Investigation of the role of medial frontal cortex during episodic encoding in young and older adults

David Maillet
Integrated Program in Neuroscience
McGill University, Montreal

July 2014

A thesis submitted to McGill University in partial fulfillment of the requirements for the degree of Ph.D. in Neuroscience

Table of contents

Abstract 6

Résumé 7

Acknowledgements 10

Preface and Contribution of Authors 11

1. Introduction 13

  1.1. Anatomical definition of mFC 14

  1.2. Episodic memory encoding 16

    1.2.1. Definition and brief history 16

    1.2.2. Activation in mFC during episodic encoding in young adults 18

  1.3. Association between mFC and task-unrelated thoughts in young adults 20

    1.3.1. Task-unrelated thoughts 20

    1.3.2. Terminology 21

    1.3.3. Occurrence and impact of TUT on task performance 22

    1.3.4. Evidence that mFC is involved in TUT in young adults 25

    1.3.5. Evidence that mFC is involved in TUT during episodic encoding in young adults 26

  1.4. Association between mFC and self-referential encoding in young adults 26

  1.5. Reconciling distinct perspectives regarding the role of mFC during episodic encoding 28

  1.6. Aging 30

    1.6.1. Age-related changes in episodic memory 30

    1.6.2. Age-related changes in mFC during episodic encoding 31

    1.6.3. Age-related changes in TUT 33

    1.6.4. Age-related changes in self-referential processing 35

  1.7. Overview of the four studies in this Thesis 37

  1.8. References 39

2. Study 1: Dissociable roles of default-mode regions during episodic encoding 50

  2.1 Preface 50

  2.2 Abstract 50

  2.3. Introduction 51

  2.4. Methods 55

2.4.1. Subjects 55
2.4.2 Behavioral methods 55
2.4.3. fMRI data acquisition 58
2.4.4. Event trial classification 59
2.4.5. Reaction time 60
2.4.6. Retrieval performance 60
2.4.7. fMRI data preprocessing 61
2.4.8. fMRI general linear model 61
2.4.9. fMRI analysis of regions involved in the main effect of subsequent memory, encoding task, and subsequent memory by encoding task interaction 62
2.4.10. fMRI analysis of regions involved in TUT 63
2.5. Results 64
2.5.1. Encoding reaction time 64
2.5.2. Retrieval accuracy and reaction time 65
2.5.3. fMRI results: Main effect of encoding task 67
2.5.4. Main effect of subsequent source memory 69
2.5.5. Task by subsequent source memory interaction 71
2.5.6. Regions involved in exhibiting TUT during episodic encoding 72
2.6. Discussion 73
2.6.1. Behavioral results 73
2.6.2. Left dorsomedial PFC and angular gyrus are activated to a greater extent in correct vs. incorrect encoding across tasks 75
2.6.3. Left ventral mPFC is activated to a greater extent in correct vs. incorrect encoding using a pleasantness task 77
2.6.4. PCC is involved both in encoding failure and exhibiting TUT 78
2.7. Conclusions 81
2.8. References 81
3. Study 2: Age-related changes in the three-way correlation between anterior hippocampus volume, whole-brain patterns of encoding activity and subsequent context retrieval 88
3.1. Preface 88
3.2. Abstract 89
3.3. Introduction 90
3.4. Methods 92

3.4.1. Subjects 92
3.4.2. Behavioral procedure 93
3.5. Results 98
3.5.1. Neuropsychological results 98
3.5.2. Behavioral results 99
3.5.3. Volumetric results 100
3.5.4. PLS results 101
3.6. Discussion 107
3.6.1. Young adults: three-way association between HH volume, encoding activity and retrieval accuracy 108
3.6.2. Older adults: reduced HH volume, and altered HH volume–activity–accuracy association .. 112
3.6.3. Conclusions 116
Disclosure statement 117
Acknowledgments 118
3.7. References 118
3.8. Suffix 127
4. Study 3: Age-related changes in frequency of mind-wandering and task-related interferences during memory encoding and their impact on retrieval 130
4.1. Abstract 130
4.2. Introduction 130
4.2.1. Mind-wandering and task-related interferences in older adults during memory encoding. 133
4.3. Method 136
4.3.1. Participants 136
4.3.2. Stimuli 136
4.3.3. Procedure 136
4.3.4. Data analysis 139
4.4. Results 140
4.4.1. Outliers 140
4.4.2. Encoding results 141
4.4.3. Retrieval results 144
4.4.4. Relationship between thought frequency at encoding and retrieval Pr-H: Younger adults' results 146

4.4.5. Older adults' results 147

4.5. Discussion 148

4.5.1. Young adults: Encoding task influences the content of ongoing thoughts 148

4.5.2. Older adults: Reduction in frequency of MW and TRI at encoding 151

4.5.3. Conclusion 155

4.6. References 155

4.7. Suffix 163

5. Study 4: Age-related differences in brain activity during the subsequent memory paradigm: a meta-analysis 163

5.1. Abstract 163

5.2. Introduction 164

5.3. Methods 169

5.3.1. Study selection 169

5.3.2. ALE analyses 170

5.4. Results 172

5.4.1. Study characteristics 172

5.4.2. ALE of age-invariant effects 175

5.4.3. ALE of young>old effects 179

5.4.4. ALE of old>young effects 179

5.5. Discussion 181

5.5.1. Old vs. young subsequent memory effects 184

5.5.3. Young and older adults often exhibit reversed effects in these regions 187

5.5.4. Old vs. young subsequent memory effects are associated with worse performance 190

5.5.5. Additional factors of consideration and limitations 191

5.6. Conclusions 193

5.7.References 193

6. General Discussion 203

6.1. Future directions 207

6.2. Limitations 209

6.3. References 210

Abstract

In recent years, many studies have assessed the neural correlates of episodic memory encoding. A recent meta-analysis of these studies in young adults found that activation in a number of regions including the medial frontal cortex (mFC) was greater during encoding events later forgotten vs. remembered. It has been suggested that activation in this region reflects task-unrelated thoughts that are detrimental to one's performance on episodic memory (EM) tasks. However, not all studies have reported that activation in mFC is detrimental to EM task performance. In a few studies that have used self-referential encoding tasks (e.g. pleasantness judgements), activation in mFC was greater for remembered vs. forgotten events. These studies suggest that mFC may be involved in self-referential evaluation of encoding stimuli which benefits later EM. Thus previous studies have provided conflicting evidence regarding the association between mFC activation at encoding and EM performance in young adults. Studies assessing age-related differences in activation during episodic encoding have reported age-related increases in activation in the mFC. Consistent with the young adult literature, two competing interpretations have been proposed: 1) this activation may reflect increased frequency of task-unrelated thoughts in older adults, or 2) that this activation reflects an increased tendency for older adults to process the encoding events in a self-referential manner.

This thesis describes four studies investigating the role of mFC during episodic encoding in young and older adults. In study 1, I report that activation in left ventral mFC was highest during successful self-referential encoding, intermediate during unsuccessful encoding, and lowest during successful encoding using a non-self-referential (semantic) encoding task in young adults. It is suggested that in young adults, ventral mFC activation reflects self-referential processes that can either benefit encoding (if directed to the encoding stimuli) or be detrimental to it (if directed to task-unrelated thoughts). In study 2, I assessed age differences in the neural correlates of episodic encoding using a self-referential task. Activation in a network involving mFC was related to better memory performance in young, but not older adults. In study 3, I report that older adults exhibit less task-unrelated thoughts compared to young adults during episodic encoding, inconsistent with the possibility that age-related increases in mFC reflect an increase in task-unrelated thoughts. In study 4, I performed a meta-analysis of age-related differences in activation during episodic encoding. I found that older adults consistently over-activate a region of mFC during successful encoding that in young adults is involved in unsuccessful encoding. It is suggested that older adults over-activate a set of regions including mFC during episodic encoding because of an increase in evaluative and personal thoughts and feelings related to the encoding events themselves, which they do not label as task-unrelated, and which do not necessarily result in good performance in memory tasks.

Résumé

Récemment, plusieurs études ont examiné les corrélats neuronaux de l’encodage épisodique. Une méta-analyse de ces études chez les jeunes adultes a démontré que plusieurs régions du cerveau, incluant le cortex frontal médian (cFM), est plus activé lors d’évènements qui seront oubliés vs. ceux dont les participants se souviendront. Il est possible que l’activité dans cette région du cerveau est liée à la présence de pensées n’ayant pas rapport avec la tâche en cours (e.g. dérive attentionnelle). Par contre, d’autres études ayant utilisé des tâches d’encodage subjectives (e.g. juger si les mots sont plaisants) ont démontré que l’activité dans le cFM est plus élevée pour les mots dont les participants se sont souvenus vs. ceux qu’ils ont oubliés. Ces études suggèrent que le cFM est impliqué dans l’encodage subjectif. Ainsi, les études précédentes ont fourni des

résultats contradictoires concernant l'association entre l'activation cFM lors de l’encodage et la performance des participants lors de tâches de mémoires. D’autres études examinant les différences aux corrélats neuronaux se produisant lors du vieillissement normal ont démontrées que l’activité dans le cFM est plus élevée chez les personnes âgées vs. les jeunes adultes. Deux interprétations de ce phénomène ont été suggérées : 1) l’activation plus élevée chez les personnes âgées peut refléter le fait que ces derniers ont plus de dérives attentionnelle, ou 2) l’activation plus élevée chez les personnes âgées peut refléter le fait que ces derniers portent attention à des détails plus subjectifs des évènements.

Dans cette Thèse, je présente quatre études investiguant le rôle du cFM lors de l’encodage chez les jeunes adultes et les personnes âgées. Dans l’étude 1, j’ai trouvé que l’activité dans le cFM était plus élevé lors de l’encodage subjectif réussi, intermédiaire lors de l’encodage non-réussi (les mots oubliés), et à son plus bas niveau lors de l’encodage non-subjectif réussi. Je propose que le cFM est impliqué dans des procédés de référence personnels subjectifs (*self-referential processing)* qui peuvent soit bénéficier l’encodage (si ces procédés sont dirigés vers les mots) ou avoir un effet négatif sur l’encodage (si ces procédés sont impliqués dans la dérive attentionnelle*)*. Dans l’étude 2, j’ai examiné les différences d’activité dans le cFM chez les personnes jeunes vs. âgées lors de l’encodage subjectif. J’ai trouvé qu’un niveau d’activité élevé dans le cFM bénéficie l’encodage de visages seulement chez les personnes jeunes, mais pas chez les personnes âgées. Dans l’étude 3, j’ai trouvé que les personnes âgées ont moins de dérives attentionnelle que les personnes jeunes lors de l’encodage. Dans l'étude 4, j'ai effectué une méta-analyse des différences d’activation lors de l’encodage chez les personnes jeunes vs. âgées. J'ai trouvé que le mFC a un niveau d’activation plus élevé pour l’encodage réussi vs. non-réussi chez les personnes âgées, mais un niveau d’activation plus élevé pour l’encodage non-réussi vs. réussi chez les jeunes adultes. Il est suggéré que les personnes âgées ont un niveau d'activation plus élevé dans le mFC vs. les jeunes adultes lors de l'encodage réussi parce que les personnes âgées encode ces évènements en ayant des pensés plus personnelles et subjectives vis-à-vis ceux-ci.

Acknowledgements

I would first like to thank my supervisor M. Natasha Rajah. I am indebted to you for the continuous support and encouragement, especially when things were not going very well. Thank you for helping me develop my critical thinking abilities. The studies in this thesis would never have been possible if you had not always encouraged me to think on my own, even during my undergraduate project and master's project. Thank you for being open-minded; I do not think the majority of professors would have been open to conducting studies on mind-wandering.

Thanks to Dr. Jens Prussner and Dr. Mathieu Brodeur for being members on my advisory committee and for providing helpful feedback and suggestions on this thesis.

Thanks to Luc, Raf, Dave, Nick, Angela, Renee, Maria, Karina, Diana, Alex, Lizzy, Lindsay, Stamatoula and all the other students in Natasha's lab. You guys kept me sane, and we had awesome times together!

Et finalement, un merci particulier à maman, papa et François. Vous m'avez toujours supporté dans mes décisions et vous m'avez permis de me concentrer pleinement sur mes études. Papa, si jamais tu lis cette thèse, tu peux remplacer les mots « older adults » par « less young adults ».

Preface and Contribution of Authors

This thesis contains four manuscripts, listed below. All manuscripts have been published in peer-reviewed academic journals. They all constitute distinct contributions to knowledge.

Maillet, D. and M. N. Rajah (2014). "Dissociable roles of default-mode regions during episodic encoding." Neuroimage 89: 244-255.

David Maillet designed the experiment, recruited and tested all subjects, performed all data analysis and wrote the paper.

Natasha Rajah supervised and funded the project and assisted in the manuscript writing in an editorial capacity.

Maillet, D. and M. N. Rajah (2011). "Age-related changes in the three-way correlation between anterior hippocampus volume, whole-brain patterns of encoding activity and subsequent context retrieval." Brain Res 1420: 68-79.

David Maillet performed all data analysis and wrote the paper.

Natasha Rajah designed and funded the experiment and oversaw data analysis and writing of the manuscript

Maillet, D. and M. N. Rajah (2013). "Age-related changes in frequency of mind-wandering and task-related interferences during memory encoding and their impact on retrieval." Memory 21(7): 818-831.

David Maillet designed the experiment, recruited and tested all subjects, performed all data analysis and wrote the paper.

Natasha Rajah supervised and funded the project and assisted in the manuscript writing in an editorial capacity.

Maillet, D. and M. N. Rajah (in press). Age-related differences in brain activity during the subsequent memory paradigm: a meta-analysis. Neuroscience & Biobehavioral Reviews.

David Maillet came up with the idea for the meta-analysis, performed the literature review, performed all data analysis and wrote the paper.

Natasha Rajah supervised the manuscript writing in an editorial capacity.

1. Introduction

Episodic memory encoding refers to the process by which an event is converted into an internal representation referred to as the memory trace, or engram, that can later be retrieved (Tulving, 1972). In recent years, many studies have assessed the neural correlates of episodic memory encoding in young and older adults using functional magnetic resonance imaging (fMRI). The most widely used paradigm that has been used in these studies is the subsequent memory paradigm, in which brain activation during encoding events that are later remembered is contrasted with brain activation during encoding events later forgotten (Wagner et al., 1998). A recent meta-analysis of 74 studies using the subsequent memory paradigm in young adults found that activation in medial frontal cortex (mFC) is not reliably activated during successful vs. unsuccessful encoding; instead, mFC was found to be consistently activated in unsuccessful vs. successful encoding (Kim, 2011). It has been suggested that mFC may be involved in task-unrelated thoughts (e.g. thinking about what one will do following the experiment) detrimental to episodic encoding (e.g., Shrager, Kirwan, & Squire, 2008). However, this hypothesis has never been directly tested.

Furthermore, it is not the case that activation in mFC is always greater in unsuccessful vs. successful encoding. In a few studies that have used self-referential encoding tasks (e.g. pleasantness judgements), the reverse has been reported: activation in mFC is greater for successful vs. unsuccessful encoding (e.g., Leshikar & Duarte, 2012; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). In these studies, it was suggested that mFC is involved in evaluation of the encoding material in relation to the self, which helps promotes successful memory. In summary, previous studies have provided conflicting evidence regarding the role of mFC during episodic encoding. The first goal of this thesis was to assess the role of mFC in episodic encoding in young adults in self-referential evaluation of encoding events vs. task-unrelated thoughts.

With healthy aging, there is a reduction in the ability to encode (i.e. learn) and remember events from one's personal life. In spite of this behavioural reduction, studies assessing age-related changes in the neural correlates of episodic encoding have reported that older adults over-recruit some brain regions compared to young adults. In particular, older adults have often been found to over-recruit mFC (Dennis, Daselaar, & Cabeza, 2007; Duzel, Schutze, Yonelinas, & Heinze, 2011; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Gutchess et al., 2005; Kensinger & Schacter, 2008; Kukolja, Thiel, Wilms, Mirzazade, & Fink, 2009; Leshikar, Gutchess, Hebrank, Sutton, & Park, 2010; H. Park, Kennedy, Rodrigue, Hebrank, & Park, 2013). One possibility is that older adults over-recruit mFC during encoding because they exhibit more task-unrelated thoughts (TUT) compared to young adults (Grady et al., 2006; Leshikar et al., 2010). Another possibility is that older adults over-recruit mFC during encoding because they have a tendency to focus more on the personal relevance and meaning of encoding stimuli compared to young adults (Kensinger & Schacter, 2008). The second goal of this thesis was to provide evidence for or against these two competing perspectives.

In the following sections, I first specify which anatomical region the term mFC will be used to refer to. I then provide an overview of the research implicating mFC in episodic memory, TUT and self-referential processing in young adults. Finally, I consider how aging may alters these processes, and present the rationale for the four experiments in this thesis.

1.1. Anatomical definition of mFC

In the current thesis, I use the term medial frontal cortex (mFC) to refer to the medial portion of the prefrontal cortex as well as the anterior cingulate cortex. This corresponds to Brodmann areas (BA) 24 and 32, as well as the medial portion of BA 9 and 10. There is no universally accepted method for determining which part of BA9 and BA10 are medial, and which are lateral. In the current thesis, peak coordinates with an X coordinate ranging between -20 and 20 will be considered as medial. Peaks in frontal cortex with an x of +- 20 will be considered lateral, and are of no interest in the current thesis.

The primary reason for considering this region, spanning multiple BA's, as a whole, is that it seems to be recruited to a similar extent by the tasks of interest in the current thesis. The similarity of activation peaks in mFC related to 1) successful self-referential encoding, 2) unsuccessful encoding, 3) age-related over-activations at encoding, and 4) TUT is illustrated in Figure 1.1, and considered in much greater detail in the rest of the Introduction. This figure makes it clear that there is no obvious clustering of activation peaks in any sub-region of mFC in any of these "contrasts" – rather, all of them span BA10, BA32, the anterior portion of BA24, and the ventral portion of medial BA9. This is not meant to imply that distinct sub-regions of mFC do not play dissociable functional roles; only that within the episodic encoding literature, there is no a-priori reason to focus on any sub-region in particular.

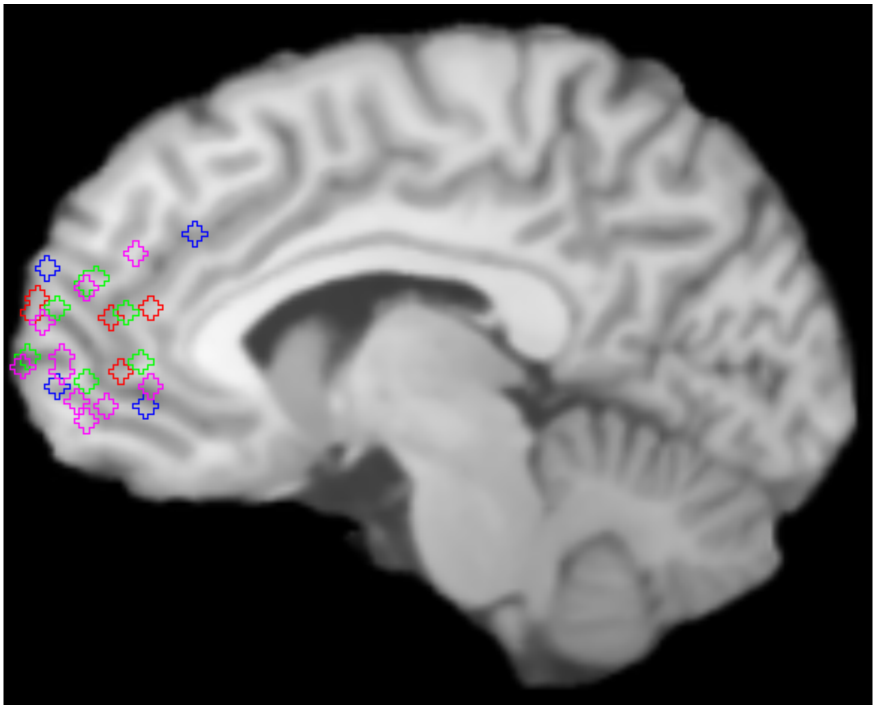

Figure 1.1: Activation peaks in mFC reported by studies investigating successful encoding using a self-referential task (red), unsuccessful encoding (green), task-unrelated thoughts (blue) and age-related over-activation during episodic encoding (pink). All coordinates had an X coordinate ranging from -20 to +20. Studies included for successful self-referential encoding: Leshikar et al., 2011; Shrager et al., 2008; Schott et al., 2011, Zierhut et al., 2010; Macrae et al., 2004. Studies included for unsuccessful encoding: Wagner et al., 2001; Kim et al., 2010; Park & Rugg, 2008; Schott et al., 2006. Studies included for task-unrelated thoughts: Christoff et al., 2009; Stawarczyk et al., 2011. Studies included for age-related over-activations: Gutchess et al. 2005, Grady et al. 2006, Dennis et al. 2007, Kensinger and Schacter 2008, Kukolja et al. 2009, Leshikar et al. 2010, Duzel et al. 2011, Park et al. 2013.

1.2. Episodic memory encoding

1.2.1. Definition and brief history

Episodic memory refers to our ability to store (encode) and retrieve information about personally experienced events that occurred at a specific time and place (e.g. my 8 year old birthday party). The term was first coined by Tulving (1972), who described episodic memory as distinct from semantic memory, which refers to memory for factual knowledge about the word that is devoid of its context of acquisition (e.g. the prime minister of Canada is Stephen Harper). Another distinguishing feature between episodic and semantic memory is that only the former is thought to be accompanied by a subjective sense of mental time travel (Tulving, 2002).

Episodic *encoding* is the process by which an event is converted into a internal representation referred to as the memory trace, or engram, that can later be retrieved (Tulving, 1972). A framework that has been very influential in understanding episodic encoding, and which is of particular interest in the current thesis, is the levels of processing framework (F. I. M. Craik & Lockhart, 1972). According to this framework, the strength and persistence of a memory trace is a by-product of the analysis that occurred at encoding. Specifically, memory trace persistence is proposed to be directly related to the depth to which a stimulus was analyzed when it was first encountered. Depth is defined as the degree of semantic or cognitive analysis, i.e., the forming of associations between the stimulus and personal knowledge.

Evidence in support of the depth of processing framework was elegantly demonstrated in a series of 10 experiments by F. Craik and Tulving (1975). A series of words was presented to subjects, one at a time, and depth of analysis was manipulated by asking subjects to answer different questions for each word: a) structural questions (Is the word in capital letters?), b) phonemic questions (does the word rhyme with the word “weight”) or c) semantic questions (e.g. Is this word a type of fish?; Would the word fit in this sentence?). Memory for each word was later tested. Words that had been encoded using the semantic questions, which required a focus on the meaning of stimuli (resulting in higher elaboration), were remembered more often relative to words that had been encoded using structural and phonemic questions. Other experiments in this paper indicated that memory retrieval accuracy is not well predicted by intention to learn, the amount of effort/difficulty of the encoding task or the amount of time spent making the encoding judgement. Rather, it is the qualitative nature of the encoding task, that is, the extent to which it promotes depth of processing, that most significantly influences retention.

The levels of processing approach has had a lasting impact of the field of episodic encoding, including in more recent neuroimaging studies of episodic encoding. In a typical functional magnetic resonance imaging (fMRI) experiment of episodic encoding, participants are presented with a list of items to encode one at a time (e.g. pictures, words, faces). After a delay, subjects are given a memory test in which, typically, they are presented with the encoding items again and must distinguish them from novel lures. While encoding, participants are almost always given a specific judgement to perform. For example, in a recent review of the encoding and fMRI literature in young adults (Kim, 2011), only 4 studies out of the 74 reviewed studies (5.5%) did not provide a specific encoding task for subjects to perform during encoding. Of the remaining studies, 28 (40%) were semantic in nature (e.g. man-made/natural judgement, living/non-living judgement). 18 (26%) studies used spatial strategies, while visualization strategies were used in 8 (11.76%) studies. Thus, in accordance with the levels of processing framework, the near totality of studies in the encoding and fMRI literature have asked subjects to focus on a particular aspect of encoding stimuli, most commonly its semantic meaning.

1.2.2. Activation in mFC during episodic encoding in young adults

The method that has most often been used to identify brain regions involved in successful encoding in fMRI studies is to contrast activation during encoding of items that were later remembered vs. items later forgotten. This contrast between remembered vs. forgotten events has been termed “subsequent memory effect (SME)” or “difference in memory” (Wagner et al., 1998). In the review alluded to in the previous section, Kim (2011) performed a meta-analysis of 74 studies that have measured SME in young adults. Across all studies, SME were identified in bilateral medial temporal lobes, bilateral visual cortex, bilateral superior parietal lobes and left ventrolateral PFC. More targeted analyses were also performed to determine whether SME differ as a function of stimulus type (word vs. picture) and whether encoding was associative (e.g. word pairs, face-name association), or not (e.g. a single word). However, because of a lack of studies, the author did not examine whether SME differed as a function of encoding instruction. Verbal vs. pictorial SME were found in left PFC, while the reverse contrast was associated with bilateral medial temporal lobes and fusiform gyrus. Associative vs. item encoding was associated with posterior ventrolateral PFC and left medial temporal lobe while the reverse contrast was associated with activation in fusiform gyrus. In summary, these results indicate that successful encoding varies according to stimulus type, and whether encoding is associative or not – however, successful encoding was not associated with activation in mFC in any condition.

Kim (2011) also examined whether there were regions that were consistently more activated during encoding items later forgotten vs. remembered. Sixteen of the 74 studies reviewed had conducted such a contrast. It was found that mFC, PCC, precuneus, bilateral inferior parietal lobes, left lateral temporal cortex and bilateral lateral superior PFC were more activated during forgotten vs. remembered events. The author noted the similarity between these regions and regions of the default-mode network (DMN) (Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). In the current thesis, “DMN” is used to refer to a set of regions including mFC, posterior cingulate, precuneus, bilateral inferior parietal lobes and lateral temporal cortex that are often co-activated with one another during cognitive tasks (Shulman et al., 1997), such as encoding failure. Thus, in this thesis, the term DMN is simply used as shorthand to refer to a set of regions, rather than implying something in particular about the properties or function of these regions. Kim (2011) suggested that increased activation in these regions may reflect an "internal processing mode" that is detrimental to episodic encoding, which instead relies on an "external processing mode".

In summary, Kim's meta-analysis suggests that mFC is not involved in successful episodic encoding in young adults. Instead, activation in this region is consistently higher when encoding items are later forgotten vs. remembered. Kim suggests that regions involved in unsuccessful encoding may be involved in an "internal processing mode", but does not specify what subjects may be "processing" in this mode. One possibility is that when subjects do not successfully encoding events, they are in an internal processing mode in which they are processing task-unrelated thoughts (TUT). In the following section, I present the concept of TUT, and describe evidence that their occurrence may account for increased activation in forgotten vs. remembered events in mFC in young adults.

1.3. Association between mFC and task-unrelated thoughts in young adults

1.3.1. Task-unrelated thoughts

The mind wanders. As you read this thesis, it is likely that your mind will frequently wander to other topics such as an event that happened earlier today (e.g. a discussion with a colleague/family member), or an event that will happen in the future (e.g. what you will have for lunch tomorrow). It has been estimated that 30% to 50% of all waking thoughts represent some form of mind-wandering, and mind-wandering persists during all activities in which it has been tested (Killingsworth & Gilbert, 2010). Despite its ubiquity, relatively little research has been conducted on this topic, until very recently. Indeed, at the time of writing this paragraph, a search for the term “mind-wandering” on Pubmed returned 183 publications, 83% of which were published in the past five years. Similarly, a search for the term “task-unrelated thoughts” returned 43 publications, 72% of which were published in the past five years. One consequence of the novelty of this topic of investigation is that the terminology has not been properly established, and can be quite confusing. For example, in the literature, the terms “task-unrelated thought”, “stimulus-independent thought”, “mind-wandering” and “daydreaming” are sometimes used interchangeably, but other times used to refer to different categories of thoughts. Thus, in the next, section I first define the terms that will be used in the current thesis.

1.3.2. Terminology

The full breadth of thoughts that people experience, the phenomenological dimensions according to which they should be described, and the best way to categorize them is still a matter of controversy (for reviews, see Callard, Smallwood, & Margulies, 2012; Christoff, 2012; Klinger, 2013; Schooler et al., 2011; Smallwood, 2013; Smallwood & Andrews-Hanna, 2013; Smallwood, Brown, Baird, & Schooler, 2011; Smallwood & Schooler, 2006; Szpunar, Moulton, & Schacter, 2013). In the current thesis, I use a conceptual division of thought types proposed by Stawarczyk and colleagues (2011; 2011). Specifically, thought types are classified along two dimensions: 1) Task-relatedness (related or unrelated) and 2) Stimulus-dependency (stimulus dependent or stimulus independent). First, task-related and stimulus-dependent thoughts are thoughts related to being concentrated on the ongoing task (i.e. being on-task). Second, “task-related interferences” refers to task-related and stimulus-independent thoughts. These are interfering thoughts related to the appraisal of the current task (e.g. thinking about how long, boring, or hard the task is, thinking about how one is doing on the task, thinking about when it will end). Third, “distractions” are task-unrelated and stimulus-dependent thoughts, and refer to monitoring of sensory perceptions/sensations irrelevant to the current task (e.g. thinking about scanner noise, thinking about how uncomfortable one is in the scanner, thinking about being cold/hot, hungry etc.). “Mind-wandering” is reserved for a type of thought that is both task-unrelated and stimulus-independent (e.g. thinking about personal concerns, something that happened in the past, something that might happen in the future etc.). Finally, I use the term “task-unrelated thought” (TUT) to refer to all types of thoughts not relevant to successfully performing the ongoing task (task-related interferences, distractions and mind-wandering). Although it may seem contradictory that “task-related interferences” are a component of “task-unrelated thought”, I use the term “task-unrelated thought” to refer to thoughts that do not contribute to successful encoding of words, rather than thoughts unrelated to the task itself.

