates versus WM for cued singletons.

Grey matter volume. Given that we compared a group of 19 older adults against 38 younger adults (19 synaesthetes and 19 controls) and had an unequal gender distribution across our 57 participants (male: N = 23; female: N = 34), we calculated each participants' total grey matter (GM) volume in millilitre (ml). This value was subsequently entered as a covariate in all second-level fMRI analyses to implicitly account for age- (Lemaitre et al., 2005; Raz et al., 2005) and gender-related (Luders et al., 2002) GM volume differences. Total GM volume was calculated from the subject-specific GM masks in native space, which were obtained following the segmentation of participants' high resolution structural T1 images.

Second-level analyses. To analyse brain activity associated with WM maintenance of retrieved pair-associates (DPA-task) and WM maintenance of cued singletons (DMS-task), the results of the single-subject analyses were taken to group-level. Using a 3 (group) x 2 (task) factorial ANOVA, we examined task effects using the contrast images DPAd>DPAb and DMSd>DMSb. To this end, a conjunction analysis was computed to investigate task-independent regions that are commonly activated during DPA and DMS-related WM. An F-test was computed to examine the main effects between the two tasks. Unless otherwise specified, all results were thresholded at $p < 0.05$ (FWE) and a voxel extent of k = 5 voxels. Exclusive masks were created for the average activity across DPA and DMS, as well as for the DPA and DMS-task separately, using a t-contrast across groups and a lenient threshold of $p < 0.01$ (uncorrected). Group effects were then computed using an F-contrast and were inclusively masked with the respective task effects. A suprathreshold of $p < 0.001$ (uncorrected), k= 5 voxels was applied to all group

effects. Thus, the masking ensured that *a)* group differences showed significant activations above zero within task-related regions and *b)* activity was reported at a more stringent threshold, as voxels had to survive the thresholds of the task effect as well as the group effect (Daselaar et al., 2010).

ROI-analyses. ROI analyses were carried out for DPA and DMS-related WM to examine group differences in two visual regions, the cuneus and inferior temporal cortex, which were previously found to be involved in WM and visual imagery (Albers et al., 2013; Han et al., 2013; Soto et al., 2012). Anatomical masks of the left and right cuneus and left and right inferior temporal cortex were selected from the WFU PickAtlas v2.4 [(http://www.nitrc.org/projects/wfu_pickatlas/; (Maldjian et al., 2003)]. Using the 3 (group) x 2 (task) factorial ANOVA described above, we calculated the main effect of group using an F-contrast, whilst inclusively masking the effect with the cuneus and inferior temporal cortex, respectively. Results of the ROI-analyses are reported at a threshold of $p < 0.001$ (uncorrected), $k = 5$ voxels. Using the rfx-plot toolbox (Gläscher, 2009) available in SPM8, we then extracted contrast estimates for each group and task to conduct subsequent post hoc analyses using SPSS.

Whole brain regression analyses with VVIQ-scores. To quantify the relationship between subjective imagery and WM-related brain activity, six simple regression analyses (3 groups x 2 tasks) were performed in SPM8: for each group, the respective contrast images DPAd>DPAb and DMSd>DMSb were entered as the criterion variable and participants' mean VVIQ-scores were entered as the predictor variable. Two t-contrasts were specified for each model in order to examine brain areas that show a) positive and b) negative correlations of VVIQ-scores with WM-related activity. The resulting images were thresholded at $p < 0.001$ (uncorrected) and a voxel extent of $k = 5$ voxels.

5.4 Results

5.4.1 Behavioural results

DPA and DMS, scanning performance. Figure 2 illustrates participants' task performance during scanning, showing the percent accuracy (averaged across Hits and Correct rejections) for each group in response to DPA-trials (dissimilar pair-associates) and DMS-trials. The mean accuracy-rate in the DPA-task was highest for young adults (M = 92.70 %; SE = 2.16 %), followed by synaesthetes (M = 84.55 %; SE = 4.39 %) and older adults (M = 73.85 %; SE = 5.26 %). In the DMS-task, the mean accuracy-rate was M = 96.21 % (SE = 1.21 %) for young adults, M = 96.49 % (SE = 1.37 %) for synaesthetes, and M = 96.38 % (SE = 1.25 %) for older adults. Accuracy scores of DPA and DMS-trials were entered as dependent variables into a 3x2 between-subjects ANOVA, with group (young adults, older adults, synaesthetes) and task (DPA, DMS) as factors. There was a significant main effect of group, $F[2,108] = 4.696$, $p = .011$, $\eta_p^2 = 0.080$. Tukey post hoc tests revealed that young adults differed significantly from older adults ($p = 0.008$), while no significant difference was found between synaesthetes and older adults ($p = 0.167$), or between young adults and synaesthetes ($p = 0.443$). A highly significant main effect of task ($F[1,108] = 26.074$, $p < .001$, $\eta_p^2 = 0.194$) suggested that the DPA-task was more demanding than the DMS-task. However, there was also a significant interaction between group and task, $F[2,108] = 4.809$, $p = .010$, $\eta_p^2 = 0.082$. Figure 2 illustrates the interaction, showing that young adults performed at a comparable level across the two tasks, while older adults and synaesthetes showed better performance at the DMS than at the DPA task.

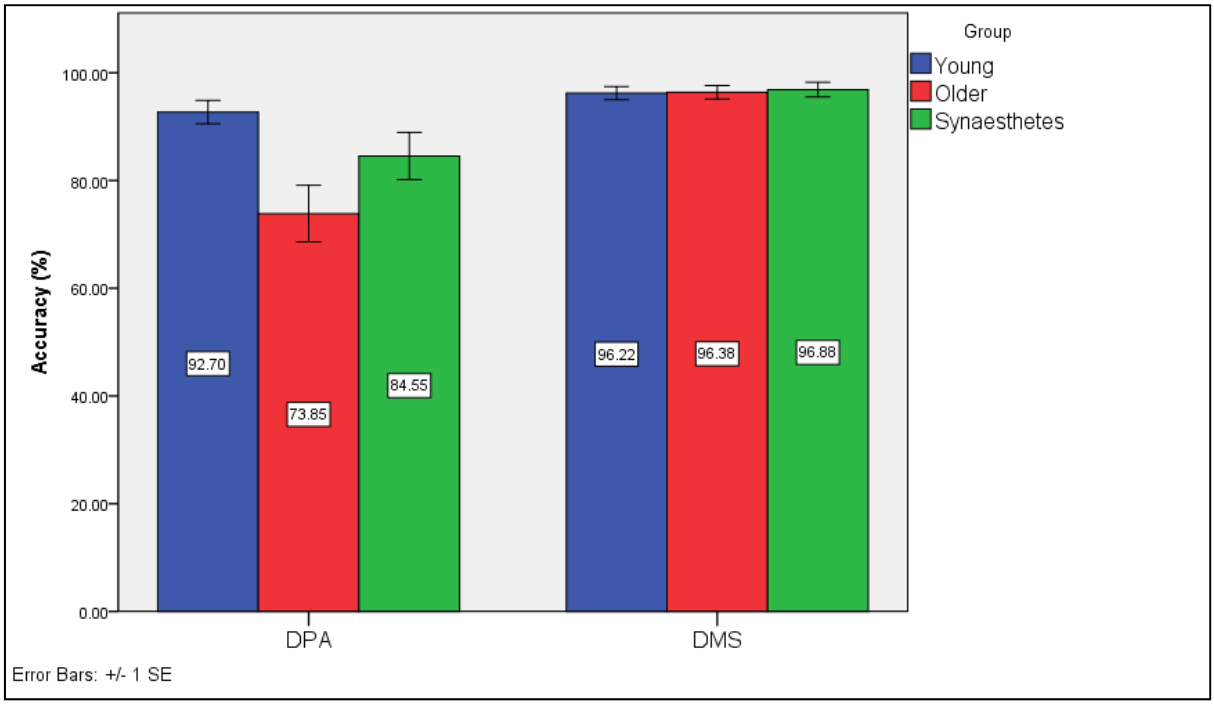


Figure 2. Mean Accuracy-rate of retrieved pair-associates and maintained cue-images during the DPA and DMS-task, respectively. Error bars indicate the standard error of the mean.

Response times (RT) were analysed for all accurate trials (Hits and Correct rejections) and were entered as dependent variables into a 3x2 between-subjects ANOVA, with group (young adults, older adults, synaesthetes) and task (DPA, DMS) as factors. As can be seen in Figure 3, the mean RT in the DPA-task was M = 751.73 ms (SE = 64.27 ms) for synaesthetes, M = 756.31 ms (SE = 50.37 ms) for young adults, and M = 1018.62 ms (SE = 69.47 ms) for older adults. In the DMS-task, the mean RT was M = 489.82 ms (SE = 34.23 ms) for young adults, M = 499.29 ms (SE = 34.71 ms) for synaesthetes, and M = 668.63 ms (SE = 41.61 ms) for older adults. Overall, RTs were lower in the DMS than in the DPA-task. The ANOVA yielded a significant main effect of group, $F[2,108] = 11.884$, $p < .001$, $\eta_p^2 = 0.180$. Tukey post hoc tests revealed that young adults and synaesthetes differed significantly from older adults (both $p < 0.001$), while no significant difference was found between young adults and synaesthetes ($p = 0.999$). There was also a significant main effect of task ($F[1,108] = 46.621$, $p < .001$, $\eta_p^2 = 0.302$), but no group by task interaction, $F[2,108] = 0.515$, $p = .599$, $\eta_p^2 = 0.009$.

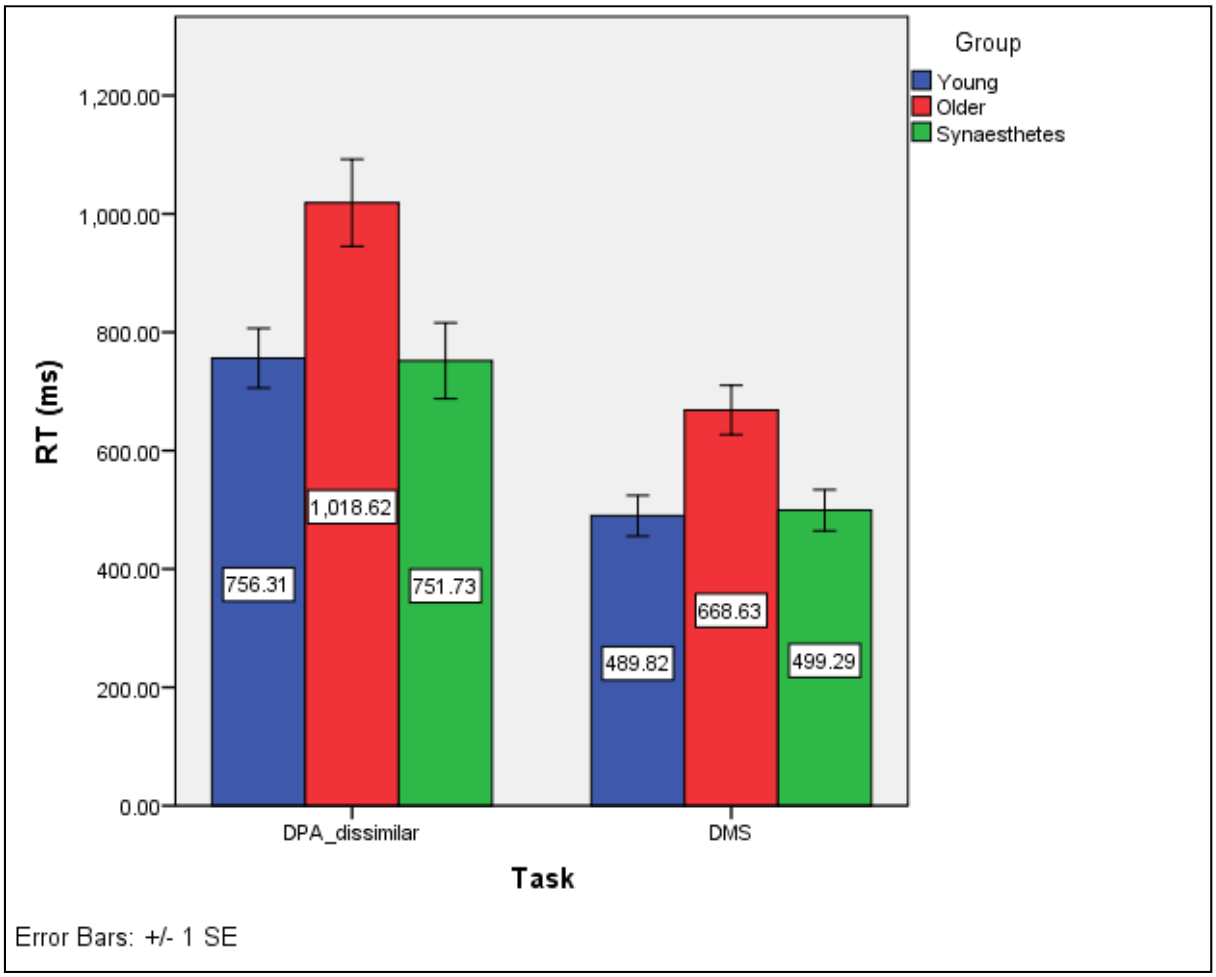


Figure 3. Mean Response times (RT) of retrieved pair-associates and maintained cue-images during the DPA and DMS-task, respectively. All RTs represent accurate responses (Hits and Correct rejections). Error bars indicate the standard error of the mean.

VVIQ Results. Our prediction that synaesthetes would show higher subjective visual imagery than the other two groups was not supported: older adults (M = 4.05; SE = 0.138) provided higher mean-ratings on the VVIQ, and thus higher vividness of imagery, than synaesthetes (M = 3.83; SE = 0.112). Young adults (M = 3.75; SE = 0.127) reported lowest visual imagery. A one-way ANOVA with group (young adults, older adults, synaesthetes) as the between subject factor revealed no significant group difference on the VVIQ-scores, $F[2,54] = 1.518$, $p = .228$.

Based on previous research showing that the vividness of visual imagery supports memory retrieval (D'Angiulli et al., 2013) and is related to better WM (Baddeley and Andrade, 2000), we investigated whether any of our groups would show a relationship between subjective imagery and accuracy and/or between

subjective imagery and RT on the DPA and DMS-task. To this end, we correlated the VVIQ-scores of each group (young adults, older adults, synaesthetes) with the accuracy-scores of the DPA and the DMS-task, respectively. For the DPA-task, there was no relationship between VVIQ-scores and retrieval accuracy in young [r = 0.197; p = 0.210 (1-tailed)] and older adults [r = 0.158; p = 0.259 (1-tailed)]. However, for synaesthetes we found a medium and marginally significant positive correlation between VVIQ-scores and retrieval accuracy, r = 0.387; p = 0.051 (1-tailed), suggesting that synaesthetes with better memory retrieval benefitted from vivid visual imagery. In the DMS-task, none of the groups showed a significant relationship between VVIQ-scores and WM-performance [young: r = 0.349; p = 0.072 (1-tailed); old: r = -0.195; p = 0.212 (1-tailed); synaesthetes: r = 0.222; p = 0.181]. Next, we correlated the VVIQ-scores of each group with the average RTs of the DPA and the DMS-task, respectively. We found no significant relationship between VVIQ-scores and RT for either group or task (all p > 0.05, one-tailed).

5.4.2 fMRI results

Task effects. The results of our conjunction analysis revealed substantial overlap of brain regions for DPA and DMS-related WM. Consistent with previous research, these areas encompassed lateral regions of the PFC, including bilateral precentral gyrus (BA6), bilateral inferior frontal (BA44/45) and left middle frontal regions (BA46/9), supplementary motor area, inferior parietal cortex and the caudate nucleus (Curtis et al., 2004; Ranganath et al., 2004; Vilberg and Rugg, 2012). We also predicted to find activation differences between our two WM-tasks, based on research showing differential neural activity for different types of information maintained in WM (Curtis et al., 2004; D'Esposito, 2007; Ranganath et al., 2004). In line with this prediction, our 3 (group) x 2 (task) mixed ANOVA yielded a main effect of task (F-contrast) in the medial and lateral prefrontal cortex (PFC), the temporal-parietal junction, cingulate and parietal cortex (see Table 1). Post hoc tests revealed that this activity was driven by DMS-related WM (t-contrast: DMSd>DMSb **>** DPAd>DPAb), while the opposite t-contrast for DPA-related WM (DPAd>DPAb **>** DMSd>DMSb) yielded no effect. Our results replicate previous findings (Curtis et al., 2004; Ranganath et al., 2004) and extend these to abstract achromatic stimuli: The

pure working memory condition of the DMS-task showed activity over and above DPA-related WM in regions that have previously been associated with visual imagery (Daselaar et al., 2010; Huijbers et al., 2011).

Table 1. Main effect of Working Memory Type

Brain region	MNI coordinates *x*	*y*	*z*	*F-value*	Cluster size (voxels)
Right Superior Medial Gyrus	6	62	10	34.50	35
Right Superior Medial Gyrus	9	59	1	34.14	
Right Postcentral Gyrus	27	-37	55	34.34	29
Right Postcentral Gyrus	24	-37	64	30.88	
Right Postcentral Gyrus	30	-31	49	29.44	
Posterior Cingulate Gyrus	-12	-22	37	44.29	22
Left Anterior Cingulate Cortex	-6	44	-2	35.77	16
Left Primary Motor Cortex	-24	-25	52	31.74	13
Left Middle Temporal Gyrus	-51	-73	13	28.29	9
Left Middle Temporal Gyrus	-51	-73	19	27.61	
Left Middle Temporal Gyrus	-48	-70	16	27.47	
Right Paracentral Lobule	6	-37	70	35.42	6
Right Precentral Gyrus	27	-25	64	26.74	6
Right Temporal-Parietal Junction	45	-31	22	30.47	5
Right Supramarginal Gyrus	63	-22	19	28.08	5

MNI coordinates represent the location of the peak voxels. The peak voxels of each cluster with the cluster size are followed by separate maxima (8mm apart) within the cluster. Results were thresholded at $p < 0.05$, FWE-corrected with a minimum cluster size of 5 voxels.

Group effects. Our 3 (group) x 2 (task) mixed ANOVA yielded a significant main effect of group on WM (averaged across the DPA and DMS-task) in the left middle frontal gyrus (BA9; peak in MNI: -24 8 49) and the left precentral gyrus (BA6; peak in MNI: -27 -25 67). The interaction between group and task was not significant. However, separate one-way ANOVAs for each task revealed that the group differences were modulated by task difficulty, as predicted. For the DMS-task (Figure 4) we found a significant group effect in the left middle frontal gyrus (BA 9; peak in MNI: -21 8 52), while the more cognitively demanding DPA-task (Figure 5) yielded a significant group effect in the anterior left middle frontal gyrus (BA 10; peak in MNI: -30 62 4) and right inferior frontal sulcus (peak in MNI: 30 11 34). No other group differences were detected. To examine the group differences more closely, we extracted contrast estimates from the identified peak voxels of each task using the rfxplot toolbox (Gläscher, 2009) and computed Tukey post hoc tests. Figures 4 and 5 illustrate that older adults showed greater mean activity in frontal regions relative to young adults and synaesthetes in both tasks, as expected. However, while the enhanced activity in the left middle frontal gyrus was non-significantly different in older relative to young adults in the DPA-task (BA10: old > young: $p = 0.683$) and only marginally significant in the DMS-task (BA9: old > young, $p = 0.062$), the enhanced activation in older adults relative to synaesthetes was always significant (DPA, BA10: $p = 0.001$; DMS, BA9: $p = 0.001$). Moreover, for both tasks we found significantly enhanced activity in the left middle frontal gyrus in young adults relative to synaesthetes (DPA, BA10: $p = 0.008$; DMS, BA9: $p = 0.026$). Thus, the results are in line with our predictions, suggesting greater efficiency in synaesthetes that is less dependent on top-down control mechanisms from WM-related areas in PFC. By contrast, Tukey post hoc tests on the right inferior frontal sulcus revealed enhanced activity in older adults relative to synaesthetes ($p = 0.001$) and young adults ($p = 0.003$), suggesting an age-related compensation in right-hemispheric frontal regions (Cabeza et al., 2002), while the difference between synaesthetes and young adults was not significant ($p = 0.931$).

DMS-task, Main Effect of Group

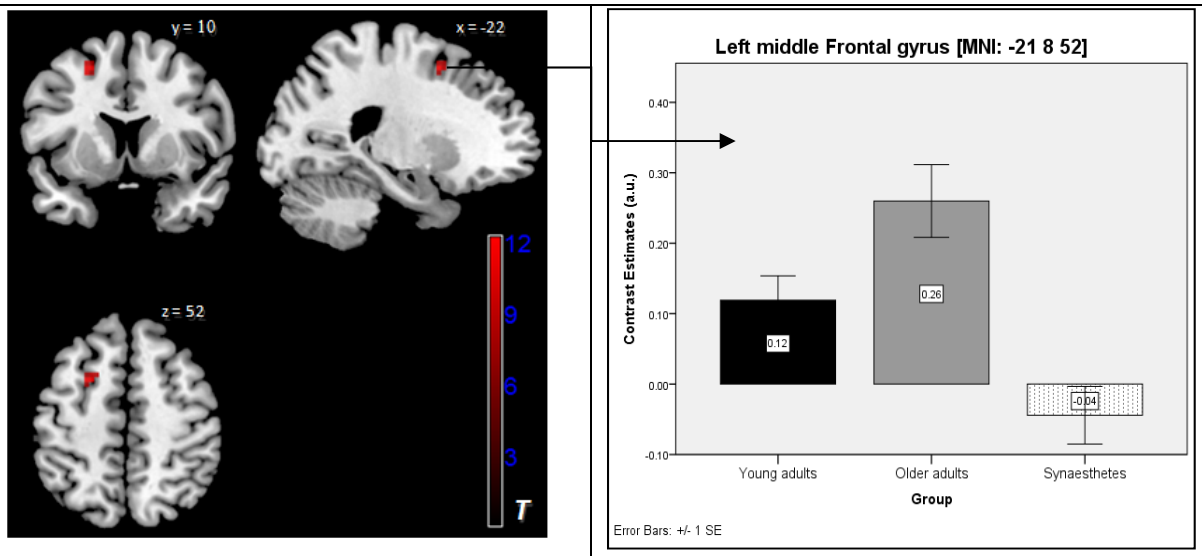


Figure 4. Left: Main effect of group shown for the DMS-task during the delay-period (DMS > DMSb, suprathresholded at p<0.001, uncorrected, k = 5 voxels, and masked with DMS > DMSb, thresholded at p<0.01, uncorrected. Right: contrast estimates extracted from the peak voxel of the left middle frontal gyrus.

DPA-task, Main Effect of Group

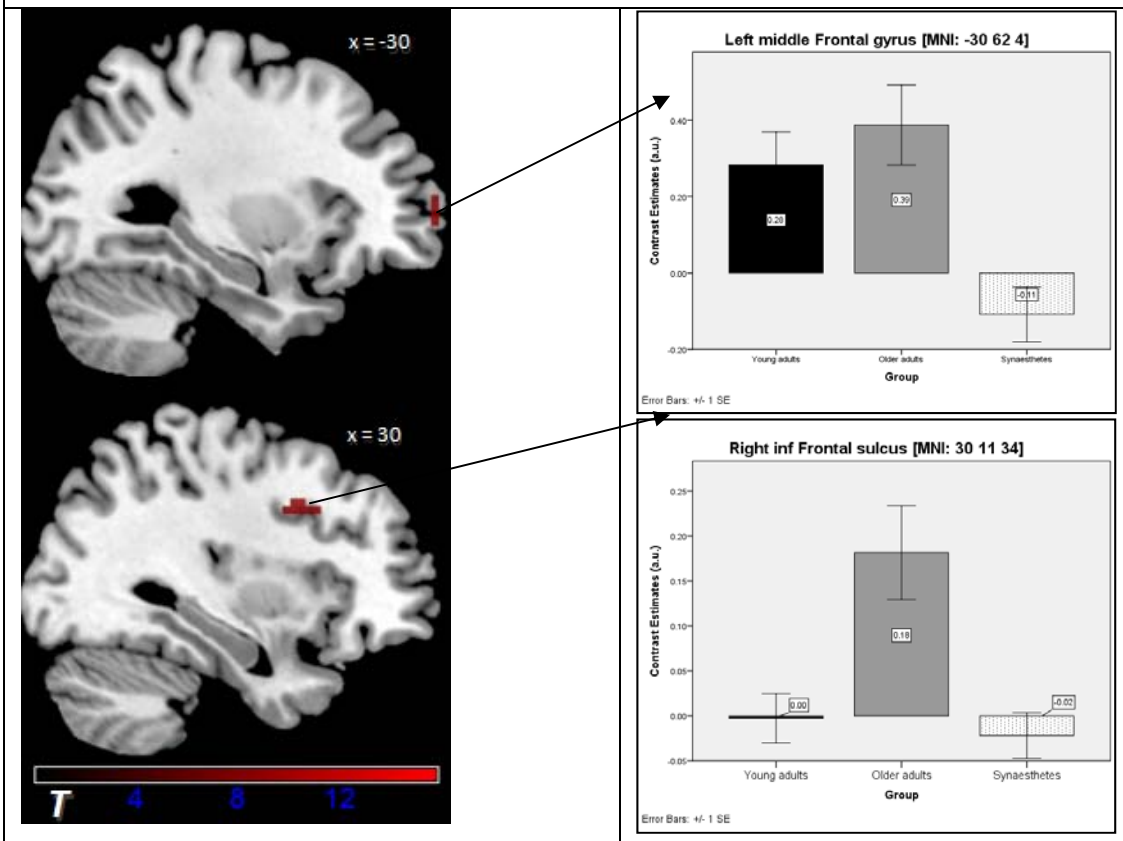
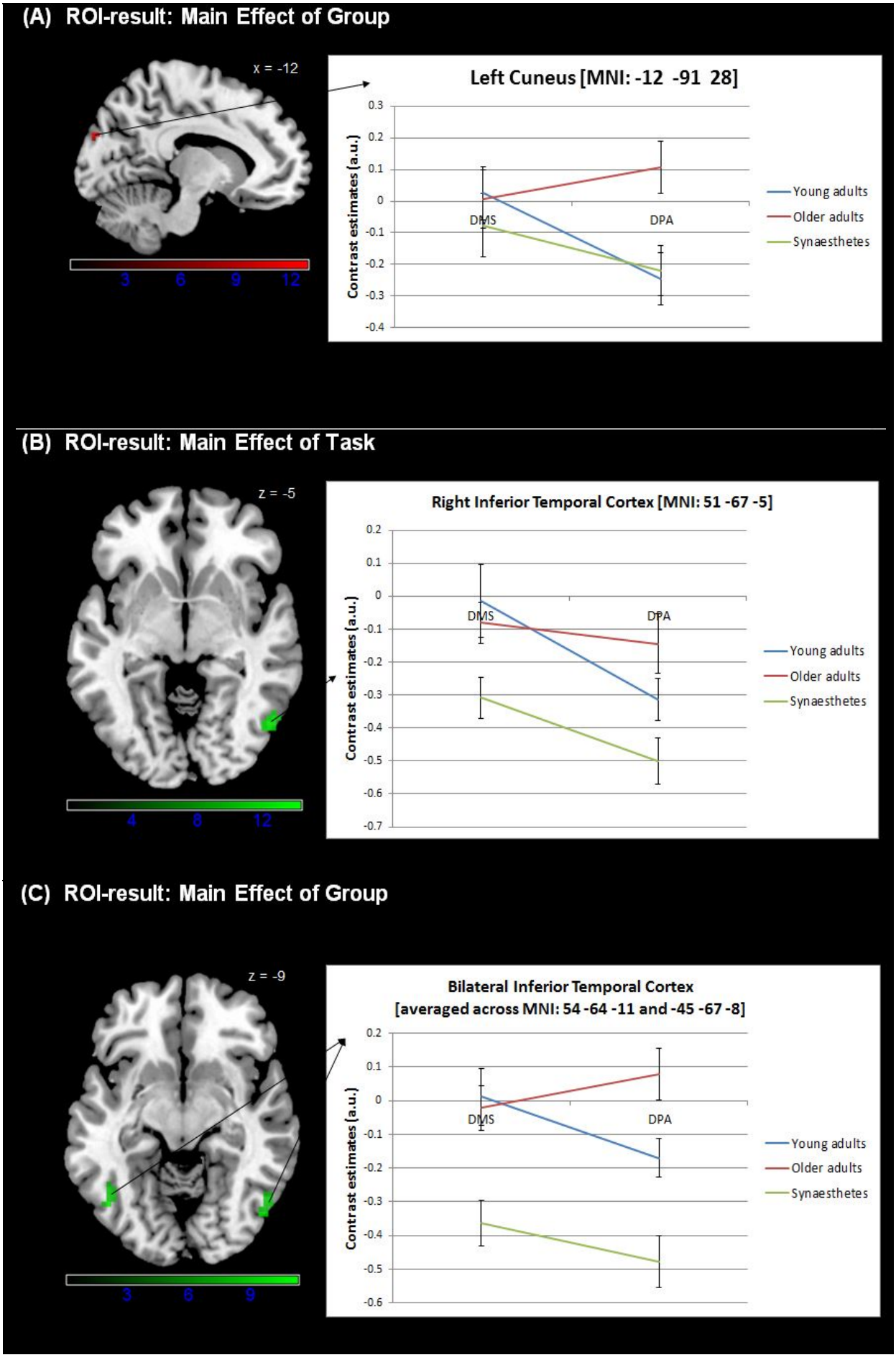


Figure 5. Left: Main effects of group shown for the DPA-task during the delay-period (DPA > DPAb, suprathresholded at p<0.001, uncorrected, k = 5 voxels, and masked with DPA > DPAb, thresholded at p<0.01, uncorrected. Right: contrast estimates extracted from the peak voxel of the left middle frontal gyrus (top) and the right inferior frontal sulcus (bottom).

ROI-results. Figure 6 illustrates the results of the cuneus and inferior temporal (IT) cortex, showing activation differences for each group and task. For the IT-cortex, the results of our 3 (group) by 2 (task) mixed ANOVA in SPM8 yielded a significant main effect of task in the right IT (peak in MNI: 51 -67 -5), a significant main effect of group bilaterally (right peak in MNI: 54 -64 -11; left peak in MNI: -45 -67 -8) and a task by group interaction in the right IT (peak in MNI: 51 -55 -17). Tukey post hoc tests were carried out using contrast estimates of the respective peak coordinates. Results revealed that the main effect of task was driven by DMS-related WM, which yielded significantly greater activity than DPA-related WM across groups, $F[1,108] = 8.279$, $p = .005$, $\eta_p^2 = 0.071$. For the main effect of group, Tukey post hoc tests were carried out on the averaged activity of peak coordinates across the left and right IT. The group effect was driven by the synaesthetes, who showed significantly lower activity than young adults ($p = 0.003$) and older adults ($p < 0.001$), while the difference between young and older adults was not significant ($p = 0.518$). The significant interaction between task and group, $F[2,108] = 7.550$, $p = .001$, $\eta_p^2 = 0.123$, revealed that the DPA-task yielded greater activity than the DMS-task in older adults' right IT-cortex, while young adults showed greater IT-activity during the DMS than during the DPA-task. The synaesthetes' activation pattern was more balanced across the two tasks, showing a negligible activation increase for DPA-related relative to DMS-related WM in right IT-cortex (see Figure 6).

For the cuneus, the results of our 3 (group) by 2 (task) mixed ANOVA yielded no significant main effect of task, or task by group interaction. However, there was a significant main effect of group in the left cuneus (peak in MNI: -12 -91 28). Tukey post hoc tests on contrast estimates of the peak coordinate revealed that the cuneus activity (averaged across DPA and DMS) in older adults relative to synaesthetes was marginally significant ($p = 0.054$), while the difference between young and older adults ($p = 0.140$), or between synaesthetes and young adults ($p = 0.904$) did not approach significance.