1.3.3. Occurrence and impact of TUT on task performance

Several theories have been proposed to explain why TUT occur during task performance, two of which will be discussed here. First, according to the goal theory of current concerns hypothesis (Klinger, 2013; Klinger, Gregoire, & Barta, 1973), TUT occur because the individual has concerns and goals that extend beyond the present moment. Mental experiences at any given moment are directed to the most salient feature, whether they are external (i.e. ongoing events) or internal (i.e. personal thoughts). Although experimenters may like to believe participants in his experiment are fully devoted to performing their experiment, this is likely not to be the case. Consistent with this model, the majority of TUTs are highly personal in nature, and frequency of TUT has been associated with motivation and interest in performing the task (Klinger, 2013).

A second proposal, the executive failure hypothesis (McVay & Kane, 2009, 2010, 2012), suggests that successfully performing a cognitive task requires executive control processes that reduce distractions of both internal (e.g. TUT) and external (e.g. distracting stimuli) nature. Thus, TUT occur when there is a failure in inhibitory control processes. This suggestion is supported primarily by the finding of a negative relationship working memory capacity and frequency of TUT during the performance of demanding cognitive tasks (McVay & Kane, 2012; Smallwood, 2013).

While the models discussed in previous paragraphs offer explanations regarding why TUT occurs, a third model, the perceptual decoupling hypothesis, has been put forth to explain why TUT can negatively affect performance on certain tasks (Smallwood & Schooler, 2006). According to this perspective, maintaining attention to an internal train of thought (a TUT) relies on some of the same domain-general cognitive processes that are involved in maintaining attention to an external task, such as a working memory task. "Domain-general processes" is a widely used concept in cognitive neuroscience used to explain why the brain can process a wide array of content (e.g. words or pictures), and can be involved in a wide array of cognitive tasks (e.g. episodic memory vs. working memory) using a smaller set of underlying processes (Rajah, Ames, & D'Esposito, 2008; Smallwood, 2013). Thus, according to this perspective, the maintenance of TUT relies on some of the same cognitive mechanisms involved in maintaining attention to an ongoing external task. For example, working memory has been proposed to be involved both in a wide range of externally-driven cognitive tasks (Baddeley, 1992), but also in maintaining an internal train of thought (Smallwood & Schooler, 2006). Since some of the same cognitive processes may be involved in TUT and external task-performance, and because the brain has limited resources, a competing relationship is proposed to exist between attention to the external environment (e.g. an ongoing task) and attention to TUT. The amount of time spent exhibiting TUT vs. exhibiting attention to the external environment is proposed to be directly related to the demands on external attention required by an ongoing task. In situations demanding a high level of external attention, the amount of time spent engaging in TUT may be reduced, since domain-general cognitive processes are required to ensure the continuity of an externally generated sequence of thought. In contrast, when demands on external attention are low, domain-general cognitive processes can be used to sustain an internally-generated sequence of thought as individuals' minds wander. TUTs may thus only negatively impact task performance when they occur in a situation in which the demands on external attention are moderate to high (e.g. reading tasks, working-memory tasks), rather than low (taking a shower, walking, doing a highly repetitive or practiced task).

Episodic encoding may be one such situation where frequency of TUT may negatively impact task performance, since forming new episodic memories cannot be performed "automatically" (i.e. requires consciousness). This relationship is intuitive: most people have had the experience of having their minds wander during a class, meeting or conversation, which in turn results in poor memory for the external events that occurred during this time. The few studies that have measured rates of TUT during episodic memory tasks have indeed found evidence for a detrimental effect (Seibert & Ellis, 1991; Smallwood, Baracaia, Lowe, & Obonsawin, 2003). For example, in one study three groups of participants received happy, neutral, or sad mood inductions, and then performed a memory recall task for letters (Seibert & Ellis, 1991). Following retrieval, participants were asked to list all the thoughts that they had during the task. The happy and sad groups produced more task-unrelated thoughts relative to the neutral group, and the proportion of these thoughts was negatively related to recall performance in all three groups (correlations ranged from r = -0.58 to -0.69). In another experiment, participants viewed shorts lists of 12 words, followed by "thought probes" (Smallwood et al., 2003). When a thought probe appears on the screen, the subject is asked to report what he/she was thinking about the moment thought probe came on screen. Following each list of 12 words and the thought probe, subjects performed an old/new recognition test in which they must distinguish the 12 studied words from 8 novel lures. Participants were split into those experiencing mind-wandering and those that didn't, and the mind-wandering group exhibited significantly more false alarms at retrieval (falsely responding that a new item had been studied at encoding).

1.3.4. Evidence that mFC is involved in TUT in young adults

A few studies have directly measured the neural correlates of TUT during task performance (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Mason et al., 2007; Stawarczyk, Majerus, Maquet, et al., 2011). Mason et al. (2007) had participants perform a working memory task twice in an fMRI scanner. The first time, the task was novel to subjects, while the second time, they had received extensive practice on it. Greater activation in mFC was found in the practiced vs. the novel task. Moreover, rates of mind-wandering, as measured using retrospective questionnaire following each fMRI session, were higher in the practiced vs. the novel task. Finally, mind-wandering rates were positively correlated with activation in several DMN regions including mFC. Christoff et al. (2009) and Stawarczyk, Majerus, Maquet, et al. (2011) both measured TUT rates during a sustained attention to response task using thought probes. In both studies, TUT episodes were operationalized as 10 second epochs preceding thought probes in which subjects subjectively reported exhibiting a TUT. These TUT episodes were contrasted to 10 second epochs preceding thought probes in which subjects reported being on-task. Christoff et al. (2009) reported increased activation in several regions including mFC preceding TUT reports. Stawarczyk, Majerus, Maquet, et al. (2011) used a design almost identical to the one used by Christoff, except that they gave subjects different options to choose from during thought probes. Rather than simply indicating whether they were on-task or off-task, subjects were asked whether they were on-task, mind-wandering, exhibiting task-related interferences or exhibiting distractions. All TUT types recruited mFC, but mind-wandering recruited this region to the greatest extent.

1.3.5. Evidence that mFC is involved in TUT during episodic encoding in young adults

There is no neuroimaging study that has measured rates of TUT during episodic encoding. Thus it is unclear whether the finding that mFC is involved in mind-wandering during working memory (Mason et al., 2007) and attention tasks (Christoff et al., 2009; Stawarczyk, Majerus, Maquet, et al., 2011) extends to episodic encoding. However, indirect evidence of mFC's role in TUT during episodic encoding comes from the meta-analysis by Kim (2011) described earlier. This meta-analysis indicated that mFC is consistently activated to a greater extent in subsequently forgotten vs. remembered events. Thus although the hypothesis has never directly been tested, several findings converge to suggest that mFC may be involved in TUT during episodic encoding in young adults: 1) activation in mFC is generally higher during unsuccessful vs. successful encoding (Kim, 2011), 2) behavioural studies indicate that TUT during encoding lead to reduced retrieval performance (Seibert & Ellis, 1991) 3) mFC is involved in task-unrelated thoughts in working memory and attention tasks (Christoff et al., 2009; Mason et al., 2007).

1.4. Association between mFC and self-referential encoding in young adults

Although there exists considerable evidence that mFC activation is detrimental to episodic encoding, this association does not extend to all encoding tasks. Instead, studies that have instructed participants to encode events by determining whether adjectives are descriptive of themselves (Macrae et al., 2004), or by making a pleasantness judgement (Leshikar & Duarte, 2012; Schott et al., 2011; Shrager et al., 2008; Zierhut et al., 2010) have reported that activation in mFC is greater for successful vs. unsuccessful encoding. The authors of these studies have interpreted mFC activation as being involved in self-referential evaluation of the encoding material. That is, both the adjective task and the pleasantness tasks involve contemplation of an aspect of oneself (personality traits, preferences). The precise role of mFC in self-referential judgements is a matter of intense debate in the literature (for recent reviews, see Andrews-Hanna, Smallwood, & Spreng, 2014; Cook, 2014; D'Argembeau, 2013; Legrand & Ruby, 2009; Northoff, 2011; Northoff, Qin, & Feinberg, 2011; Northoff, Qin, & Nakao, 2010; Qin & Northoff, 2011; Roy, Shohamy, & Wager, 2012) and is beyond the scope of this thesis, but may include valuation (D'Argembeau, 2013), evaluation that is not self-specific (Legrand & Ruby, 2009), or conceiving the affective meaning of events (Roy et al., 2012).

Furthermore, it has been demonstrated that performing such self-referential judgements is a very effective way to encode information. Symons and Johnson (1997) conducted a meta-analysis that revealed that making either the pleasantness judgement of the adjective self-judgement results in superior memory compared to semantic judgements (i.e. man-made/natural judgement) and other-referential judgements (judging whether an adjective is descriptive of a well-known person). It was suggested that self-referential encoding tasks promote superior memory compared to other tasks because they promote both elaboration and organisation of the encoding material (while other tasks may only promote one or the other). Elaboration refers to attending to the meaning of a word, and forming associations between the word and personal knowledge, or semantic memory. Organisation refers to grouping items together within a list (e.g. grouping all fruits together and all the animals together). Because the concept of oneself is so well developed, and since people constantly use it in their daily lives, some have suggested that processing information in a self-relevant way is the "normal" processing mode (Catrambone, Beike, & Niedenthal, 1996). In turn, the ease of processing information in relation to oneself, and the richness of the self as a concept may make it easy to elaborate ("e.g. I like this word because…") and organise (e.g. "I like both bananas and oranges, but I dislike both apples and tomatoes") information.

Although is it clear that self-referential encoding tasks lead to superior recall compared to traditional (i.e. semantic) encoding tasks, these tasks have not often been used in neuroimaging studies. For example, in the meta-analysis by Kim (2011), only 3 out of 74 used such a task. Thus, one possibility as to why mFC was not identified in this meta-analysis as supporting successful encoding is that the encoding tasks used in these experiments (mostly semantic) did not recruit cognitive processes subserved by this region.

1.5. Reconciling distinct perspectives regarding the role of mFC during episodic encoding

I have so far presented evidence that mFC is activated to a greater extent in successful vs. unsuccessful encoding when the encoding task is self-referential, but is activate to a greater extent in unsuccessful vs. successful encoding when the encoding task is not self-referential (e.g. semantic). I am not aware of any study that has attempted to reconcile these results. A working model for activation in mFC during episodic encoding is presented in Figure 1.2. Specifically, I suggest the following possibility. The mFC is involved in self-referential evaluation. Activation in mFC is greatest during successful encoding using a self-referential task, when subjects are explicitly asked to perform such evaluation. Activation in mFC is at an intermediate level during unsuccessful encoding, irrespective of the encoding task, because TUT (which occur to a greater extent during unsuccessful encoding) tend to be highly self-referential (Klinger, 2013). Finally, activation in mFC is lowest during successful encoding using semantic/perceptual encoding tasks, since these tasks do not involve any self-referential evaluation.

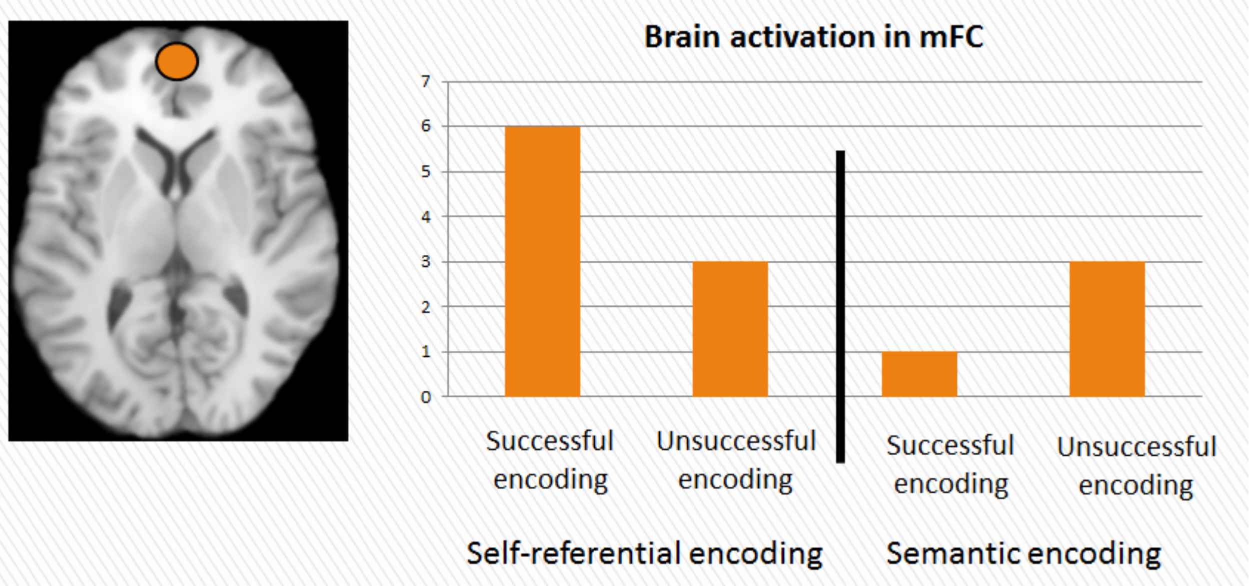

Figure 1.2: Working model for activation in mFC during successful vs. unsuccessful encoding in young adults. Activation in a hypothetical region of mFC is shown for successful and unsuccessful encoding involving a self-referential and a semantic task.

Although this model can potentially explain findings in young adults, it leads to an ambiguous situation when trying to interpret age-related over-activations in mFC during encoding tasks. That is, given that mFC has been associated with both self-referential evaluation of encoding stimuli and TUT in young adults, it is unclear which cognitive process older adults are up-regulating when over-recruiting this region. In the next section, I first consider the effects of aging on episodic memory, and then discuss age-related changes in self-referential encoding and TUT.

1.6. Aging

1.6.1. Age-related changes in episodic memory

Healthy older adults (60-80 year old) exhibit reductions in episodic memory compared to young adults (20-35 years old) (F. I. M. Craik, 1991; F. I. M. Craik & Salthouse, 2000). Moreover, reductions in episodic memory are among the most commonly reported complaints in aging and can significantly degrade quality of life (Mol et al., 2007). Several different theories have been used to explain these reductions. For example, based on the well-documented finding that older adults are disproportionately impaired on memory for associations compared to memory for items (Spencer & Raz, 1995), some have suggested that older adults exhibit a specific deficit in binding together the different features that make up a complex memory (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000). Other theories posit that older adults exhibit deficits in episodic memory tasks because of a decline in domain-general processes involved in a broad range of cognitive tasks. For example, the resource deficit theory suggests that older adults have less resources available to them to perform cognitive tasks (F. I. M. Craik, 1983). The inhibition deficit theory postulates that older adults are less able than young adults to prevent irrelevant information from entering working memory (Hasher & Zacks, 1988a). This results in increased attention being paid to information irrelevant to the current goal, to the detriment of goal-related information. This “mental clutter” is thought to be detrimental to encoding since less attention is focused on the relevant information to be encoded (Hasher & Zacks, 1988a). It is also thought to be detrimental at retrieval because of greater competition among related ideas and memories (Hasher & Zacks, 1988a).

1.6.2. Age-related changes in mFC during episodic encoding

At the time at which this thesis was started, only one study had examined age-related changes in successful episodic encoding using a self-referential task (Gutchess, Kensinger, & Schacter, 2010). Young and older adults encoded adjectives while judging if they were descriptive of themselves, or descriptive of Albert Einstein. At retrieval, subjects were asked to remember in which condition each adjective had been studied in. Surprisingly young adults exhibited greater activation in mFC in forgotten vs. remembered adjectives in the self-referential condition, while the reverse was true for the Einstein condition. These findings are inconsistent with many previous studies indicating that mFC is involved in self-referential encoding (Leshikar & Duarte, 2012; Macrae et al., 2004; Schott et al., 2011; Zierhut et al., 2010). Furthermore, older adults showed the exact opposite pattern, that is greater activation in mFC in remembered vs. forgotten items *in the self-referential condition*, and the opposite for the Einstein condition. The authors noted the peculiarity of their results, and suggested that it may have reflected that fact that both a "self" encoding condition and an "other" (Einstein) encoding condition were included in the same study, while previous studies have only included a "self" condition. The requirement to distinguish at retrieval between the self vs. other judgements performed at encoding, which rely on similar regions of DMN including mFC, may have influenced the results. Moreover, the authors suggested that age differences may reflect fundamental differences in the way individuals encode information about the self and others across age groups.

During episodic encoding of stimuli using orienting tasks that are not self-referential (i.e. semantic, perceptual), older adults commonly over-recruit the medial FC (Dennis et al., 2007;

Duzel et al., 2011; Grady et al., 2006; Gutchess et al., 2005; Kensinger & Schacter, 2008; Kukolja et al., 2009; Leshikar et al., 2010; H. Park et al., 2013). In these studies, the encoding task was to: judge whether picture stimuli contain water (Gutchess et al., 2005; H. Park et al., 2013), judge whether pictures/words are large/small or represent a living/non-living entity (Grady et al., 2006), judge which semantic category a word belongs to (Dennis et al., 2007), judge whether objects depicted in a picture would fit in a cabinet drawer (Kensinger & Schacter, 2008), judge whether objects are natural/artificial (Kukolja et al., 2009), or judge whether scenes are indoor/outdoor (Leshikar et al., 2010). These types of semantic/perceptual tasks do not recruit mFC in young adults (Kim, 2011). Thus, it is not simply the case that older adults over-recruit regions that young adults also recruit at encoding; rather, recruitment of mFC in these studies is *age-unique* (Maillet & Rajah, 2013).

It is important to understand that the finding of an age-related increase in activation in mFC in these studies was not their main focus. Rather, studies in the field of age-related differences in episodic encoding have predominantly focused on changes in medial temporal lobes, lateral PFC and visual cortex. Thus in almost all studies showing age-related changes in mFC, this change was not predicted, and was not the main interest of the study (for exception, see Kensinger & Schacter, 2008). This is important in understanding the interpretations that were given in these studies. For example, Leshikar et al. (2010) suggest age-related increases in regions including mFC may reflect age-related increases in mind-wandering even though mind-wandering was not measured in this study. Gutchess et al. (2005) attributes this change to increased sensitivity to fine distinctions among stimuli in older adults, even though there is no measure of visual discrimination in this study. Grady et al. (2006) suggests it may reflect increased monitoring of internal/external milieus, even though these factors were not measured.

Other studies have interpreted age-related increases in mFC as a failure to deactivate regions of default-mode network in older adults (Duzel et al., 2011; Kukolja et al., 2009; H. Park et al., 2013). In these studies, it is often unclear why age-related increases in mFC are interpreted as "failures" in older adults. There exists very little evidence to determine whether age-related increases in activation in this region are beneficial or detrimental to performance in older adults. In the following sections I review theoretical and behavioural evidence consistent with each of the two propositions made in this thesis: that older adults exhibit increased activation in mFC because of 1) an age-related increases in TUT frequency or 2) an age-related increase in focus on the self-relevance of encoding material.

1.6.3. Age-related changes in TUT

If one wishes to argue that age-related increases in activation in mFC during episodic encoding are due to an increase in TUT in older adults, then it should first be demonstrated that older adults do in fact exhibit an increase, rather than a decrease in TUT during task performance. TUT is a novel topic of investigation which is not yet very well understood, even in young adults. As such, theoretical models of aging and memory may have limited utility for making predictions regarding age-related changes in TUT during episodic encoding. For example, as discussed earlier, McVay & Kane have suggested that TUT occur during cognitive tasks because of a failure in inhibitory control (McVay & Kane, 2009, 2010, 2012). Thus, it follows that if older adults have a deficit in inhibitory control (Hasher & Zacks, 1988b), they may exhibit an increase in TUT compared to young adults. This suggestion has been put forward recently by proponents of this theory (Clapp & Gazzaley, 2012). However, Smallwood (2013; 2006) has argued that working memory is required for the maintenance of the TUT episode. Thus if older adults have reduced attentional resources compared to young (F. I. M. Craik, 1983), and use up a greater proportion of these resources on the encoding task than young (Anderson, Craik, & Naveh-Benjamin, 1998), then they may have fewer resources available for sustaining TUT compared to young adults. Finally, Klinger (2013) has suggested that TUT may occur because the individual has goals that extend beyond the current task. If this is the case, differences in the types of goals that young and older adults have, or age-related differences in motivation to perform cognitive tasks may also affect alter frequency or type of TUT experienced (Jackson & Balota, 2012).

When this thesis was started in 2011, there was very little empirical evidence available to distinguish between these possibilities. To my knowledge, only 2 studies examined age-related differences in TUT frequency; neither in the context of an episodic memory task. Giambra (1973) asked 135 males aged 17-77 to answer a 344-item daydreaming questionnaire in daily life. An age-related reduction in daydreaming frequency was found, although daydreaming stayed high throughout life. Giambra (1989) also reported an age-related decrease in mind-wandering during 5 laboratory experiments containing thought probes during a vigilance task in which subjects had to identify a target rectangle amongst square lures. A negative correlation between age and mind-wandering was found in all five experiments. The studies by Giambra provide evidence for an age-related reduction in TUT. However, to my knowledge no study has measured frequency of TUT during an episodic encoding task. Thus, many reasons could be invoked to suggest that older adults may exhibit more TUTs during episodic encoding tasks. Perhaps a task with meaningful stimuli (e.g. words, rather than picture of squares/rectangles) would trigger more TUT in older adults. The vigilance task used by Giambra was not challenging for either age group; perhaps a more challenging task such as episodic encoding would alter TUT rates disproportionately in one age group vs. another. Perhaps older adults, because they are especially sensitive to their memory abilities, would exhibit more thoughts related to their performance in the ongoing task (i.e. task-related interferences). In summary, the evidence to date suggests an age-related decreases in TUT; however, no study has measured age-related differences in TUT frequency in an episodic memory experiment.

1.6.4. Age-related changes in self-referential processing

In this section, I review behavioural evidence that older adults may spontaneously focus more on personal meaning and relevance of incoming information compared to young adults. In contrast to the age-related reductions seen in cognitive domains such as episodic memory and working memory, emotional regulation is preserved with age, and may even be enhanced (Carstensen, 1992; Carstensen, Fung, & Charles, 2003). Rates of depression and anxiety are lower in older adults (Jorm, 2000), while life satisfaction increases with age (Diener & Lucas, 1999). Older adults experience fewer worries about financial and social events (Powers, Wisocki, & Whitbourne, 1992). Older adults rate more events and stimuli as positive, and also remember more positive vs. negative events (Gutchess, Kensinger, Yoon, & Schacter, 2007; Mather, 2012; Mather & Carstensen, 2005; Mather & Knight, 2005). The socioemotional selectivity theory (Carstensen, 1992; Carstensen et al., 2003) suggests that these age-related changes may be due to perceived life expectancy. Young adults, who have their lives ahead of them, focus on “expansive goals”: knowledge acquisition, developing new skills, long-term goal planning and making new contacts. Older adults, realizing that do not have much time left, instead direct their attention and efforts to maximizing emotionally meaningful goals. According to this theory, what drives old age is a desire to derive meaning and satisfaction from life.

This focus on emotional regulation and deriving meaning and satisfaction may spontaneously influence the features of events that older adults focus on. For example, Todd et al. (2012) recently suggested that affect-biased attention, the predisposition to attend to certain categories of affectively salient stimuli over others, may be a key component of emotional regulation. The authors suggested that affect-biased attention acts in a proactive manner as an affective filtering process. Thus, because of their focus on emotional regulation, it is possible that older adults are predisposed to automatically focus on the personal relevance and meaning of encoding stimuli and later remember these features. For example, in one study where young and older couples were asked to describe a past vacation, older couples reported more subjective details regarding such as descriptions of people while younger couples reported more factual information such as specific itineraries (Gould & Dixon, 1993). In another study, young vs. older adults reported more perceptual and contextual details about an event experienced in the lab (e.g. "The picnic basket was blue"), while older adults reported more thoughts and feelings (e.g. "I would never have packed such a sparse picnic basket") compared to young (Hashtroudi, Johnson, & Chrosniak, 1990). In a third study, young and older adults were asked to justify why they said that they had seen particular stimuli in a memory test; that is, they were asked what specifically they were basing this decision on (Comblain, D'Argembeau, Van der Linden, & Aldenhoff, 2004). Older adults attributed more of their "remember" responses to a recollection of their initial emotional reaction/feelings to the stimulus, compared to young

These studies suggest that older adults may remember more subjective information (e.g. interpretations, meaning, feelings) compared to young, who might instead remember specific perceptual details, contextual and facts. However, it is unclear from these findings if this bias occurs only at the time of retrieval, or whether it is caused by differences in how young and older originally attended to information. A fourth study provides evidence that attentional focus at encoding may play a role. Gaesser, Sacchetti, Addis, and Schacter (2011) showed young and older adults pictures depicting people engaged in a particular activity. In one condition, subjects were either asked to 1) use the picture as a cue to remember an event from their own lives in the past 5 years, 2) use the picture as a cue to imagine an event that may occur in the future or 3) simply describe the picture, reporting only what was literally depicted, without embellishment. Across all conditions, older adults reported less specific details, but more “semantic information” and inferences (e.g. speculating about the temperature, providing explanation for people’s actions), even in the picture description task, in which they were specifically instructed not to do so. Moreover, age-related changes in picture description, that is, in how young and older adults originally perceive events, accounted for a large portion of age-related differences in remembering the past and imagining the future. The authors suggested that older adults prioritize personal meaning rather than a precise reiteration of events. This study is consistent with the suggestion that differences in the qualitative details of events spontaneously processed by older vs. young adults significantly influences later memory. Thus, it is possible that age-related increase in mFC during episodic encoding reflects this increased tendency to prioritize personal meaning.

1.7. Overview of the four studies in this Thesis

In the following sections, I present four studies that assessed the role of mFC during episodic encoding in young and older adults: the first assessed the role of mFC in young adults, while the other three assessed age-related changes in this region.

Study 1: In study 1, young adults were asked to encode word stimuli using either a semantic or a self-referential encoding task. This paradigm allowed an explicit test of the model in Figure 1. That is, I hypothesized that mFC would exhibit a task X subsequent memory interaction, due to this region being involve in successful vs. successful encoding only in the self-referential task, but not in the semantic encoding task. Moreover, this study is the first to measure the neural correlates of TUT during an episodic encoding task. This allowed testing the hypothesis that regions typically involved in unsuccessful encoding (e.g. posterior cingulate) are involved in exhibiting TUT.

Study 2: One reason for which it is difficult to understand age-related increases in activation in mFC during episodic encoding is that the encoding tasks that have been used in the literature are semantic, or perceptual (see previous section). These encoding tasks do not recruit mFC in young adults. Greater insight into age-related changes in mFC may be gained by additionally examining age-related changes in a task that recruits this region in both age groups (i.e. a self-referential encoding task). For instance, if older adults do over-recruit mFC because they spontaneously focus on more self-referential aspects of the encoding events, then age-related differences in activation in this region may be expected to disappear when *both* age groups are explicitly asked to encode events in this manner. In the second study in this thesis, I present the first study to examine age-related differences in the association between encoding activity and subsequent retrieval performance with a pleasant/unpleasant encoding task; a task which has been shown to recruit mFC in young adults (e.g., Gusnard, Akbudak, Shulman, & Raichle, 2001). I hypothesized that in both age groups, increased encoding activation in mFC would be positively correlated with retrieval performance;

Study 3: Although some fMRI studies have interpreted age-related increases in mFC as reflecting increases in TUT (Grady et al., 2006; Leshikar et al., 2010) it is interesting to note that no study, behavioural of neuroimaging, has ever compared frequency of TUT in young vs. older adults during a memory task. In the Study 3, I present the first between-group behavioural analysis of age-related differences in frequency of TUT during encoding. Based on the limited evidence available in this area of research before this thesis was started (Giambra, 1973, 1989), I hypothesized that older adults would exhibit a reduction in TUT compared to young adults during episodic encoding; which would be inconsistent with the suggestion that age-related increases in mFC represent an age-related increase in TUT.

Study 4: The field of aging and episodic memory encoding has focused almost exclusively on lateral PFC, medial temporal lobes and occipital cortex (for reviews, see Cabeza, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; D. C. Park & Gutchess, 2005; Rajah & D'Esposito, 2005). Age-related changes in mFC during episodic encoding, although seemingly consistent to me, have largely been ignored. The fourth study in this thesis is an exhaustive quantitative meta-analysis of age-related changes in studies that have used the subsequent memory contrast. The main goal of this analysis was to objectively demonstrate that older adults consistently over-activate mFC during episodic encoding studies, and if this is the case, to determine precisely which sub-region of mFC is over-activated.

1.8. References

Anderson, N. D., F. I. M. Craik and M. Naveh-Benjamin (1998). "The attentional demands of encoding and retrieval in younger and older adults: 1. Evidence from divided attention costs." Psychol Aging **13**(3): 405-423.

Andrews-Hanna, J. R., J. S. Reidler, C. Huang and R. L. Buckner (2010). "Evidence for the default network's role in spontaneous cognition." J Neurophysiol **104**(1): 322-335.

Baddeley, A. (1992). "Working memory." Science **255**(5044): 556-559.

Buckner, R. L. (2012). "The serendipitous discovery of the brain's default network." Neuroimage **62**(2): 1137-1145.

Buckner, R. L., J. R. Andrews-Hanna and D. L. Schacter (2008). "The brain's default network: anatomy, function, and relevance to disease." Ann N Y Acad Sci **1124**: 1-38.

Callard, F., J. Smallwood and D. S. Margulies (2012). "Default Positions: How Neuroscience's Historical Legacy has Hampered Investigation of the Resting Mind." Front Psychol **3**: 321.