(A) ROI-result: Main Effect of Group
x = -12
3
6
9
12
Left Cuneus [MNI: -12 -91 28]
Contrast estimates (a.u.)
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
DMS
DPA
Young adults
Older adults
Synaesthetes
(B) ROI-result: Main Effect of Task
z = -5
4
8
12
Right Inferior Temporal Cortex [MNI: 51 -67 -5]
Contrast estimates (a.u.)
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
DMS
DPA
Young adults
Older adults
Synaesthetes
(C) ROI-result: Main Effect of Group
z = -9
3
6
9
Bilateral Inferior Temporal Cortex
[averaged across MNI: 54 -64 -11 and -45 -67 -8]
Contrast estimates (a.u.)
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
DMS
DPA
Young adults
Older adults
Synaesthetes

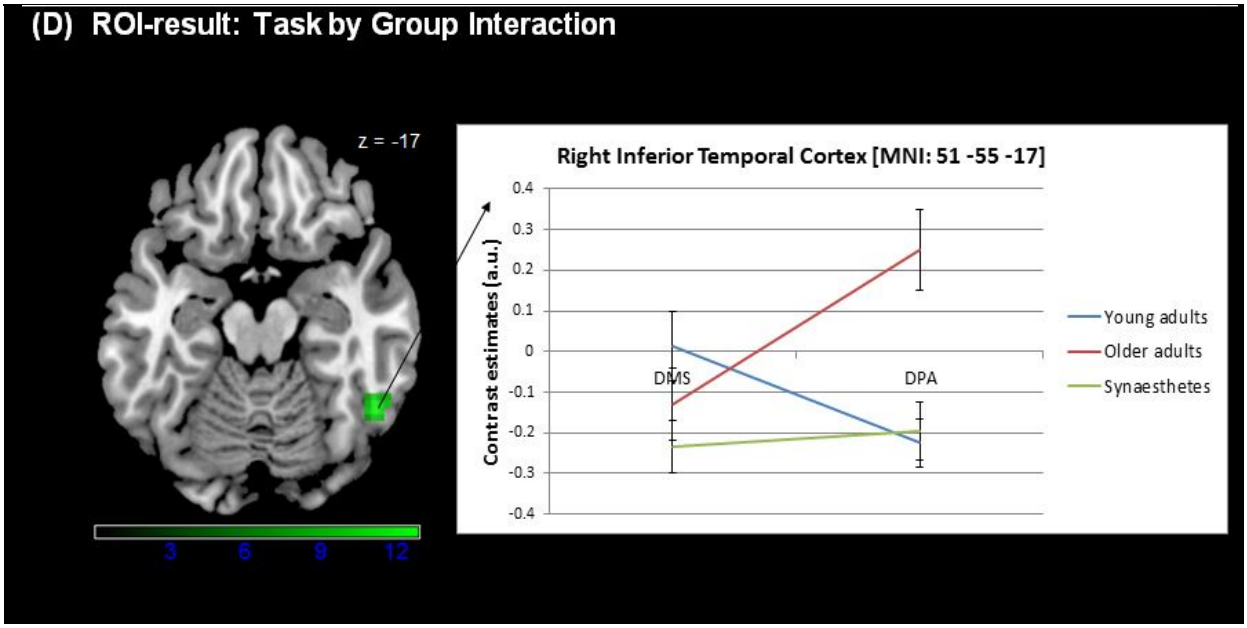


Figure 6. ROI-results of the cuneus (A) and the inferior temporal cortex (B-D). (A) Left: Main effect of group in the cuneus during the delay-period for DMS and DPA-related WM. A) Right: Contrast estimates extracted from the peak voxel of the cuneus, showing the relative activation difference for young adults, older adults and synaesthetes on DMS and DPA-related WM. (B-D) Left: Main effect of task, main effect of group, and task by group interaction, respectively, are shown for the inferior temporal cortex. (B and D) Right: Contrast estimates extracted from the peak voxels of the inferior temporal cortex, showing the relative activation differences for each task (DMS, DPA), group (young, old, synaesthetes), and interaction between task and group, respectively. (C) Right: Main effect of group presented with the average activity across the peak voxels of the left and right inferior temporal cortex. Results are thresholded at $p<0.001$ (uncorrected), $k = 5$ voxels, and rendered on the individual subjects' brain available in MRIcron. a.u. = arbitrary units.

Whole brain regression analyses with VVIQ-scores. Figure 7 presents the results of the whole brain regression analysis of participants' VVIQ-scores with the DPA-task (DPAd>DPAb). In line with our predictions, we found a positive correlation between younger adults' VVIQ-scores and memory-related brain regions, such as the right anterior inferior temporal and right inferior frontal gyrus (BA45). By contrast, the synaesthetes' VVIQ-scores were negatively related to posterior visual and attention-related areas, such as the left cuneus and the right inferior parietal lobe. For older adults we found a negative correlation between VVIQ-scores and the left middle and superior temporal cortex. For the DMS-task (Figure 8), we found a positive correlation between young adults' VVIQ-scores and the right posterior hippocampus and the cerebellum, while synaesthetes showed a negative correlation between VVIQ-scores and visual and attention-related areas, such as the bilateral lingual and left middle occipital gyrus, as well as the left postcentral gyrus. Older adults showed a negative correlation between VVIQ-scores and the left anterior insula.

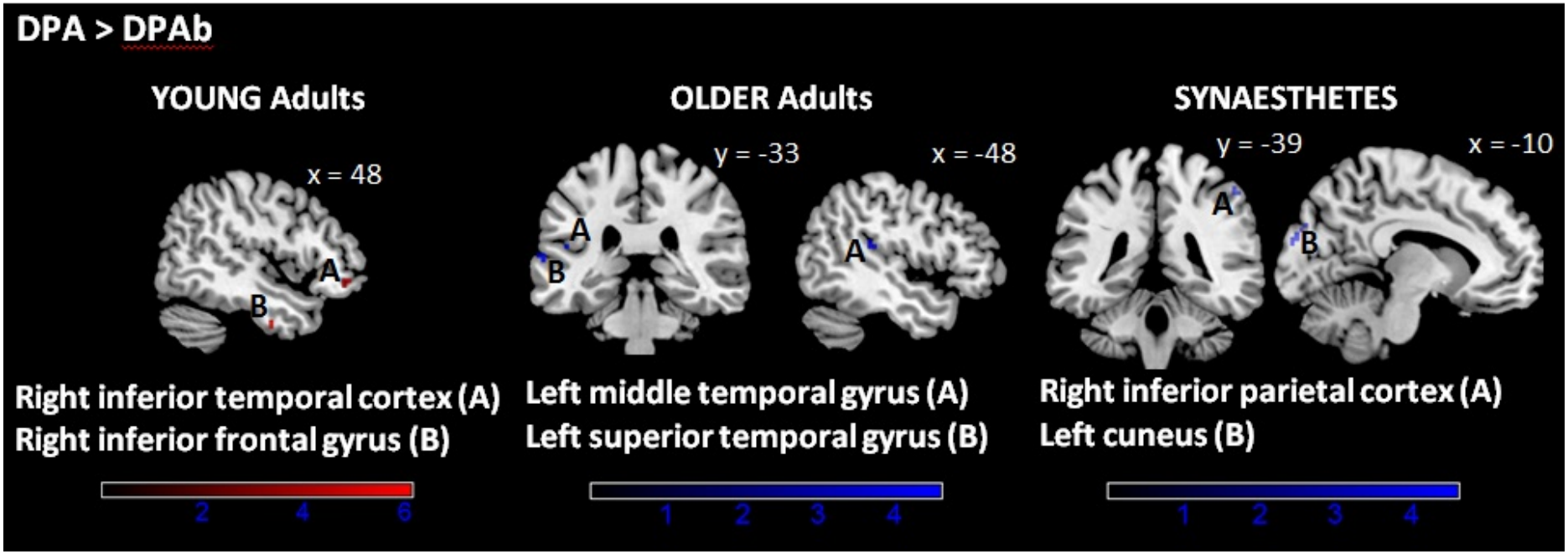


Figure 7. Whole brain correlations between VVIQ-scores and delay-activity during the DPA-task (DPA > DPAb) for young adults, older adults and synaesthetes. Positive correlations are shown in red colour, negative correlations in blue colour. All images thresholded at $p < 0.001$, uncorrected, $k = 5$ voxels.

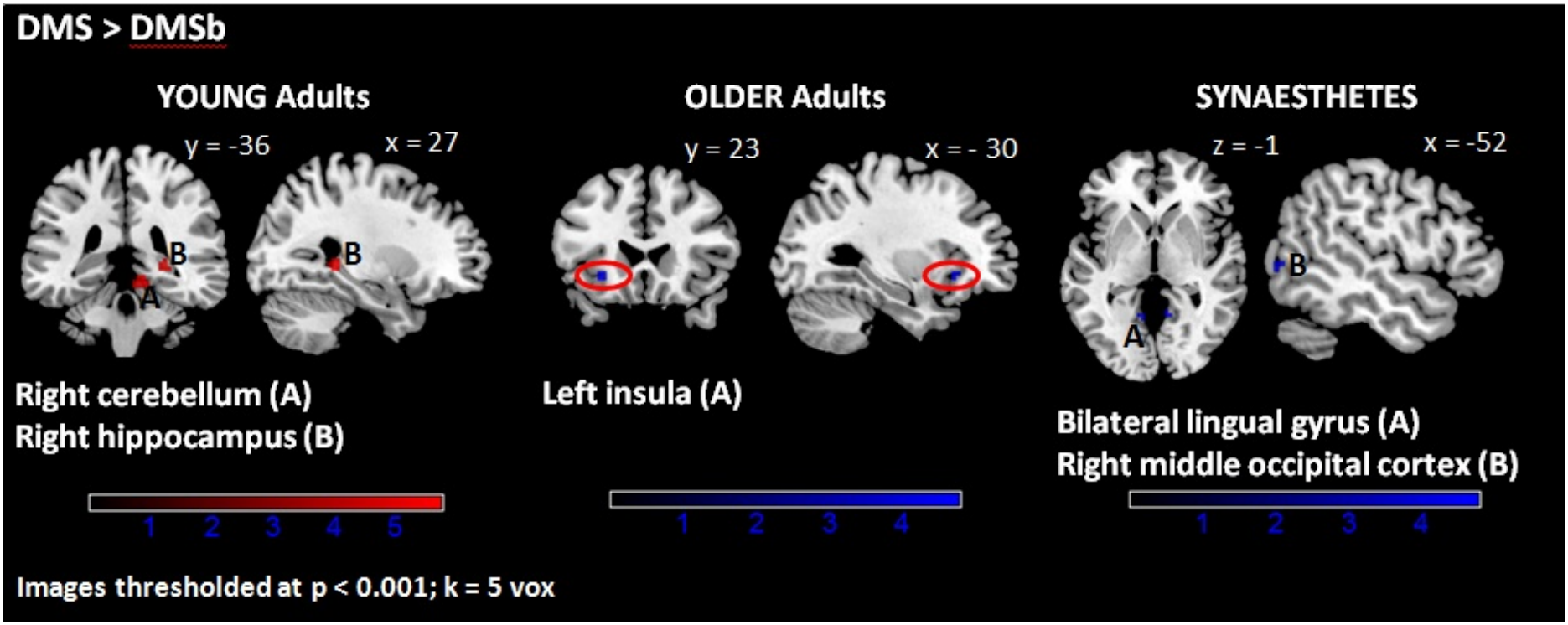


Figure 8. Whole brain correlations between VVIQ-scores and delay-activity during the DMS-task (DMS > DMSb) for young adults, older adults and synaesthetes. Positive correlations are shown in red colour, negative correlations in blue colour. All images thresholded at $p < 0.001$, uncorrected, $k = 5$ voxels.

5.5 Discussion

The present fMRI study used a novel between-group design with young synaesthetes, young and older adults to investigate the neural correlates of visual working memory (WM), as well as differences in subjective visual imagery as a WM-related strategy. By including synaesthetes and older adults we were able to investigate differential activity in prefrontal cortex (PFC) and posterior sensory regions as they relate to visual WM and visual imagery.

Results of two WM-tasks, DMS (maintenance of cued images, low WM-load) and DPA (maintenance of retrieved images from memory, high WM-load) demonstrated that the neural correlates of WM are task-dependent [cf. (Curtis et al., 2004)]. DMS-related WM yielded greater activity in a number of frontal-parietal regions than DPA-related WM, while no effect was found when contrasting DPA-related against DMS-related WM. Although the enhanced activity during the low WM-load DMS-task appears counterintuitive, the results are in line with previous research (Ranganath et al., 2004). WM of retrieved pair-associates might be more prone to fading and result in reduced signal strength than WM of perceptually cued stimuli. The significantly higher accuracy and lower RTs in the DMS relative to the DPA-task further support this interpretation and reflect the greater cognitive demands of retrieval-related WM.

With respect to group effects, we observed evidence of enhanced neural efficiency in synaesthetes relative to young and older adults, which was manifested by reduced activity in prefrontal cortex (PFC) across the two WM-tasks. Moreover, the group differences found in PFC reflected the specific type of WM: the DMS-task yielded a significant group effect in the left middle frontal gyrus (BA 9), which is classically associated with the maintenance of information in WM, including the reactivation of just-seen, transiently stored material (Curtis and D'Esposito, 2003; Raye et al., 2002). Older adults, who activated this region more strongly than synaesthetes ($p=0.001$) and young adults ($p=0.062$), might have compensated the behavioural WM-performance, which did not differ between groups. The fact that young adults also showed enhanced activity relative to synaesthetes highlights the effect of synaesthesia, indicating greater WM-related efficiency in synaesthetes that is less dependent on top-down control mechanisms. Our findings are in line with the

sensory recruitment model of WM (Serences et al., 2009), suggesting that enhanced neural sensitivity in posterior visual regions (as in synaesthesia) alleviated top-down control functions from PFC.

The DPA-task yielded two group effects, one in the right inferior frontal sulcus and another in the left middle frontal gyrus, corresponding to the lateral region of BA10. We attribute the group differences in the inferior frontal sulcus to a specific age-related dedifferentiation, given the enhanced activity in older adults relative to both, young adults and synaesthetes. Aging has been associated with a hemispheric asymmetry, whereby older adults show less left-lateralized activity than young adults, often activating additional right frontal regions whilst performing the same cognitive process (Cabeza, 2002). The group effect in BA10, which has been associated with the recollection of contextual details in associative memory tests (Simons et al., 2005a; Simons et al., 2005b), reflects memory-related processing differences inherent in the DPA-task. Although the instruction was to use the cue for retrieval and the delay for maintaining the retrieved pair-associates, it is likely that some participants continued to re-activate the to-be-maintained information during the delay-period. In this sense, the group differences found in lateral BA10 reveal the additional memory demands imposed by DPA-related over DMS-related WM. Interestingly, young and older adults showed significantly enhanced activity in BA10 relative to synaesthetes, suggesting that it was the specific retrieval-related maintenance subserved by this region, during which synaesthetes demonstrated greater efficiency. It is worth noting that our behavioural data for the DPA-task yielded significantly higher accuracy in young relative to older adults, while synaesthetes performed non-significantly better than older adults and non-significantly poorer than young adults. Thus, the significant reduction of activity in synaesthetes' BA10 relative to the other two groups cannot be attributed to an extreme behavioural discrepancy, but instead corroborates the synaesthetes' efficiency in DPA-related WM. The fact that we only analysed successful and confident trials adds further confidence to the synaesthetes' enhanced efficiency in WM. This interpretation raises the question why synaesthetes, albeit showing greater neural efficiency, only demonstrated mediocre performance in the DPA-task? In answering this question, the behavioural results need to be explained within the context of associative memory rather than WM alone. Specifically, the DPA-task was preceded by an associative learning paradigm, in which participants acquired the

correct combination of pair-associates in their own pace. The results of this task revealed an associative learning advantage of synaesthetes (reported in Chapter 3), who required fewer numbers of Runs and showed a specific learning advantage in response to dissimilar pair-associates, both of which were significant relative to older adults. By contrast, young adults performed non-significantly better than older adults and demonstrated average encoding that was (non-significantly) below that of synaesthetes. The fact that we did not find a behavioural advantage of synaesthetes at retrieval can therefore be attributed to a speed-accuracy trade-off: the low number of Runs during associative learning, and thus, the reduced stimulus exposure, might have prevented synaesthetes from a behavioural advantage at recognition. In this respect, the WM results of the present study (in particular those of the DPA-task) merely allow making inferences about differences in the activation patterns, but cannot be used as a predictor for long-term memory performance. Similarly, since the DMS-task yielded high performance accuracy across groups (> 95%), the group differences found in BA9 are indicative of strategy differences between groups to arrive at successful WM, rather than of performance differences in WM due to differential neural activity.

The present study allowed us to advance the sensory recruitment model, demonstrating that enhanced neural sensitivity in synaesthetes' occipito-temporal regions (Barnett et al., 2008) not only resulted in reduced top-down control from PFC, but also in reduced activity in sensory regions *per se*: our ROI-analyses revealed that synaesthetes showed significantly less activity in the cuneus and the IT-cortex relative to young and older adults across WM-tasks. Importantly, no significant difference was observed in these ROIs for the comparison of young and older adults, indicating that the group effect cannot be attributed to age-related neural broadening in the ventral-visual-stream (Park et al., 2012), but rather suggests individual differences pertaining to synaesthesia. Specifically, synaesthetes were previously found to show grey and white-matter differences in IT-cortex relative to controls (Banissy et al., 2012; Jancke et al., 2009; Rouw et al., 2011; Weiss and Fink, 2009), as well as greater excitability (Terhune et al., 2011) and enhanced sensitivity (Barnett et al., 2008) in primary visual cortex, which are likely to account for reduced activity in these regions. Our results suggest bottom-up effects of posterior sensory regions to WM, whereby enhanced sensory-perceptual mechanisms (as in synaesthetes) contribute to an efficient WM-network. Moreover, our results mitigate previous

ambiguities from studies comparing only young and older adults. For instance, age-related WM-impairments have often been attributed to reduced neural specificity in ventral visual cortex due to a failure of top-down signalling from PFC (Gazzaley et al., 2005; Kalkstein et al., 2011). However, older adults experience reduced neural specificity in ventral visual cortex even in the absence of WM-demands (Goh, 2011; Park et al., 2004; Park et al., 2012), making it difficult to ascribe WM-contributions entirely to PFC. Combining synaesthesia and aging demonstrates that top-down signalling interacts with sensitivity in posterior sensory regions, showing bidirectional effects on visual WM.

5.5.1 Group differences in visual imagery

An important link to the synaesthetes' WM-efficiency is the use of visual imagery, which they were previously found to experience more vividly than non-synaesthetes (Barnett and Newell, 2008; Meier and Rothen, 2013; Simner, 2013; Whitaker et al., 2014). Using the Vividness of Visual Imagery Questionnaire [VVIQ; (Marks, 1973)], our groups did not differ on subjective imagery ratings. One possibility for this finding is that the VVIQ might be a less reliable measure when administered across different participant populations. Athough the VVIQ has been tested for reliability (Marks, 1973), these measures were taken within the same population (young adults). Previous studies showed that different participant populations behave differently when introspecting subjective experiences. For example, older adults tend to give higher confidence ratings than young adults on tasks of visual perception (Palmer et al., 2014) and memory (Dodson et al., 2007; McDonough et al., 2014), despite comparable task performance. This phenomenon might extent to the subjective experience of visual imagery. Indeed, our group of older adults reported higher mean vividness ratings than synaesthetes and young adults, but showed no advantage in performance accuracy, RT and neural signal on either WM-task.

Our whole-brain correlations between participant's VVIQ-scores and brain activity during DMS and DPA-related WM demonstrated that the neural pathway of visual WM is guided by strategy [cf. (Hales and Brewer, 2012); (Rothmayr et al., 2007)], as well as age- and individual differences. In both WM-tasks, young adults showed a positive correlation between VVIQ-scores and WM in higher-order brain regions that are involved in memory and semantic processing, including the hippocampus (DMS-task) and the anterior inferior temporal and PFC (DPA-task) (Henson et al., 1999; Zhu et al., 2012). In other words, young adults with higher subjective imagery relied on memory-based rather than visual-based strategies and demonstrated greater effort (enhanced activity) in using imagery during WM. A different imagery strategy was adopted by older adults, whose VVIQ-scores correlated negatively with the left anterior insula during the DMS-task. The insular cortex is involved in emotional awareness (Gu et al., 2013) and was previously found to show enhanced activation during imagery of emotional events (Caria et al., 2007). Speculatively, the reduced activation in older adults reporting high visual imagery

might reflect the non-emotional content of our fractal stimuli, coupled with reduced emotional concerns about performance, particularly in the low-demanding DMS-task. During the DPA-task, older adults' VVIQ-scores correlated negatively with activation in the auditory cortex: the higher the vividness ratings, the lower the activation in the superior temporal gyrus. Similar findings have been reported by (Amedi et al., 2005) in young adults, showing interaction effects in visual and auditory cortex: during visual imagery, activation in visual regions was enhanced, while it was suppressed in auditory cortex. By contrast, auditory imagery showed a trend towards enhanced activation in auditory and reduced activation in visual regions. One possibility for our finding might be that those older adults with higher vividness ratings relied more on auditory cortex suppression to facilitate visual imagery, especially during the high-demanding DPA-task. This converges with our ROI-results, in which we found higher average activation in older adults' cuneus and IT-cortex relative to the other two groups. This effect was only found during DPA-related WM, indicating that visual imagery in demanding WM-contexts taxed the visual system of older adults. Synaesthetes were the only group in which subjective imagery ratings correlated with visual WM in visual regions. Visual imagery has classically been associated with activation in visual cortex (Ganis et al., 2004; Pillai et al., 2013; Slotnick et al., 2005), supporting the notion that perception and imagery are represented by the same neural substrates [for review see (Kosslyn et al., 2001)]. Specifically, our group of synaesthetes showed a negative correlation during both WM-tasks, indicating that those who reported higher subjective imagery showed reduced (efficient) activity in visual regions. Moreover, synaesthetes were the only group showing a positive correlation between VVIQ-scores and performance accuracy on the DPA-task, suggesting that good imagers of this group benefitted from using imagery during the WM-task to further boost their associative memory performance. The fact that visual imagery facilitates long-term memory (LTM) has been demonstrated before (Baddeley and Andrade, 2000; D'Angiulli et al., 2013). Likewise, previous research has shown a positive relationship between WM and LTM *per se* (Vogel and Machizawa, 2004). However, our results suggest that vivid visual imagery and efficient visual WM are underpinned by enhanced sensory-perceptual mechanisms in synaesthetes, as they correlated in posterior visual regions. Our data extent the sensory recruitment model of WM (Serences et al., 2009), showing that enhanced sensitivity in posterior visual regions (as in synaesthesia) resulted in reduced activity

in occipito-temporal cortex and lower top-down demands from PFC, while reduced sensitivity (as in old age) showed the opposite effect. Future research should investigate the impact of differential sensory-perceptual mechanisms between young synaesthetes, young and older adults on the effective connectivity between frontal and occipito-temporal regions during visual WM.

In conclusion, our results revealed prefrontal and occipito-temporal contributions to visual WM that reflected the differences in visual perception and imagery between synaesthetes, young and older adults. This is the first fMRI study to investigate the neural correlates of visual WM in synaesthetes, allowing us to examine the influence of perception on WM, as well as performance on associative retrieval. Results showed that while WM-maintenance *per se* was most efficient in synaesthetes (showing reduced activity in prefrontal cortex and visual regions relative to young and older adults), it was not predictive of faster or more accurate associative retrieval. Thus, WM made no direct contribution to associative memory. Subjective visual imagery correlated with visual regions during WM-maintenance as well as with retrieval accuracy in synaesthetes, but not in young and older adults. Our fMRI-data point to an underlying common cause, driven by enhanced sensory-perceptual functions (as in synaesthesia), that supports higher-level cognitive processes including visual WM, imagery and associative retrieval.

Chapter 6: General Discussion

6.1 Overview

In this thesis we tested two memory models, the modular account (Squire and Wixted, 2011) and the representational account of memory (Bussey and Saksida, 2007). While the modular account of memory envisages a conceptual and anatomical division of memory and perception, the representational account of memory proposes a perceptual-mnemonic continuum of stimulus representations along the VVS. In Chapters 2 - 5, we tested these two accounts using a novel between-group design (synaesthetes, young and older adults) and fractal pair-associates that differed in perceptual similarity. We investigated a range of different cognitive processes, including associative encoding, retrieval, recognition and working memory.

In Chapter 2, we tested our 3 participant groups behaviourally and demonstrated that i) the similarity manipulation was effective in placing differential demands on memory and perception, and ii) the achromatic abstract fractal pair-associates, which did not elicit any colour responses in synaesthetes, yielded a subtle memory advantage in synaesthetes relative to older adults, which was not found between synaesthetes and young adults, or between young and older adults. This finding suggested a generic rather than a synaesthesia-specific memory advantage, which arises from enhanced perceptual mechanisms and is therefore best interpreted with the representational account of memory.

In Chapter 3, we built on the design and stimuli of the behavioural study and examined the neural correlates of associative retrieval and recognition using fMRI. In order to test the representational account of memory, we mapped out the entire VVS and carried out region-of-interest (ROI) and whole brain analyses. Across associative retrieval and recognition, our findings yielded group differences in posterior occipito-temporal regions, but not in the MTL. Specifically, synaesthetes showed reduced activity during retrieval, and enhanced activity during recognition relative to the other two groups. This suggests that enhanced perceptual mechanisms afford greater efficiency at top-down retrieval as well as greater sensitivity during bottom-up recognition. Our results support the notion of a perceptual-mnemonic continuum as envisaged by the representational account of memory, showing a direct contribution of perceptual mechanisms to visual associative memory based on the examples of synaesthesia and aging.

The modular account of memory emphasises a role of the hippocampus in declarative memory (Squire, 1994). In Chapter 4, we tested the modular memory account by examining the effects of associative retrieval on hippocampal activation and neocortical connectivity in a group of young and older adults. Older but not young adults showed a significant hippocampal activation increase during dissimilar pair-retrieval, indicating age-related deficits in discriminating dissimilar pair-associates among a set of familiar stimuli. Moreover, we found hippocampal connectivity with specific networks that i) compensated for age-related perceptual deficits in the similar condition, and ii) modulated flexibly in young adults according to stimulus type (similar and dissimilar pair retrieval). Our results support a representational rather than a modular view of memory, suggesting a role of the hippocampus in memory and perception that was modulated by age as well as task difficulty (perceptual similarity of the stimulus set).

Given that working memory (WM) and visual imagery play a role in long-term memory (Baddeley and Andrade, 2000), we examined the neural correlates of visual WM in our three groups in Chapter 5. Moreover, we correlated participants' subjective visual imagery ratings with brain activity during WM-maintenance. Synaesthetes showed reduced WM-related activity in prefrontal cortex and early visual regions relative to young and older adults. Subjective visual imagery correlated with activation in visual regions during WM-maintenance, as well as with retrieval accuracy in synaesthetes, but not in young and older adults. The results further demonstrated the synaesthetes' efficiency in tasks requiring top-down support (i.e. WM and visual imagery), and revealed the facilitating effects of enhanced sensory-perceptual mechanisms on visual associative memory.

Throughout our work, the results supported the perceptual-mnemonic view and extended the representational account of memory to posterior regions of the VVS. However, our findings leave a number of unanswered questions for the theoretical context of the representational memory account, which we discuss next.

6.2 Effects of stimulus similarity on PRC signal change during associative retrieval and recognition

Perhaps the most curious finding of our fMRI study in Chapter 3 was the absence of a stimulus type effect on PRC activation during associative retrieval and recognition. In line with the stimulus type principle envisaged by the representational account of memory, converging evidence from neuroimaging (Devlin and Price, 2007; Ryan et al., 2012), neuropsychology (Barense et al., 2007; 2012) and non-human primate research (Buckley et al., 2001; Bussey et al., 2002); Bussey et al., 2003) supports a role of the PRC in the perceptual discrimination of stimuli with large feature overlap. Specifically, the PRC acts as a convergence zone that unitises features into coherent objects (Bussey and Saksida, 2002) and is therefore particularly suitable in resolving feature ambiguity. In an attempt to demonstrate PRC engagement in our visual associative memory paradigm, we manipulated fractal pair-associates in visual similarity: visually dissimilar pair-associates were expected to tax the hippocampus based on its involvement in pattern separation (Rolls, 2013; Yassa and Stark, 2011) and in the recollection of stimuli from dissimilar domains (Mayes et al., 2007). By contrast, similar pair-associates were predicted to engage the PRC based on its sensitivity to minimal feature changes (Gonsalves et al., 2005; Henson et al., 2003). However, our ROI results in Chapter 3 revealed no significant differences between hippocampal and perirhinal activation, and there was no significant activation difference within the PRC in response to similar and dissimilar pair-associates. This applied to associative retrieval (Figure 5a; Chapter 3) as well as associative recognition (Figure 8; Chapter 3) and was found for all groups. How can this effect be explained? One interpretation is that the lack of different PRC responses might have been an effect of stimulus presentation. The dominant procedure in perceptual paradigms is to present discriminant stimuli simultaneously [e.g. (Bussey et al., 2003; Devlin and Price, 2007; O'Neil et al., 2009)]. Presumably, simultaneous stimulus presentation affords direct bottom-up comparisons to assist PRC in resolving feature ambiguity. By contrast, our DPA-task displayed one image at the time and the matching similar pair-associate either had to be retrieved from memory (at the cue stage), or recognised in the absence of the cue stimulus (at the target stage). The additional memory demands posed by this task might have blurred the fine-grained differences between similar pair-associates, resulting in PRC

activation that neither differed from hippocampal activation, nor showed differences between stimulus types (similar and dissimilar pairs). Interestingly, Watson and colleagues (Watson et al., 2012a) reported increased perirhinal activation during an associative memory task for similarity-matched objects. However, this fMRI study recorded PRC activation during incidental encoding, suggesting that activation increases in response to subsequently recognised objects were related to bottom-up perceptual processes and not, as in our case, to top-down memory processes.

An alternative interpretation of our finding is that the relatively long delay period of 8 seconds between cue and target might have converted our associative retrieval task to an item recognition test in the similar condition. In this case, the PRC would represent each of the fractal images as unitised objects at the time of encounter (i.e. at cue and target stages), but lose its sensitivity to fine-grained feature changes over the delay and show no activation changes. This is in line with an fMRI study by (Staresina and Davachi, 2010), where encoding of unitised objects in context showed enhanced activation in PRC, while encoding of fragmented objects in context activated posterior visual regions. Presumably, representation of fractal images as individual objects would yield consistent activation levels in PRC, as was found in our DPA-task, and could explain the lack of activation differences between similar and dissimilar pair-associates, and between PRC and hippocampus.

6.3 Effects of aging and synaesthesia on PRC signal change during associative retrieval and recognition

A second unexpected finding in Chapter 3 was the lack of activation differences in PRC due to aging and/or synaesthesia. Although the relationship between synaesthesia and perceptual sensitivity in PRC has not previously been examined, evidence from older adults suggests a reduction in PRC function, concomitant with an age-related perceptual decline. For example, Ryan et al. (2012) scanned young and older adults during a perceptual object matching task. Older adults performed significantly more poorly than young adults on ambiguous stimuli with high feature overlap, and showed significantly reduced PRC activation. Given the disparate sensory-perceptual abilities between our three groups, the similar pair-associates might have resulted in reduced activation in older adults (cf. Ryan et al., 2012), while synaesthetes might have been more sensitive to fine-grained feature

changes, showing enhanced activation in PRC during associative retrieval and/or recognition. However, following the argument developed in section 6.2, the sequential stimulus presentation might have been insensitive in bringing out the activation differences that are typically observed in PRC with simultaneous stimulus presentations in perceptual discrimination tasks (Bussey and Saksida, 2003; O'Neil et al., 2009; Devlin and Price, 2007; Ryan et al., 2012).

A further important issue to consider was the influence of group differences in regional grey matter (GM) volume that could potentially influence activation differences in the PRC. Aging is typically associated with GM volume reductions, including the hippocampus and neighbouring rhinal cortices (Raz et al., 2005). Structural changes in GM volume can account for BOLD activation differences. For instance, Kalpouzos et al. (2012) found that local GM atrophy in older adults' occipital cortex accounted for reduced activation during encoding, whilst atrophy in dorsolateral PFC accounted for enhanced activation during retrieval. By constrast, synaesthetes have larger GM volume than controls, which is frequently reported in the fusiform gyrus (Banissy et al., 2012; Jancke et al., 2009; Rouw et al., 2011; Weiss and Fink, 2009). The effects of structural differences on brain function have been demonstrated by (O'Hanlon et al., 2013) in a combined structural and functional MRI study: two regions exhibiting enlarged GM volume in synaesthetes relative to controls (lateral occipital and posterior fusiform gyrus) were associated with significantly reduced BOLD responses in response to black letter processing. Given the sensory-perceptual differences between old age and synaesthesia, it is plausible that the PRC shows GM volume variations that might in turn attenuate activation differences between groups. The results of our regional GM volume analysis partially exclude this possibility, revealing only age-related, but not synaesthesia-specific GM volume differences in PRC (see Figure 7 in the Appendix). Moreover, to further minimise any structural confounds on brain activity, each participants' ROI-specific GM matter volume was entered as a covariate in our fMRI analyses to account for age- (Lemaitre et al., 2005; Raz et al., 2005) and gender-related (Luders et al., 2002) GM volume differences. Thus, the non-significant group effect on PRC activation reported in Chapter 3 might best be interpreted with the effects of stimulus presentation: sequential presentation of stimuli with high feature overlap, as in our DPA-paradigm, was less effective in taxing the PRC than the simultaneous stimulus

presentations used in perceptual discrimination tasks (Saksida and Bussey, 2010; Ryan et al., 2012; Devlin et al., 2007).

Two methodological issues might further explain the non-significant group and stimulus effects on PRC activation: the first relates to scanner sensitivity and the second to signal dropout. Regarding scanner sensitivity, our data were acquired at low field strength (1.5T) and at a conventional resolution of 3.0 mm isotropic voxels. Lower field strength reduces the signal-to-noise ratio (SNR) during data collection, thereby affecting the sensitivity of stimulus-dependent BOLD signal changes relative to stimulus-independent fluctuations in the BOLD signal. Similiarly, the relatively low spatial resolution of 3 x 3 x $3mm^3$ voxel size is less specific to the functional properties in small regions such as PRC compared to high resolution imaging at 1 x 1 x $1mm^3$ voxel sizes (Carr et al., 2010). To alleviate some of these potential issues, we ensured that the acquired signal was limited to specific ROIs by using non-smoothed images in our ROI-analysis.

The second issue relating to signal dropout is of particular concern when imaging the MTL (Olman et al., 2009). Signal dropout is caused by inhomogeneities in the magnetic field, which often occur at tissue boundaries to air-filled cavities. The vicinity of the ear-canals and the sphenoid sinus make the MTL a candidate region for signal dropout, with the ERC and PRC as the most severely affected regions (Olman et al., 2009). A recent fMRI study by (Lech and Suchan, 2014) employed a visual discrimination task to examine MTL contributions to visual perception. While the authors found evidence for hippocampal involvement during visual discrimination, no significant perirhinal activations (at a lenient threshold of $p < 0.01$, uncorrected) could be detected. The authors attributed the lack of perirhinal activation to signal dropouts, an issue that might well account for our findings in Chapter 3. However, contrary to Lech and Suchan's findings, PRC activation in our study was significant across groups and conditions (at a threshold of $p < 0.005$, uncorrected), with the exception of the dissimilar non-match condition during associative recognition, where we lowered the PRC activation threshold to $p < 0.05$ (uncorrected). Moreover, Lech and Suchan's data were acquired using a 3T scanner and at a higher spatial resolution (voxel size = 1.65 mm × 1.65 mm × 3 mm), thus having a higher SNR than in our data. By comparing our results with those of Lech and Suchan (2014), we therefore gain confidence that the non-significant group and stimulus effects in PRC

were due to differences in stimulus presentation rather than low SNR or signal dropout.