Carstensen, L. L. (1992). "Motivation for social contact across the life span: a theory of socioemotional selectivity." Nebr Symp Motiv **40**: 209-254.

Carstensen, L. L., H. H. Fung and S. T. Charles (2003). "Socioemotional Selectivity Theory and the Regulation of Emotion in the Second Half of Life." Motivation and Emotion **27**(2): 103-123.

Catrambone, R., D. Beike and P. Niedenthal (1996). "Is the Self-Concept a Habitual Referent in Judgments of Similarity?" Psychological Science **7**: 158-163.

Chalfonte, B. L. and M. K. Johnson (1996). "Feature memory and binding in young and older adults." Mem Cognit **24**(4): 403-416.

Christoff, K. (2012). "Undirected thought: Neural determinants and correlates." Brain Res **1428**: 51-59.

Christoff, K., A. M. Gordon, J. Smallwood, R. Smith and J. W. Schooler (2009). "Experience sampling during fMRI reveals default network and executive system contributions to mind wandering." Proc Natl Acad Sci U S A **106**(21): 8719-8724.

Clapp, W. C. and A. Gazzaley (2012). "Distinct mechanisms for the impact of distraction and interruption on working memory in aging." Neurobiol Aging **33**(1): 134-148.

Comblain, C., A. D'Argembeau, M. Van der Linden and L. Aldenhoff (2004). "The effect of ageing on the recollection of emotional and neutral pictures." Memory **12**(6): 673-684.

Craik, F. and E. Tulving (1975). "Depth of Processing and the Retention of Words in Episodic Memory." Journal of Experimental Psychology: General **104**(3): 268-294.

Craik, F. I. M. (1983). "On the transfer of information from temporary to permanent memory." Philosophical Transactions of the Royal Society of London **302**(1110): 341-358.

Craik, F. I. M. (1991). Memory functions in normal aging. Memory disorders: Research and clinical practice T. Yanagihara and R. C. Petersen. New York, Dekker.

Craik, F. I. M. and R. S. Lockhart (1972). "Levels of Processing - Framework for Memory Research." Journal of Verbal Learning and Verbal Behavior **11**(6): 671-684.

Craik, F. I. M. and T. A. Salthouse (2000). The Handbook of Aging and Cognition. Mahwah, NJ, Lawrence Erlbaum Associates.

D'Argembeau, A., F. Collette, M. Van der Linden, S. Laureys, G. Del Fiore, C. Degueldre, A. Luxen and E. Salmon (2005). "Self-referential reflective activity and its relationship with rest: a PET study." Neuroimage **25**(2): 616-624.

Delamillieure, P., G. Doucet, B. Mazoyer, M. R. Turbelin, N. Delcroix, E. Mellet, L. Zago, F. Crivello, L. Petit, N. Tzourio-Mazoyer and M. Joliot (2010). "The resting state questionnaire: An introspective questionnaire for evaluation of inner experience during the conscious resting state." Brain Res Bull **81**(6): 565-573.

Dennis, N. A., S. Daselaar and R. Cabeza (2007). "Effects of aging on transient and sustained successful memory encoding activity." Neurobiol Aging **28**(11): 1749-1758.

Diaz, B. A., S. Van Der Sluis, S. Moens, J. S. Benjamins, F. Migliorati, D. Stoffers, A. Den Braber, S. S. Poil, R. Hardstone, D. Van't Ent, D. I. Boomsma, E. De Geus, H. D. Mansvelder, E.

J. Van Someren and K. Linkenkaer-Hansen (2013). "The Amsterdam Resting-State Questionnaire reveals multiple phenotypes of resting-state cognition." Front Hum Neurosci **7**: 446.

Diener, E. and R. E. Lucas (1999). Personality and subjective well-being. Well-being: The foundations of hedonic psychology. D. Kahneman, E. Diener and N. Schwarz. New York, Russell Sage Foundation.

Duzel, E., H. Schutze, A. P. Yonelinas and H. J. Heinze (2011). "Functional phenotyping of successful aging in long-term memory: Preserved performance in the absence of neural compensation." Hippocampus **21**(8): 803-814.

Gaesser, B., D. C. Sacchetti, D. R. Addis and D. L. Schacter (2011). "Characterizing age-related changes in remembering the past and imagining the future." Psychol Aging **26**(1): 80-84.

Giambra, L. M. (1973). "Daydreaming in males from seventeen to seventy-seven: A preliminary report." Proceedings of the Annual Convention of the American Psychological Association: 769-770.

Giambra, L. M. (1989). "Task-unrelated-thought frequency as a function of age: a laboratory study." Psychol Aging **4**(2): 136-143.

Gould, O. N. and R. A. Dixon (1993). "How we spent our vacation: Collaborative storytelling by young and older adults." Psychology and Aging **6**(93-99).

Grady, C. L., M. V. Springer, D. Hongwanishkul, A. R. McIntosh and G. Winocur (2006). "Age-related changes in brain activity across the adult lifespan." J Cogn Neurosci **18**(2): 227-241.

Greicius, M. D., B. Krasnow, A. L. Reiss and V. Menon (2003). "Functional connectivity in the resting brain: a network analysis of the default mode hypothesis." Proc Natl Acad Sci U S A **100**(1): 253-258.

Gusnard, D. A., E. Akbudak, G. L. Shulman and M. E. Raichle (2001). "Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function." Proc Natl Acad Sci U S A **98**(7): 4259-4264.

Gutchess, A. H., E. A. Kensinger and D. L. Schacter (2010). "Functional neuroimaging of self-referential encoding with age." Neuropsychologia **48**(1): 211-219.

Gutchess, A. H., E. A. Kensinger, C. Yoon and D. L. Schacter (2007). "Ageing and the self-reference effect in memory." Memory **15**(8): 822-837.

Gutchess, A. H., R. C. Welsh, T. Hedden, A. Bangert, M. Minear, L. L. Liu and D. C. Park (2005). "Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity." J Cogn Neurosci **17**(1): 84-96.

Hasher, L. and R. T. Zacks (1988). "Working memory, comprehension, and aging: A review and a new view." The psychology of learning and motivation **22**: 193-225.

Hasher, L. and R. T. Zacks (1988). "Workng memory, comprehension, and aging: a review and a new view." The psychology of learning **22**: 193-225.

Hashtroudi, S., M. K. Johnson and L. D. Chrosniak (1990). "Aging and qualitative characteristics of memories for perceived and imagined complex events." Psychol Aging **5**(1): 119-126.

Jackson, J. D. and D. A. Balota (2012). "Mind-wandering in younger and older adults: Converging evidence from the sustained attention to response task and reading for comprehension." Psychol Aging **27**(1): 106-119.

Jorm, A. F. (2000). "Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span." Psychol Med **30**(1): 11-22.

Kensinger, E. A. and D. L. Schacter (2008). "Neural processes supporting young and older adults' emotional memories." J Cogn Neurosci **20**(7): 1161-1173.

Killingsworth, M. A. and D. T. Gilbert (2010). "A wandering mind is an unhappy mind." Science **330**(6006): 932.

Kim, H. (2011). "Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies." Neuroimage **54**(3): 2446-2461.

Kim, H. (2012). "A dual-subsystem model of the brain's default network: self-referential processing, memory retrieval processes, and autobiographical memory retrieval." Neuroimage **61**(4): 966-977.

Klinger, E. (2013). "Goal Commitments and the content of thoughts and dreams: basic principles." Front Psychol **4**: 415.

Klinger, E., K. C. Gregoire and S. G. Barta (1973). "Physiological correlates of mental activity: eye movements, alpha, and heart rate during imagining, suppression, concentration, search, and choice." Psychophysiology **10**(5): 471-477.

Kukolja, J., C. M. Thiel, M. Wilms, S. Mirzazade and G. R. Fink (2009). "Ageing-related changes of neural activity associated with spatial contextual memory." Neurobiol Aging **30**(4): 630-645.

Leshikar, E. D. and A. Duarte (2012). "Medial prefrontal cortex supports source memory accuracy for self-referenced items." Soc Neurosci **7**(2): 126-145.

Leshikar, E. D., A. H. Gutchess, A. C. Hebrank, B. P. Sutton and D. C. Park (2010). "The impact of increased relational encoding demands on frontal and hippocampal function in older adults." Cortex **46**(4): 507-521.

Macrae, C. N., J. M. Moran, T. F. Heatherton, J. F. Banfield and W. M. Kelley (2004). "Medial prefrontal activity predicts memory for self." Cereb Cortex **14**(6): 647-654.

Maillet, D. and M. N. Rajah (2013). "Association between prefrontal activity and volume change in prefrontal and medial temporal lobes in aging and dementia: a review." Ageing Res Rev **12**(2): 479-489.

Mason, M. F., M. I. Norton, J. D. Van Horn, D. M. Wegner, S. T. Grafton and C. N. Macrae (2007). "Wandering minds: the default network and stimulus-independent thought." Science **315**(5810): 393-395.

Mather, M. (2012). "The emotion paradox in the aging brain." Ann N Y Acad Sci **1251**: 33-49.

Mather, M. and L. L. Carstensen (2005). "Aging and motivated cognition: the positivity effect in attention and memory." Trends Cogn Sci **9**(10): 496-502.

Mather, M. and M. Knight (2005). "Goal-directed memory: the role of cognitive control in older adults' emotional memory." Psychol Aging **20**(4): 554-570.

McVay, J. C. and M. J. Kane (2009). "Conducting the train of thought: working memory capacity, goal neglect, and mind wandering in an executive-control task." J Exp Psychol Learn Mem Cogn **35**(1): 196-204.

McVay, J. C. and M. J. Kane (2010). "Does mind wandering reflect executive function or executive failure? Comment on Smallwood and Schooler (2006) and Watkins (2008)." Psychol Bull **136**(2): 188-197; discussion 198-207.

McVay, J. C. and M. J. Kane (2012). "Why does working memory capacity predict variation in reading comprehension? On the influence of mind wandering and executive attention." J Exp Psychol Gen **141**(2): 302-320.

Mevel, K., B. Landeau, M. Fouquet, R. La Joie, N. Villain, F. Mezenge, A. Perrotin, F. Eustache, B. Desgranges and G. Chetelat (2013). "Age effect on the default mode network, inner thoughts, and cognitive abilities." Neurobiol Aging **34**(4): 1292-1301.

Mol, M., M. Carpay, I. Ramakers, N. Rozendaal, F. Verhey and J. Jolles (2007). "The effect of perceived forgetfulness on quality of life in older adults; a qualitative review." Int J Geriatr Psychiatry **22**(5): 393-400.

Naveh-Benjamin, M. (2000). "Adult age differences in memory performance: tests of an associative deficit hypothesis." J Exp Psychol Learn Mem Cogn **26**(5): 1170-1187.

Nyberg, L., A. R. McIntosh, R. Cabeza, L. G. Nilsson, S. Houle, R. Habib and E. Tulving (1996). "Network analysis of positron emission tomography regional cerebral blood flow data: ensemble inhibition during episodic memory retrieval." J Neurosci **16**(11): 3753-3759.

Park, H., K. M. Kennedy, K. M. Rodrigue, A. Hebrank and D. C. Park (2013). "An fMRI study of episodic encoding across the lifespan: changes in subsequent memory effects are evident by middle-age." Neuropsychologia **51**(3): 448-456.

Powers, C. B., P. A. Wisocki and S. K. Whitbourne (1992). "Age differences and correlates of worrying in youth and elderly adults." The Gerontologist **32**: 82-88.

Qin, P. and G. Northoff (2011). "How is our self related to midline regions and the default-mode network?" Neuroimage **57**(3): 1221-1233.

Raichle, M. E. (2009). "A paradigm shift in functional brain imaging." J Neurosci **29**(41): 12729-12734.

Raichle, M. E. (2010). "Two views of brain function." Trends Cogn Sci **14**(4): 180-190.

Raichle, M. E., A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard and G. L. Shulman (2001). "A default mode of brain function." Proc Natl Acad Sci U S A **98**(2): 676-682.

Rajah, M. N., B. Ames and M. D'Esposito (2008). "Prefrontal contributions to domain-general executive control processes during temporal context retrieval." Neuropsychologia **46**(4): 1088-1103.

Rajah, M. N., D. Crane, D. Maillet and D. Floden (2011). "Similarities in the patterns of prefrontal cortex activity during spatial and temporal context memory retrieval after equating for task structure and performance." Neuroimage **54**(2): 1549-1564.

Schooler, J. W., J. Smallwood, K. Christoff, T. C. Handy, E. D. Reichle and M. A. Sayette (2011). "Meta-awareness, perceptual decoupling and the wandering mind." Trends Cogn Sci **15**(7): 319-326.

Schott, B. H., T. Wustenberg, M. Wimber, D. B. Fenker, K. C. Zierhut, C. I. Seidenbecher, H. J. Heinze, H. Walter, E. Duzel and A. Richardson-Klavehn (2011). "The relationship between level of processing and hippocampal-cortical functional connectivity during episodic memory formation in humans." Hum Brain Mapp **34**(2): 407-424.

Seibert, P. S. and H. C. Ellis (1991). "Irrelevant thoughts, emotional mood states, and cognitive task performance." Mem Cognit **19**(5): 507-513.

Shulman, G. L., J. A. Fiez, R. L. Buckner, F. M. Miezin, M. E. Raichle and S. E. Peterson (1997). "Common blood flow changes across visual tasks: II.: decreases in cerebral cortex." Journal of Cognitive Neuroscience **9**: 648-663.

Smallwood, J. (2013). "Distinguishing how from why the mind wanders: a process-occurrence framework for self-generated mental activity." Psychol Bull **139**(3): 519-535.

Smallwood, J. and J. Andrews-Hanna (2013). "Not all minds that wander are lost: the importance of a balanced perspective on the mind-wandering state." Front Psychol **4**: 441.

Smallwood, J., S. F. Baracaia, M. Lowe and M. Obonsawin (2003). "Task unrelated thought whilst encoding information." Conscious Cogn **12**(3): 452-484.

Smallwood, J., K. Brown, B. Baird and J. W. Schooler (2011). "Cooperation between the default mode network and the frontal-parietal network in the production of an internal train of thought." Brain Res.

Smallwood, J. and J. W. Schooler (2006). "The restless mind." Psychol Bull **132**(6): 946-958.

Spencer, W. D. and N. Raz (1995). "Differential effects of aging on memory for content and context: a meta-analysis." Psychol Aging **10**(4): 527-539.

Stawarczyk, D., S. Majerus, M. Maj, M. Van der Linden and A. D'Argembeau (2011). "Mind-wandering: phenomenology and function as assessed with a novel experience sampling method." Acta Psychol (Amst) **136**(3): 370-381.

Stawarczyk, D., S. Majerus, P. Maquet and A. D'Argembeau (2011). "Neural correlates of ongoing conscious experience: both task-unrelatedness and stimulus-independence are related to default network activity." PLoS One **6**(2): e16997.

Symons, C. S. and B. T. Johnson (1997). "The self-reference effect in memory: a meta-analysis." Psychol Bull **121**(3): 371-394.

Szpunar, K. K., S. T. Moulton and D. L. Schacter (2013). "Mind wandering and education: from the classroom to online learning." Front Psychol **4**: 495.

Todd, R. M., W. A. Cunningham, A. K. Anderson and E. Thompson (2012). "Affect-biased attention as emotion regulation." Trends Cogn Sci **16**(7): 365-372.

Tulving, E. (1972). Episodic and semantic memory. Organization of memory. E. Tulving and W. Donaldson. New York, Academic Press**:** 381-403.

Tulving, E. (2002). "Episodic memory: from mind to brain." Annu Rev Psychol **53**: 1-25.

Wagner, A. D., D. L. Schacter, M. Rotte, W. Koutstaal, A. Maril, A. M. Dale, B. R. Rosen and R. L. Buckner (1998). "Building memories: remembering and forgetting of verbal experiences as predicted by brain activity." Science **281**(5380): 1188-1191.

Zierhut, K., B. Bogerts, B. Schott, D. Fenker, M. Walter, D. Albrecht, J. Steiner, H. Schutze, G. Northoff, E. Duzel and K. Schiltz (2010). "The role of hippocampus dysfunction in deficient memory encoding and positive symptoms in schizophrenia." Psychiatry Res **183**(3): 187-194.

2. Study 1: Dissociable roles of default-mode regions during episodic encoding

2.1 Preface

Please note that the following manuscript differs slightly from the one published in Neuroimage in April 2014. Following publication, I detected an error in how the onset vectors for the "Pleasantness Incorrect" condition were coded. This error resulted in approximately 45% of onset vectors being incorrectly coded for this condition only. I have fixed this error, and in the following sections, I present the updated results. An erratum has been submitted to Neuroimage with the following results.

2.2 Abstract

We investigated the role of distinct regions of the default-mode network (DMN) during memory encoding with fMRI. Subjects encoded words using either a strategy that emphasized self-referential (pleasantness) processing, or one that emphasized semantic (man-made/natural) processing. During encoding subjects were intermittently presented with thought probes to evaluate if they were concentrated and on-task or exhibiting task-unrelated thoughts (TUT). After the scanning session subjects performed a source retrieval task to determine which of two judgments they performed for each word at encoding. Source retrieval accuracy was higher for words encoded with the pleasantness vs. the man-made/natural task and there was a trend for higher performance for words preceding on-task vs. TUT reports. fMRI results show that left dorsal medial PFC and left angular gyrus activity was greater during successful vs. unsuccessful encoding during both encoding tasks. Greater activity in ventral medial PFC was related successful vs. unsuccessful encoding only in the pleasantness task. In contrast, posterior

cingulate and right temporoparietal junction were activated to a greater extent in unsuccessful vs. successful encoding across tasks. Finally, activation in posterior cingulate and bilateral dorsolateral prefrontal cortex was related to TUT across tasks; moreover, we observed a conjunction in posterior cingulate between encoding failure and TUT. We conclude that DMN regions play dissociable roles during memory formation, and that their association with subsequent memory may depend on the manner in which information is encoded and retrieved

2.3. Introduction

The default-mode network (DMN) refers to a set of regions including medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), inferior parietal lobes (IPL), and lateral temporal cortex (LTC) (Buckner et al., 2008). A formal characterization of this network came from task-based meta-analyses which found that these regions were activated to a greater extent during passive resting-state conditions compared to a variety of externally-driven and cognitively demanding tasks, such as visual search and episodic memory retrieval (Nyberg et al., 1996 and Shulman et al., 1997). More recently, similar task-related reductions in activity in DMN regions has been reported during episodic encoding studies (e.g., Daselaar et al., 2004). Furthermore, a recent meta-analysis indicated that increased activation in all major DMN regions during episodic encoding, including ventral medial PFC, PCC, bilateral IPL and LTC is predictive of retrieval failure (Kim, 2010). It has been suggested that since successful encoding requires externally-directed attention, activation in DMN regions should be suppressed, reflecting down-regulation of task-unrelated thoughts (TUT) (Daselaar et al., 2009 and Shrager et al., 2008), defined here as thoughts that are not relevant to encoding items. This suggestion is consistent with behavioral evidence indicating that the frequency of TUT at encoding is negatively correlated with retrieval performance in young adults (Maillet and Rajah, 2013 and Seibert and Ellis, 1991); and is also compatible with evidence that DMN regions are involved in TUT at rest and during some cognitive tasks such as the sustained attention to response task (Andrews-Hanna et al., 2010a, Christoff et al., 2009 and Stawarczyk et al., 2011). However, to our knowledge, the hypothesis that activation in DMN regions during episodic encoding reflects TUT has never been directly tested.

Furthermore, although the majority of the literature indicates that activation in DMN regions is suppressed during successful episodic encoding, these studies have mostly used semantic encoding tasks, such as judging whether words are man-made/natural (Kim, 2010). Such tasks are known to deactivate DMN regions (e.g., Lustig et al., 2003). In contrast, increased activation in some DMN regions has been observed during successful encoding when the encoding task emphasized subjective evaluation of stimuli in relation to oneself. For example, successful encoding using both pleasantness judgments, or judging whether adjectives are descriptive of oneself have both been associated with activation in mPFC (e.g., Leshikar and Duarte, 2012, Macrae et al., 2004, Maillet and Rajah, 2011, Shrager et al., 2008 and Zierhut et al., 2010) and at least one study using pleasantness judgments has also reported correct subsequent memory effects in IPL (Schott et al., 2011). Moreover, encoding using such self-referential strategies results in better memory compared to semantic and perceptual encoding tasks (e.g., Leshikar and Duarte, 2012 and Maillet and Rajah, 2013). It has been suggested that this increase in memory is due to the superior organizational and elaborative processes associated with encoding information in relation to the self (Rogers et al., 1977 and Symons and Johnson, 1997). In contrast, in another fMRI study where subjects encoded words using a pleasantness judgment, it was found that activation in left mPFC predicted retrieval success; but, activation in right mPFC, PCC/precuneus, and bilateral temporoparietal junction predicted retrieval failure (Shrager et al., 2008). Taken together, these studies suggest that when self-referential encoding strategies are used, a subset of DMN regions may be involved in encoding success, while a distinct set of regions may be involved in encoding failure, perhaps due to TUT.

These results are consistent with evidence that the DMN can be fractionated into distinct subsystems, only some of which are preferentially recruited during self-referential processing. For example, Andrews-Hanna et al. (2010b) reported that a dorsal medial PFC subsystem, which included regions such as dorsal medial PFC, LTC, temporal pole and temporoparietal junction was preferentially activated when people made self-relevant decisions. In addition, Andrews-Hanna et al. (2010b) identified a distinct subsystem, which included retrosplenial cortex and IPL, that was preferentially engaged when individuals constructed mental scenes based on memory. More recently, Qin and Northoff (2011) performed a quantitative meta-analysis indicating that in contrast to other DMN regions, only the ventral anterior cingulate (ACC) was preferentially recruited during self-referential decisions. In another meta-analysis, Kim (2012) reported evidence that a subsystem including anterior medial PFC and posterior cingulate mainly supports self-referential processes, while regions including IPL and LTC were involved in memory retrieval. Thus, although there is some inconsistency, these results converge to suggest a particularly important role of mPFC in self-referential processes, which is in agreement with studies indicating that this region is involved in encoding success when items are encoded in relation to the self.

These prior studies also suggest that other DMN regions, including PCC, IPL and LTC, are involved in encoding failure regardless of whether the encoding task is self-referential or semantic because the cognitive processes subserved by these regions are recruited to a greater extent during TUT relative to encoding items using these strategies. Previous studies suggest that the content of TUT during the performance of a cognitive task in an fMRI scanner is varied and may include: mind-wandering (e.g. thoughts about the past or the future), distractions involving monitoring of the internal or external environment (e.g. thinking about how hungry one is, thinking about scanner noise etc.), and task-related interferences (e.g. thoughts related to the appraisal of the current task) (Stawarczyk et al., 2011). These thoughts may recruit cognitive processes that have been associated with PCC, LTC and IPL such as, scene construction (Hassabis et al., 2007), memory retrieval (Kim, 2012 and Wagner et al., 2005), internally focused attention (Buckner et al., 2008), prospection (Addis et al., 2007), and monitoring of internal/external milieus (Raichle et al., 2001).

The current study was designed to investigate the role of distinct DMN regions during encoding of word stimuli. We used fMRI to examine regional activity while subjects performed self-referential (pleasantness) and semantic (man-made/natural judgment) encoding of verbal stimuli. We pseudo-randomly inserted thought probes throughout the encoding task that asked subjects to provide self-reports of their current mental state (Christoff et al.,2009 and Stawarczyk et al., 2011). During thought probes, subjects reported whether they were focused on task, or whether they were exhibiting TUT (i.e. mind-wandering, task-related interferences or distractions) (Stawarczyk et al., 2011). Ten minutes after fMRI scanning, subjects performed a source memory retrieval task for encoded stimuli.

The first goal of this study was to directly test the hypothesis that due to its involvement in self-referential processes, mPFC would be activated to a greater extent in successful vs. unsuccessful encoding of verbal items when a pleasantness but not when a man-made/natural encoding strategy is used. Also, based on findings that retrosplenial cortex/PCC, IPL and LTC may be recruited during in processes such as construction of mental scenes (Andrews-Hanna et al., 2010b and Hassabis et al., 2007) and/or memory retrieval (Kim, 2012 and Wagner et al., 2005), and that these regions have been involved in encoding failure even when a self-referential task is used (Shrager et al., 2008), we predicted that these regions would be activated to a greater extent in unsuccessful vs. successful encoding of word stimuli independently of the task. In addition, we tested the hypothesis that the DMN regions activated in unsuccessful vs. successful encoding would also be activated to a greater extent when subjects were off-task (exhibiting TUT) vs. on-task. To identify the neural correlates of TUT during episodic memory encoding, we contrasted the activation in encoding trials preceding TUT (off-task) reports with the activation in encoding trials preceding on-task reports. Reaction times for the events preceding thoughts probes were used as an objective measure for whether the TUT episode, whose occurrence was measured during the thought probe, extended to the preceding encoding event. Specifically, we predicted that if this was the case, encoding trials in which TUT occurred would be associated with longer reaction times vs. those where no TUT occurred.

2.4. Methods

2.4.1. Subjects

Twenty-one, right-handed, healthy adults (age range 18–30, mean age = 23.33, 12 women) participated in the study. Participants reported no history of psychiatric illness, neurological disorders, or substance abuse and were healthy at time of testing. Participants had a minimum of high school education (mean education = 16.35 year). Volunteers were recruited with advertisements on university websites in the city of Montreal. All participants signed a consent form approved by the ethics boards of the Douglas Mental Health University Institute.

2.4.2 Behavioral methods

Participants visited the Douglas Mental Health University Institute on two separate occasions. In the first session, they completed a series of neuropsychological tasks including the Montreal Cognitive Assessment Scale (Nasreddine et al., 2005) (cut-off > 25) and the Beck Depression Inventory (Beck, 1987 and Beck et al., 1961) (cut off < 10). They also completed the Edinburgh inventory (Oldfield, 1971), and were all right-handed according to this test. Finally, participants performed a practice version of the fMRI task in a mock MRI scanner, which familiarized them with the memory task and thought classification prior to the fMRI session (session two).

Participants returned for a second session to perform an episodic memory task for words, while undergoing fMRI scanning. The MRI session consisted of an anatomical scan (5 min) and 4 fMRI encoding runs (each 10 min 20 s). Thus, in total, the encoding portion of the experiment lasted approximately 41 min. The stimuli used in the memory task were 414 French nouns of 3–11 letters, taken from Desrochers and Thompson (2009) and the OMNILEX database (http://www.omnilex.uottawa.ca/scrServices.asp). The experiment was carried out in French, given that Montreal is a primarily French-speaking city. In total, 414 nouns were used: 276 served as encoding words, while the other 138 were used as distractors at retrieval. Half of the words were used in the pleasantness task, while the other half was used in the man-made/natural task. The words were not switched across the pleasantness and man-made/natural task for different subjects. However, T-tests indicated that words used in pleasantness encoding, man-made/natural encoding and words used as distractors in the retrieval task were matched for number of letters (mean with standard deviation: 6.46 (1.82), 6.68 (1.67) and 6.60 (1.74) respectively), number of syllables (mean with standard deviation: 2.05 (0.68), 2.02 (0.72) and 2.00 (0.71) respectively), frequency ratings (mean with standard deviation: 3.49 (1.15), 3.30 (1.11) and 3.47 (1.08) respectively) and imageability ratings (mean with standard deviation: 4.48

(1.5), 4.43 (1.62) and 4.62 (1.56) respectively). Half of the words in all tasks represented man-made objects (e.g., pencil, computer, car), and the other half were natural (e.g., cat, apple, rose).

During each encoding run, subjects were presented with words, one at a time, in the center of the screen for 2.5 s/word. They were asked to answer one of two questions for each word during encoding: 1) determine whether it was man-made (semantic encoding task) or 2) judge if they think the word was pleasant (self-referential encoding task). The question to be answered on any given trial was indicated by an appropriate cue, presented below each word ("Pleasant?" or "Man-made?"). For both encoding tasks, participants answered "yes" with button 1 and "no" with button 2. Encoding trials were separated by a variable inter-trial interval (ITI) of either 2.2, 4.0, or 6.7 s (mean = 4.3 s) which served to add jitter to the fMRI acquisition sequence, allowing dissociation of event-related changes in BOLD activity (Dale, 1999). Participants were informed that a retrieval task would follow; thus encoding was intentional. Participants had also performed a practice version of the task during the first session, so they were fully aware of the upcoming nature of the retrieval task. Participants performed the same encoding task for 4, 5, 6 or 7 consecutive words. After 4–7 words, there was a 2.5 sec ITI, followed by a thought probe was presented on screen for 7 s. Following the thought probe, the encoding task was switched for the next 4–7 words.

During the thought probe subjects were asked to report the type of thought that they were experiencing the moment the probe came on screen (Christoff et al., 2009 and Stawarczyk et al., 2011). In accordance with the methods used by Stawarczyk et al. (2011), subjects chose between 1) being concentrated on the task, 2) mind-wandering (e.g. I thought about my personal worries, I thought about something that happened in the past or future, etc.), 3) task-related interferences (e.g. I thought about how long, boring, easy or hard the task was, etc.), or 4) thinking about internal distractions (e.g. feeling uncomfortable, thinking about back pain, etc.) or external distractions (e.g. thinking about scanner noise). Note that we use the term “task-unrelated thought (TUT)” to refer to mind-wandering, task-related interferences and distractions. Although it may appear contradictory that we included task-related interferences as a component of task-unrelated thought, our use of the term TUT is meant to refer to a collection of thoughts that are not relevant to encoding words, rather than thoughts unrelated to the task itself. Participants were familiarized with the thought classification, and given examples of each category during the practice session. In total, there were 54 thought probes across the four encoding runs (13 or 14 per run).

Approximately 10 min following the end of the encoding task, subjects performed a source memory retrieval task outside of the scanner. During retrieval, all 276 encoding words (138 in the pleasantness task, and 138 in the man-made/natural task), mixed with 138 new words, were presented one at a time. Each word appeared on-screen for 4.5 s, followed by a fixed 1 s ITI. Subjects were asked to choose whether each word was 1) old and studied in the pleasantness task, 2) old and studied in the man-made task, 3) old (but no recall of the encoding task) or 4) new. The correct response was 1) on 33.3% of trials, 2) on 33.3% of trials and 4) and 33.3% of trials.

2.4.3. fMRI data acquisition

The MRI and fMRI data were collected using a 3 T Siemens Trio scanner at the Douglas Mental Health University Institute Brain Imaging Centre. A standard whole-head coil was used, and cushions were inserted to stabilize head motion. A high-resolution structural scan was acquired using a 5.03 min gradient-echo (GRE) sequence (TR = 2300 ms, TE = 2.98 ms, flip angle = 9, 172 1 mm sagittal slices, field of view = 256 mm, 1mm × 1mm × 1mm resolution). Following the structural scan, subjects performed the aforementioned episodic memory task during four 10.26 min runs while blood-oxygen-level-dependent (BOLD) images were acquired using a fast echo-planar imaging (EPI) pulse sequence (TR = 2000 ms, TE = 30 ms, field of view = 256 mm, in-plane resolution = 4 × 4 × 4mm). 308 fMRI volumes were acquired in each of the four encoding runs, for a total of 1232 in the experiment.

2.4.4. Event trial classification

We analyzed the behavioral data in a way that matched the fMRI data analysis (see later section). Specifically, the 276 encoding events were divided into those directly preceding the thought probes (n = 54), and those that did not (n = 222). Words directly preceding thought probes were classified as either “on-task” or “off-task”, depending on the answer provided during the thought probe. Off-task trials were those in which subjects responded that they were exhibiting any type of TUT (mind-wandering, task-related interferences or distractions), while on-task trials were those in which they responded that they were concentrated on the task, irrespective of subsequent memory. The encoding trials that did not directly precede thought probes were divided into “correct pleasantness encoding” (PleasCor), “incorrect pleasantness encoding” (PleasIncor), “correct man-made/natural encoding” (ManCor) and “incorrect man-made/natural encoding” (ManIncor). Correct events were those words that were subsequently remembered and attributed to the correct encoding task (correct source). Incorrect events were all other events types, in which the source was forgotten (source misattribution, item recognition with no recollection of source, and missed words). We chose to combine these events types due to the small number of “misses” in the pleasantness task (mean = 14). As noted in a previous study using this methodology, this means that our behavioral and fMRI results distinguish encoding events for which the source was later remembered vs. forgotten, but do not speak to the question of events later attracting a correct recognition judgment without source vs. misses (Gottlieb et al., 2010). However, we did conduct exploratory analyses using only misses, reported in section 3.2.3.

2.4.5. Reaction time

We analyzed encoding reaction time data primarily to test the hypothesis that encoding trials directly preceding on-task reports would be associated with faster reaction times compared with encoding trials preceding off-task reports. A two-tailed paired samples *t*-test was used to assess this hypothesis. A separate two-way encoding task (man-made/natural vs. pleasantness) by subsequent memory (correct vs. incorrect) ANOVA was used to analyze RT on the remaining encoding trials which did not directly precede the thought probes.

We also examined whether retrieval RT differed as a function of encoding task or subsequent memory. A two-way encoding task (man-made/natural vs. pleasantness) by subsequent memory (correct vs. incorrect) ANOVA was used to analyze the retrieval RT.

2.4.6. Retrieval performance

We analyzed the retrieval performance data in order to answer two questions: 1) is source memory better for words encoded in the pleasantness vs. man-made/natural task and 2) is source memory better for words directly preceding on-task vs. off task reports. We analyzed retrieval performance using an index which assessed the probability of correctly remembering the source, while correcting for response bias. Specifically, for each task, retrieval performance was computed as (% Source Hit — (% source misattribution + % false alarm)/2). A two-tailed paired *t*-test was used to compare retrieval performance in the two tasks, for words which did not directly precede the thought probes.

The (% Source Hit — (% source misattribution + % false alarm)/2) measure could not be used to compare performance on encoding trials preceding on-task vs. off-task reports; this is because “false alarms” cannot be attributed to on-task or off-task trials (they can only be attributed to the pleasantness or the man-made/natural task). Thus, to compare performance on on-task vs. off-task trials, we compared proportion of source hits, source misattributions and misses using paired *t*-tests.

2.4.7. fMRI data preprocessing

Pre-processing and analysis of the fMRI data was conducted in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Images from the first 10 s of each run were discarded to control for field inhomogeneities. All scans were then spatially realigned to the first scan, using a 6 parameter (rigid body) transformation. Next, the scans were normalized to the MNI EPI template in SPM8, resampled to 2 mm cubic voxels and smoothed using an 8 mm full-width at half maximum (FWHM) kernel.

2.4.8. fMRI general linear model

For each subject, seven regressors were modeled in an event-related manner ($t = 0$), convolved with the SPM canonical hemodynamic response function and its temporal derivative, and entered into a general linear model (GLM) regression analysis. Encoding events directly preceding the thought probes ($n = 54$) were analyzed separately from other encoding events ($n = 222$), and classified as either “on-task” or “off-task”, depending on the answer provided during the thought probe. Because of the small amount of trials available, we did not examine on-task and off-task events separately for each encoding task. The thought probes themselves were also modeled as a regressor, but were not analyzed further (Christoff et al., 2009). The encoding trials that did not directly precede thought probes were divided into “correct pleasantness encoding” (PleasCor), “incorrect pleasantness encoding” (PleasIncor), “correct man-made/natural encoding” (ManCor) and “incorrect man-made/natural encoding” (ManIncor). Correct events were those words that were subsequently remembered and attributed to the correct encoding task (correct source). Incorrect events were all other events types, in which the source was forgotten (source misattribution, old with no recollection of source, and forgotten words). Serial correlations were accounted for using an autoregressive AR(1) model. A high-pass filter cut-off of 128 was used, and no global normalization was performed. Finally, movement parameters were included as regressors of no interest.

Two separate second level random effect fMRI analyses were conducted. The first analysis was conducted on the encoding trials which did not directly precede thought probes (classified as PleasCor, PleasIncor, ManCor and ManIncor), while the second was conducted on encoding trials directly preceding the probes (classified as on-task or off-task). Results were considered significant if they exhibited $p < .001$ with a cluster size greater than 10 voxels (Forman et al., 1995).

2.4.9. fMRI analysis of regions involved in the main effect of subsequent memory, encoding task, and subsequent memory by encoding task interaction

The first fMRI analysis used data from all 21 subjects included in this study. We performed the following 4 t-contrasts for each subject: PleasCor vs. baseline, PleasIncor vs. baseline, ManCor vs. baseline and ManIncor vs. baseline. These contrasts were entered in a two-way subsequent source memory-by-encoding task repeated measures ANOVA. We assessed brain regions involved in the main effect of encoding task, the main effect of subsequent source memory and the encoding task-by-subsequent source memory interaction. Main effects were exclusively masked with the subsequent memory-by-encoding task F interaction at a very liberal threshold ($p < 0.05$) to ensure that they were not driven by it (e.g., Prince et al., 2009).

2.4.10. fMRI analysis of regions involved in TUT

For the second fMRI analysis, we used a sub-sample of 14 subjects (out of 21) that had at least 14 on-task and 14 off-task events to examine the brain regions involved in exhibiting TUT (mean of 26 on-task and 27 off-task events across the 14 subjects). First, 2 t contrasts were performed for each subject (off-task vs. on-task and on-task vs. off-task). Next, two one-sample group level t-tests were performed on these t-contrasts to test the null hypothesis that there were no differences in activation between these conditions. Although we acknowledge that this is a relatively small sample size, a similar sample size ($n = 15$) was used in a previous study of mind-wandering (Christoff et al., 2009). In addition, the regions identified in our TUT contrast were largely overlapping with those found in previous studies (Christoff et al., 2009 and Stawarczyk et al., 2011).

Finally, to assess the regions involved both in encoding failure and in exhibiting TUT, we performed a conjunction in SPM8 between the off-task vs. on-task and the main effect of encoding failure (both contrasts individually thresholded at $p < 0.001$). The conjoint probability for the conjunction is very conservative ($p < 0.00001$) (Fisher, 1950 and Lazar et al., 2002).
We used Mango (http://ric.uthscsa.edu/mango/download.html) and Caret (http://brainvis.wustl.edu/wiki/index.php/Main_Page) to display the fMRI results for the Figures. Marsbar (http://marsbar.sourceforge.net/) was used to extract parameter estimates of the ROIs plotted in Fig. 2.

2.5. Results

2.5.1. Encoding reaction time

Encoding reaction times are listed in Table 1. We analyzed the impact of encoding task-type (man-made/natural vs. pleasantness) and subsequent memory (correct vs. incorrect) on encoding RT using a two-way task repeated measures ANOVA. There was a significant task-by-subsequent source memory interaction ($F(1,20) = 10.982$, $p = 0.003$, $\eta^2 p = 0.354$). There were no significant main effects of subsequent source memory ($F(1,20) = 0.127$, $p = 0.725$, $\eta^2 p = 0.006$) or task-type ($F(1,20) = 0.82$, $p = 0.777$, $\eta^2 p = 0.004$) on encoding RT. The significant interaction was due to subjects responding faster during correct vs. incorrect events in the pleasantness task ($F(1,20) = 15.879$, $p = 0.001$, $\eta^2 p = 0.443$), with no such effect in the man-made/natural task ($F(1,20) = 2.476$, $p = 0.131$, $\eta^2 p = 0.110$).

Table 1.
Reaction time with standard error.

	Pleasant Correct	Pleasant Incorrect	Man-made Correct	Man-made Incorrect	On-Task	Off-Task
Encoding Reaction Time (ms)	1621 (55)	1686 (55)	1673 (67)	1621 (61)	1486 (52)	1668 (97)
Retrieval Reaction Time (ms)	2096 (85)	2278 (90)	2272 (84)	2186 (94)	2129 (74)	2110 (94)

Note: This table presents the mean encoding reaction times in for each condition, with standard error in parentheses. “On-Task” refers to encoding events preceding thought probes in which subjects reported being concentrated on the task. “Off-task” refers to encoding events preceding thought probes in which subjects reported exhibiting task-unrelated thoughts.

We also compared encoding RT for words preceding on-task reports vs. off-task reports. Subjects responded that they were on-task on 51% of probes, and off-task on 48% of probes. This proportion was similar when thought probes followed the man-made/natural encoding task (49% on-task, 51% off-task) and the pleasantness encoding task (52% on-task, 47% off-task). Across encoding tasks, TUT were composed of 18% mind-wandering, 31% task-related interferences and 50% internal/external distractions. To be consistent with the fMRI data, we examined RT in the encoding trials preceding on-task vs. off-task trials, collapsed across encoding task type and TUT type. A repeated measures ANOVA revealed that subjects responded significantly faster in the encoding trials preceding on-task vs. off task reports ($F(1,20) = 10.821$, $p = 0.004$, $\eta^2p = 0.351$). This result supports our interpretation that the TUT episode encompassed the encoding trial preceding the thought probe.

2.5.2. Retrieval accuracy and reaction time

The proportion of correct source, source misattribution, words recognized without the source, misses and false alarms is listed in Table 2. A paired *t*-test on the (% Source Hit — (% source misattribution + % false alarm)/2) measure indicated that source memory performance was better for words encoded in the pleasantness vs. man-made/natural task ($F(1,20) = 59.462$, $p < 0.001$, $\eta^2p = 0.748$). As can be seen in Table 2, the reduced source memory performance in the man-made/natural task is attributable to a greater amount of misses in this task ($T(1,20) = 57.699$, $p < 0.001$, $\eta^2p = 0.743$); there were no differences in either source misattributions ($T(1,20) = 0.71$, $p = 0.944$) or words recognized without the source ($T(1,20) = 1.66$, $p = 0.112$).

Table 2.

Retrieval accuracy performance with standard error.

Response type	Pleasantness task	Man-made task	On-task	Off-task
% Source Hit	0.57 (0.04)	0.38 (0.03)	0.51 (0.03)	0.44 (0.04)
% Recognition, no source	0.21 (0.03)	0.23 (0.03)	0.21 (0.04)	0.24 (0.03)
% Misses	0.13 (0.02)	0.30 (0.03)	0.19 (0.02)	0.25 (0.03)
% Source misattribution	0.09 (0.02)	0.09 (0.02)	0.09 (0.02)	0.07 (0.02)
% False alarms	0.03 (0.01)	0.03 (0.01)		
% Source Hit—((% false alarm + % source misattribution)/2)	0.51 (0.04)	0.31 (0.03)		

Note: This table presents the retrieval performance data for each condition. “Recognition, no source” refers to words when subjects correctly responded that they had seen a word before, but did not remember its source. “Source misattribution” refers to responding that a word studied in the pleasantness task was studied in the man-made/natural task and vice-versa. “On-Task” refers to retrieval performance for encoding words preceding thought probes in which subjects reported being concentrated on the task. “Off-task” refers to retrieval performance for encoding words preceding thought probes in which subjects reported exhibiting task-unrelated thoughts.

A two-way repeated measures ANOVA on retrieval RT with factors of task (man-made/natural vs. pleasantness) and subsequent memory (correct vs. incorrect) revealed a significant interaction ($F(1,20) = 23.939$, $p < 0.001$, $\eta^2 p = 0.545$), but not main effect of task ($F(1,20) = 2.516$, $p = 0.128$, $\eta^2 p = 0.112$) or subsequent memory ($F(1,20) = 0.296$, $p = 0.592$, $\eta^2 p = 0.015$). The interaction was due to significantly faster RT in correct retrieval events studied in the pleasantness vs. man-made task ($F(1,20) = 14.789$, $p = 0.001$, $\eta^2 p = 0.425$), but faster RT for incorrect events in the man-made vs. the pleasantness task (F(1,20) = 10.193, p = 0.005, η^2p = 0.338).

We also examined retrieval performance for words preceding on-task vs. off-task reports. As explained in the methods section, we directly compared proportion of source hits, source misattributions and misses using t-tests. Subjects exhibited more source hits for on-task vs. off task trials (F(1,20) = 5.837, p = 0.025, η^2p = 0.226). Although subjects exhibited numerically higher source misattributions in on-task vs. off-task trials, this difference was not significant (F(1,20) = 0.763, p = 0.393). Subjects exhibited significantly more misses for off-task vs. on task trials (F(1,20) = 5.447, p = 0.03, η^2p = 0.214). Finally, we also examined whether retrieval RT differed according to on-task vs. off-task reports at encoding. We found no significant difference in retrieval RT between words preceding on-task vs. off-task reports at encoding (F(1,20) = 0.112, p = 0.741, η^2p = 0.006). Thus in summary, in addition to being associated with higher *encoding* reaction times (previous section), encoding trials preceding off-task reports were also associated with subtle changes in subsequent memory compared to on-task trials (more misses and less source hits).

2.5.3. fMRI results: Main effect of encoding task

The main effect of encoding task identified regions which were activated to a greater extent when making a pleasantness vs. man-made/natural judgment or vice-versa, independent of whether subjects correctly remembered the source of encoding events or not. A group of regions including anterior mPFC, bilateral inferior/middle temporal gyri, bilateral angular gyri, PCC and bilateral cerebellum was identified in the pleasantness vs. the man-made/natural task. In contrast, greater activation in the man-made/natural vs. the pleasantness task was identified in bilateral

bilateral intraparietal sulcus and right lateral PFC. A complete list of regions identified by the main effect of task can be found in Table 3.

Table 3. ANOVA encoding task main effect.

Hemisphere	Brain region	Brodmann area	MNI coordinates	Cluster size	Peak T value
Pleasantness vs. man-made/natural encoding task					
Left	Anterior medial superior PFC	8/9	-6 54 44	4655	9.51
			-6 58 16		8.56
			-6 58 30		8.26
Left	Middle/Inferior Temporal Gyrus	21/20	-60 -14 -24	1482	6.66
			-30 14 -22		6.18
			-38 18 -20		5.45
Right	Cerebellum		30 -84 -36	427	6.44
Left	Posterior Cingulate	23/30	-4 -50 28	729	5.31
			-10 -52 6		4.07
Right	Temporal pole	38/21	48 12 -36	125	5.06
			54 4 -34		4.67
			58 2 -26		4.13
Left	Angular gyrus/ Middle Temporal Gyrus	39	-56 -66 28	699	5.01
			-60 -62 16		3.94
			-64 -48 26		3.31
Right	Middle Temporal Gyrus	22/21	50 -38 0	261	4.54
Left	Inferior Frontal Gyrus	44/45	-52 22 12	51	3.95
Right	Middle temporal gyrus/Lateral occipital cortex	39/19	58 -64 20	148	3.9
			50 -78 10		3.88
Right	Cerebellum		46 -60 -44	12	3.66
Right	Cerebellum		6 -54 -50	13	3.62
Left	Cerebellum		-28 -84 -36	24	3.59
Man-made/natural vs. pleasantness encoding task					

Hemisphere	Brain region	Brodmann area	MNI coordinates	Cluster size	Peak T value
Right	Intraparietal sulcus	40/7	44 -44 48	919	5.29
Left	Intraparietal sulcus	40/7	-36 -44 44	634	4.38
			-44 -40 48		4.14
			-42 -46 54		3.94
Right	Middle frontal gyrus	6	32 8 56	205	4.05
Right	Middle frontal gyrus	6/9	46 14 32	188	4.03
			40 8 32		3.62
Right	Insula		28 22 2	14	3.74
Right	Insula		28 26 -4	18	3.72
Right	Frontal pole	10	36 54 10	93	3.69

Note: This table presents the random effects within-group SPM8 results. The t-values represent the value for the local maxima which had a $p < .001$ and spatial extent threshold of $k > 10$. The cluster size refers to the total number of voxels included in the voxel cluster. The stereotaxic coordinates are measured in mm.

2.5.4. Main effect of subsequent source memory

Regions including medial anterior PFC, left angular gyrus and left inferior PFC were activated to a greater extent in correct vs. incorrect source memory encoding, independently of encoding task. In contrast, the right precuneus/PCC, right temporoparietal junction, right insula and right superior frontal gyrus were activated to a greater extent during incorrect vs. correct source encoding events. A complete list of regions identified by the main effect of subsequent source memory can be found in Table 4.

Table 4.

ANOVA main effect of subsequent source memory.

Hemisphere	Brain region	Brodmann area	MNI Coordinates	Cluster size	Peak T value
Correct vs. incorrect source encoding					
Left	Inferior Frontal Gyrus	47/45	-34 30 -10	1554	6.33
			-42 26 -2		5.96
			-48 24 12		5.7
Left	Caudate		-12 10 10	1259	6.24
			14 10 6		4.28
			16 12 14		4.22
Left	Anterior medial superior PFC	8/9	-12 34 56	809	4.64
			-6 30 50		4.16
			-8 56 26		3.96
Left	Middle Frontal Gyrus	6	-42 12 54	80	4.43
Right	Cerebellum		40 -68 -42	340	4.33
			32 -72 -42		4.19
Left	Parahippocampal Gyrus/ Cerebellum	36	-24 -34 -26	187	4.32
Left	Angular gyrus	39	-46 -66 28	92	3.95
Right	Inferior Frontal Gyrus	47	36 34 -14	25	3.67
Incorrect vs. correct source encoding					
Right	Temporoparietal junction	39/40/22	56 -52 12	607	4.88
			58 -44 34		4.08
			58 -40 22		3.65
Right	Precuneus / posterior cingulate	7	6 -68 60	1800	4.73
			6 -78 50		4.6
			8 -68 50		4.53
Right	Superior frontal gyrus	6	22 2 58	92	3.92
			32 -2 58		3.45
Right	Insula	13	48 12 -4	46	3.56
Right	Inferior Parietal Lobule	40	58 -32 44	16	3.55
Left	Posterior Cingulate	31	-18 -66 20	11	3.4

Note: This table presents the random effects within-group SPM8 results. The t-values represent the value for the local maxima which had a $p < .001$ and spatial extent threshold of $k > 10$. The cluster size refers to the total number of voxels included in the voxel cluster. The stereotaxic coordinates are measured in mm.

2.5.5. Task by subsequent source memory interaction

The task by subsequent source memory interaction identified regions that were related to correct vs. incorrect source encoding in the pleasantness, but not the man-made/natural task, and vice-versa (Table 5). Left ventral mPFC (anterior cingulate/frontal pole) was activated to a greater extent in correct vs. incorrect source encoding only in the pleasantness task (F(1,20)=6.991, p=0.016, $n^2p = 0.259$, but to a greater extent in incorrect vs. correct source encoding in the man-made task (F(1,20)=5.491, p=0.03, $n^2p = 0.215$. On the other hand, left precentral gyrus and middle frontal gyrus were involved in correct vs. incorrect source encoding only in the man-made task ($p < 0.0005$ in both regions), while there was no such difference in the pleasantness task ($p > 0.18$ in both regions).

Table 5. ANOVA interaction: Regions involved in correct source encoding only in the pleasantness task.

Hemisphere	Brain region	Brodmann area	MNI coordinates	Cluster size	Peak T value
Interaction: Correct vs. incorrect source only in the pleasantness task					
Left	Anterior cingulate/ Medial frontal pole	9	-2 56 8	34	3.58
Interaction: Correct vs. incorrect source only in the man-made task					
Left	Precentral Gyrus	6	-40 6 30	146	4.23
Left	Middle Frontal Gyrus	46	-52 28 24	66	4.21

Note: This table presents the random effects within-group SPM8 results. The t-values represent the value for the local maxima which had a $p < .001$ and spatial extent threshold of k > 10. The cluster size refers to the total number of voxels included in the voxel cluster. The stereotaxic coordinates are measured in mm.

2.5.6. Regions involved in exhibiting TUT during episodic encoding

We examined the brain regions related to exhibiting TUT by contrasting activation in encoding trials preceding off-task vs. on task-reports (Table 6). Increased activity in PCC lingual gyrus, dorsal anterior cingulate, right insula and bilateral DLPFC was observed during encoding events preceding off- vs on-task events. We observed no significant increases in brain activity during encoding events preceding on-task vs. off-task reports at $p < 0.001$.

Table 6.

Brain regions involved in task-unrelated thoughts.

Hemisphere	Brain region	Brodmann area	MNI coordinates	Cluster size	Peak T value
Left	Middle Frontal Gyrus	8	-34 38 38	58	5.14
Left	Posterior Cingulate	31/19/23	-10 -68 22 -22 -58 0 -14 -62 12	191	4.76 4.7 4.37
Bilateral	Cuneus/ lingual gyrus	17/19	0 -72 14	117	4.76
			6 -70 0		4.04
Right	Thalamus		20 -26 0	11	4.52
Right	Insula		38 0 -20	12	4.46
Right	Middle/Superior Frontal Gyrus	8	32 46 34	76	4.44
Right	Dorsal anterior cingulate	32	4 16 40	21	4.16

Note: This table presents the random effects within-group SPM8 results. The t-values represent the value for the local maxima which had a $p < .001$ and spatial extent threshold of k > 10. The cluster size refers to the total number of voxels included in the voxel cluster. The stereotaxic coordinates are measured in mm.

We conducted a conjunction analysis to determine whether the regions activated in encoding events preceding off-task vs. on-task reports overlapped with regions involved in incorrect vs. correct encoding (both individual contrasts thresholded at $p < 0.001$). A single region in PCC ([− 14 66 22], cluster size = 1) was identified in the conjunction. When both contrasts were thresholded at $p<0.005$, the cluster size increased to 127 voxels.

2.6. Discussion

The goal of this study was to investigate the role of distinct DMN regions in episodic memory encoding. Subjects encoded word stimuli using a self-referential (pleasantness) and a semantic (man-made/natural) task. During encoding subjects were intermittently presented with thought probes to evaluate if they were concentrated and on-task or exhibiting task-unrelated thoughts (TUT). In the next sections we first discuss the behavioral results, and then discuss the fMRI results in relation to our specific hypotheses.

2.6.1. Behavioral results

Behavioral results indicated that retrieval performance was better for words encoded self-referentially vs. semantically, consistent with previous research (e.g., Leshikar and Duarte, 2012 and Maillet and Rajah, 2013). Encoding RT was significantly faster for successfully vs. unsuccessfully encoded words in the self-referential, but not the semantic task. It is possible that words for which subjects can more easily judge as pleasant or not, because they are more salient/meaningful for a given participant, are easier to remember than words for that are harder for subjects to classify as pleasant/unpleasant. On the other hand, the easiness with which a word can be classified as man-made or natural may not have an influence of whether this word will be remembered or not. In addition*, retrieval* RT was significantly faster for source hits in the pleasantness vs. the semantic task, but faster for incorrect events in the man-made vs. pleasantness task. These results may indicate that for words that were correctly retrieved, retrieval judgments were easier to make in the pleasantness vs. the man-made task, perhaps because these memories were stronger. On the other hand, if memories were indeed stronger for words encoded in the pleasantness task vs. man-made task, this may have resulted in subjects hesitating more in the pleasantness vs. the man-made retrieval task for incorrect events (considering that they may have in fact have judged this word as pleasant/unpleasant) before ultimately making a mistake.

Our behavioral results indicate that TUT is frequent during episodic memory encoding. Indeed, subjects reported exhibiting a TUT on 48% of thought probes. In comparison, another study reported that subjects experienced TUTs on approximately 68% of thought probes during a sustained attention to response task (SART) (Stawarczyk et al., 2011). This reduction in TUT during episodic memory encoding may be due to this task being more demanding than the SART, which is quite repetitive and monotonous (Smallwood and Schooler, 2006). Moreover, 50% of TUTs in our study were internal/extraction distractions. This indicates that the majority of TUTs during episodic encoding in an fMRI scanner in young adults may be related to monitoring of internal and external milieus, rather than mind-wandering or thoughts related to the appraisal of the task. Finally, we found an association between TUT and performance on the memory task. First as we had predicted, RT for words preceding on-task reports were significantly faster than those preceding TUT reports. Second, we found that subjects exhibited more source hits and fewer misses for encoding trials preceding on-task vs. off-task reports, consistent with prior evidence of a negative relationship between TUT and memory performance (Maillet and Rajah, 2013, Seibert and Ellis, 1991 and Smallwood et al., 2003).

2.6.2. Left dorsomedial PFC and angular gyrus are activated to a greater extent in correct vs. incorrect encoding across tasks

We had not predicted that any DMN region would be activated to a greater extent in correct vs. incorrect encoding across tasks. Based on previous findings, one would instead expect a particularly important role for the left inferior frontal gyrus in successful encoding of verbal material (Kim, 2010 and Wagner et al., 1998). In agreement with these findings, the most prominent region involved in encoding success across tasks was a large region in left inferior frontal gyrus. This may reflect the role of this region in controlled semantic elaboration, which promotes successful verbal encoding (Wagner et al., 1998).

Interestingly however, we also found encoding success effects across encoding tasks in DMN regions including dorsomedial PFC and, left angular gyrus. This result was unexpected, given that neither of these regions is usually involved in encoding success when semantic encoding strategies are used. One possibility is that these regions were involved in encoding success because of the specific requirements of the source retrieval task. In the current study, the source retrieval task required subjects to identify which of two encoding judgments had been performed on a given word. In other words, the retrieval task required subjects to distinguish which of two cognitive operations (i.e. task-relevant thoughts) they had performed on a given word at encoding (Johnson et al., 1993). This is different from retrieval tasks traditionally used in the literature that only require subjects to recall whether or not a stimulus was seen or not — in these cases, retrieval of the cognitive operation performed at encoding is not required. Similarly, retrieval of the cognitive operations is not required in other source retrieval tasks that emphasize memory for perceptual aspects of the stimuli (e.g. determining if a word presented in red or green/on the left or right). Thus one possibility is that task-independent encoding success effects in anterior medial PFC and angular gyrus reflects internally directed attention to task-relevant cognitive operations at encoding which was necessary for successful source recollection. This suggestion is compatible with proposals that the angular gyrus is involved in internally focused attention (but note that this role is typically emphasized at retrieval, e.g. Daselaar et al., 2009 and Wagner et al., 2005).

Another study that assessed subsequent memory for encoding task (distinguishing between words and pictures judged as living/non-living vs. smaller/bigger than a shoebox) also identified a very similar region of left dorsomedial PFC to the one observed in the current study (Dulas and Duarte, 2011). In addition, we note that previous studies have also implicated this region specifically in *retrieval* of which of two encoding tasks was performed (Dobbins and Wagner, 2005 and Simons et al., 2005). For example, in Simons et al. (2005), at encoding, subjects either judged whether stimuli were pleasant/unpleasant or related more to entertainment or politics. Two source retrieval tasks were administered: in one, subjects had to remember which of the two encoding tasks they had performed on the stimulus, while in the other, they had to remember whether the stimulus had been presented on the left or right of the screen (spatial source). Compared to the spatial source task, recollection of encoding task recruited left anterior medial PFC. The authors suggested that this region may be involved in the coordinated control of internally generated information. Thus, when considered along with findings from other studies, our results suggest that the anterior medial PFC may be important both in encoding and retrieving the cognitive operation performed on encoding stimuli. Furthermore, our results emphasize that the association between encoding activation in regions of DMN, such as dorsomedial PFC and angular gyrus, and retrieval performance may critically depend on the nature of the retrieval task (Morris et al., 1977, Rugg et al., 2008 and Tulving and Thompson, 1973).