6.4 Synaesthesia-specific structural and functional differences in anterior inferior temporal gyrus

With respect to structural differences, our group of synaesthetes showed significantly larger GM volume relative to young and older adults in the left anterior IT (Figure 7, Appendix). We also observed partial overlap between differences in structure and function (cf. O'Hanlon et al. 2013): during retrieval, synaesthetes showed significantly lower signal change relative to young and older adults in the left and right anterior IT. Similarly, during recognition, synaesthetes showed significanlty higher signal change relative to young and older adults in the right anterior IT. Our data are consistent with findings of impaired recognition memory after bilateral cooling or ablation of anterior IT in monkeys (Bachevalier and Mishkin, 1994; Horel et al., 1987), indicating that this region is critically involved in memory tasks [see also (Li et al., 1993)]. Note that we found activation differences between groups even *after* accounting for GM volume differences, suggesting true functional differences that might underpin the synaesthetes' enhanced perceptual-mnemonic abilities relative to controls. Specifically, the underrecruitment observed in this region at associative retrieval (Figure 5, Chapter 3) further corroborates the synaesthetes' efficiency during top-down processes that were found in early visual regions (Chapters 3 and 4), while the overrecruitment at recognition (Figure 8, Chapter 3) supports enhanced sensitivity during bottom-up perceptual processes (Chapters 2 and 3).

How can we explain the synaesthesia-specific activation differences in the anterior IT? The anterior IT is located laterally to the PRC and is considered the most anterior unimodal visual area in the VVS (Gross et al., 1972; Suzuki, 2010). In the macaque monkey, this brain region corresponds to area TE, which was found to contain pair-coding neurons (albeit significantly less than the neighbouring area 36 in PRC) that respond to fractal pair-associates (Naya et al., 2003; Hirabayashi et al., 2013). Specifically, within TE, Hirabayashi et al. (2013) demonstrated early hierarchical coding of emergent feature representations, whereby feature-processing cells compute and relay novel information to more complex pair-associative cells that

are selectively responsive to the feature. Given the low resolution of fMRI relative to single unit recordings, it might not be surprising that the weak conjunctive feature function subserved by the anterior IT showed no effect of age on associative retrieval or recognition. However, synaesthetes might show heightened neural specificity in anterior regions of the VVS that are shaped by enhanced processing mechanisms in early visual regions (cf. Hubbard et al., 2011). This is consistent with neurophysiological studies showing that feature categorization training in macaques selectively tuned neurons in anterior IT towards features that were diagnostic of a certain category [(Sigala, 2004; Sigala and Logothetis, 2002); see also (Sigala et al., 2002) for converging monkey and human evidence]. Since synaesthesia is a form of expert perceptual and mnemonic shaping of cortical mechanisms (Rothen et al., 2012; Rouw et al., 2011) we consider it plausible that synaesthetes show enhanced specificity in more selective visual processing regions such as the anterior IT. Such neural specificity would return the respective signal reductions and increases observed in our group of synaesthetes during associative retrieval and recognition. Speculatively, the synaesthetes' enhanced sensitivity in anterior IT might have contributed to feature conjunctions in a such way to eliminate the group differences further upstream in PRC (as discussed in section 6.3), where feature conjunctions are typically observed (Bussey and Saksida, 2002).

Following the synaesthetes' activation differences at retrieval and recognition, we further observed activation differences in anterior IT for specific types of stimuli: activation decrease at retrieval was only observed in the dissimilar condition, while activation increase at recognition was merely present in the similar condition. One interpretation of this finding is that the coarse feature overlap inherent in dissimilar pair-associates might have been required for detection in anterior IT during top-down retrieval (at the cue stage). By contrast, high feature overlap inherent in the similar condition might have been sufficient for detection during bottom-up recognition. Specifically, at recognition, participants are provided with a perceptual target that had already been maintained over the delay, thereby affording perceptual discrimination of fine-grained features. Taken together, our group of synaesthetes processed fractal images according to the perceptual or mnemonic properties demanded by recognition and retrieval, which is consistent with the perceptual-mnemonic view envisaged by the representational account of memory (Bussey and Saksida, 2007).

6.5 Towards the representational account of memory and perception

The primary aim of this thesis was to advance our conceptual understanding of memory and perception, with an emphasis on establishing the neural correlates underpinning the cognitive processes involved in visual associative memory. Two fundamentally different memory models were tested and served as frameworks for the interpretation of our results: the modular account (Squire and Wixted, 2011) and the representational account of memory (Bussey and Saksida, 2007). Using the examples of synaesthesia and aging, we demonstrated across four experiments (Chapters 2 – 5) that sensory-perceptual abilities translated into visual associative memory, which is consistent with the representational account of memory.

The novel contribution of this thesis was two-fold: first, our studies contribute to the synaesthesia literature, extending synaesthesia-specific theories of perception to associative memory (Rothen et al., 2012). Second, our results extend the representational account of memory to posterior regions in the VVS by showing differences between synaesthetes, young and older adults in early visual regions during associative retrieval, recognition and working memory.

6.5.1 Behavioural support for the representational account of memory

Our two behavioural investigations in Chapters 2 and 3 revealed that associative learning and memory were underpinned by sensory-perceptual differences between synaesthetes, young and older adults. The fact that we found perceptual influences on learning and memory across two behavioural paradigms (with different participants), further adds to the reliability of our findings. Moreover, across the two studies we manipulated the perceptual-mnemonic demands of our trial-and-error learning paradigm, with direct influences on stimulus discriminability and on the effectiveness of learning and memory. For example, in Chapter 2, participants engaged in a two alternative forced-choice associative learning task *without* prior stimulus exposure. Here, we found a learning advantage of synaesthetes relative to older adults in the similar condition that was not found for the comparison of young and older adults. By contrast, in Chapter 3, participants

received a one-off exposure to the stimulus pairs that was followed by a four alternative forced-choice task. In this study, synaesthetes showed a learning advantage in the dissimilar condition relative to older adults. Thus, the additional stimulus exposure (in Chapter 3) enabled the synaesthetes to extract perceptual cues of abstract pair-associates a priory, which subsequently assisted in discriminating dissimilar pair-associates from a range of other dissimilar shapes. In other words, by manipulating the perceptual-mnemonic demands of our trial-and-error learning paradigm, we were able to demonstrate the effects of perception on stimulus discriminability. Comparing the associative retrieval results across our two studies leads to similar conclusions: slower learning of dissimilar pair-associates by synaesthetes in the two alternative forced-choice task (Chapter 2) translated into a retrieval advantage of dissimilar pair-associates relative to older adults. By contrast, faster learning of dissimilar pair-associates by synaesthetes in the four alternative forced-choice task (Chapter 3) yielded no significant retrieval advantage relative to the other two groups. Instead, we found that young adults, who required a larger number of Runs during learning, outperformed the other two groups at retrieval. What our findings demonstrate is that enhanced perceptual learning, whether caused by synaesthesia or through enhanced training and stimulus exposure, translated into improved associative retrieval, which is consistent with the perceptual-mnemonic view of the representational account of memory (Bussey and Saksida, 2007).

6.5.2 fMRI support for the representational account of memory

Our comparison of young synaesthetes, young and older adults offered a novel approach to manipulating sensory-perceptual mechanisms between groups and testing the effects of this manipulation on the neural correlates of memory. Group differences at associative retrieval and recognition (Chapter 3) were most prominent in early visual areas, including the cuneus and occipital-temporal regions. These regions converge with areas in which synaesthetes show enhanced sensitivity (Barnett et al., 2008) and excitability (Terhune et al., in press; Terhune et al., 2011), and in which older adults demonstrate reduced neural specificity (Park et al., 2004; Park et al., 2010; Park et al., 2012). Posterior visual regions have classically been ascribed a role in visual perception by the modular account of memory, with no envisaged function in visual memory (Squire, 1994). However, the fact that we found

group differences in occipital-temporal areas during associative retrieval and recognition, suggests that memory and perception are underpinned by a continuum of neural substrates in the ventral visual stream, as outlined by the representational account of memory (Bussey and Saksida, 2007). Further support for this argument is warranted by the synaesthetes' reverse activation patterns during retrieval and recognition: the synaesthetes' reduced activation relative to controls during associative retrieval suggested that the enhanced sensitivity in visual cortex gave rise to a more differentiated and efficient neural network. By contrast, the enhanced activity in early visual regions during recognition reflected the synaesthetes' enhanced sensitivity to external, behaviourally relevant stimuli. In other words, the synaesthetes' approach to memory (retrieval and recognition) was driven by the underlying perceptual sensitivity in occipito-temporal cortex.

Similar findings were observed in Chapter 5 when examining the neural correlates of WM and visual imagery. Across two WM-tasks, we found reduced frontal and occipital-temporal activation in synaesthetes relative to controls (young and older adults), suggesting that enhanced perceptual mechanisms (as in synaesthesia) required less top-down control from PFC and showed greater specificity in early visual regions during WM-maintenance. This effect was further borne out in a significant group by task interaction in the IT-cortex: Older adults showed enhanced activity relative to young adults during DPA-related WM, while activity during DMS-related WM was comparable between the two groups. DPA-related WM involved the retrieval and maintenance of dissimilar pair-associates, therefore posing additional memory demands over DMS-related WM. The older adults' enhanced activity might reflect reduced age-related neural specificity and/or efficiency of neural networks in IT-cortex (Park et al., 2004; Park et al., 2010; Park et al., 2012) that made the discriminability and maintenance of stimuli from a set of dissimilar pair-associates particularly challenging. Compared to controls, the synaesthetes' activation in IT-cortex did not differ between DMS and DPA-related WM. This might reflect the heightened neural specificity in synaesthetes, showing enhanced representations of fractal images in IT-cortex that were less affected by discriminability.

Taken together, our findings across two fMRI studies (Chapters 3 and 5) show that when cognitive processes were directed towards internal representations (associative retrieval and DPA-related WM), synaesthetes showed reduced activation

in posterior regions of the VVS. These brain areas coincide with the location where synaesthesia-specific processing advantages emerge (Barnett et al., 2008; Terhune et al., in press). Our findings are consistent with the suggested link between perception and memory in synaesthesia (Rothen et al., 2012), showing that the same neural substrates that facilitate perceptual processing in synaesthetes underpin their generic memory advantage for non-synaesthesia inducing stimuli. Within the theoretical context of associative memory, the findings of our between-group design extend the perceptual-mnemonic principle of the representational account of memory to posterior visual regions. Moreover, our findings demonstrated that the synaesthetes' perceptual processing advantages might underpin an overall network efficiency across the brain, manifested with reduced activation in frontal regions during WM (Figures 4 and 5, Chapter 5) and associative retrieval (Figure 4, Chapter 3), as well as by reduced parietal activation during associative retrieval (Figure 4, Chapter 3).

In Chapter 4 we demonstrated that the perceptual-mnemonic principle of the representational memory account extended to the hippocampus. Comparing a group of young and older adults, we tested the modular account of memory in its prediction that the hippocampus has a role in declarative memory, but is not involved in visual perception (Squire and Wixted, 2011). In young adults, the hippocampus showed a stable activation pattern in response to similar and dissimilar pairs, but exhibited different functional coupling with neocortical regions to support associative retrieval of varying memory load. Contrary to suggestions by the modular account of memory, this finding indicated a perceptual role of the hippocampus in response to fractals that was unaffected by the discriminability of well-trained similar and dissimiliar stimulus pairs. Instead, retrieval accuracy of stimuli with varying stimulus discriminability was determined by the strength and the dynamics of hippocampal connectivity with other neocortical regions (cf. King et al., 2015). The fact that older adults showed a significant activation increase in response to dissimilar relative to similar pair retrieval suggests an attempt to compensate a perceptual deficit in discriminating dissimilar pair-associates from a range of familiar stimuli. The age-related perceptual deficit of the hippocampus was further evident by a deficient allocation of hippocampal resources to other cortical networks: older adults reached a resource ceiling at low memory load by hippocampal coupling with frontal-parietal regions, which in young adults was only observed at high memory load. Our findings

suggest a role for the hippocampus in the perceptual discrimination of complex stimuli, which is consistent with the representational account of memory (Bussey and Saksida, 2007).

6.6 Limitations and Future Directions

The results of our behavioural and fMRI investigations are based on a between-group design that includes a specific sample of the population (grapheme-colour synaesthetes) and a small stimulus set, which therefore bear some limitations to the inferences we can draw about associative memory.

The reason why our group differences were mainly found in posterior visual regions (across retrieval, WM and recognition) might be due to the fact that grapheme-colour synaesthesia is a trait most susceptible to low-level stimulus changes that are manifested in early visual regions. These posterior regions are also the location where synaesthesia effects have been reported (e.g. the letter and colour area), and where enhanced processing mechanisms originate (in early visual cortex, Barnett et al., 2008; Terhune et al. 2011; Terhune et al., in press). Likewise, the neural dedifferentiation in older adults' occipital-temporal regions (Goh, 2011; Park and McDonough, 2013) counteract the synaesthetes' enhanced specificity precisely in these areas. Thus, by comparing synaesthetes against older adults, our studies were designed to reveal the perceptual-mnemonic processes in posterior regions of the VVS, but were limited in detecting differences in MTL regions. Related to this argument is the sequential stimulus presentation in our DPA and DMS-paradigm, which did not elicit activation differences within PRC and between PRC and the hippocampus, as discussed in sections 6.2 and 6.3. To overcome these limitations, future research should use between-group designs and memory tasks targeting the MTL. For example, future studies could employ a design that compares young adults, middle aged and older adults in order to capture the transient effects of reduced perception on memory [cf. (Evans et al., 2014)]. Moreover, studies could use memory experts to compare retrieval strategies for visual stimuli with varying levels of discriminability [cf. (Minati and Sigala, 2013)]. In order to tease out the effects of similarity on MTL regions, future recognition tests might benefit from simultaneous stimulus presentations rather than using a DPA paradigm as in our studies. With

respect to synaesthesia, future memory research should aim for a between-group design that compares young and older synaesthetes against young and older controls, thereby allowing parallel comparisons of the effects of aging and synaesthesia on the neural correlates of associative retrieval.

Although we showed a generic memory advantage in synaesthetes (by using achromatic abstract stimuli that did not elicit synaesthesia), it cannot be ruled out that the effects are largely due to an entirely different network in synaesthetes that cannot easily be extrapolated to the general population. Enhanced intrinsic functional connectivity in synaesthetes relative to controls (Dovern et al., 2012) as well as different white-matter distributions across the synaesthetic brain (Whitaker et al., 2014) could have influenced the activation differences between young and older adults in such a way that they were not merely an effect of enhanced perceptual mechanisms in posterior visual regions, but supported by a wider network. Given that this was the first fMRI investigation of synaesthesia and generic memory, future research could examine if memory in synaesthetes is indeed underpinned by the same neural substrates that give rise to synaesthesia. For example, we predict that an fMRI study, which tests synaesthetes on verbal memory tasks that induce colour photisms, would find activation in colour area V4, as was demonstrated by numerous fMRI studies testing synaesthetes in the perceptual domain (Rouw et al., 2011). Using this approach would therefore not only extend the synaesthesia literature from perception to memory, but further probe and verify the perceptual-mnemonic view of the representational memory account.

Two further methodological limitations of our project are worth noting. The first relates to the fMRI data acquisition using a 1.5T scanner, and the second to the small stimulus set of 8 pair-associates.

In section 6.3 we discussed the issues of data acquisition at low field strength (1.5T) and at a conventional resolution of 3 x 3 x 3mm^3 isotropic voxels. While low field strength reduces the signal-to-noise ratio (SNR) during data collection, the relatively low spatial resolution of 3 x 3 x 3 mm^3 voxel size is less specific to the functional properties occurring within each voxel. Specifically, the lower spatial resolution might be problematic for imaging small ROIs, such as subregions in the MTL. While this problem can be alleviated with high resolution functional imaging at

1 x 1 x 1 mm^3 voxel sizes (Carr et al., 2010), it comes at the cost of longer data acquisition and might therefore only be appropriate for research questions targeting specific ROIs. Given that our fMRI studies addressed broader questions relating to the neural correlates of VAM (and included whole-brain and ROI analysis), the use of high resolution fMRI, or imaging specific sections of the brain (e.g. the MTL) would have been inappropriate. Perhaps more important for the comparison of findings is to bear in mind that result similarities and/or differences between studies might be underpinned by scanner and data acquisition parameters rather than physiology [see example comparison between our findings and those of Lech and Suchan (2014) discussed in section 6.3]. Given that this is the first fMRI study examining synaesthetes on a memory paradigm, future studies that build on our research are therefore particularly advised to evaluate their findings in the light of potential scanner and data acquisition differences over and above the differences relating to the neural correlates in synaesthesia.