2.6.3. Left ventral mPFC is activated to a greater extent in correct vs. incorrect encoding using a pleasantness task

The main effect of encoding task indicated that the medial PFC, PCC, bilateral angular gyrus, bilateral LTC and cerebellum were activated to a greater extent when making a pleasantness vs. man-made/natural judgment during verbal encoding, independent of whether subjects correctly remembered the source of encoding events or not. However, it is unlikely that all these regions are involved specifically in self-referential processes. Indeed, prior experimental studies (Grady et al., 2012 and Grigg and Grady, 2010) in addition to recent meta-analysis (Qin and Northoff, 2011) have indicated that most of these DMN regions are recruited not only when making self-referential judgments, but also when making judgements about personally known people, and about widely-known but not personally known figures. Thus in the current study, it is possible that some of these DMN regions may have been recruited in during pleasantness vs. man-made/natural encoding due to their more general involvement in internally directed attention and/or subjective evaluation processes (Buckner et al., 2008, Legrand and Ruby, 2009 and Spreng, 2012).

Furthermore, although many DMN regions were recruited to a greater extent in a pleasantness vs. man-made/natural encoding, only the ventral mPFC was involved in successful encoding uniquely in the pleasantness task. On the other hand, this region was involved in encoding failure in the man-made encoding task. Thus one possibility is that this region was involved in successful encoding only in the pleasantness task due to its involvement in self-referential evaluation of verbal encoding stimuli (e.g., Andrews-Hanna et al., 2010b). In contrast, self-referential evaluation of verbal material in the man-made/natural task may have been detrimental to source memory retrieval, since it could have led to a source misattribution (judging that one had encoded a word in the pleasantness task instead of the man-made/natural task).

2.6.4. PCC is involved both in encoding failure and exhibiting TUT

A major goal of this study was to test that hypothesis that the DMN regions activated to a greater extent in incorrect vs. correct encoding would be activated to a greater extent in encoding trials preceding off-task vs. on-task reports. In the current study, encoding failure was associated with increased activity in precuneus, PCC and right temporoparietal junction. All of these regions are commonly associated with encoding failure (Kim, 2010). Furthermore, exhibiting TUT was associated with increased activation in lingual gyrus, bilateral dorsolateral PFC and a region of PCC which overlapped with the one involved in incorrect source encoding. Thus, the same region of PCC was involved in encoding failure and exhibiting TUT during episodic encoding. The exact cognitive mechanism subserved by this region of PCC during episodic encoding is unclear. One possibility is that PCC is involved in "scene construction" processes, or memory retrieval, necessary when an individual imagines an alternate scenario from the one currently being experienced (Andrews-Hanna et al., 2010b, Buckner and Carroll, 2007, Hassabis and Maguire, 2009, Hassabis et al., 2007 and Wagner et al., 2005). Alternatively, given that the majority of TUT in the current experiment were related to thinking about internal/external distractions (e.g. thinking about MRI scanner noise, or how uncomfortable one is in the scanner), PCC may also be involved in monitoring of the internal and external milieus (Raichle et al., 2001 and Stawarczyk et al., 2011).

Apart from PCC, we observed a mismatch between regions involved in exhibiting TUT and in encoding failure. Specifically, exhibiting TUT was related to bilateral DLPFC and dorsal ACC activation, while encoding failure was related to activation in right temporoparietal junction. Although not the focus of our study, DLPFC regions similar to the ones we observed in the current study during TUT (MNI: [− 34 38 38] and [32 46 34]) were identified in a meta-analysis of encoding failure (TAL: [− 36 30 38] and [34 32 42]) (Kim, 2010). Christoff et al. (2009) observed DLPFC and dorsal ACC involvement in mind-wandering episodes during a sustained attention to response task, and proposed that activation in these regions may reflect either 1) multitasking (coordination of TUT and task performance), 2) conflict detection aimed at bringing attention back to the task or 3) detecting conflict with the TUT episode itself. Alternatively, this region may be involved in monitoring of internal and external milieus. In contrast to DLPFC, right temporoparietal junction was involved in encoding failure but not in TUT. Thus our experiment does not offer any explanation for the involvement of this region in encoding failure.

No regions were identified in the on-task vs. off-task contrast in our study. One may have expected regions activated in correct vs. incorrect events to also be activated in encoding events preceding on-task vs. off-task reports. We have noted that differences in retrieval performance for encoding events preceding on-task vs. off-task events were very subtle; in other words, successful encoding sometimes occurred even when subjects reported being off-task (and vice-versa), possibly diluting the effect. Another possibility, although speculative, is that subjects are also encoding the contents of their off-task thoughts, thus recruiting regions part of traditional encoding networks. Both of these factors could have contributed to the null results in this study.

In closing, we would like to re-emphasize some of the main limitations of the current study. First we used a small sample of subjects ($n = 14$) to examine activation during off-task vs. on-task events. Second, for all fMRI contrasts in the current study, we used an uncorrected threshold of $p < 0.001$. Using this threshold, it is possible that some of the results reported in this paper are false positives; however we believe that the use of this threshold in the current study represented a good compromise between type 1 and type 2 errors. Further studies are required to replicate these findings and to see whether they generalize to other types of encoding tasks. Third, in the current study, we collapsed across different TUT types; it would be interesting to examine activation during different types of TUT to determine the relative involvement of distinct brain regions in specific thought types during episodic encoding. Finally, in the current fMRI study there was a fixed ITI of 2.5 sec between the on- and/or off-task encoding events and the subsequent thought probe. In rapid event-related fMRI studies variable ITIs between events are recommended for optimally discriminate activity associated with neighbouring event-types. Thus, due to the fixed ITI between on- and/or off-task events and the thought probe, it may be that there was residual activity related to the thought probe which was associated with on- and/or off-task events. However, we do not think this was the case since: i) residual activity associated with the thought probe would have to be correlated with either the on- and/or off-task events, for this to occur, and ii) off- and on-task events were both followed by identical thought probes, so activity associated with the probe would likely be controlled for in a contrast of these event-types. Moreover, previous studies, employing similar designs, have reported activity in similar brain regions during mind-wandering (Christoff et al., 2009 and Stawarczyk et al., 2011).

2.7. Conclusions

In summary, our experiment presents evidence that DMN play dissociable roles during episodic encoding of verbal material. In contrast to the general finding that all major DMN regions are involved in encoding failure (Kim, 2010), our experiment demonstrates that many of these regions, including left ACC, left anterior medial PFC and left angular gyrus can are involved in encoding success in some memory paradigms. We propose that the encoding strategy used, as well as the specific requirements of the retrieval task may be critical in determining the nature of the association between activation in specific DMN regions and retrieval success. For example, in the current study, left ventral mPFC was involved in encoding success only in the pleasantness task, suggesting that these regions were modulated primarily by the nature of the *encoding* task. Left dorsomedial PFC and left angular gyrus were involved in encoding success across tasks. As previously discussed, this may reflect the role of these regions in internally-directed attention to cognitive operations (i.e. task-relevant thoughts), which was a specific requirement of the subsequent source *retrieval* task. Finally, our experiment also demonstrates for the first time an overlap between encoding failure and exhibiting TUT in the PCC.

2.8. References

Addis, D. R., Wong, A. T., & Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia, 45*(7), 1363-1377.

Andrews-Hanna, J. R., Reidler, J. S., Huang, C., & Buckner, R. L. (2010). Evidence for the default network's role in spontaneous cognition. *J Neurophysiol, 104*(1), 322-335.

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron, 65*(4), 550-562.

Beck, A. T. (1987). *Beck Depression Inventroy*. TX: The Psychological Corporation.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry, 4*, 561-571.

Blumenfeld, R. S., & Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist, 13*(3), 280-291.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38.

Buckner, R. L., & Carroll, D. C. (2007). Self-projection and the brain. *Trends Cogn Sci, 11*(2), 49-57.

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc Natl Acad Sci U S A, 106*(21), 8719-8724.

Dale, A. M. (1999). Optimal experimental design for event-related fMRI. *Hum Brain Mapp, 8*(2-3), 109-114.

Daselaar, S. M., Prince, S. E., & Cabeza, R. (2004). When less means more: deactivations during encoding that predict subsequent memory. *Neuroimage, 23*(3), 921-927.

Daselaar, S. M., Prince, S. E., Dennis, N. A., Hayes, S. M., Kim, H., & Cabeza, R. (2009). Posterior midline and ventral parietal activity is associated with retrieval success and encoding failure. *Front Hum Neurosci, 3*, 13.

Desrochers, A., & Thompson, G. L. (2009). Subjective frequency and imageability ratings for 3,600 French nouns. *Behav Res Methods, 41*(2), 546-557.

Dobbins, I. G., & Wagner, A. D. (2005). Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. *Cereb Cortex, 15*(11), 1768-1778.

Dulas, M. R., & Duarte, A. (2011). The effects of aging on material-independent and material-dependent neural correlates of contextual binding. *Neuroimage, 57*(3), 1192-1204.

Fisher, R. A. (1950). *Statistical methods for research workers*. London: Oliver & Boyd.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med, 33*(5), 636-647.

Gottlieb, L. J., Uncapher, M. R., & Rugg, M. D. (2010). Dissociation of the neural correlates of visual and auditory contextual encoding. *Neuropsychologia, 48*(1), 137-144.

Grady, C. L., Grigg, O., & Ng, C. (2012). Age differences in default and reward networks during processing of personally relevant information. *Neuropsychologia, 50*(7), 1682-1697.

Grigg, O., & Grady, C. L. (2010). The default network and processing of personally relevant information: converging evidence from task-related modulations and functional connectivity. *Neuropsychologia, 48*(13), 3815-3823.

Hassabis, D., Kumaran, D., & Maguire, E. A. (2007). Using imagination to understand the neural basis of episodic memory. *J Neurosci, 27*(52), 14365-14374.

Hassabis, D., & Maguire, E. A. (2009). The construction system of the brain. *Philos Trans R Soc Lond B Biol Sci, 364*(1521), 1263-1271.

Huijbers, W., Vannini, P., Sperling, R. A., C, M. P., Cabeza, R., & Daselaar, S. M. (2012). Explaining the encoding/retrieval flip: memory-related deactivations and activations in the posteromedial cortex. *Neuropsychologia, 50*(14), 3764-3774.

Johnson, M. K., Hashtroudi, S., & Lindsay, D. S. (1993). Source monitoring. *Psychol Bull, 114*(1), 3-28.

Kim, H. (2010). Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI studies. *Neuroimage*.

Kim, H. (2012). A dual-subsystem model of the brain's default network: self-referential processing, memory retrieval processes, and autobiographical memory retrieval. *Neuroimage, 61*(4), 966-977.

Lazar, N. A., Luna, B., Sweeney, J. A., & Eddy, W. F. (2002). Combining brains: a survey of methods for statistical pooling of information. *Neuroimage, 16*(2), 538-550.

Legrand, D., & Ruby, P. (2009). What is self-specific? Theoretical investigation and critical review of neuroimaging results. *Psychol Rev, 116*(1), 252-282.

Leshikar, E. D., & Duarte, A. (2012). Medial prefrontal cortex supports source memory accuracy for self-referenced items. *Soc Neurosci, 7*(2), 126-145.

Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., . . . Buckner, R. L. (2003). Functional deactivations: change with age and dementia of the Alzheimer type. *Proc Natl Acad Sci U S A, 100*(24), 14504-14509.

Macrae, C. N., Moran, J. M., Heatherton, T. F., Banfield, J. F., & Kelley, W. M. (2004). Medial prefrontal activity predicts memory for self. *Cereb Cortex, 14*(6), 647-654.

Maillet, D., & Rajah, M. N. (2011). Age-related changes in the three-way correlation between anterior hippocampus volume, whole-brain patterns of encoding activity and subsequent context retrieval. *Brain Res, 1420*, 68-79.

Maillet, D., & Rajah, M. N. (2013). Age-related changes in frequency of mind-wandering and task-related interferences during memory encoding and their impact on retrieval. *Memory, 21*(7), 818-831.

Morris, C. D., Bransford, J. D., & Franks, J. J. (1977). Levels of processing versus transfer appropriate processing. *J. Verbal Learn. Verbal Behav, 16*, 519-533.

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc, 53*(4), 695-699.

Nyberg, L., McIntosh, A. R., Cabeza, R., Nilsson, L. G., Houle, S., Habib, R., & Tulving, E. (1996). Network analysis of positron emission tomography regional cerebral blood flow data: ensemble inhibition during episodic memory retrieval. *J Neurosci, 16*(11), 3753-3759.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Prince, S. E., Dennis, N. A., & Cabeza, R. (2009). Encoding and retrieving faces and places: distinguishing process- and stimulus-specific differences in brain activity. *Neuropsychologia, 47*(11), 2282-2289.

Qin, P., Di, H., Liu, Y., Yu, S., Gong, Q., Duncan, N., . . . Northoff, G. (2010). Anterior cingulate activity and the self in disorders of consciousness. *Hum Brain Mapp, 31*(12), 1993-2002.

Qin, P., & Northoff, G. (2011). How is our self related to midline regions and the default-mode network? *Neuroimage, 57*(3), 1221-1233.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682.

Rogers, T. B., Kuiper, N. A., & Kirker, W. S. (1977). Self-reference and the encoding of personal information. *J Pers Soc Psychol, 35*(9), 677-688.

Rugg, M. D., Johnson, J. D., Park, H., & Uncapher, M. R. (2008). Encoding-retrieval overlap in human episodic memory: a functional neuroimaging perspective. In W. S. Sossin, J.-C. Lacaille, V. F. Castellucci & S. Belleville (Eds.), *Essence of Memory* Amsterdam: Elsevier Science.

Schott, B. H., Wustenberg, T., Wimber, M., Fenker, D. B., Zierhut, K. C., Seidenbecher, C. I., . . . Richardson-Klavehn, A. (2011). The relationship between level of processing and hippocampal-cortical functional connectivity during episodic memory formation in humans. *Hum Brain Mapp, 34*(2), 407-424.

Seibert, P. S., & Ellis, H. C. (1991). Irrelevant thoughts, emotional mood states, and cognitive task performance. *Mem Cognit, 19*(5), 507-513.

Shrager, Y., Kirwan, C.B., & Squire, L.R. (2008). Activity in both hippocampus and perirhinal cortex predicts the memory strength of subsequently remembered information. *Neuron, 59*(4), 547-553.

Shulman, G. L., Fiez, J. A., Buckner, R. L., Miezin, F. M., Raichle, M. E., & Peterson, S. E. (1997). Common blood flow changes across visual tasks: II.: decreases in cerebral cortex. *Journal of Cognitive Neuroscience, 9*, 648-663.

Simons, J. S., Owen, A. M., Fletcher, P. C., & Burgess, P. W. (2005). Anterior prefrontal cortex and the recollection of contextual information. *Neuropsychologia, 43*(12), 1774-1783.

Smallwood, J., Baracaia, S. F., Lowe, M., & Obonsawin, M. (2003). Task unrelated thought whilst encoding information. *Conscious Cogn, 12*(3), 452-484.

Smallwood, J., & Schooler, J. W. (2006). The restless mind. *Psychol Bull, 132*(6), 946-958.

Spreng, R. N. (2012). The fallacy of a "task-negative" network. *Front Psychol, 3*, 145.

Stawarczyk, D., Majerus, S., Maquet, P., & D'Argembeau, A. (2011). Neural correlates of ongoing conscious experience: both task-unrelatedness and stimulus-independence are related to default network activity. *PLoS One, 6*(2), e16997.

Symons, C. S., & Johnson, B. T. (1997). The self-reference effect in memory: a meta-analysis. *Psychol Bull, 121*(3), 371-394.

Tulving, E., & Thompson, D. M. (1973). Encoding specificity and retrieval processes in episodic memory. *Psychol. Rev, 80*, 352-373.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., . . . Buckner, R. L. (1998). Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*(5380), 1188-1191.

Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci, 9*(9), 445-453.

Zierhut, K., Bogerts, B., Schott, B., Fenker, D., Walter, M., Albrecht, D., . . . Schiltz, K. (2010). The role of hippocampus dysfunction in deficient memory encoding and positive symptoms in schizophrenia. *Psychiatry Res, 183*(3), 187-194.

3. Study 2: Age-related changes in the three-way correlation between anterior hippocampus volume, whole-brain patterns of encoding activity and subsequent context retrieval

3.1. Preface

As alluded to in the introduction of this thesis, one reason that it is difficult to understand age-related increases in activation in mFC during episodic encoding is that the encoding tasks that have been used in the literature are semantic, or perceptual. These encoding tasks do not recruit mFC in young adults. Greater insight into age-related changes in mFC may be gained by additionally examining age-related changes in a task that recruits this region in both age groups (i.e. a self-referential encoding task). In the following study, young and older adults were asked to encode face stimuli using a pleasantness judgement. This allowed the study of age-related differences in the association between brain activation at encoding and retrieval accuracy when both age groups are asked to encode information using a self-referential judgement.

However, this study was not originally designed to answer questions regarding the association between activation in mFC and memory performance in young vs. older adults. Rather, the question of interest was to investigate how age-related differences in activation during memory encoding are associated with declines in anterior hippocampus volume and memory performance. Three memory tasks were administered to subjects: an item recognition task, a spatial context memory task (memory for spatial location) and a temporal context memory tasks (memory for the order in which events occur). These tasks were originally chosen to assess age-differences in activation in encoding tasks assessing item specific (face stimuli) vs. item-context associations (face-location or face-time). Therefore, the introduction and discussion of this manuscript primarily focus on the association between the hippocampus and such item-context associations.

Although the following manuscript emphasizes hippocampus-context memory associations, the data and analyses performed are well suited to answer questions pertinent to this thesis. Specifically, in all three memory tasks, subjects were asked to encode the events using a pleasantness judgement. Moreover, activation in the whole brain was correlated to retrieval accuracy. This data is thus adequate to answer the question of whether increased activation in mFC is related to better memory performance in both age groups when a self-referential encoding task is used. **I have included an extra section following the Reference section of the manuscript specifically addressing how the results reported are relevant to this question.**

3.2. Abstract

Age-related declines in memory for context have been linked to volume loss in the hippocampal head (HH) with age. However, it remains unclear how this volumetric decline correlates with age-related changes in whole-brain activity during context encoding, and subsequent context retrieval. In the current study we examine this. We collected functional magnetic resonance imaging data in young and older adults during the encoding of item, spatial context and temporal context. HH volume and subsequent retrieval performance was measured in all participants. In young adults only there was a positive three-way correlation between larger HH volumes, better memory retrieval, and increased activity in right hippocampus, right ventrolateral prefrontal cortex (VLPFC) and midline brain regions during episodic encoding. In contrast, older adults exhibited a positive three-way association between HH volume, generalized activity in bilateral

hippocampus and dorsolateral PFC across all encoding tasks, and subsequent spatial context retrieval. Young adults also engaged this network, but only during the most difficult temporal context encoding task and activity in this network correlated with subsequent temporal context retrieval. We conclude that age-related volumetric reductions in HH disrupted the structure–function association between the hippocampus and activity in the first general encoding network recruited by young adults. Instead, older adults recruited those brain regions young adults only engaged for the most difficult temporal task, at lower difficulty levels. This altered pattern of association correlated with spatial context retrieval in older adults, but was not sufficient to maintain context memory abilities overall.

3.3. Introduction

Compared with young adults, older adults exhibit a disproportionate behavioral deficit in associative memory tasks, such as spatial and temporal context memory tasks (Naveh-Benjamin, 2000, Rajah et al., 2010b and Spencer and Raz, 1995). In young adults, there is substantial neuroimaging evidence implicating the hippocampus (Diana et al., 2007 and Eichenbaum et al., 2007), particularly its anterior portion, in associative encoding (Jackson and Schacter, 2004, Prince et al., 2005 and Sperling et al., 2003). Healthy older adults exhibit volumetric reductions in anterior hippocampus (hippocampus head; HH), which has been related to poorer retrieval of spatial and temporal context information with age (Rajah et al., 2010a). In addition, under-recruitment of the hippocampus during associative encoding in older adults predicts poorer subsequent memory for associations (Dennis et al., 2008). These findings indicate that region-specific changes in the structure and function of the hippocampus with age may contribute to associative memory deficits in healthy older versus younger adults.

It is generally accepted that the hippocampus contributes to encoding through interactions with neocortex (Eichenbaum, 2000, Moscovitch, 1992, Paller, 2002 and Rugg et al., 2008). Supporting this view, neuroimaging studies in young adults have revealed that the hippocampus is functionally coupled with sensory areas, the prefrontal cortex (PFC), and parietal cortex at encoding (McCormick et al., 2010, Rajah et al., 1999 and Ranganath et al., 2005). Recent studies have reported age-related changes in the whole-brain networks coupled with hippocampus during associative encoding (Dennis et al., 2008 and Leshikar et al., 2010). For example, during a source encoding task, one study reported that older adults exhibited less connectivity between hippocampus and posterior regions, such as posterior cingulate and parietal lobe, but increased connectivity of hippocampus with PFC (Dennis et al., 2008).

Thus, independent studies have established that volumetric reductions in anterior hippocampus and age-related changes in hippocampal connectivity at encoding are associated with poorer associative memory in healthy older adults (Dennis et al., 2008 and Rajah et al., 2010a). However, it remains unknown how individual differences in anterior hippocampal volumes directly influence encoding-related activity in this region and other brain regions implicated in context encoding, and how this affects subsequent context retrieval accuracy in young adults. Furthermore the impact of healthy aging on this three-way pattern of associations has not been directly tested. The current study was designed to address these issues. Young and older adults underwent functional magnetic resonance imaging during item, spatial context and temporal context encoding using face stimuli. In all tasks, the orienting task was a subjective pleasant/neutral judgment to each face. In addition, we used multivariate partial least squares

(PLS; McIntosh et al., 2004) in the current study to examine the three-way association between HH volumes (which were determined in a previous study (Rajah et al., 2010a)), encoding-related fMRI activation, and retrieval accuracy for item recognition, spatial context and temporal context tasks. In young adults, we hypothesized that larger HH volume would be related to increased activation in a whole-brain encoding network including ventrolateral PFC and medial PFC, and to subsequent retrieval accuracy. We also hypothesized that age-related volumetric reductions in HH would alter the three-way association between HH volume, encoding activity, and subsequent retrieval, which may contribute to the episodic memory deficits observed in healthy older adults (Glisky and Kong, 2008 and Naveh-Benjamin, 2000).

3.4. Methods

3.4.1. Subjects

22 young (age range, 19–34, mean = 23.5) and 21 older (age range, 60–80, mean = 67.48) subjects participated in the study. Volunteers were right-handed and fluent in English. They were administered a battery of neuropsychological tests which included the Language and Social Background Questionnaire (LSBQ; Bialystok et al., 2005 and Bialystok et al., 2007), the Mini-Mental Status Exam (MMSE; Folstein et al., 1975), the Beck Depression Inventory (BDI; Beck, 1987 and Beck et al., 1961), the Geriatric Depression Scale (GDS; Brink et al., 1982), the Cognitive Assessment Scale for the Older Adults (CASE; Geneau and Gjedde, 1996), the California Verbal Learning Task (CVLT) long-form free recall, CVLT long-form category assisted free recall and CVLT long-term recognition (Delis et al., 1987 and Delis et al., 1988). Independent sample *T*-tests were conducted to assess any age differences on these measures. Exclusion criteria for the elderly sample included family history of Alzheimer's disease, the diagnosis of diabetes, the presence of cataracts or glaucoma, high cholesterol levels left untreated

in the past 2 years, and high or low blood pressure left untreated in the past 2 years. All participants signed a consent form, and the study was approved by the ethics boards of the Douglas Hospital, the Montreal Neurological Institute and McGill University.

3.4.2. Behavioral procedure

Subjects were told that they would be participating in a memory study for non-famous, age-variant human faces. The experiment consisted of 24 encoding lists of 12 face stimuli, 8 per encoding task, each followed by a 1 minute break, and a retrieval task. This yielded a total of 96 encoding events, and 48 retrieval events for each task. During encoding, subjects were presented with twelve face stimuli, one at a time, for 2 s, either on the left or right of the computer screen. They were asked to rate each face as being pleasant (button 1) or neutral (button 2). They were also asked to intentionally encode the stimuli for an upcoming item recognition, spatial context or temporal context retrieval task. The encoding phase was identical across all tasks, but subjects were informed of which retrieval task would follow. Faces were presented in black and white, were cropped from the neck upward and were rated as pleasant or neutral by two independent raters. More details about stimulus construction are described by Rajah et al. (2008).

After each encoding list, a 1 minute distraction task followed, in which subjects were asked to alphabetize two simultaneously presented words. This was followed by an item recognition, spatial context or temporal context retrieval task. In all three tasks, two faces were simultaneously presented on the top and bottom of the computer screen. In the recognition task, one of these was “old” (had been previously seen by the subject) and the other was new. Depending on the retrieval cue, the subject was asked to respond to the old/new face. In the spatial context memory task, two “old” faces were presented, one of which had appeared on the left side of the screen at encoding and the other on the right. Subjects were asked to respond to the face that had been presented on the left/right, depending on the retrieval cue. In the temporal context memory task, subjects were presented with two "old" faces and, depending on the retrieval cue, asked to respond to the one that had been presented most/least recently. Hence, two alternative forced-choice decisions were made in all three retrieval tasks. Stimuli were presented in such a way that spatial information could not inform a temporal judgment and vice versa. They were also oriented vertically to avoid masking effects. Two group (2) × task (3) mixed ANOVAs were performed to assess main effects and group by task interactions in 1) encoding reaction time (RT) and 2) retrieval accuracy. Post-hoc tests were conducted to clarify the results.

3.4.3. fMRI procedure

3.4.3.1. Data acquisition

Structural and functional images were acquired using a 3T Siemens Trio scanner at the Montreal Neurological Institute. T1-weighted image volumes were acquired at the start of the experiment using a 9.35 min gradient-echo (GRE) ADNI (Alzheimer's Disease Neuroimaging Initiative) sequence (TR 2300 ms, TE 2.94 ms, flip angle 30°, 160 1 mm sagittal slices, 1 × 1 × 1.2 mm voxels, field of view — FOV = 256 mm^2). BOLD images were acquired using a fast echo-planar imaging (EPI) pulse sequence (TR = 2000 ms, TE = 30 ms, FOV = 256 mm^2, matrix size = 64 × 64, in-plane resolution = 4 × 4 mm, 340 whole brain acquisitions/11:20 min run) while subjects performed the aforementioned behavioral tasks.

3.4.3.2. Structural image processing and analysis

Images were converted to MNC format and subsequently processed in DISPLAY software (Collins et al., 1994 and Pruessner et al., 2000). In order to make comparisons between subjects and groups, all structural scans underwent signal-intensity normalization, non-uniformity correction, and linear transformation into standard stereotaxic space using the MNI template prior to volume segmentation (Collins et al., 1994, Collins et al., 1998, Pruessner et al., 2000 and Sled et al., 1998). Two independent raters segregated the hippocampus into tail, body and head (HH) portions using the protocol outlined by Pruessner et al., 2000 and Pruessner et al., 2001. The volume of each sub-region was then averaged across the two hemispheres. Only average ((Left + Right) / 2) HH volume is of interest in the current study. Intra-class correlation (3, 1, ICC; Shrout and Fleiss, 1979) was conducted to assess interrater and intrarater reliability of HH volume measures. Furthermore, a 2-way age-group × sex ANOVA was conducted to assess the effects of these factors on HH volume.

3.4.3.3. Functional image processing and analysis

Images were converted to ANALYZE format and subsequently pre-processed in SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Functional images were spatially realigned to the first image, spatially normalized to the MNI EPI-template available in SPM2, and smoothed using 10 mm full-width half maximum (FWHM) isotropic Gaussian kernel. The smoothed images were used in the spatio-temporal partial least squares (PLS) analysis (McIntosh et al., 2004), performed using the PLSGUI software (http://www.rotman-baycrest.on.ca/index.php?section=84). For all our analyses, we included only encoding events that were successfully remembered during retrieval.

3.4.3.4. Spatio-temporal behavior PLS

The goal of the present study was to assess the relationship between HH volume, whole-brain encoding activation and retrieval accuracy. To investigate whole-brain performance-related networks related to HH volume, we used the “Behavior PLS” option in PLSGUI (ST-bPLS; McIntosh et al., 2004 and Protzner and McIntosh, 2007). This procedure allows the investigation of the covariance between brain activation, task design and a set of exogenous variables. In this case, the two exogenous variables were HH volume, and accuracy in each of the three retrieval tasks. ST-bPLS identifies a set of mutually orthogonal LVs which maximally relates the activation data to these variables.

Each subject's fMRI data was entered into a matrix, referred to as data matrix, or “datamat”. The rows of the datamat represent the mean data for one subject in one condition. In the present experiment, there were three conditions: item recognition, spatial and temporal context tasks. The columns of the datamat contain data for each voxel, at each of 7 time lags. Each time lag contains data for a 2 second period, with the first time lag coinciding with an event onset. Hence, we considered activation for 14 s after event onset, to encapsulate the entire breadth of the hemodynamic response function (HRF). The datamat's rows are organized such that conditions are nested within each subject, and the columns are organized such that time lags are nested within each voxel. All the subjects' data matrices were then stacked together into a single, between group datamat.

This datamat was then cross-correlated with a matrix containing the average HH volume, and accuracy scores for each task and each subject. Singular value decomposition (SVD) was then applied to this correlation matrix, to generate latent variables (LVs) which consist of a singular value, a singular image and a correlation profile for both HH volume and retrieval accuracy. The correlation profile shows how accuracy and HH volume correlate with the pattern of brain activity identified in the singular image in young and older adults. The singular image indicates which brain voxels exhibit the strongest correlation in activity with accuracy and HH volume in young and older adults at each time lag after event onset. A singular image consists of negative and positive brain saliences, which are numerical weights assigned to each voxel at each time lag, and represents a spatio-temporal pattern of whole-brain activity for the entire time series (seven 2 s TRs/time lags after event-onset). Brain regions with positive voxel saliences are positively related to the correlation profile for accuracy and HH volume depicted for young and older adults for a given LV, and those with negative voxel saliences are negatively related to the correlation profiles. Thus the relationship between the singular image and the correlation profile is symmetrical. The singular value indicates the strength of the correlation between encoding-related activity in all brain voxels and the two exogenous variables.