The choice of our stimulus set with 8 pair-associates was determined by our aim to examine the neural correlates of *successful associative retrieval*. Unlike recognition paradigms that typically employ several hundred pair-associates (Kirwan and Stark, 2004), 8 pair-associates can be learned to criterion within reasonable time of approximately 30 minutes. Specifically, our choice was based on well-known visual associative memory tests that typically employ between 6 pairs [Wechsler Memory Scale (Wechsler, 1987), Visual association test (Lindeboom, 2001)] and 8 pairs [Cambridge Automated Neuropsychological Battery, pair-associate learning – CANTAB PAL (Blackwell et al., 2004)]. The small stimulus set enabled us to achieve high performance accuracy in our DPA-paradigm across synaesthetes, young and older adults. This ensured a high number of trials to be included in the fMRI analysis (increasing signal strength) and to effectively examine the neural correlates of successful associative retrieval. However, using a small stimulus set limited us in our ability to address questions relating to false memory (examining false alarms) or forgetting (examining misses), given the small number of unsuccessful trials in our data. To further test the representational account of memory and examine the perceptual-mnemonic mechanisms during false memory and forgetting, future research should employ recognition paradigms with larger stimulus sets (Kirwan and Stark, 2004).

6.7 Implications

6.7.1 Implications for dementia

The findings reported in this thesis, which support the representational account of memory, have implications for our understanding of dementia. Dementia is still largely associated with MTL lesions affecting long-term declarative memory processes, based on the longstanding taxonomy of the modular account of memory (Squire, 1994). However, as reviewed in the General Introduction (section 1.2.3), neuropsychological studies reveal that MTL patients are not merely impaired in memory, but also show deficits in perception (Saksida and Bussey, 2010). Moreover, memory deficits are not just the result of MTL lesions, but can be found after lesions in posterior regions of the VVS: as discussed in section 6.4, non-human primate data demonstrates a role of the anterior IT in perceptual categorization of visual objects (Sigala and Logothetis, 2002), as well as in visual object recognition (Li et al., 1993). Moreover, the evidence suggests that the impairments in memory and perception are stimulus-specific and reflect the type of dementia sustained by patients. For instance, Lee et al. (2006) showed that patients with Alzheimer's Disease (AD), who had atrophy in the hippocampus but not the PRC, performed poorly on spatial scene discriminations but were able to discriminate faces. By contrast, patients with semantic dementia (SD), with atrophy in the PRC but not the hippocampus, performed poorly on face but not spatial scene discriminations. This compelling double dissociation is in line with the representational-hierarchical view [Figure 4 in section 1.2.3 (Saksida, 2009)] showing that perirhinal lesions impair feature discriminations of objects and faces, while hippocampal lesions impair discriminations of progressively more complex spatial elements (see also (Lee et al., 2005). Our research extended the representational-hierarchical view to posterior visual brain regions, showing double-dissociations in associative retrieval, recognition and WM that were underpinned by differences in perceptual abilities in aging and synaesthesia. The implication of this research is that dementia should not be treated as a categoric memory problem, but one that is also underpinned by perceptual deficits. The so-called declarative memory problems experienced by hippocampal patients such as H.M. (Scoville and Milner, 1957) are only confirming the representational-hierarchical view in its suggestion that hippocampal damage would

yield the most severe perceptual-mnemonic problems, given its location at the apex of the visual processing hierarchy and its related function in processing complex object, spatial, and presumably also conceptual associations. On the other hand, priming effects observed in object and colour recognition tests, as found in H.M. (Milner, 1970) and patients with AD (Lloyd-Jones, 2005), are considered non-declarative by the modular account of memory (Squire, 1994). However, the priming effects are clearly indicative of visual memory, with the difference that these recognition problems are not resolved by the hippocampus but at lower levels of the visual hierarchy. In line with our research showing perceptual and memory differences in posterior visual processing regions between aging and synaesthesia, dementia might better be defined according to the perceptual-mnemonic deficits observed in patients, rather than be classified as a declarative or non-declarative memory problem.

6.7.2 Implications for cognitive interventions

Reframing our understanding of dementia within the perceptual-mnemonic view (Bussey and Saksida, 2007) has important implications for cognitive interventions in preventing or arresting memory decline in aging in dementia, respectively. The desired aim of most cognitive intervention studies is to develop training regimes that show transfer effects to other cognitive processes (Park and Bischof, 2013). However, based on the stimulus-type principle envisaged by the representational account of memory, transfer effects across different stimulus types would not necessarily be expected, because the same neural substrates involved in perceptual processing of specific classes of stimuli are also involved in their higher level mnemonic processing (i.e. WM, visual imagery, associative memory; (cf. Owen et al., 2010). Yet, the prevailing lack of theoretical guidance often leads to poor design and vague result interpretations in cognitive training studies. For instance, Buschkuehl et al. (2008) trained older adults on a visual WM-task using coloured squares and animal stimuli. Transfer effects were found on a mental tracking task with coloured dots, and on a visual free recall task. However, no transfer was found when the test stimuli were of entirely different nature, including a digit-span or verbal free recall test. The authors concluded that "*since the transfer to WM was limited to the visual domain, we assume that the overall transfer to WM was not strong enough*

to also result in reliable transfer effects in episodic memory or in transfer effects that go beyond the visual domain. [...] it might be that more efficient WM training would be able to yield stronger performance increases in episodic memory" (Buschkuehl et al., 2008; p. 705). However, the results of this study more likely suggest that training on specific types of (visual) stimuli strengthened the representations of these stimuli in the underpinning neural substrates, which subsequently improved visual WM and visual memory alike. We suggest that future cognitive interventions might benefit from systematic matching of stimuli and brain regions for which training is desired. For example, it could be envisaged that perceptual detection tasks of stimulus features would target early visual regions; visual discrimination tasks with complex features would target the PRC, and spatial navigation tasks might target the hippocampus. With the implementation of specific stimulus types in intervention studies, we would then expect transfer effects from the visual perceptual to the visual memory domain, based on the perceptual-mnemonic principle of the representational memory account. In fact, these effects have been demonstrated, as described in the above study by Buschkuehl et al. (2008), as well as by others. For instance, Berry et al. (2010) trained older adults on perceptual discrimination of high spatial frequency Gabor patches with low-level features such as changing orientation and colour. Following training, the trained group outperformed the control group on the perceptual task, as expected. However, relative to the control group, the trained group also performed significantly better on a visual WM-task that used similar low-level features such as moving dots. Moreover, EEG recordings during the WM-task revealed a significant decrease in the N1-amplitude for trained participants vs. controls, which was not present before the training. The N1 is an early visual component that is sensitive to visual and motion stimuli. Berry et al.'s findings therefore suggest transfer effects of visual perception to visual WM-tasks, underpinned by neural plasticity in corresponding early visual processing regions. Interestingly, neural plasticity in early visual cortex (V1 –V3) can also be induced by using visual imagery, i.e. in the absence of external perceptual stimuli. Providing neurofeedback, Geraint Rees and colleagues (Scharnowski et al., 2012) trained young adults in imagining high spatial frequency Gabor patterns in order to up-regulate visual cortex activity in one hemisphere. Compared to a control group and a group of non-successful imagers, the successful up-regulators were able to sustain up-regulation without neurofeedback in subsequent transfer trials, and showed

significantly enhanced perceptual sensitivity in detecting near-threshold stimuli presented to the contralateral hemifield of the trained cortical region. Thus, consistent with the representational view of memory (Bussey & Saksida, 2007), these results show a feature-selective stimulus representation that can selectively be refined to meet perceptual as well as mnemonic (imagined) demands in posterior regions as early as V1.

The above findings also relate to synaesthesia, which is manifested with enhanced sensitivity in early visual regions, resulting in altered perception (Barnett et al., 2008), enhanced memory for non-synaesthesia inducing shapes (Pfeifer et al., 2014), as well as more efficient retrieval and visual imagery strategies in visual cortex (Chapters 3 and 5). Taken together, cognitive interventions should be targeted to individual needs and might take the form of various designs and stimuli depending on the brain structure to be refined. Guided by the theoretical principles of the representational memory account (Bussey and Saksida, 2007), future cognitive interventions that systematically match the stimuli with the underlying neural representations would be expected to show transfer effects from perception to higher-level mnemonic processes.

6.8 Conclusion

In conclusion, the results of our four experiments advance our conceptual understanding of memory and perception and extend the representational account of memory to posterior visual regions in the brain. Using three participant groups (young adults, young synaesthetes and older adults), each of which have their respective strengths and weaknesses in memory and perception, we demonstrated that enhanced perceptual mechanisms (as in synaesthesia) translated into improved VAM. Specifically, this was shown across four constituent cognitive processes involved in VAM: visual associative learning, retrieval, recognition and working memory. Behaviourally, we found improved associative learning and retrieval that was facilitated by enhanced perceptual mechanisms, induced either via synaesthesia or via enhanced training and stimulus exposure. In fMRI, we found that internally directed memory processes (WM and associative retrieval) were associated with reduced activation in synaesthetes' posterior visual regions, reflecting greater neural

efficiency in synaesthetes relative to controls. By contrast, externally directed memory processes (associative recognition) were associated with enhanced activation in posterior visual regions, reflecting the synaesthetes' enhanced sensitivity that was previously found in early visual cortex for perceptual tasks (Barnett et al., 2008). Finally, our comparison of young and older adults suggested a role for the hippocampus in the perceptual discrimination of complex stimuli, which challenges the modular account of memory in its prediction that the hippocampus is purely involved in long-term declarative memory processes. Together with other empirical data (Bussey and Saksida, 2007; Saksida and Bussey, 2010), our findings point to the need for a revision of the role of posterior visual regions in perception and the hippocampus in memory, and put forward a perceptual-mnemonic continuum in brain regions along the VVS that represents specific feature complexity and classes of stimuli.

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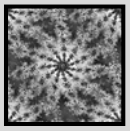
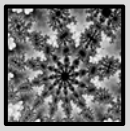
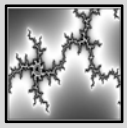
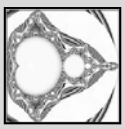
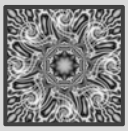
Appendix

Stimulus selection

Visually similar pair-associates					
		Similarity rating			**Similarity rating**
1a	1b		5a	5b	
		4.35 (0.93)			3.80 (0.89)
2a	2b		6a	6b	
		4.25 (0.79)			3.70 (0.80)
3a	3b		7a	7b	
		4.15 (0.81)			3.65 (0.98)
4a	4b		8a	8b	
		3.85 (0.74)			3.20 (0.83)

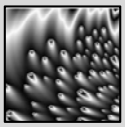
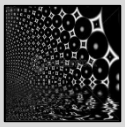
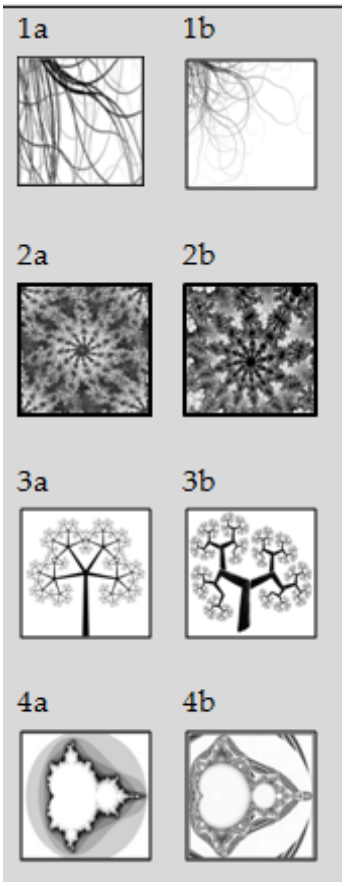
Visually dissimilar pair-associates					
		Similarity rating			**Similarity rating**
9a	9b		13a	13b	
		1.00 (0.00)			1.35 (0.59)
10a	10b		14a	14b	
		1.05 (0.22)			1.45 (0.51)
11a	11b		15a	15b	
		1.25 (0.44)			1.45 (0.60)
12a	12b		16a	16b	
		1.30 (0.57)			1.60 (0.68)

Figure 1. Mean ratings (and standard deviations) of visual similarity for the set of 16 pair-associates considered for the fMRI study. Ratings were given on a 5-point Likert-scale, with 5 indicating highest similarity and 1 indicating lowest similarity.
Using a Wilcoxon signed-rank test, results demonstrated that the eight visually similar pair-associates were rated significantly higher in visual similarity (M = 3.87; SD = .38) compared to the eight visually dissimilar pair-associates (M = 1.31; SD = .20); significance z = -2.52; *p(two-tailed)* = .012. We selected four pictures from each category with the highest and lowest scores respectively (see Figure 2 below).

Selected stimuli.

Similar pairs.



Dissimilar pairs.

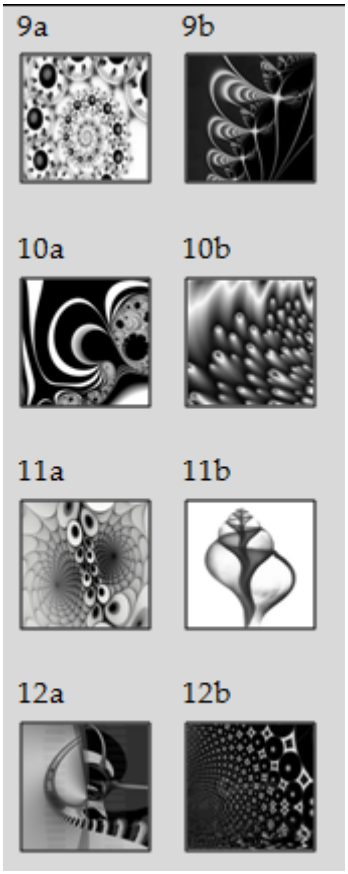


Figure 2. The 4 similar and 4 dissimilar pair-associates included in the study.

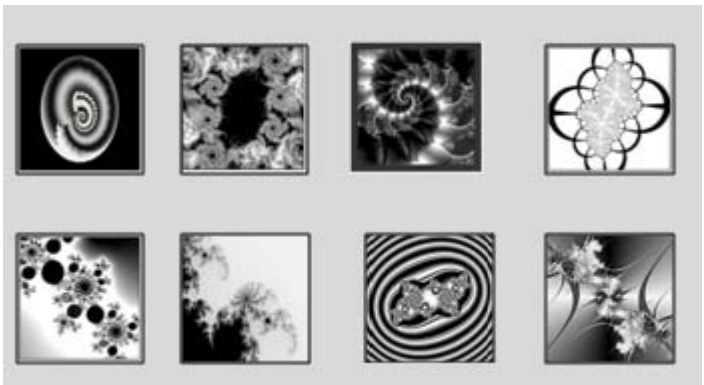


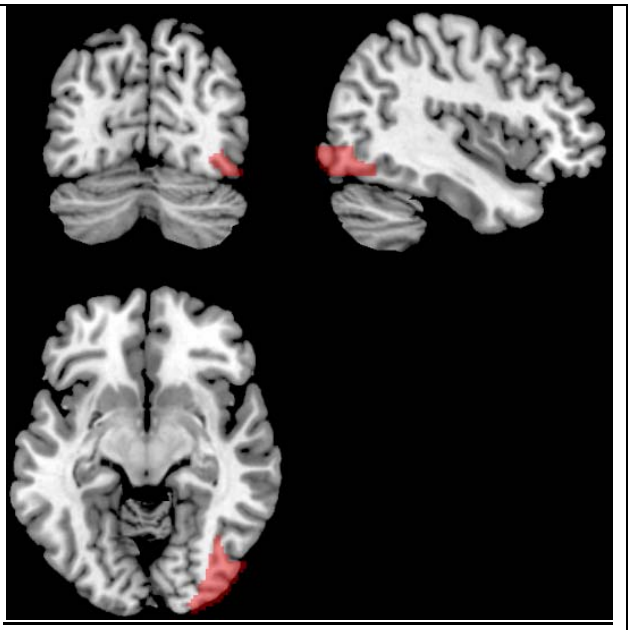
Figure 3. Eight individual fractal images used for the DMS-task.