The statistical significance of each LV pair was determined by conducting 500 permutation tests, on the singular values, which represented the proportion of the covariance matrix accounted for by each LV pair (McIntosh and Lobaugh, 2004, McIntosh et al., 1998, McIntosh et al., 1999 and McIntosh et al., 2004). Permutations were conducted with sampling without replacement so that the event-type order was rearranged for each subject. The probability that the permuted singular values exceed the observed singular values was calculated and only LVs for which this probability was $p < 0.05$ were deemed significant. To identify dominant and stable voxels within a dot product image, a bootstrap analysis of standard errors was conducted (Efron and Tibshirani, 1986). We conducted 100 bootstrap samples, which allowed us to identify voxels that reliably contributed to the experimental effect within each LV. We considered local maxima within the medial temporal lobes (MTL) to be reliable if they were above a 3 ($p < 0.005$) threshold (cluster size > 5). For local maxima outside the MTL, we used a more restrictive threshold of 3.5 ($p < 0.0005$) with a spatial extent of 15 or more voxels. Peak coordinates were converted from MNI to Talairach space, and the Tailarach and Tournoux atlas (Talairach and

Tournoux, 1988) was used to identify the Brodmann area (BA) localizations of significant activations.

3.5. Results

The neuropsychological, behavioral and volumetric results have been reported elsewhere (Rajah et al., 2010a and Rajah et al., 2010b). However, because we added 1 young subject for the current analysis, we present the updated results.

3.5.1. Neuropsychological results

Results are shown in Table 1. The independent samples *T*-test for CASE score was significant, t(33) = 3.048, p = 0.005. However, both group means were above the 94 score cut-off for individuals with 15+ years of education. The independent samples *T*-test for long form free recall CVLT was also significant, t(39) = 3.217, p < 0.005. This is consistent with studies indicating older adults have a deficit in free recall (Craik and Salthouse, 2000). There were no other significant differences between the groups on neuropsychological tests.

Table 1. Group means for education and neuropsychological measures

Group		EDU	MMSE	BECK	GDS	CASE	LFCVLT	LCRCVLT	RGCVLT
Young adults	Mean	16.14	29.50	2.95	1.05	98.76*	13.90*	13.40	15.45
	S.E.	0.27	0.23	0.88	0.34	0.34	0.42	0.44	0.22
Older adults	Mean	15.29	29.38	4.19	0.90	97.28*	11.10*	12.00	15.10
	S.E.	0.56	0.19	0.78	0.21	0.35	0.75	0.73	0.32

Note: This table presents the group means and standard errors (S.E.) for education (EDU) in years, and other psychological measures taken. MMSE = mini-mental status examination; GDS = Geriatric Depression Scale; CASE = Cognitive Assessment Scale for the Older Adults, LFCVLT = CVLT, long-form free recall; LCRCVLT = CVLT, long-form category assisted recall; RGCVLT = CVLT, long-term recognition. Significant group differences ($p < 0.05$) are highlighted with asterisks.

3.5.2. Behavioral results

Encoding RT and retrieval accuracy results are shown in Table 2. A group (2) × task (3) mixed ANOVA revealed a significant interaction $F(2,82) = 7.024$, $p < 0.005$ in encoding RT for the pleasantness judgment. Post-hoc *T*-tests revealed that young adults responded significantly faster than older adults in during item encoding, $t(41) = -2.483$, $p < 0.05$ and spatial context encoding $t(41) = -2.257$, $p < 0.05$, but not during temporal context encoding $t(41) = -1.295$, $p > 0.05$. Post-hoc, within-group, one-way ANOVAs for task indicated that both young and older adults exhibited task differences in RT (young: $F(2,42) = 32.351$, $p < 0.001$, older adults: $F(2,40) = 12.831$, $p < 0.001$). Post-hoc *T*-tests on the within-group ANOVA in young revealed that they exhibited significantly faster RT during item encoding, compared to both spatial ($t(21) = -5.568$, $p < 0.001$) and temporal ($t(21) = -7.693$, $p < 0.001$) context encoding, and also exhibited faster RT during spatial versus temporal context encoding, $t(21) = -2.634$, $p < 0.05$. On the other hand, while older also exhibited significantly faster RT during item encoding versus both spatial ($t(20) = -4.388$, $p < 0.001$) and temporal ($t(20) = 4.324$, $p < 0.001$) context encoding, they did not exhibit a significant difference in RT between spatial and temporal context encoding, $t(20) = 1.758$, $p > 0.05$.

Table 2.

Mean encoding reaction time and retrieval accuracy data with standard error.

		Recognition	Spatial context	Temporal context
Young adults	Encoding reaction time	1257.48 (56)	1354.83 (64)	1406 (64)
	Retrieval accuracy	0.94 (0.11)	0.89 (0.17)	0.82 (0.22)
Older adults	Encoding reaction time	1464.79 (62)	1563.14 (66)	1464.5 (67)
	Retrieval accuracy	0.93 (0.10)	0.80 (0.19)	0.68 (0.21)

Note: Accuracy values shown are the proportion correct per task type with SE. Reaction time values are shown in milliseconds per task type with SE.

A group (2) × task (3) mixed ANOVA revealed a significant interaction F(2,82) = 16,248 $p < 0.001$, in retrieval accuracy scores. Post-hoc *T*-tests that revealed the interaction was due to there being no difference in recognition accuracy between the two groups, t(41) = 0.327, p = 0.745, but a significant difference in spatial accuracy, t(41) = 3.677, p = 0.001 and temporal accuracy, t(41) = 4867, $p < 0.001$. A post hoc linear trend analysis was run to determine if there was a linear decrease in accuracy across recognition, spatial and temporal tasks. The analysis revealed that there was a linear trend × group interaction, F(1,41) = 31.328, $p < 0.001$. The interaction was due to their being a smaller, albeit still significant linear trend in young, F(1,21) = 40.08, $p < 0.001$ than in older adults, F(1,20) = 221.432, $p < 0.001$.

3.5.3. Volumetric results

The volumetric results for this sample have been previously published (Rajah et al., 2010a). From this study, the interrater measurements for average HH was 0.91 (Rajah et al., 2010a). The interrater measurement for raters 1 and 2 was of 0.98 and 0.84, respectively. These measurements were within publishable range.

The 2-way ANOVA revealed that young adults had significantly larger HH volumes compared to older adults, F(1,39) = 8.858, $p < 0.05$. There was no significant sex main effect.

3.5.4. PLS results

The between-group PLS identified two significant ($p < 0.05$) LVs. The singular image, representing voxels with stable and significant activation, and the correlation profile for the first LV (LV1; $p < 0.05$; percent cross-block covariance accounted for = 16.76%), representing brain–accuracy and brain–HH volume correlations by task are shown in Fig. 1. Local maxima for this LV are presented in Table 3.

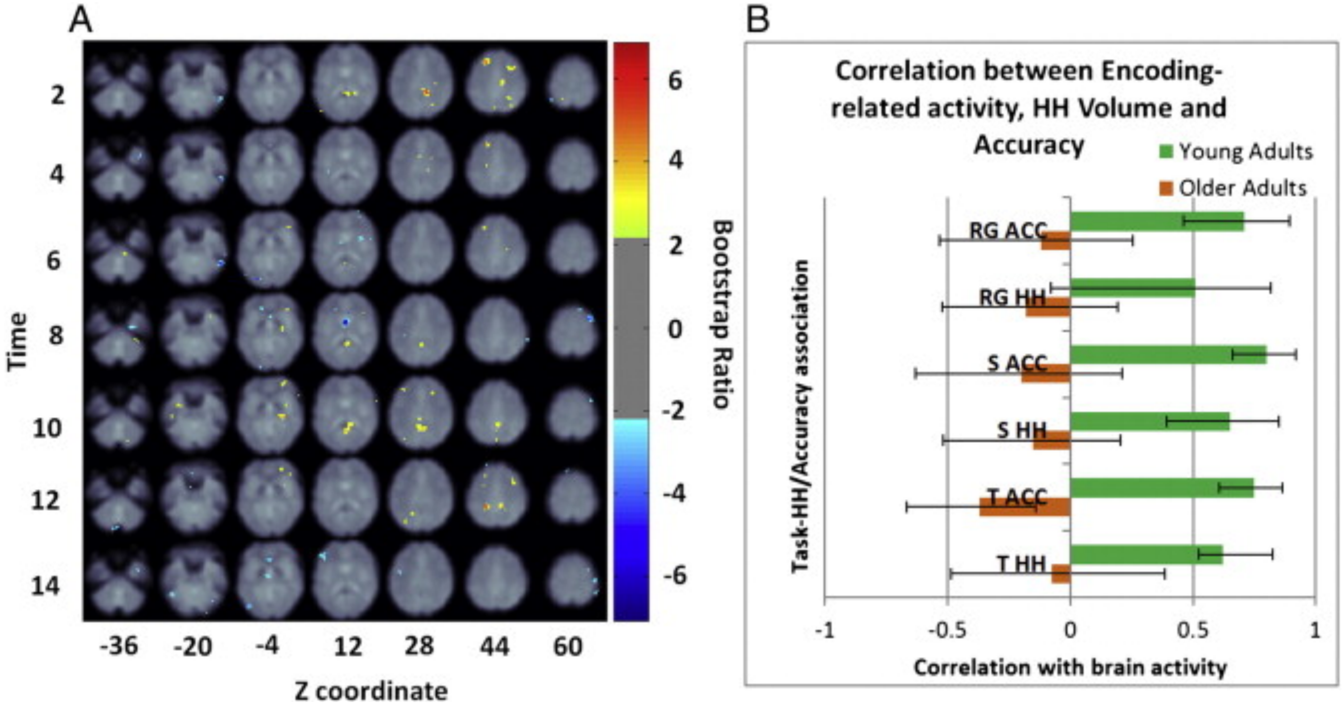

Fig. 1.

Singular image and the correlation profile for LV1 of the between-group PLS. A) The singular image for LV1 at a bootstrap of 3.5 ($p < 0.0005$), which reflects stable and significant activations at 2 to 14 s after event onset. Z coordinates are reported in mm in MNI space. The color-bar represents the color code for the colorized activations on the singular image. Regions colored in red–orange–yellow are positively related with the experimental effect presented in (B). Regions colored in blue are negatively related with the experimental effect presented in (B). B) Correlation profile for LV1. The correlation profile shows how accuracy and HH volume correlate with the pattern of brain activity identified in the singular image in young and older adults. RG = Recognition, S = Spatial context, T = Temporal context, ACC = Accuracy, HH = Average hippocampus head volume.

Table 3.

Local maxima for LV1 of the ST-bPLS analysis.

Lag	BSR	Cluster size	X	Y	Z	Hem	Gyral location	Brodmann area
Positive saliences: in young, regions in which activity positively correlates with retrieval accuracy in all tasks and HH volume in the spatial and temporal tasks.								
1	6.87	66	− 20	29	32	Left	Medial prefrontal	BA 9
1	6.52	97	0	− 38	17	Medial	Retrosplenial cortex	BA 29/30
1	5.71	22	8	− 21	38	Right	Cingulate gyrus	BA 24
1	4.62	15	44	− 33	35	Right	Inferior parietal lobe	BA 40
1	4.59	24	36	18	43	Right	Middle frontal gyrus	BA 8
1	4.34	21	12	− 65	25	Right	Precuneus	
2	5.91	16	− 20	33	35	Left	Medial frontal cortex	BA 8/9
3	4.85	15	44	35	− 8	Right	Inferior frontal gyrus	BA 47
3	4.36	15	20	− 33	− 32	Right	Cerebellum	
4	4.41	44	0	− 49	21	Medial	Retrosplenial cortex	BA 29/30
4	4.13	16	24	7	− 10	Right	Putamen	
5	4.94	186	4	− 50	10	Right	Retrosplenial cortex	BA 29/30
5	4.79	15	12	− 21	38	Right	Posterior cingulate	BA 31
5	3.40	9	24	− 35	− 8	Right	Hippocampus	

Lag	BSR	Cluster size	X	Y	Z	Hem	Gyral location	Brodmann area
6	5.69	15	− 20	− 37	42	Left	Posterior cingulate	BA 31
6	4.59	31	0	− 40	46	Medial	Precuneus	BA 7
Negative saliences: in young, regions in which activity negatively correlates with retrieval accuracy in all tasks and with HH volume in the spatial and temporal tasks.								
3	− 6.52	16	− 48	− 81	4	Left	Occipital gyrus	BA 19
3	− 5.25	15	59	− 51	− 14	Right	Fusiform gyrus	BA 37
3	− 3.88	15	− 20	− 11	19	Left	Thalamus	
4	− 7.06	111	0	4	11	Medial	Caudate nucleus	
4	− 6.58	33	40	15	58	Right	Premotor cortex	BA 6
4	− 5.50	52	32	− 10	− 37	Right	Inferior temporal gyrus	BA 20
4	− 4.71	19	− 16	3	70	Left	Premotor cortex	BA 6
6	− 6.99	28	− 8	− 91	− 32	Left	Cerebellum	
7	− 6.82	57	16	11	69	Right	Premotor cortex	BA 6
7	− 6.65	43	− 48	− 78	− 3	Left	Occipital gyrus	BA 19
7	− 5.36	15	0	27	− 8	Medial	Anterior cingulate	BA 32
7	− 4.85	35	− 44	36	13	Left	Inferior frontal gyrus	BA 45/46
7	− 4.44	7	28	− 25	− 26	Right	Parahippocampal gyrus	BA 36
7	− 4.38	20	− 63	− 51	− 11	Left	Fusiform gyrus	BA 37
7	− 4.35	26	44	− 66	− 7	Right	Occipital gyrus	BA 19
7	− 4.22	18	36	7	59	Right	Premotor cortex	BA 6

Note: Temporal lag represents the time interval (2 s each) after event-onset, when a cluster of voxels exhibited a peak bootstrap ratio reflecting the identified effect. The bootstrap ratio threshold (BSR) was set to +/− 3 for the hippocampus (HC), and +/− 3.5 for all other areas. The spatial extent refers to the total number of voxels included in the voxel cluster (threshold =/>5 for HC and =/>15 for all other areas). The stereotaxic coordinates are reported in Talairach coordinates, in mm, and the Brodmann Areas (BA) were determined by reference to Talairach and Tournoux (1988). Hem = Hemisphere.

LV1 identified a pattern of encoding-related activity in young adults that was significantly correlated with both HH volume and subsequent memory accuracy for all task types (right side of Fig. 1B), although the confidence interval representing the correlation between HH volume and activity during item encoding suggests this association was not significant. In young adults increased activity in positive salience brain regions and decreased activity in negative salience brain regions was significantly correlated with larger HH volumes and higher retrieval accuracy. In older adults, this effect was inverted and was not significant as indicated by the wide error bars crossing the zero-correlation mark. Regions of positive brain salience in LV1 included right hippocampus, right VLPFC, putamen and a number of regions thought to be part of the default-mode network (Buckner et al., 2008 and Greicius et al., 2003), including precuneus, posterior cingulate, medial PFC and retrosplenial cortices. Negative brain salience regions included, bilateral occipital cortex, fusiform gyrus, and bilateral premotor cortex.

The second LV (LV2; $p < 0.001$; percent cross-block covariance accounted for = 23.50%) identified a three-way interaction effect that reflected group differences in encoding activity which in turn were also differentially correlated with HH volume and subsequent memory effects in young versus older adults (for a list of local maxima, see Table 4, for singular image and correlation profile, see Fig. 2). No positive saliences were identified for this LV at the threshold specified. Thus we focus only on the pattern associated with negative saliences in the two age groups. In older adults, LV 2 identified a pattern of whole brain activity that was related to HH volume in all tasks, but to retrieval accuracy only in the spatial context memory task. In young adults, this same pattern of whole brain activity was identified during temporal context encoding and increased activity in these regions was significantly correlated with increased temporal retrieval accuracy and to larger HH volumes. These negative salience regions included bilateral hippocampus, left parahippocampal gyrus, bilateral premotor cortex, right VLPFC, bilateral dorsolateral PFC (DLPFC), bilateral anterior PFC, left fusiform gyrus and bilateral middle temporal gyrus (BA21).

Table 4.

Local maxima for LV2 of the ST-bPLS analysis.

Lag	BSR	Cluster size	X	Y	Z	Hem	Gyral location	Brodmann area (BA)
Negative saliences: regions in which activity in the temporal task positively correlates with retrieval accuracy and HH volume in young, and in which activity during the spatial task correlates with accuracy and HH volume in older adults.								
1	− 5.46	21	− 59	1	22	Left	Premotor cortex	BA 6
1	− 4.77	22	12	− 15	4	Right	Thalamus	
1	− 4.34	39	48	− 16	− 3	Right	Superior temporal gyrus	BA 22
2	− 4.45	18	− 4	15	69	Left	Premotor cortex	BA 6
2	− 4.41	29	− 8	− 46	6	Left	Retrosplenial cortex	BA 29
3	− 4.50	15	48	6	33	Right	Inferior frontal gyrus	BA 44
3	− 4.26	19	12	− 76	33	Right	Occipital gyrus	BA 19
3	− 3.11	13	− 32	− 16	− 9	Left	Hippocampus	
4	− 7.91	1384	− 44	− 31	2	Left	Middle temporal gyrus	BA 21
4	− 6.32	526	4	− 44	43	Right	Precuneus	
4	− 6.18	26	− 24	3	− 20	Left	Parahippocampal gyrus	BA 28
4	− 5.22	31	32	66	8	Right	Anterior frontal	BA 10
4	− 5.15	42	− 28	62	1	Left	Anterior frontal	BA 10
4	− 4.20	25	− 59	− 62	7	Left	Fusiform gyrus	BA 37
5	− 6.98	81	− 44	− 20	− 9	Left	Middle temporal gyrus	BA 21
5	− 6.26	439	− 36	− 56	− 34	Left	Cerebellum	
5	− 5.63	40	− 55	− 7	11	Left	Precentral gyrus	BA 42/6

Lag	BSR	Cluster size	X	Y	Z	Hem	Gyral location	Brodmann area (BA)
5	− 5.29	565	8	− 80	33	Right	Occipital gyrus	BA 19
5	− 5.20	112	51	43	15	Right	Anterior dorsolateral	BA 46/10
5	− 4.99	48	− 40	52	23	Left	Anterior dorsolateral	BA 9/10
5	− 4.93	15	51	− 68	− 30	Right	Cerebellum	
5	− 4.63	27	− 32	58	− 3	Left	Anterior frontal	BA 10
5	− 4.63	129	51	− 15	4	Right	Superior temporal gyrus	BA 22
5	− 4.43	124	63	− 39	− 11	Right	Middle temporal gyrus	BA 21
5	− 4.04	34	24	− 20	60	Right	Precentral gyrus	BA 4
6	− 6.72	321	44	− 32	− 9	Right	Hippocampus	
6	− 5.49	196	32	− 87	− 23	Right	Cerebellum	
6	− 5.38	62	− 32	− 28	− 25	Left	Cerebellum	
6	− 4.67	29	− 12	2	33	Left	Anterior cingulate	BA 24
6	− 4.66	60	− 59	− 27	9	Left	Superior temporal gyrus	BA 42
6	− 4.23	25	− 28	− 87	− 26	Left	Cerebellum	
6	− 4.20	21	− 51	− 59	− 7	Left	Fusiform gyrus	BA 37
7	− 5.64	46	− 59	− 51	− 1	Left	Middle temporal gyrus	BA 21
7	− 4.82	22	24	− 1	63	Right	Premotor cortex	BA 6

Note: Temporal lag represents the time interval (2 s each) after event-onset, when a cluster of voxels exhibited a peak bootstrap ratio reflecting the identified effect. The bootstrap ratio threshold (BSR) was set to +/− 3 for the hippocampus (HC), and +/− 3.5 for all other areas. The spatial extent refers to the total number of voxels included in the voxel cluster (threshold =/>5 for HC and =/>15 for all other areas). The stereotaxic coordinates are reported in Talairach coordinates, in mm, and the Brodmann Areas (BA) of the peak coordinate were determined by reference to Talairach and Tournoux (1988). Hem = Hemisphere.

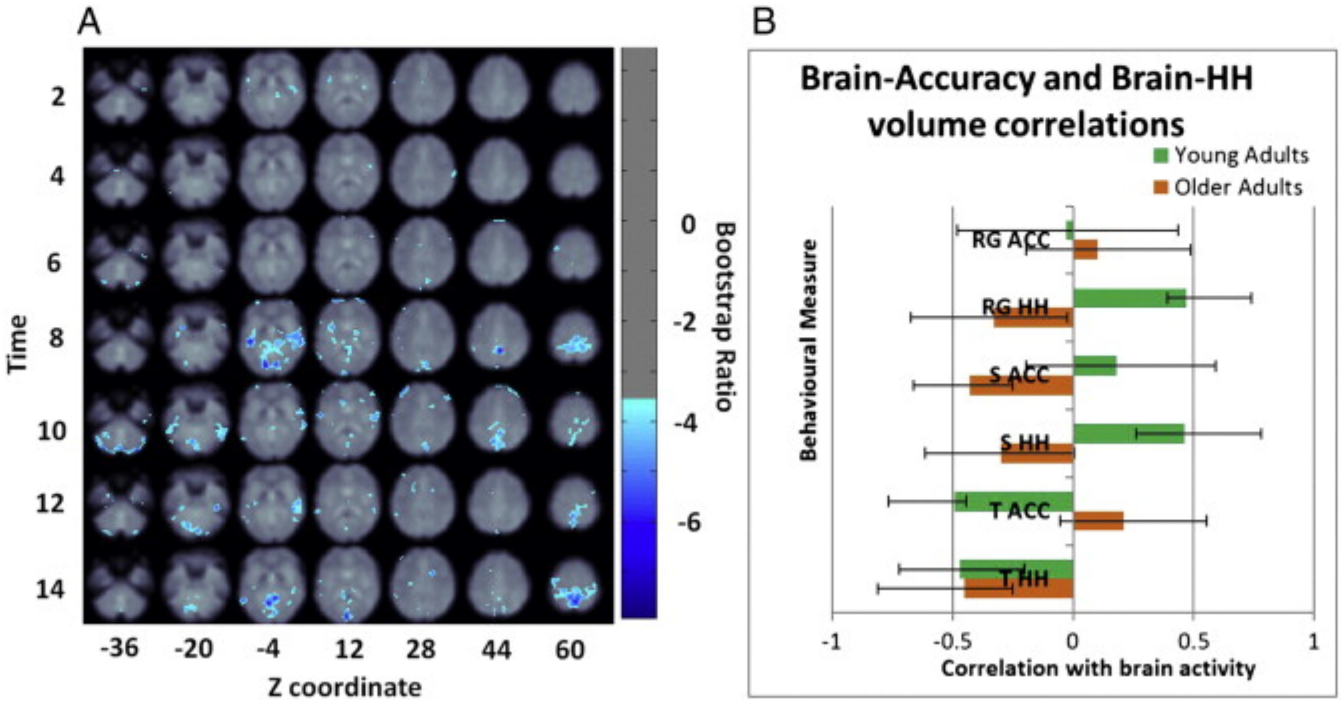

Fig. 2.

Singular image and correlation profile for LV2 of the between-group PLS. A) The singular image for LV2 at a bootstrap of 3.5 ($p < 0.0005$), which reflects stable and significant activations at 2 to 14 s after event onset. Z coordinates are reported in mm in MNI space. The color-bar represents the color code for the colorized activations on the singular image. Regions colored in red–orange–yellow are positively related with the experimental effect presented in (B). Regions colored in blue are negatively related with the experimental effect presented in (B). B) Correlation profile for LV2. The correlation profile shows how accuracy and HH volume correlate with the pattern of brain activity identified in the singular image in young and older adults. RG = Recognition, S = Spatial context, T = Temporal context, ACC = Accuracy, HH = Average hippocampus head volume.

3.6. Discussion

The first goal of this study was to examine the three-way association between individual differences in HH volume, activity in whole-brain encoding networks and retrieval accuracy in young adults. We predicted that HH volume would be related to performance-related networks in the two context tasks, due to the associative nature of these encoding tasks. In addition we were interested in determining if age-related context memory deficits are related to alterations in this three-way association with age; as a result of age-related gray matter volume loss in the HH. Volumetric results confirmed that older adults exhibited a significant decrease in HH volume.

Retrieval accuracy results revealed that compared to young adults, older adults performed equivalently on item recognition, but performed worse on both spatial and temporal context tasks, consistent with prior reports of an age-related deficit in context memory (Spencer and Raz, 1995). Furthermore, in both groups, accuracy across the item recognition, spatial context and temporal context tasks followed a decreasing linear trend. In young adults, RT for the pleasantness judgment at encoding followed the opposite trend, being fastest during item encoding and slowest during temporal context encoding. In older adults, RT was significantly faster in the item recognition task compared to both context tasks, but was not significantly different between the spatial and temporal context tasks.

The between-group PLS analysis identified two significant LVs, both of which reflected group differences in brain activity–accuracy and brain activity–HH volume correlations. In the following sections we first present a detailed interpretation of the results obtained from young adults. We then discuss how healthy aging impacts HH volume and alters the pattern of association between HH volume, encoding activity and subsequent memory retrieval.

3.6.1. Young adults: three-way association between HH volume, encoding activity and retrieval accuracy

The first LV from the PLS analysis identified a pattern of structure–function–behavior associations that was unique to young adults. Specifically, this LV identified a network of brain regions which exhibited greater activity during all encoding tasks, as a function of larger HH volume. Furthermore, increased activity in this context encoding network correlated with subsequent retrieval accuracy. Therefore, in young adults LV1 identified a general episodic encoding network that was positively correlated with HH volume, and was associated with subsequent retrieval.

The brain regions identified in LV 1 included right hippocampus and right VLPFC (BA 47). Activity in hippocampus and VLPFC has been routinely reported in studies of subsequent memory (Kim, 2011) and the interaction between these two regions is thought to be important to successful encoding (Simons and Spiers, 2003). Therefore, young adults with larger HH volumes activated these two nodes of a traditional face encoding network (Rajah et al., 1999) to a greater degree, and increased activity in this network correlated with increased subsequent retrieval.
Of additional interest is that many of the brain regions identified in LV 1 were located along the midline: medial PFC, posterior cingulate, precuneus and retrosplenial cortices. These brain regions have been characterized as being part of the default mode network (DMN), which has been defined as a set of functionally connected brain regions that exhibit task-induced deactivation and increase activation at rest (Buckner et al., 2008, Deco et al., 2011 and Raichle and Snyder, 2007). Although the role of the DMN in cognition remains unclear, there is some evidence that this network engaged during mind-wandering and self-referential processing (Addis et al., 2009, Buckner et al., 2008 and Christoff et al., 2009). Interestingly, a recent meta-analysis of encoding activity found that all regions of the DMN are associated with subsequent forgetting (Kim, 2011). It was suggested that activation of these regions at encoding may reflect mind-wandering, or lapses in attention, thus leading to poorer subsequent memory (Kim, 2011). However, this association does not extend to all encoding tasks, as increased activation in midline DMN regions has also been reported to predict subsequent memory when a subjective, social or self-referential orientation task is employed at encoding (Harvey et al., 2007, Macrae et al., 2004 and Mitchell et al., 2004). In the current study subjects made a subjective pleasantness

judgment during encoding. Therefore, it is possible that the observed positive correlation between larger HH volume and increased activity in hippocampus, VLPFC and midline brain regions during all encoding tasks, reflected the ability of young adults with larger HH volumes to more effectively encode face stimuli using the self-referential subjective pleasantness judgment associated with these stimuli; which in turn benefitted these subjects' subsequent retrieval.

Young adults also activated a second network of brain regions, but only during temporal context encoding (LV 2 from the PLS analysis). Activity in this network was positively correlated with having large HH volume and with better subsequent temporal context retrieval. Brain regions exhibiting this pattern of association in young adults included bilateral hippocampus and bilateral DLPFC. In the current study, young adults exhibited significantly longer RT during temporal context encoding than during the encoding of item and spatial context, likely reflecting additional processing/effort during this task. Moreover, young adults performed the worst on the subsequent temporal context retrieval task, compared to spatial context retrieval and item recognition. Therefore, the temporal context task was the most difficult task at encoding and retrieval in young adults. Increased DLPFC activity has been associated with increases in task effort and concomitant demands on strategic processing (Rajah et al., 2008), and increased hippocampal activity has been associated with increases in the number of associations formed at encoding (Staresina and Davachi, 2008). Moreover, in a recent study, Blumenfield et al. observed greater DLPFC activity during the encoding of inter-item relations versus the encoding of item-specific details/associations (Blumenfeld et al., 2011). However, it is unclear if in that study subjects found the encoding or retrieval of inter-item relations more difficult than item-specific context encoding and retrieval. Taken together these findings suggest that in the current study temporal context encoding required the additional recruitment of brain regions related to implementing a strategy for forming inter-item relations, which is necessary for encoding the relative recency of items (increased DLPFC activity) and for the actual formation of these additional relational associations (increased hippocampal activity). The PLS results also indicate that young adults with larger HH volumes were better able to recruit this second network during temporal context encoding and this benefitted their subsequent temporal context retrieval. Furthermore, our behavioral data suggest that encoding and retrieving inter-item relations (i.e. in the temporal context task) was more difficult than encoding and retrieving item-specific associations (i.e. in the spatial context task) in young adults.

In summary, the young adult results indicate that HH volume was associated with increased activity in two distinct encoding-related networks, identified in LV1 and LV2. The first network (LV1) included right hippocampus, right VLPFC and midline brain regions. Increased activity in this network was positively correlated with HH volume and retrieval accuracy, across all tasks. Thus, this LV identified a general encoding network which was engaged when subjects were required to encoded face stimuli using a subjective judgment of pleasantness decision. Individual differences in HH volume in young adults were also positively correlated with a second network of brain regions that exhibited greater activity only during temporal context encoding only (LV2). This network included bilateral hippocampus and DLPFC, regions thought to be important for forming inter-item associations during temporal context encoding. Interestingly, increased activity in this second relational encoding network was also positively correlated with better subsequent temporal context retrieval accuracy in young adults. Therefore in young adults, individual differences in HH volume were positively correlated with increased activity in both general encoding and relational encoding networks, and with subsequent episodic retrieval. These results are consistent with models that emphasize hippocampus–neocortical interactions as the key mediator of memory formation (Alvarez and Squire, 1994 and Eichenbaum, 2000).

3.6.2. Older adults: reduced HH volume, and altered HH volume–activity–accuracy association

We had previously reported the hippocampal volumetric results for HH, hippocampal body and hippocampal tail of this sample (Rajah et al., 2010a). In this previous study we noted that older adults exhibited significantly reduced HH volume compared to young adults. The current study indicates that there was also an age-related change in the association between HH volume, encoding-related activity and retrieval accuracy. Specifically, LV 1 from the PLS results shows that older adults did not exhibit a significant three-way association between HH volume, activity in the general encoding network engaged by young adults, which included VLPFC and DMN regions, and subsequent retrieval.

As noted above, activity in VLPFC is thought to be important for mediating successful face encoding. The young adult results (see above) indicate that having larger HH volumes was correlated with increased encoding activity in right VLPFC, which correlated with successful subsequent context retrieval. The right VLPFC has been postulated to play an important role in mediating episodic encoding (Machizawa et al., 2010), and prior studies have shown that age-related deficits in VLPFC activity during encoding are related to subsequent retrieval deficits (Dennis et al., 2008 and Grady et al., 1995). Interestingly, Logan et al. have previously reported that under-recruitment of VLPFC during encoding in older compared to younger adults, can be ameliorated if a semantic encoding strategy is employed; but this amelioration of VLPFC activity did not remove the age-related deficit in subsequent retrieval (Logan et al., 2002). This raises the possibility that even when under-recruitment in VLPFC is corrected for in older adults, there remains an underlying deficit which prevents successful encoding. Our results suggest that this underlying deficit may be HH volume loss, which in turn disrupts the positive associations between the HH volume and activity in VLPFC and other brain regions (discussed below) that are important for successful memory encoding, particularly context encoding.

In addition to this age-related change in VLPFC activity during encoding, several studies have demonstrated age-related changes in DMN regions at encoding (de Chastelaine et al., 2011, Duverne et al., 2009,Gutchess et al., 2010 and Miller et al., 2008). These studies have reported either attenuation of activation/deactivation in these regions, or a reversal of the relationship between activation and subsequent memory with age. For example, during an item encoding task for adjective stimuli encoded in reference to a friend, Gutchess et al. (2010) reported subsequent memory effects in medial PFC, anterior cingulate and posterior cingulate cortices in young, but subsequent forgetting effects in the same areas in older adults. Furthermore, this pattern of results was inverted when the adjectives were encoded in a self-referential manner. In the present study, we found that midline DMN regions did not contribute to subsequent memory in older adults, and further demonstrated that in contrast with young adults, activity in these regions in older adults was not related to HH volume. Taken together, our results indicate that there is a disruption of the three-way association between encoding activity in right VLPFC and DMN, HH volume and subsequent retrieval with age, which may be due to reduced volume in HH.

However, in the current study, we also observed preserved structure–function associations between HH volume and increased activity in brain regions identified in LV 2 from the PLS analysis, which included bilateral hippocampus and DLPFC. However, in older adults this pattern of association was observed *during all encoding tasks*; in young adults, this pattern of encoding activity was correlated with larger HH volume only during temporal context encoding. This suggests that there was a more generalized recruitment of this network in older adults, compared to young adults during memory encoding. Moreover, increased activity in this network was correlated with subsequent spatial context retrieval in older adults. In young adults, activity in this network was positively correlated with subsequent temporal context retrieval.

In young adults, increased encoding activity in bilateral hippocampus and DLPFC during temporal context encoding was interpreted as reflecting the engagement of an inter-item relational strategy and associative encoding processes during this most difficult, temporal context encoding task. If it is assumed that the functional processes mediated by distinct brain regions remain constant with increasing age (Rajah and D'Esposito, 2005), then our current results suggest that older adults with larger HH volumes engaged relational strategies and associative encoding processes during all encoding tasks, which may reflect attempted compensation for the aforementioned deficits in structure–function associations in a general context encoding network (see above). This altered pattern of recruitment was directly correlated with improved subsequent spatial context retrieval, albeit at a reduced level compared to young adults. Moreover, it is possible that this altered pattern of structure–function association supported the maintenance of item recognition at the levels equivalent to young adults, but due to behavioral ceiling effects the correlation with behavior was not observed in older adults.

Our older adult results are broadly consistent with the neural inefficiency hypothesis (Morcom et al., 2007), and compensation-related utilization of neural circuits hypothesis (CRUNCH) of aging (Reuter-Lorenz and Cappell, 2008), and suggest that due to processing inefficiencies, older adults recruit additional brain regions to perform easier tasks, such as the spatial context memory task, which young adults recruit to perform more difficult tasks, such as the temporal context memory task in the current study. As a result older adults have limited resources to perform these more difficult tasks, and thus exhibited the greatest deficit on temporal context memory tasks (Craik and Byrd, 1982).

It is noteworthy that in the current study older adult performed worse than young adults on context retrieval. Therefore, it is questionable whether the same pattern of encoding activation results would be observed if context retrieval accuracy was matched between age groups. Keeping in mind that our current analyses included *both* behavior and HH volume as covariates of interest in the PLS analysis, it is possible that if older adults performed equivalently *and had preserved HH volumes*, then the patterns of activity observed would be indistinguishable from the young since there would be no group differences in either neural or behavioral measures. However, if young and older adults' context retrieval performance was matched, but age-related differences in HH volume were still present, it is unclear what outcome would have been observed since no study to date has examined fMRI activity during context *encoding*, when subsequent context retrieval was matched in young and older adults. One possibility, given our current interpretation that older adults did not show the three-way association identified in LV1 for young adults due to HH volume reduction with age, is that even if subsequent context retrieval was equated between age groups, older adults would not exhibit a significant three-way association between HH volume, retrieval accuracy and encoding activity in brain regions identified in LV1, since HH volume deficits would still be present. In contrast, given that we interpreted older adults' over-generalized recruitment of LV2 as reflecting functional compensation for the aforementioned disruption, it is possible that if there was age-equivalence in subsequent context retrieval, then older adults would continue to over-generalize and possibly over-recruit brain regions identified in LV2, particularly DLPFC, during all encoding tasks. This prediction is supported by previous studies that have examined encoding activity when performance on a subsequent item recognition task was matched and reported over-recruitment in DLPFC (Dennis et al., 2007, Gutchess et al., 2005 and Morcom et al., 2003). For example, Dennis et al. (2007) reported greater event-related over-recruitment in left DLPFC in older versus younger adults during successful encoding, when subsequent retrieval performance was matched.Gutchess et al. (2005) reported over-recruitment of DLPFC, particularly left DLPFC, in older versus younger adults during the encoding of complex scenes when subsequent item recognition was matched.

However, Morcom et al. (2003) observed that over-recruitment of bilateral DLPFC in older, versus younger adults, during encoding, was independent of whether performance was matched between age groups. This suggests that over-recruitment of DLPFC may not be performance related in older adults. Furthermore, in the aforementioned encoding studies (Dennis et al., 2007, Gutchess et al., 2005 and Morcom et al., 2003), over-recruitment of medial PFC and age-equivalent recruitment of VLPFC (areas identified in LV1, see Table 3) were also reported. Therefore, it is also possible that under conditions in which subsequent context retrieval was equivalent between young and older adults, that older adults would over-recruit PFC regions from LV1 (the general encoding network in young adults), despite having HH volume reductions. To discriminate between these alternative possibilities a future study examining the association between HH volume, context encoding activity, and subsequent context retrieval in young and older adults needs to be conducted in which both age groups perform equivalently in context retrieval.

3.6.3. Conclusions

This study demonstrated that there are group differences in the three-way association between larger HH volume, whole-brain encoding activity and subsequent retrieval accuracy in young and older adults. Young adults recruited a general encoding network that included right hippocampus, right VLPFC and midline brain regions which positively correlated with having a larger HH volume, and subsequent retrieval accuracy. Young adults also recruited a second network which included bilateral hippocampus and bilateral DLPFC specifically during the most demanding temporal encoding task, which may have reflected the use of additional relational encoding resources in this task. In contrast, older adults exhibited volumetric reductions in HH and altered associations between HH volume and encoding-related activity in VLPFC and midline brain regions, which may have contributed to diminished performance on both context memory tasks. However, we observed that older adults with larger HH volumes may have attempted to compensate for this deficit by recruiting the network that young adults reserved for the most difficult temporal context tasks, *during all encoding tasks* (Cabeza et al., 1997 and Grady, 1996). This generalization of structure–function association between HH volume and bilateral hippocampal and DLPFC activity correlated with improved spatial context retrieval, but retrieval performance on this task and the temporal context tasks remained significantly lower in older versus younger adults; thus highlighting that there are limitations to compensation with age.

Disclosure statement

There are no conflicts of interest for any of the authors regarding the study presented in this article. All authors have reviewed the contents of the manuscript being submitted and approve of its contents and validate the accuracy of the data. The data contained in the manuscript being submitted has not been previously published nor has it been submitted elsewhere, and will not be submitted elsewhere, while under consideration in Brain Research.

Acknowledgments

This work was supported by the Canadian Institutes of Health Research (CIHR) — Operating Grant #82036 awarded to M. N. Rajah.

3.7. References

Addis, D. R., Pan, L., Vu, M. A., Laiser, N., & Schacter, D. L. (2009). Constructive episodic simulation of the future and the past: distinct subsystems of a core brain network mediate imagining and remembering. *Neuropsychologia, 47*(11), 2222-2238.

Alvarez, P., & Squire, L. R. (1994). Memory consolidation and the medial temporal lobe: a simple network model. *Proc Natl Acad Sci U S A, 91*(15), 7041-7045.

Beck, A. T. (1987). *Beck Depression Inventroy*. TX: The Psychological Corporation.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry, 4*, 561-571.

Bialystok, E., Craik, F. I., & Freedman, M. (2007). Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsychologia, 45*(2), 459-464.

Bialystok, E., Craik, F. I., Grady, C., Chau, W., Ishii, R., Gunji, A., et al. (2005). Effect of bilingualism on cognitive control in the Simon task: evidence from MEG. *Neuroimage, 24*(1), 40-49.

Blumenfeld, R. S., Parks, C. M., Yonelinas, A. P., & Ranganath, C. (2011). Putting the pieces together: the role of dorsolateral prefrontal cortex in relational memory encoding. *J Cogn Neurosci, 23*(1), 257-265.

Brink, T., Yesavage, J., Lum, O., Heersema, P., Adey, M., & Rose, T. (1982). Screening tests for geriatric depression. *Clinical Gerontologist, 1*, 37-44.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38.

Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., et al. (1997). Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *Journal of Neuroscience 17*(1), 391-400.

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc Natl Acad Sci U S A, 106*(21), 8719-8724.

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr, 18*(2), 192-205.

Collins, P., Roberts, A. C., Dias, R., Everitt, B. J., & Robbins, T. W. (1998). Perseveration and strategy in a novel spatial self-ordered sequencing task for nonhuman primates: effects of excitotoxic lesions and dopamine depletions of the prefrontal cortex. *J Cogn Neurosci, 10*(3), 332-354.

Craik, F. I. M., & Byrd, M. (1982). Aging and cognitive deficits: The role of attentional resources. In F. I. M. Craik & S. Trehub (Eds.), *Aging and cognitive processes* (pp. 191-211). New York: Plenum Press.

Craik, F. I. M., & Salthouse, T. A. (2000). *The Handbook of Aging and Cognition*. Mahwah, NJ: Lawrence Erlbaum Associates.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Curr Opin Neurobiol, 16*(6), 693-700.

de Chastelaine, M., Wang, T. H., Minton, B., Muftuler, L. T., & Rugg, M. D. (2011). The Effects of Age, Memory Performance, and Callosal Integrity on the Neural Correlates of Successful Associative Encoding. *Cereb Cortex*.

Deco, G., Jirsa, V. K., & McIntosh, A. R. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat Rev Neurosci, 12*(1), 43-56.

Delis, D. C., Cullum, C. M., Butters, N., Cairns, P., & Prifitera, A. (1988). Wechsler memory scale-revised and california verbal learning test: Convergence and divergence. *The Clinical Neuropsychologist, 2*(188-196).

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *The California Verbal Learning Test- Research Edition*. New York: Psychological Corporation.

Dennis, N. A., Daselaar, S., & Cabeza, R. (2007). Effects of aging on transient and sustained successful memory encoding activity. *Neurobiol Aging, 28*(11), 1749-1758.

Dennis, N. A., Hayes, S. M., Prince, S. E., Madden, D. J., Huettel, S. A., & Cabeza, R. (2008). Effects of aging on the neural correlates of successful item and source memory encoding. *J Exp Psychol Learn Mem Cogn, 34*(4), 791-808.

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends Cogn Sci, 11*(9), 379-386.

Duverne, S., Habibi, A., & Rugg, M. D. (2008). Regional specificity of age effects on the neural correlates of episodic retrieval. *Neurobiol Aging, 29*(12), 1902-1916.

Duverne, S., Motamedinia, S., & Rugg, M. D. (2009). The relationship between aging, performance, and the neural correlates of successful memory encoding. *Cereb Cortex, 19*(3), 733-744.

Efron, B., & Tibshirani, R. (1986). Bootstrap methods for standard errors, confidence intervals and other measures of statistical accuracy. *Statistical Science, 1*, 54-77.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci, 1*(1), 41-50.

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annu Rev Neurosci, 30*, 123-152.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Geneau, D., & Gjedde, A. (1996). *Le ''Protocole d'examen cognitif de la personne âgée - version révisée'' (PECPA-2r): Normalisation par groupes d'âge et antécédents éducationnels chez des sujets québécois francophones*. St-Hyacinthe, Québec.

Giovanello, K. S., Schnyer, D. M., & Verfaellie, M. (2004). A critical role for the anterior hippocampus in relational memory: evidence from an fMRI study comparing associative and item recognition. *Hippocampus, 14*(1), 5-8.

Glisky, E. L., & Kong, L. L. (2008). Do young and older adults rely on different processes in source memory tasks? A neuropsychological study. *J Exp Psychol Learn Mem Cogn, 34*(4), 809-822.

Grady, C. L. (1996). Age-related changes in cortical blood flow activation during perception and memory. *Annals of the New York Academy of Science, 777*, 14-21.

Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., et al. (1995). Age-related reductions in human recognition memory due to impaired encoding. *Science, 269*, 218-220.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A, 100*(1), 253-258.

Gutchess, A. H., Kensinger, E. A., & Schacter, D. L. (2010). Functional neuroimaging of self-referential encoding with age. *Neuropsychologia, 48*(1), 211-219.

Gutchess, A. H., Welsh, R. C., Hedden, T., Bangert, A., Minear, M., Liu, L. L., et al. (2005). Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *J Cogn Neurosci, 17*(1), 84-96.

Harvey, P. O., Fossati, P., & Lepage, M. (2007). Modulation of memory formation by stimulus content: specific role of the medial prefrontal cortex in the successful encoding of social pictures. *J Cogn Neurosci, 19*(2), 351-362.

Jackson, O., 3rd, & Schacter, D. L. (2004). Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *Neuroimage, 21*(1), 456-462.

Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., Inati, S., & Heatherton, T. F. (2002). Finding the self? An event-related fMRI study. *J Cogn Neurosci, 14*(5), 785-794.

Kim, H. (2010). Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI studies. *Neuroimage*.

Leshikar, E. D., Gutchess, A. H., Hebrank, A. C., Sutton, B. P., & Park, D. C. (2010). The impact of increased relational encoding demands on frontal and hippocampal function in older adults. *Cortex, 46*(4), 507-521.

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron, 33*(5), 827-840.

Machizawa, M. G., Kalla, R., Walsh, V., & Otten, L. J. (2010). The time course of ventrolateral prefrontal cortex involvement in memory formation. *J Neurophysiol, 103*(3), 1569-1579.

Macrae, C. N., Moran, J. M., Heatherton, T. F., Banfield, J. F., & Kelley, W. M. (2004). Medial prefrontal activity predicts memory for self. *Cereb Cortex, 14*(6), 647-654.

McCormick, C., Moscovitch, M., Protzner, A. B., Huber, C. G., & McAndrews, M. P. (2010). Hippocampal-neocortical networks differ during encoding and retrieval of relational memory: functional and effective connectivity analyses. *Neuropsychologia, 48*(11), 3272-3281.

McIntosh, A. R., Chau, W. K., & Protzner, A. B. (2004). Spatiotemporal analysis of event-related fMRI data using partial least squares. *Neuroimage, 23*(2), 764-775.

McIntosh, A. R., & Lobaugh, N. J. (2004). Partial least squares analysis of neuroimaging data: applications and advances. *Neuroimage, 23 Suppl 1*, S250-263.

McIntosh, A. R., Lobaugh, N. J., Cabeza, R., Bookstein, F. L., & Houle, S. (1998). Convergence of neural systems processing stimulus associations and coordinating motor responses. *Cereb Cortex, 8*(7), 648-659.

McIntosh, A. R., Rajah, M. N., & Lobaugh, N. J. (1999). Interactions of prefrontal cortex in relation to awareness in sensory learning. *Science, 284*(5419), 1531-1533.

Miller, S. L., Celone, K., DePeau, K., Diamond, E., Dickerson, B. C., Rentz, D., et al. (2008). Age-related memory impairment associated with loss of parietal deactivation but preserved hippocampal activation. *Proc Natl Acad Sci U S A, 105*(6), 2181-2186.

Mitchell, J. P., Macrae, C. N., & Banaji, M. R. (2004). Encoding-specific effects of social cognition on the neural correlates of subsequent memory. *J Neurosci, 24*(21), 4912-4917.

Morcom, A. M., Good, C. D., Frackowiak, R. S., & Rugg, M. D. (2003). Age effects on the neural correlates of successful memory encoding. *Brain, 126*(Pt 1), 213-229.

Morcom, A. M., Li, J., & Rugg, M. D. (2007). Age effects on the neural correlates of episodic retrieval: increased cortical recruitment with matched performance. *Cereb Cortex, 17*(11), 2491-2506.

Moscovitch, M. (1992). Memory and working with memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience, 4*, 257-267.

Naveh-Benjamin, M. (2000). Adult age differences in memory performance: tests of an associative deficit hypothesis. *J Exp Psychol Learn Mem Cogn, 26*(5), 1170-1187.

Paller, K. A. (2002). Cross-Cortical Consolidation as the Core Defect in Amnesia: Prospects for Hypothesis-Testing with Neuropsychology and Neuroimaging. In L. R. Squire & D. L. Schacter (Eds.), *The Neuropsychology of memory* (3rd ed.). New York: Guilford Press.

Petersson, K. M., Sandblom, J., Elfgren, C., & Ingvar, M. (2003). Instruction-specific brain activations during episodic encoding. a generalized level of processing effect. *Neuroimage, 20*(3), 1795-1810.

Prince, S. E., Daselaar, S. M., & Cabeza, R. (2005). Neural correlates of relational memory: successful encoding and retrieval of semantic and perceptual associations. *J Neurosci, 25*(5), 1203-1210.

Protzner, A. B., & McIntosh, A. R. (2007). The interplay of stimulus modality and response latency in neural network organization for simple working memory tasks. *J Neurosci, 27*(12), 3187-3197.

Pruessner, J. C., Collins, D. L., Pruessner, M., & Evans, A. C. (2001). Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. *J Neurosci, 21*(1), 194-200.

Pruessner, J. C., Li, L. M., Serles, W., Pruessner, M., Collins, D. L., Kabani, N., et al. (2000). Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. *Cereb Cortex, 10*(4), 433-442.

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage, 37*(4), 1083-1090; discussion 1097-1089.

Rajah, M. N., Ames, B., & D'Esposito, M. (2008). Prefrontal contributions to domain-general executive control processes during temporal context retrieval. *Neuropsychologia, 46*(4), 1088-1103.

Rajah, M. N., & D'Esposito, M. (2005). Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain, 128*(Pt 9), 1964-1983.

Rajah, M. N., Kromas, M., Han, J. E., & Pruessner, J. C. (2010). Group differences in anterior hippocampal volume and in the retrieval of spatial and temporal context memory in healthy young versus older adults. *Neuropsychologia, 48*(14), 4020-4030.

Rajah, M. N., Languay, R., & Valiquette, L. (2010). Age-related changes in prefrontal cortex activity are associated with behavioural deficits in both temporal and spatial context memory retrieval in older adults. *Cortex, 46*(4), 535-549.

Rajah, M. N., McIntosh, A. R., & Grady, C. L. (1999). Frontotemporal interactions in face encoding and recognition. *Brain Res Cogn Brain Res, 8*(3), 259-269.

Ranganath, C., Heller, A., Cohen, M. X., Brozinsky, C. J., & Rissman, J. (2005). Functional connectivity with the hippocampus during successful memory formation. *Hippocampus, 15*(8), 997-1005.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Direction in Psychological Science, 17*, 177-182.

Rugg, M. D., Johnson, J. D., Park, H., & Uncapher, M. R. (2008). Encoding-retrieval overlap in human episodic memory: a functional neuroimaging perspective. In W. S. Sossin, J.-C. Lacaille, V. F. Castellucci & S. Belleville (Eds.), *Essence of Memory* Amsterdam: Elsevier Science.

Schacter, D. L., Curran, T., Reiman, E. M., Chen, K., Bandy, D. J., & Frost, J. T. (1999). Medial temporal lobe activation during episodic encoding and retrieval: a PET study. *Hippocampus, 9*(5), 575-581.

Shrout, P. E., & Fleiss, J. L. (1979). Intraclass correlations: uses in assessing rater reliability. *Psychol Bull, 86*(2), 420-428.

Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nat Rev Neurosci, 4*(8), 637-648.

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging, 17*(1), 87-97.

Spaniol, J., & Grady, C. (2010). Aging and the neural correlates of source memory: over-recruitment and functional reorganization. *Neurobiol Aging*.

Spencer, W. D., & Raz, N. (1995). Differential effects of aging on memory for content and context: a meta-analysis. *Psychol Aging, 10*(4), 527-539.

Sperling, R., Chua, E., Cocchiarella, A., Rand-Giovannetti, E., Poldrack, R., Schacter, D. L., et al. (2003). Putting names to faces: successful encoding of associative memories activates the anterior hippocampal formation. *Neuroimage, 20*(2), 1400-1410.

Staresina, B. P., & Davachi, L. (2008). Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *J Cogn Neurosci, 20*(8), 1478-1489.

Talairach, J., & Tournoux, P. (1988). *Co-Planar Stereotaxic Atlas of the Human Brain*. New York: Thieme Medial Publishers, Inc.

3.8. Suffix

In the present section, I reinterpret the data from the previous manuscript in a way that is more relevant to the aims of the current thesis. At the time of publication, this manuscript was the first investigation of age-related differences in the association between encoding activation using a pleasantness task and retrieval performance. One suggestion regarding age-related over-activation in mFC in encoding tasks that are not self-referential is that, irrespective of the encoding task, older adults tend to focus more on self-referential aspects of encoding events. If this is the case, then one may expect that age-related differences in mFC activation would disappear if both age groups are explicitly asked to encode information in this manner.

This hypothesis was not supported. Activation in a network of regions including left mFC, right ventrolateral PFC and right hippocampus was related to higher retrieval accuracy (and higher anterior hippocampus volume) in young adults only. In older adults, the correlations between activation in these regions and retrieval accuracy tended to be non-significant, and if anything reversed in direction (in the temporal context task). These results are reminiscent of the only other study that has investigated age-related differences in activation in a self-referential encoding task (Gutchess et al., 2010). In this study, young and older adults encoded adjectives while judging if they were descriptive of themselves, or descriptive of Albert Einstein. At retrieval, subjects were asked to remember in which condition each adjective had been studied in. A complete reversal in the association between increased activation in mFC and memory performance was reported in this study: In young, activation was greater for remembered vs. forgotten events in the Einstein task, but activation was greater for forgotten vs. remembered events in the Self condition – this pattern was completely reversed in older adults. Taken together, these results suggest that young and older adults seem to recruit mFC in opposite manners. In tasks in which young adults tend not to recruit this region during successful encoding (e.g. during semantic encoding tasks), older adults seem to recruit it. In contrast, this study, as well as the one by Gutchess, seem to indicate that in tasks in which young adults do recruit mFC during successful encoding (e.g. during self-referential tasks), older adults do not.

One possibility to explain the present results is that both age groups recruited mFC during the pleasantness encoding task for self-referential evaluation of the face stimuli, but that this was only beneficial to retrieval performance in young adults. It is important to note that due to the specific nature of the retrieval tasks used in the present experiment, judging whether faces were pleasant or not at encoding in itself may not have been sufficient to perform the retrieval tasks adequately. The judgement may have even led to reduced cognitive resources in older adults and impeded their ability to encode the more objective aspects of the memory task. That is, judging a face as pleasant may not have helped older adults whether that face was presented on the left/right or first/second. Thus, it is possible that only young adults were able to use the pleasantness judgement in a way that helped them perform the context memory tasks. For example, young adults, may have not only judged the faces as pleasant/unpleasant, but may have also focused on the spatial/temporal aspects of this encoding event.

In the fMRI literature, it is often suggested that age-related differences in mFC activation can be attributed to increased frequency of TUT in older vs. young adults (e.g. Leshikar et al., 2010). Thus, another possibility is that activation in mFC was related to increased retrieval accuracy in young adults because young were performing self-referential evaluation of the face stimuli, while mFC activation was not (ore negatively) related to retrieval accuracy in older adults because older adults were performing self-referential evaluation of task-unrelated thoughts (e.g. thinking about one will do following the experiment). In the following experiment, I directly test the hypothesis that older adults exhibit more TUT compared to young adults during episodic memory encoding.

References

Gutchess, A. H., E. A. Kensinger and D. L. Schacter (2010). "Functional neuroimaging of self-referential encoding with age." Neuropsychologia **48**(1): 211-219.

Leshikar, E. D., A. H. Gutchess, A. C. Hebrank, B. P. Sutton and D. C. Park (2010). "The impact of increased relational encoding demands on frontal and hippocampal function in older adults." Cortex **46**(4): 507-521.

4. Study 3: Age-related changes in frequency of mind-wandering and task-related interferences during memory encoding and their impact on retrieval

4.1. Abstract

During the performance of cognitive tasks such as memory encoding, attention can become decoupled from the external environment and instead focused on internal thoughts related to the appraisal of the current task (task-related interferences; TRI), or personal thoughts unrelated to the task at hand (mind-wandering; MW). However, the association between the frequency of these thoughts experienced at encoding and retrieval accuracy in young and older adults remains poorly understood. In this study young and older adults encoded lists of words using one of two encoding tasks: judging whether words are man-made/natural (objective task), or whether they are pleasant/neutral (subjective task). We measured the frequency of TRI and MW at encoding, and related them to retrieval accuracy in both age groups. We found that encoding task influenced the type of internal thoughts experienced by young, but not older, adults: young exhibited greater MW in the subjective vs the objective task, and greater TRI in the objective vs subjective encoding task. Second, across both tasks we found marked age-related decreases in both MW and TRI at encoding, and frequency of these thoughts negatively impacted memory retrieval in young adults only. We discuss these findings in relation to current theories of ageing, attention and memory.

4.2. Introduction

During the performance of cognitive tasks, attention can become decoupled from the external environment and instead focused on one's internal train of thought (Christoff, 2012; Smallwood & Schooler, 2006). For example, participants may experience interfering thoughts related to the appraisal of the current task, (task-related interferences; TRI), or personal thoughts unrelated to the task at hand (mind-wandering; MW) (Smallwood, Davies, et al., 2004; Smallwood & Schooler, 2006; Stawarczyk, Majerus, Maj, Van der Linden, & D'Argembeau, 2011). Examples of the former are thinking about the difficulty or the length of an ongoing cognitive task, and examples of the latter are thinking about personally salient events that happened earlier in the day, or that may occur in the future. When MW and TRI occur during cognitively demanding tasks, they have been associated with reductions in task performance (McVay & Kane, 2010; Smallwood, Davies, et al., 2004; Smallwood & Schooler, 2006; Stawarczyk, Majerus, Maj, et al., 2011). Different theoretical accounts have been proposed to explain how such internal thoughts occur and why they negatively impact task performance. According to the resource competition hypothesis, MW reflects the activation of unresolved goals/current concerns and may occur automatically (without executive control) (Smallwood & Schooler, 2006). According to this perspective, the MW episode itself involves cognitive control processes; thus MW may compete with a primary cognitive task for limited cognitive resources (Smallwood, 2010; Smallwood & Schooler, 2006). On the other hand, according to the control-failure hypothesis, MW occurs during cognitive tasks following the failure of inhibitory executive control mechanisms to prevent their occurrence; however, the MW episode itself is conceived as independent of cognitive control processes, instead relying on the default-mode network (McVay & Kane, 2010).