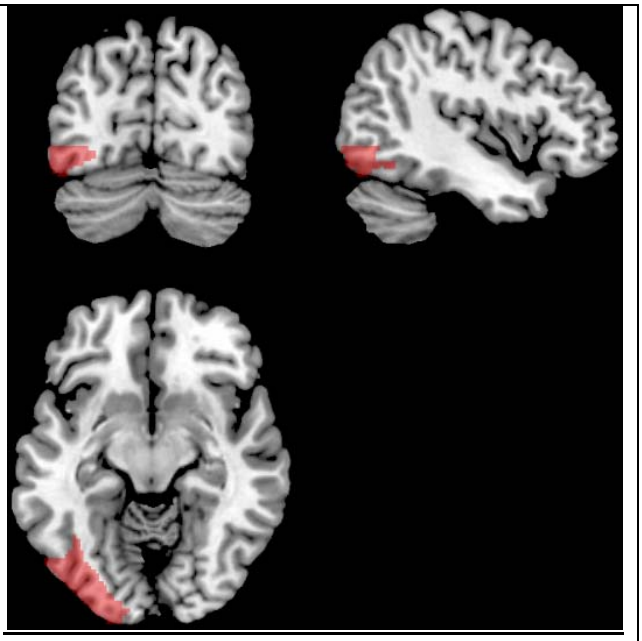
Specification of ROI-masks

Several ROIs were selected along the ventral visual pathway, which were chosen from the Anatomy toolbox v1.8, 2011 (http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html); (Eickhoff et al., 2005)) and the WFU PickAtlas v2.4 (http://www.nitrc.org/projects/wfu_pickatlas/; (Maldjian et al., 2003).

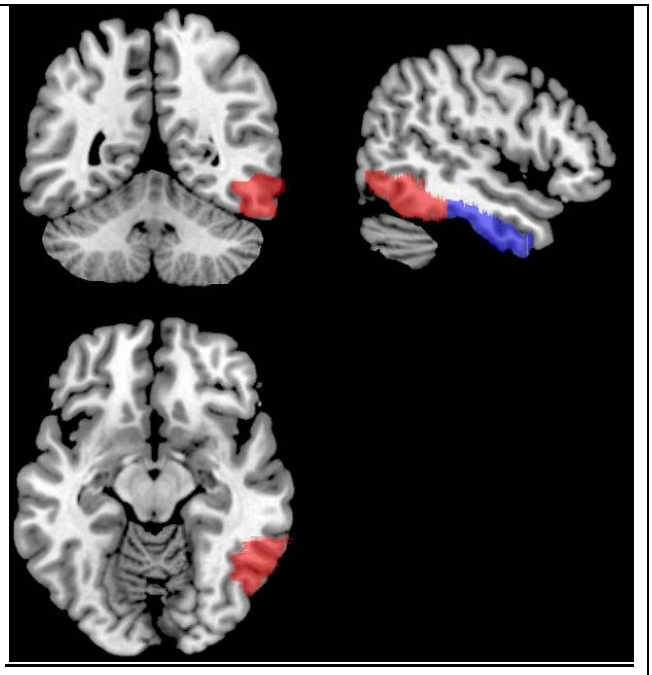
From posterior to anterior, the following MNI coordinates form the border of our ROIs:

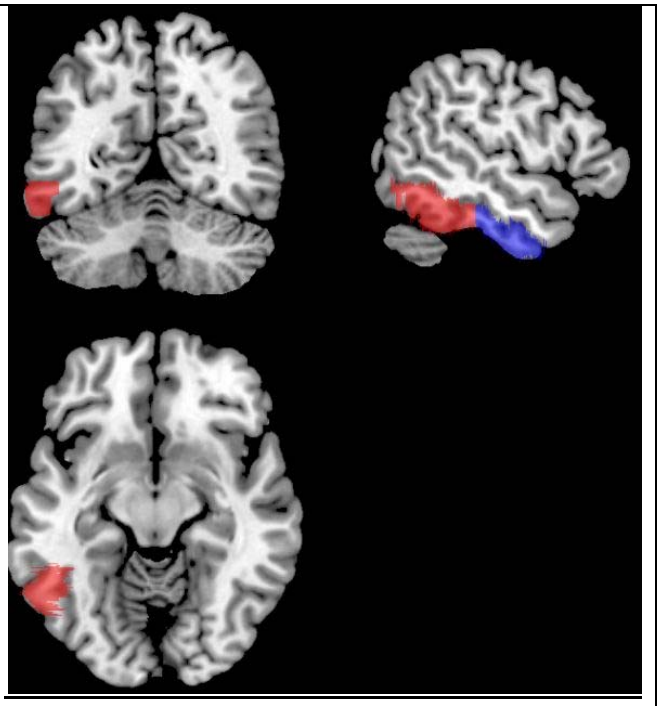
Inferior Occipital Gyrus

Right Inferior Occipital Gyrus (WFU PickAtlas) Dorsal: z= - 2 Ventral: z= - 17 Anterior: y= - 61 Posterior: y= - 101 Lateral: x=50 Medial: x=20	

Left Inferior Occipital Gyrus (WFU PickAtlas) Dorsal: z= - 1 Ventral: z= - 18 Anterior: y= - 58 Posterior: y= - 102 Lateral: x= - 56 Medial: x= - 10	

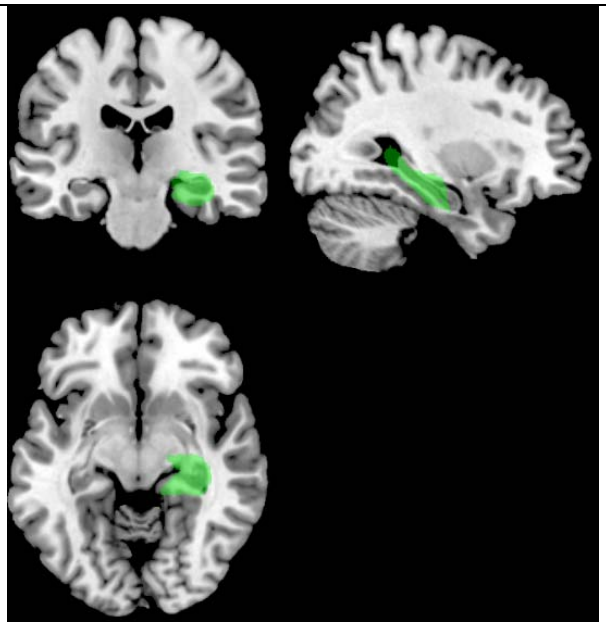
Inferior Temporal Gyrus

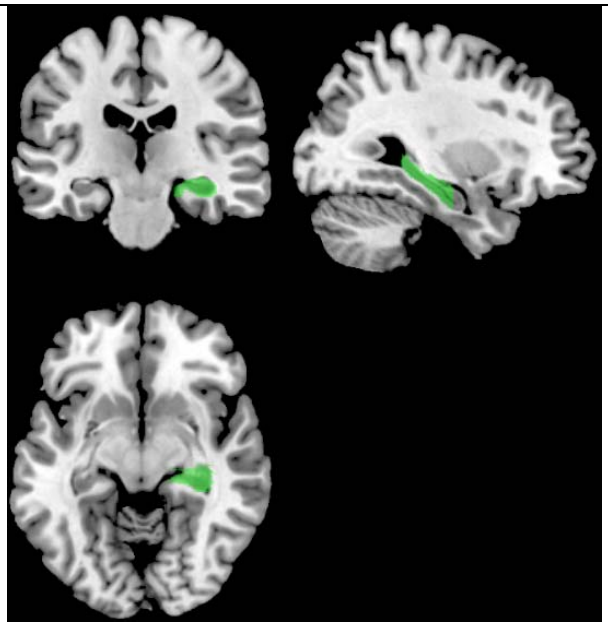
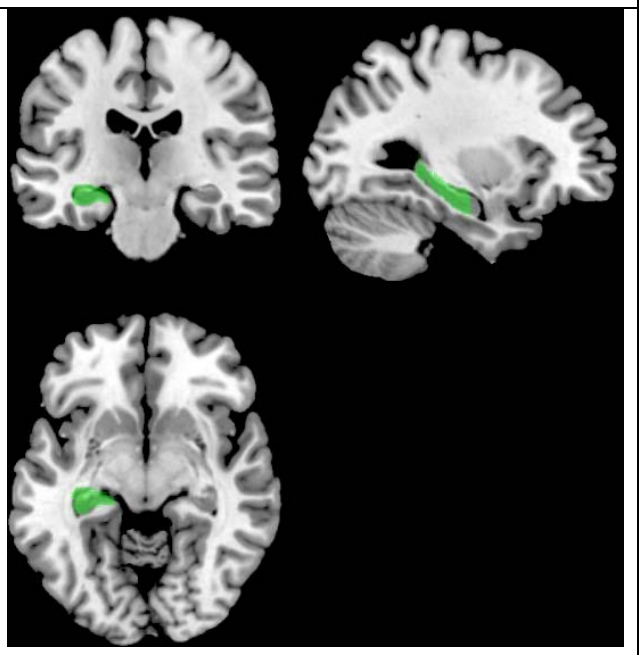
Right anterior and posterior Inferior Temporal Gyrus (WFU PickAtlas) **Anterior part :** Dorsal: z= - 13 Ventral: z= - 44 Anterior: y=11 Posterior: y= - 32 Lateral: x=68 Medial: x=26 **Posterior part:** Dorsal: z= - 3 Ventral: z= - 31 Anterior: y= - 33 Posterior: y= - 74 Lateral: x=68 Medial: x=38	

Left anterior and posterior Inferior Temporal Gyrus (WFU PickAtlas) **Anterior part:** Dorsal: z= - 16 Ventral: z= - 45 Anterior: y=15 Posterior: y= - 27 Lateral: x= - 66 Medial: x= - 31 **Posterior part:** Dorsal: z= - 6 Ventral: z= - 30 Anterior: y= - 28 Posterior: y= - 68 Lateral: x= - 71 Medial: x= - 38	

Hippocampus

The left and right hippocampus was selected from the Anatomy toolbox, encompassing the subiculum, cornu ammonis, dentate gyrus and the hippocampal-amygdala-transition-area. We applied corrections to these hippocampal ROIs in order to eliminate areas of the parahippocampal cortex, the Thalamus and the Ventricle (Example of right hippocampus shown in Box a). To correct the image, the left and right hippocampal mask of the Anatomy toolbox was overlaid on the single-subject image in MRIcron. Hippocampal masks were then handdrawn around the Toolbox masks, sparing the subiculum, but eliminating the parahippocampal cortex, Thalamus and the Ventricle (Box b and c). Two further sources were used as an anatomical guide [Cho et al., 2010, see Figure 4].

	Example right Hippocampus, Anatomy toolbox
	

	Right Hippocampus, corrected
Right Hippocampus, corrected Dorsal: z= 4 Ventral: z= - 24 Anterior: y= - 11 Posterior: y= - 40 Lateral: x=40 Medial: x=16	
	Left Hippocampus, corrected
Left Hippocampus, corrected Dorsal: z= 0 Ventral: z= - 24 Anterior: y= - 11 Posterior: y= - 40 Lateral: x= - 40 Medial: x= - 16	

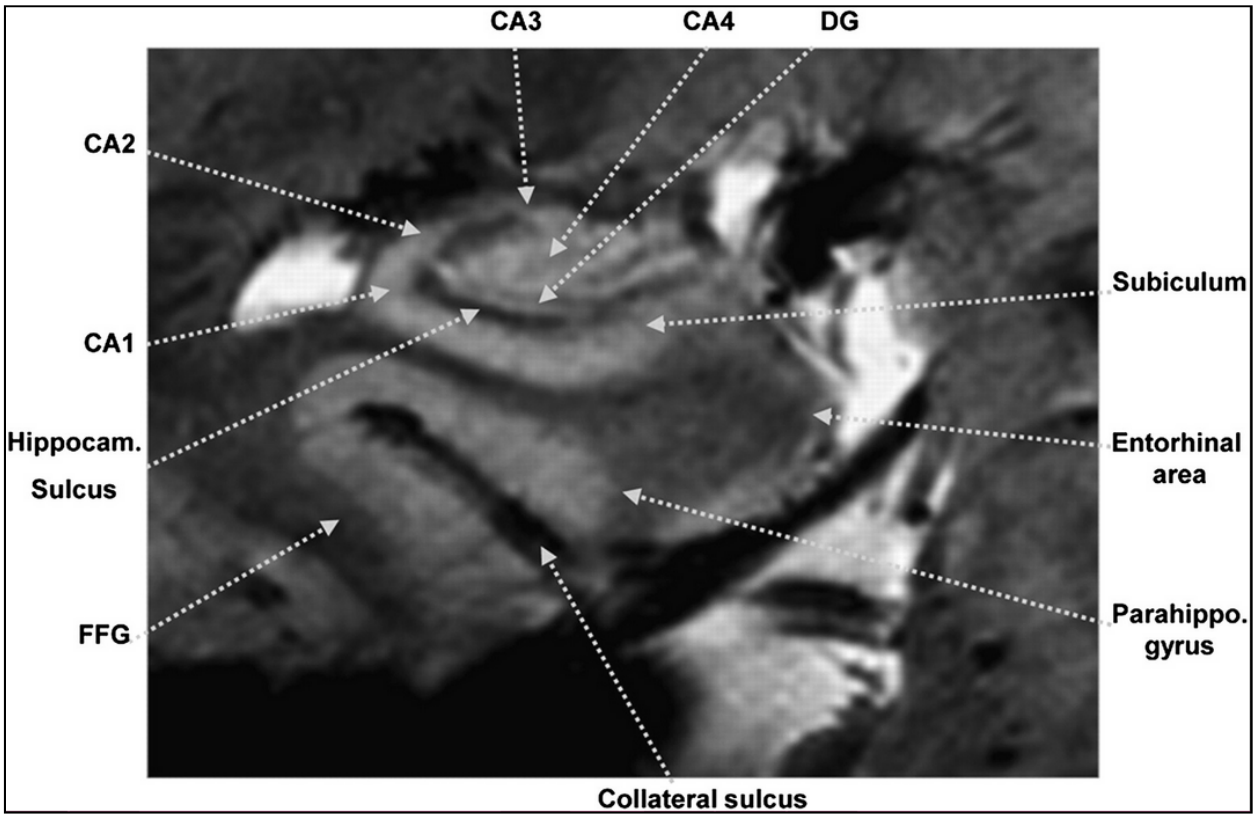


Figure 4. Coronal 7.0-T MR image of hippocampus. Hippocampal substructures such as CA1, CA2, subiculum, and CA4/DG are clearly visible. FFG = fusiform gyrus [Source: Cho et al., 2010. Substructural Hippocampal Glucose Metabolism Observed on PET/MRI. *J Nucl Med.* 2010;51:1545-1548.]

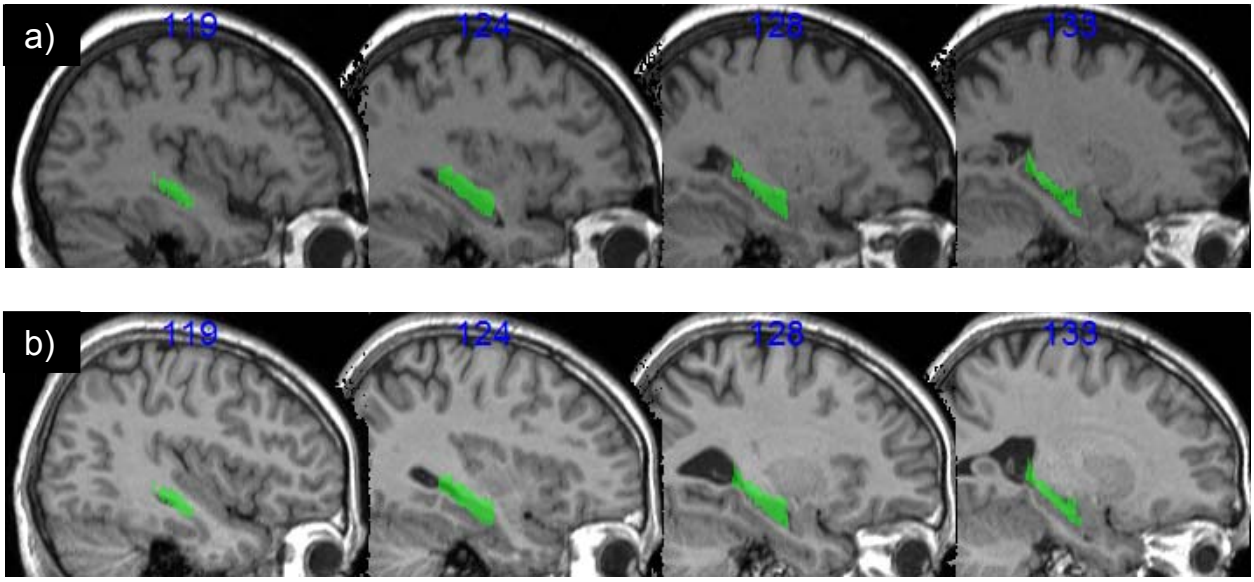
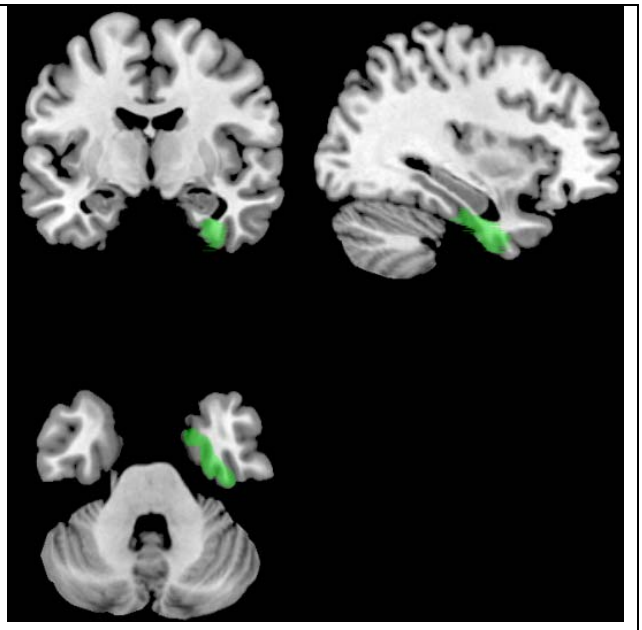
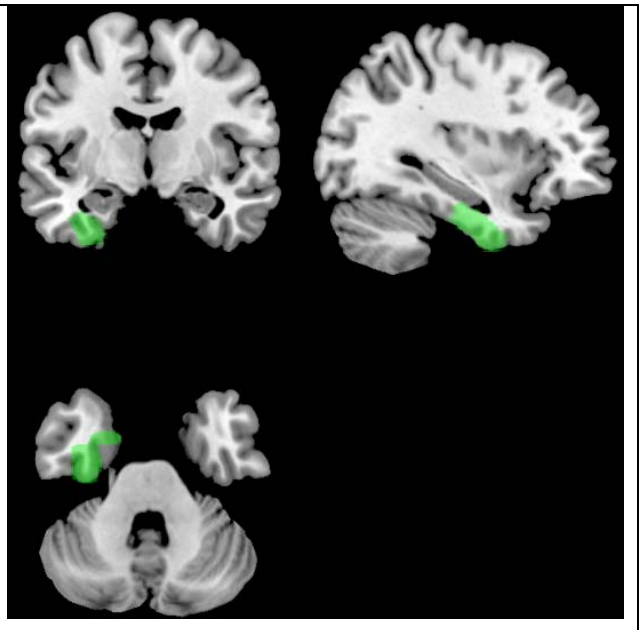


Figure 5. Corrected Hippocampal mask overlaid on two individual subjects. a) Individual subject with the least GM-volume (515.95 ml); b) Individual subject with the most GM-volume (881.40ml).

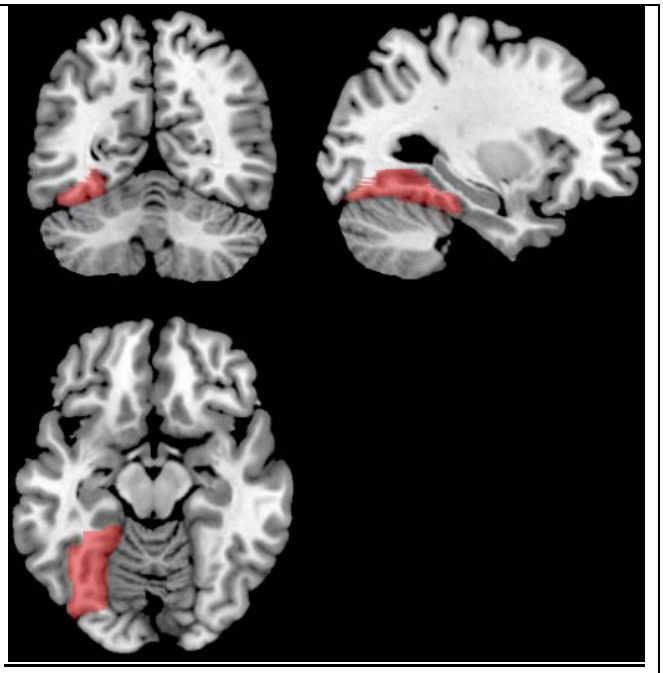
Perirhinal cortex

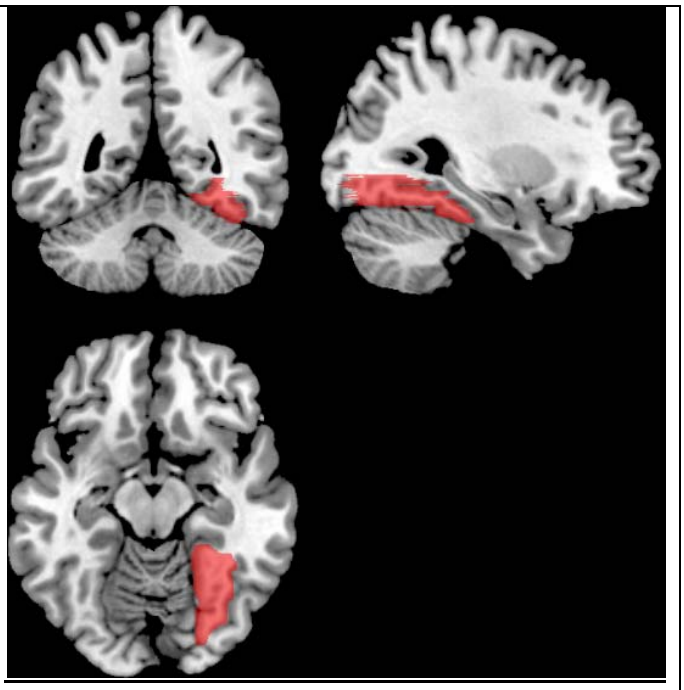
The mask for the Perirhinal cortex was taken from [Holdstock, J. S., Hocking, J., Notley, P., Devlin, J. T., and Price, C. J., 2009. Integrating visual and tactile perceptual information in the perirhinal cortex. ***Cerebral Cortex]***, available on http://www.neurolang.com/research/perirhinal-map/. The mask was separated in two unilateral masks, one for each hemisphere, bordering on the following coordinates:

Right Perirhinal cortex Dorsal: z= - 20 Ventral: z= - 52 Anterior: y= 9 Posterior: y= - 25 Lateral: x= 42 Medial: x= 17	

Left Perirhinal cortex Dorsal: z= - 20 Ventral: z= - 49 Anterior: y= 6 Posterior: y= - 24 Lateral: x= - 43 Medial: x= - 16	

Fusiform Gyrus

Left Fusiform Gyrus (WFU PickAtlas) Dorsal: z= - 3 Ventral: z= - 25 Anterior: y= - 18 Posterior: y= - 84 Lateral: x= - 49 Medial: x= - 16	

Right Fusiform Gyrus (WFU PickAtlas) Dorsal: z= - 2 Ventral: z= - 25 Anterior: y= - 15 Posterior: y= - 87 Lateral: x= 47 Medial: x= 17	

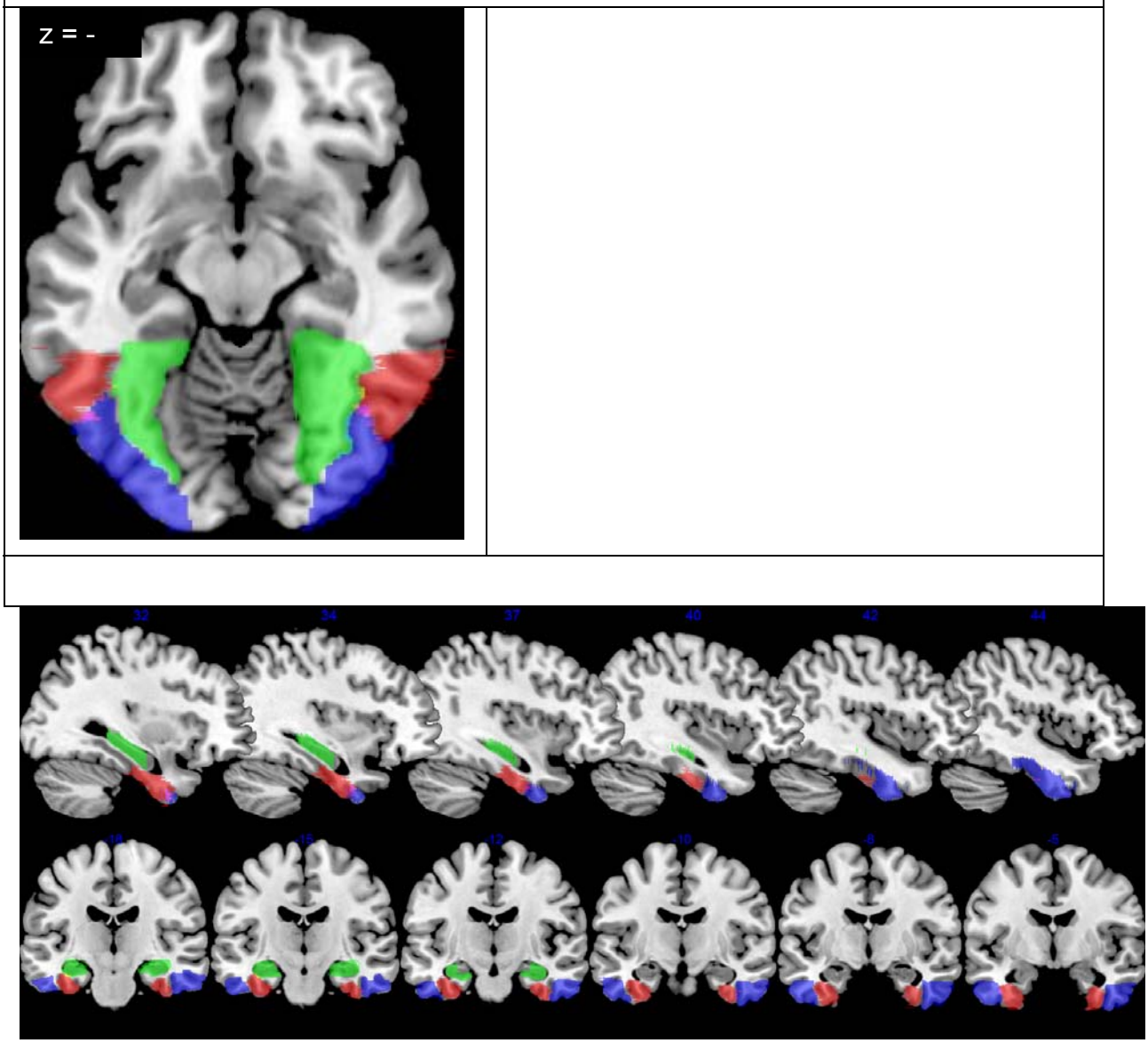


Figure 6. Six ROI masks overlaid on the individual subject's brain available in MRIcron. a) inferior occipital gyrus (blue); posterior inferior temporal gyrus (red); fusiform gyrus (green); b) Hippocampus (green); PRC (red); anterior inferior temporal gyrus (blue).

ROI Results, Grey matter

The extracted grey matter volume (ml) of each ROI was subjected to a 3 x 6 x 2 mixed ANOVA, with group (young adults, older adults, synaesthetes) as the between-subject factor and ROI (Inferior Occipital Gyrus, posterior Inferior Temporal Gyrus, Fusiform Gyrus, anterior Inferior Temporal Gyrus, PRC, Hippocampus) and hemisphere (left, right) as the within-subject factors.

Results are illustrated in Figure 7. We applied the Greenhouse Geisser correction (Greenhouse and Geisser, 1959) for non-sphericity of the within-subject variables where necessary, which is indicated by adjusted degrees of freedom. There was a significant main effect of group, $F[2,54] = 33.259$, $p < .001$, $\eta_p^2 = 0.552$. Tukey post-hoc comparisons revealed a significant difference between young and older aduts, $p < 0.001$, between synaesthetes and older adults, $p < 0.001$, but not between young adults and synaesthetes, $p = 0.981$.

Further significant effects were found as follows:

Main effect of ROI, $F[3.724, 201.088] = 6010.915$, $p < .001$, $\eta^{p2} = 0.991$

Interaction between ROI and group, $F[7.448, 201.088] = 5.051$, $p < .001$, $\eta_p^2 = 0.158$

Main effect of hemisphere, $F[1,54] = 1256.707$, $p < .001$, $\eta_p^2 = 0.959$

Interaction between hemisphere and group, $F[2,54] = 7.080$, $p < .001$, $\eta_p^2 = 0.208$

Interaction between ROIs and hemisphere, $F[3.569,192.721] = 756.816$, $p < .001$, $\eta_p^2 = 0.933$

There was no significant interaction between ROIs, hemisphere and group, $F[7.138, 192.721] = 1.030$, $p = .412$, $\eta_p^2 = 0.037$.

Significant differences between pairs of groups on individual ROIs (t-tests, reported at $p < 0.05$) are marked with an asterisk in Figure 7. In all of these ROIs, synaesthetes and young adults showed significantly higher GM volume than older adults, except in the left anterior inferior temoporal gyrus, where all 3 groups differed significantly, with synaesthetes showing the highest GM volume, followed by young adults and then older adults.

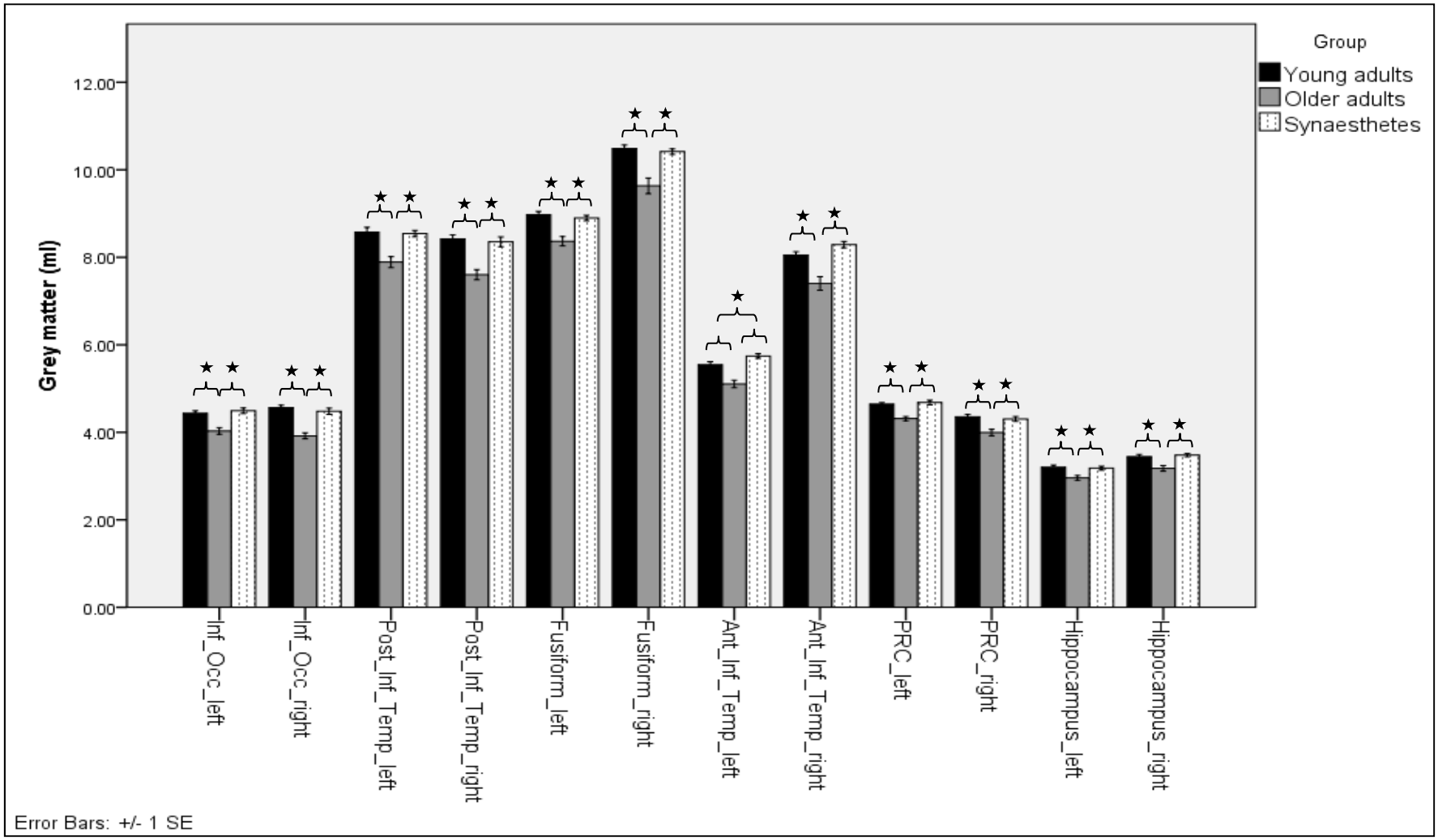


Figure 7. Mean GM volume (in ml) in 6 regions of interest, shown bilaterally for young adults, older adults and synaesthetes. Asterisks indicate significant group differences derived from t-tests on the mean GM volume for each ROI. GM = Grey matter; Inf Occ = Inferior Occipital Gyrus; Post Inf Temp = Posterior Inferior Temporal Gyrus; Fusiform = Fusiform Gyrus; Ant Inf Temp = Anterior Inferior Temporal Gyrus; PRC = Perirhinal cortex.