Most studies investigating the relationship between MW frequency and task performance have used attention tasks, such as the sustained attention to response task (SART) (Smallwood & Schooler, 2006; Stawarczyk, Majerus, Maj, et al.,2011). In contrast, relatively little is known about the impact of MW and TRI during memory encoding on retrieval performance. Intuitively one would expect that MW would have a negative effect on memory encoding; most people have had the experience of having their minds drift away from ongoing external events (e.g., a boring lecture) to more "interesting" topics such as planning an event later in the day, which in turn results in poor or no recall of the external events that occurred during this time. A few studies have indeed found a negative association between MW and memory performance in young adults (Seibert & Ellis, 1991; Smallwood, Baracaia, Lowe, & Obonsawin, 2003; Smallwood, O'Connor, Sudberry, & Obonsawin, 2007; Smallwood, Obsonsawin, et al., 2003). For example, in one study three groups of participants received happy, neutral, or sad mood inductions, and then performed a memory recall task for letters (Seibert & Ellis, 1991). Following retrieval, participants were asked to list all the thoughts that they had had during the task. The happy and sad groups produced more task-unrelated thoughts relative to the neutral group, and the proportion of these thoughts was negatively related to recall performance in all three groups. On the other hand, to our knowledge no study has assessed the impact of TRI on memory performance.

In the current study we were interested in determining whether different encoding tasks might differentially affect the rates of MW and TRI during memory encoding, and whether the frequency of these thoughts may in turn negatively impact memory retrieval. A well-replicated phenomenon in the memory literature is that encoding tasks which encourage participants to attend to the semantic meaning of stimuli ("deep" encoding) result in better memory for these stimuli relative to more "shallow" encoding tasks which instruct participants to attend to perceptual features (Craik, 1972, 2002). For example, commonly used semantic encoding tasks include making man-made/natural or living/non-living judgements on word or object stimuli. More recently it has been demonstrated that self-referential/subjective encoding tasks, such as judging whether adjectives are descriptive of oneself, or judging whether words are pleasant/neutral, also result in especially high performance on memory tasks (Rogers, Kuiper, & Kirker, 1977; Symons & Johnson, 1997). This mnemonic benefit is thought to result from elaboration and organisation of the encoding material through one's self schema (Symons & Johnson, 1997).

We hypothesised that semantic and subjective/self-referential encoding tasks might differentially affect frequency of MW and TRI. The Seibert and Ellis (1991) study described above demonstrated that pre-task conditions that bias participants towards themselves can increase rates of MW in a subsequent memory task. In this study we investigated whether the nature of the encoding task itself could modulate frequency of MW during the same task. Specifically, we hypothesised that participants would exhibit greater MW in a subjective (pleasant/neutral) vs an objective/semantic (man-made/natural) encoding task. On the other hand, it has been demonstrated that when an error is detected during task performance, participants may exhibit thoughts related to self-evaluation and performance (i.e., TRI), such as thinking about one's ability or the difficulty of the task (Smallwood, Davies, et al., 2004). Since semantic judgements are objective (i.e., have a right and a wrong answer), we hypothesised that they might result in an increased frequency of TRI relative to a subjective encoding judgement. In addition we measured reaction times for the pleasantness and man-made/natural judgements to verify whether time on task could account for these differences in thought content. Finally we hypothesised that the frequency of internal thoughts during encoding would be negatively correlated with memory performance in young adults.

4.2.1. Mind-wandering and task-related interferences in older adults during memory encoding

To our knowledge no study has assessed age-related changes in the frequency of MW and TRI during memory encoding tasks. Healthy ageing is associated with a reduction in episodic memory (Craik, 1991; Craik & Salthouse,2000). It has been hypothesised that part of older adults' memory deficits might be due to a reduction in inhibitory control (Clapp & Gazzaley, 2012; Hasher & Zacks, 1988). For example, according to the inhibition deficit theory of ageing, older adults are less able than young adults to prevent irrelevant information from entering working memory (Hasher & Zacks, 1988). This results in increased attention being paid to information irrelevant to the current goal, to the detriment of goal-related information. This "mental clutter" is thought to be detrimental to encoding since less attention is focused on the relevant information to be encoded (Hasher & Zacks, 1988). Similarly it has been proposed that during working memory maintenance older adults are more susceptible to interference caused by both external (e.g., radio playing) and internal factors (e.g., MW) (Clapp & Gazzaley, 2012). Such accounts would predict an age-related increase in MW and/or TRI during memory encoding, due a reduction in the ability to inhibit these thoughts, a result which would support the control failure hypothesis of MW (McVay & Kane, 2010).

However, another account of age-related deficits in memory tasks is that older adults have diminished attentional*resources* (Craik, 1983). For example, studies have shown that dividing the attention of young participants at encoding (and thereby reducing their available resources) results in similar deficits to those observed in older adults (Rabinowitz & Craik, 1982). Furthermore it has been demonstrated that age differences in memory tasks are reduced when a supportive environment which decreases attentional demands is provided (e.g., specific instructions to use a strategy) (Glisky, Rubin, & Davidson, 2001; Naveh-Benjamin, Brav, & Levy, 2007). Thus, if older adults have fewer attentional resources than young adults, they may use up more of these resources to perform a given task compared to young adults (Anderson, Craik, & Naveh-Benjamin, 1998), and have fewer resources available for MW, which would be consistent with the resource competition framework of MW (Smallwood, 2010; Smallwood & Schooler, 2006). Consistent with this view, age-related decreases in MW have been reported during vigilance, attention, and reading tasks (Giambra, 1989; Jackson & Balota, 2012; Krawietz, Tamplin, & Radvansky, 2012).

Thus in the current study we were interested in contrasting the predictions made by inhibition deficit vs the reduced attentional resources theories of ageing and memory. Specifically, we assessed how the nature of the encoding task would modulate thought content in older adults, and whether they would display an increase or a decrease in MW/TRI compared to young adults. First, we predicted that similarly to young adults, we would observe (1) greater MW in the subjective vs the objective task, due to this task biasing the participants' attention towards themselves, and (2) greater TRI in the objective vs the subjective task in older adults, due to this task having a performance-related component. Second, based on previous findings of an age-related decrease in MW during attention and reading tasks (Giambra, 1989; Jackson & Balota, 2012; Krawietz et al., 2012), we predicted that older adults would display a reduction in MW compared to young adults during memory encoding. On the other hand, we predicted that TRI might exhibit either no age-related change, or less of a reduction than MW. This is based on the common finding that older adults worry about their memory, and that negative attitudes and stereotypes may have a negative impact on their memory (Hess, Hinson, & Hodges, 2009; Levy, 1996; McDaniel, Einstein, & Jacoby, 2008). We reasoned that this might result in a shift of internal thought content during memory tasks away from MW to TRI in older adults (e.g., thinking about the difficulty of the task or about one's ability).

4.3. Method

4.3.1. Participants

A total of 31 young adults (age range: 18–32, mean: 22.6, 22 women) and 26 older adults (age range: 60–76, mean: 64.30, 15 women) participated in the study. One additional older adult was excluded because of a score of 21 on the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005). All participants were French–English bilingual and reported no history of neurological or psychiatric disorders. The groups did not differ in education level (young mean: 15.19, *SD*=2.48; old mean: 14.90, *SD*=2.56; *p*=.891). The mean score on the mini mental status examination (MMSE; Folstein, Folstein, & McHugh, 1975) in older adults was 29.4 (*SD*=1.06), and all of them scored 25 or higher. All participants had a score of 24 or higher on the MOCA, and there were no significant between-group difference in score on this test (young mean: 28, *SD*=1.77; old mean: 27.08, *SD*=1.96; *p*=.067).

4.3.2. Stimuli

The stimuli used in this experiment were 366 French nouns of 3–11 letters, taken from Desrochers and Thompson (2009) and the OMNILEX database (http://www.omnilex.uottawa.ca/scrServices.asp). The experiment was carried out in French, given that Montreal is a primarily French-speaking city. The words were split into four lists: two encoding lists of 122 words each, and two lists of 61 words each used as distractors at retrieval. Words in all lists were matched for frequency and imageability ratings. Half of the words in all lists represented man-made objects (e.g., pencil, computer, car), and the other half were natural (e.g., cat, apple, rose).

4.3.3. Procedure

The experiment consisted of three phases: encoding, thought questionnaire, and retrieval. Participants went through each phase twice. Thus the order of tasks was: encoding 1, thought questionnaire 1, retrieval 1, encoding 2, thought questionnaire 2, retrieval 2. At encoding participants saw 122 words, presented one at a time for 1.5 seconds each. Words at encoding and retrieval were separated by a variable inter-trial interval (2.2, 3.4, or 5 seconds; mean 3 seconds) during which a central cross was presented. In one encoding phase participants were asked to judge whether each word was pleasant/neutral (subjective task), and in the other they were asked whether words were man-made/natural (objective task), and instructed to give their answer by pressing one of two buttons. Participants were told that a memory test would follow: therefore encoding was intentional. The order of encoding tasks was counterbalanced across participants. Immediately following each encoding phase, participants answered 15 questions taken from the thinking content section of the Dundee Stress Test questionnaire (Matthews et al., 1999) (translated into French). This questionnaire has been used by previous studies to assess MW and TRI retrospectively during a task (Barron, Riby, Greer, & Smallwood, 2011; Smallwood, O'Connor, & Heim, 2005; Smallwood, O'Connor, Sudberry, Haskell, & Ballantyne, 2004). Eight of these questions measured frequency of MW, while seven measured frequency of TRI. Each question appeared on the screen for 10 seconds, and participants were asked to rate the frequency to which they experienced each thought during the encoding phase on a 1 to 5 scale (1 = never, 2 = once, 3 = a few times, 4 = often, 5 = very often). The mean score for each question in young and older adults is presented in Table 1.

Table 1 - Score on questionnaire for mind-wandering and task interferences, with standard deviation in parentheses

	Question	Young adults		Older adults	
		Subjective encoding	**Objective encoding**	**Subjective encoding**	**Objective encoding**
Mind-wandering	I thought about members of my family	2.36	1.77	1.58	1.80
	I thought about something that made me feel guilty	1.90	1.57	1.20	1.19
	I thought about personal worries	2.00	1.97	1.16	1.30
	I thought about something that made me feel angry	1.30	1.16	1.04	1.11
	I thought about something that happened earlier today	1.87	1.83	1.32	1.23
	I thought about something that happened in the recent past	1.83	1.83	1.16	1.24
	I thought about something that happened in the distant past	2.70	1.81	1.08	1.19
	I thought about something that might happen in the future	2.45	2.02	1.12	1.23
	Average Mind-wandering	2.05 (0.64)	1.79 (0.69)	1.21 (0.22)	1.29 (0.40)
Task interferences	I thought about how I should work more carefully	2.31	2.82	1.88	1.88
	I thought about how much time was left in the task	2.87	3.03	1.96	2.03
	I thought about how others have done on this task	1.40	1.73	1.36	1.46
	I thought about the difficulty of the task	2.03	2.41	1.76	2.00
	I thought about my level of ability	2.13	2.59	1.92	2.04
	I thought about the purpose of the experiment	1.87	2.21	1.64	1.65
	I thought about how I would feel if I were told how I performed	1.47	1.78	1.26	1.38
	Average Task-interference	2.00 (0.53)	2.36 (0.57)	1.68 (0.53)	1.78 (0.53)

Note: This tables lists all the questions asked to probe mind-wandering and task interferences during memory encoding. For each question, the mean score is indicated for each task and age group.

The retrieval phase started immediately following the administration of the thought questionnaire (approximately 3 minutes following encoding). Participants were presented with 183 words, one at a time, for 2.75 seconds each. Participants saw all 122 words they had seen at encoding plus 61 new words. They were asked to determine whether each word was old (previously seen at encoding) or new, as well as their confidence level, by pressing one of four buttons: 1 = Definitely old, 2 = Probably old, 3 = Definitely new, or 4 = Probably new (Dennis, Kim, & Cabeza, 2008; Duverne, Motamedinia, & Rugg, 2009). In the rest of this paper "Definitely new" and "Definitely Old" responses are referred to as high-confidence responses, while "Probably new" and "Probably old" responses are referred to as low-confidence responses.

At the end of the experiment we administered a debriefing questionnaire, in which we asked participants to rate how difficult and interesting they thought the memory tasks were on a 1 to 10 scale.

4.3.4. Data analysis

Within-group outliers for MW, TRI, and retrieval Pr were identified by using a Z score cut-off of±3, separately for each task. Outliers on any of these three variables were excluded from all analyses on the corresponding task. For completeness we also calculated data point outliers across tasks for MW and TI (i.e., two values per participant), and between-group outliers. The Shapiro–Wilk test of normality was run on MW, TRI, and retrieval Pr scores for words encoded using the objective and subjective encoding tasks. A significant result (p<.05 corrected for 12 multiple comparisons) was taken as evidence of a non-normal distribution.

Between-group differences in response rate for the encoding, retrieval, and thought questionnaire phases were each assessed using two-way Age group by task mixed ANOVAs. The frequency of MW during encoding was assessed by averaging the score given on the eight questions measuring MW, separately for each task. The frequency of TRI during encoding was assessed by averaging the score given on the seven questions measuring TRI, separately for each task. A three-way Age group (young/old) by Thought type (MW/TRI) by Task (objective/subjective) mixed ANOVA was used to assess between-group differences in thought frequency at encoding. We used gender as a covariate in this analysis since our sample in both age groups included more women than men. Note that the frequency of MW vs TRI within a task in a single age group was not of interest in the current study, since this relies on the peculiarities of the questionnaire. Therefore only between-group differences in MW and TRI, as well as within-group differences in thought frequency between tasks, were of interest. A two-way Age group by task mixed ANOVA was used to assess between-group differences in encoding reaction time (RT). We used a significance threshold of$p$<.05 for all ANOVAs. When significant interactions emerged, we performed post-hoc tests corrected for multiple comparisons using a Bonferroni correction.

Retrieval performance was assessed using the index Pr (% of hits –% of false alarms). We calculated Pr separately for high-confidence retrieval judgements (Pr-H) and for low-confidence retrieval judgements (Pr-L). Between-group differences in retrieval Pr and retrieval RT were each assessed by conducting a two-way Age group (young/old) by Task (objective/subjective) mixed ANOVA with post-hoc T-tests. Stepwise multiple regressions were used to assess the relationship between retrieval Pr (dependent variable) and MW and TRI (independent variables), separately for each task and age group.

4.4. Results

4.4.1. Outliers

Data from two young participants were unavailable for the objective task due to computer malfunction. One young participant was identified as having a TRI score 3.22 standard deviations higher than other young adults on the subjective task. The same young participant was also identified as a between-group outlier, and a data point outlier. Thus this participant was excluded from all analyses involving the subjective task. One older adult was identified as having a MW score 4.16 standard deviations higher than other older adults on the subjective task. This participant was not a between-group outlier, given young adults' higher MW rates. Still, since multiple regressions were done within group, we excluded this participant from all analyses involving the subjective task. Finally, one older participant was identified as a between-group outlier on Pr-H in the objective task (z=3.01). However, since this participant was not a within-group outlier (*z*=2.65), we included him in all analyses (note that his exclusion would not have impacted the significance of the group by task mixed ANOVA on Pr scores, the ANOVAs on encoding data, or the multiple regressions). Thus all statistical analyses were based on a sample of 30 young and 25 older adults in the subjective task, and 29 young and 26 older adults in the objective task. The Shapiro–Wilk test was significant for MW in both the subjective (*p*<.001) and the objective (*p*<.001) tasks in older adults, indicating that the MW scores were not normally distributed in this group. This caveat is addressed in a later section. The Shapiro-Wilk test did not reach significance (*p*<.004) for TRI or Pr-H in older adults, or for any variable in young adults.

4.4.2. Encoding results

Young adults responded to 99% (*SD*=1%) of trials in both the subjective and objective encoding tasks. Older adults responded to 98.42% (*SD*=1%) of trials in the subjective task and 98.99% (*SD*=1%) in the objective task. A two-way age group by task mixed ANOVA revealed there was no main effect of task, *F*(1, 53) = 0.811, *p*=.372, or age group by task interaction, *F*(1, 53) = 1.571, *p*=.551), but there was a group main effect, *F*(1, 53) = 4.94, *p*=.03, on response rates. Encoding RT results are listed in Table 2. A two-by-two mixed ANOVA revealed no significant main effects for group, *F*(1, 51) = 0.951, *p*=.334, or task, *F*(1, 51) = 0.205, *p*=.653, and no significant group by task interaction, *F*(1, 51) = 0.310, *p*=.580, in RT. Accuracy in the man-made/natural (objective) encoding was high in both groups (Young: 93.87%, *SD*=0.033; Old: 94%, *SD*=0.039; *p*=.884).

Table 2
Mean reaction time (RT), in milliseconds with standard deviation in parentheses

	Young adults		Older adults	
	Subjective task	Objective task	Subjective task	Objective task
Encoding RT	1249 (221)	1214 (235)	1184 (142)	1192 (187)
Retrieval RT	1457 (270)	1603 (197)	1574 (242)	1708 (276)

Young adults responded to 29.75 (*SD*=0.65) questions of the Dundee Stress Test assessing frequency of MW and TRI, while older adults responded to 29.16 questions (*SD*=1.25) (out of 30). This age difference reached significance,*T*(1, 51) = 2.196, *p* = .033). Mean RT for responses to the Dundee Stress Test questions was significantly faster in young adults (mean = 3902 ms, *SD*=509) compared to older adults (mean = 4320 ms, *SD*=848), *T*(1, 51) = 2.199, *p*= .032, although both groups responded well within the time limit for each question (10,000 ms).

A three-way Group by Task by Thought type mixed ANOVA revealed a main effect of group, *F*(1, 51) = 29.636,*p*<.001, a Task by Thought type interaction, *F*(1, 51) = 11.425, *p*=.001, and a third level interaction, *F*(1, 51) = 11.558, *p*=.001. These effects remained significant when gender, encoding RT, or retrieval RT was included as a covariate. The main effect of group was due to young adults exhibiting a significantly greater amount of internal thoughts compared to older adults overall. The third level interaction was due to a significant second level Task by Thought type interaction in young, *F*(1, 27) = 20.197, *p*<.001, but not in older adults (*p*=.988). In young adults this second level interaction was due to young adults exhibiting more MW during the subjective vs the objective task, T(27) = 3.40, *p*=.002, but more TRI during the objective versus the subjective task, T(27) = 2.60, *p*=.015. These effects were significant after correction for two multiple comparisons (*p*<.025). On the other hand, in older adults there was no main effect of task, *F*(1, 24) = 1.696, *p*=.205, or task by thought type interaction *p*=.988).

Previous studies have indicated that differences in task interest and task difficulty may account for age-related differences in MW frequency between young and older adults (Jackson & Balota, 2012; Krawietz et al., 2012). In the current study young and older adults rated the memory tasks as being equally difficult (young mean = 5.09,*SD*=1.81; old mean; 5.26, *SD*=2.69; *p*=.788). However, older adults rated the memory tasks as being significantly more interesting than did young adults (young mean = 5.29, *SD*=1.94; old mean; 8.17, *SD*=1.49; *p*<.001). Thus we ran an analysis of covariance (ANCOVA) to determine if the Age group main effect remained significant after accounting for task interest. This analysis revealed that although task interest accounted for some of the variance, the age difference in internal thoughts remained highly significant, *F*(1, 48) = 16.291, *p*<.001.

Given that internal thought frequency was assessed retrospectively following the encoding session (which lasted about 9.15 minutes) another possible explanation for the age-related reduction in MW/TRI frequency is that older adults failed to recall that they experienced these thoughts. To assess this possibility we examined age-related changes in MW/TRI frequency using only a subset of high-performing older adults. It has been demonstrated that a subset of the ageing population shows either no reduction or a very small reduction in memory compared to young adults (for a recent review, see Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012). In the current study we defined high-performing older adults as those performing within one standard deviation (*SD*) of the mean Pr-H of young adults in*both* retrieval tasks. A total of 10 older adults had a Pr-H within 1 *SD* of young adult's mean in the subjective task, and 9 older adults reached this criterion in the objective task. Of these, seven older adults performed within 1 *SD* in both the objective and subjective tasks; only these seven older adults were defined as high-performing. A two-way Group by task ANOVA on Pr-H scores confirmed that these high-performers scored as well as young adults in both retrieval tasks; there was no group main effect, *F*(1, 33) = 0.909, *p*=.347, or group by task interaction, *F*(1, 33) = 0.629, *p*=.433. Next we conducted a Group by Task by Thought type mixed ANOVA using this sub-sample of older adults and the full young adult sample. Similar to the ANOVA with the full older adult sample, a highly significant group main effect emerged, *F*(1, 33) = 12.874, *p*=.001, and there was also a Task by Thought type interaction, *F*(1, 33) = 4.18, *p*=.049, and a marginally significant Group by Task by Thought Type interaction, *F*(1,33) = 3.092, *p*=.088. In summary, high-performing older adults performed the memory tasks as well as young adults, but still exhibited reduced frequency of MW and TRI; thus it is unlikely that impaired retrieval can account for the age-related reduction in thought frequency that we observed in the full sample.

4.4.3. Retrieval results

Young adults responded to 99.8% (*SD*=1%) of the retrieval trials in the subjective task, and 97.3% (*SD*=2.7%) of the trials in the objective task. Older adults responded to 98.5% (*SD*=3%) of the trials in the subjective task and 99.2% (*SD*=1%) of the trials in the objective. A two-way age group by task mixed ANOVA revealed that there was no main effect of task, *F*(1, 51) = 3.469, *p*=.068, or age group, *F*(1, 51) = 0.421, *p*=.519, on response rates. However, there was a group by task interaction, *F*(1, 51) = 10.655, *p*=.02, due to young adults responding more often in the subjective task compared to the objective tasks, *T*(1, 27) = 3.519, *p*=.002, but older adults responding equally often in both tasks, *T*(1, 24) = 1.04, *p*=.309.

Retrieval RT are presented in Table 2. A two-way age group by task mixed ANOVA on RT revealed a significant effect of task, *F*(1, 51) = 47.008, *p*<.001, due to both groups responding faster in the subjective versus the objective task. There was also a main effect of age group, due to young adults responding faster overall, *F*(1, 51) = 4.434, *p* = .04. There was no group by task interaction, *F*(1, 51) = 0.596, *p*=.444.

The percentage of hits and false alarms for confident and non-confident responses in young and older adults are presented in Table 3. Retrieval Pr is also presented in this table. Pr-L was near 0 in both groups, indicating that low-confidence responses likely reflected guessing. Therefore assessment of retrieval performance focused only on high confidence (Pr-H) responses. A two-way age group by task mixed ANOVA on Pr-H responses revealed a significant main effect of task, *F*(1, 51) = 62.066, *p*<.001, due to both age groups performing better in the subjective versus the objective encoding task. There was also a main effect of group, *F*(1, 51) = 32.146, *p*<.001, due to young performing better than older adults overall. There was no group by task interaction, *F*(1, 51) = 0.042, *p*=.839.

Table 3
Percentage of hits and false alarms for high and-low confidence responses with standard deviation in parentheses

	Young adults		Older adults	
	Subjective task	Objective task	Subjective task	Objective task
High confidence Hits	0.88 (0.08)	0.80 (0.11)	0.82 (0.11)	0.68 (0.14)
High confidence False alarms	0.06 (0.07)	0.11 (0.08)	0.16 (0.14)	0.17 (0.11)
High Confidence Pr	0.83 (0.10)	0.69 (0.12)	0.65 (0.17)	0.51 (0.15)
Low-confidence hits	0.04 (0.03)	0.07 (0.05)	0.04 (0.05)	0.07 (0.09)
Low-confidence false alarms	0.07 (0.06)	0.1 (0.08)	0.04 (0.06)	0.05 (0.06)
Low-confidence Pr	-0.03 (0.07)	-0.03 (0.08)	-0.01 (0.04)	0.02 (0.06)

4.4.4. Relationship between thought frequency at encoding and retrieval Pr-H: Younger adults' results

In young adults, in the retrieval task for subjectively encoded stimuli, the correlation between Pr-H and TRI was −0.34 (*p*=.065), and the correlation between Pr-H and MW was −0.46 (*p*=.01). We conducted stepwise multiple regression to assess the effect of MW and TRI at encoding on retrieval Pr-H. The multiple regression analysis revealed that a reduced model with only MW provided the best fit for predicting Pr-H for subjectively encoded stimuli, *F*(1, 29) = 7.613, *p*=.01 (Adjusted R-square = 0.186). The addition of TRI did not significantly improve the fit of the model, T = 1.0110, *p*=.321. Figure 1a presents the regression results for the subjective task.

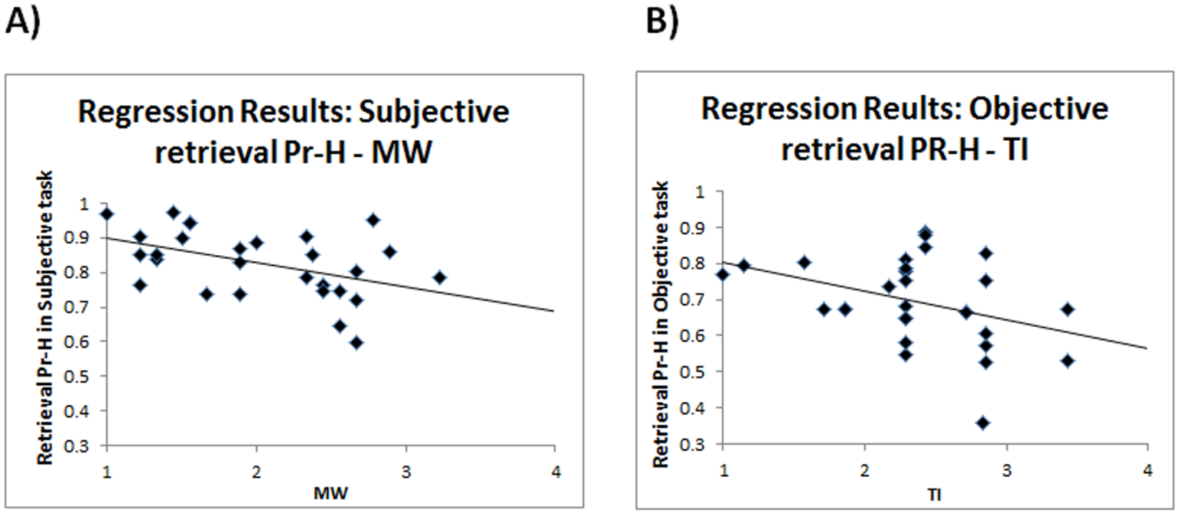

Figure 1 – Regression results in young adults. A) This figure depicts a scatter-plot of subjective retrieval Pr-H (Y-axis) against mind wandering (MW; x-axis). The linear regression line is presented in black. B) This figure depicts a scatter-plot of objective retrieval Pr-H (Y-axis) against task-related interferences (TRI; x-axis). The linear regression line is presented in black.

In the retrieval task for objectively encoded stimuli the correlation between Pr-H and TRI was −0.374 (*p*=.046), and the correlation between Pr-H and MW was −0.008 (*p*=.966). The stepwise multiple regression revealed that a model with only TRI provided the best fit for predicting Pr-H for objectively encoded stimuli, *F*(1, 27) = 4.381, *p*=.046 (Adjusted R-square = 0.108). Figure 1b presents the regression results for the objective task.

4.4.5. Older adults' results

In older adults, during the retrieval task for subjectively encoded stimuli, the correlation between Pr-H and TRI was −0.05 (*p*=.810), and the correlation between Pr-H and MW was −0.162 (*p*=.438). The multiple regression analysis did not identify a significant model for predicting Pr-H in the subjective task. During the retrieval task for objectively encoded stimuli, the correlation between Pr-H and TRI was 0.08 (*p*=.696) and the correlation between Pr-H and MW was 0.16 (*p*=.445). The multiple regression did not identify a significant model for predicting Pr-H in the objective task. However, as previously mentioned, the Shapiro–Wilk test was significant for MW in both the subjective (*p*<.001) and the objective (*p*<.001) tasks in older adults, indicating that the MW scores were not normally distributed. In the subjective tasks 9 older adults did not report MW, and in the objective task 12 older adults did not report any MW. Thus the lack of a relationship between MW and retrieval Pr in older adults may be due to a floor effect.

To address this issue we separated older adults into those who reported no MW versus those who reported at least one instance of MW (Smallwood, Baracaia, et al., 2003). Next we performed an independent sample *T*-test to assess whether those older adults reporting MW performed worse than those reporting no MW. In the subjective task 9 older adults reported no MW, and 16 older adults reported at least one instance of MW. There was no significant difference between the two groups in retrieval Pr-H (mean MW group = 0.67, *SD*=0.14; mean non-MW group = 0.64, *SD*=0.18;*p*=.68). In the objective task 12 older adults reported no MW and 14 reported at least one instance of MW. There was no significant difference between the two groups in retrieval Pr (mean MW group = 0.55, *SD*=0.13; mean non-MW group = 0.48, *SD*=0.18; *p*=.27). Thus, if anything, older adults reporting MW performed slightly better than those reporting no MW in this task.

4.5. Discussion

The purpose of this experiment was to assess the frequency of MW and TRI during objective and subjective encoding tasks, and the impact of these thoughts on subsequent memory retrieval in young and older adults. First, we found that encoding task influenced the type of thought experienced by young, but not older, adults. Young adults exhibited greater TRI in the objective vs subjective encoding task, and exhibited greater MW in the subjective vs the objective task. Second, across both tasks we found a marked age-related decrease in both types of thoughts. There were no age- or task-related differences in RT at encoding, indicating that these difference in thought frequency emerged even if the two groups performed similarly in the encoding tasks. Third, we found that frequency of internal thoughts at encoding negatively impacted memory retrieval in young adults only. We first discuss the results in young adults, and next consider age-related changes in these relationships.

4.5.1. Young adults: Encoding task influences the content of ongoing thoughts

In the current study retrieval performance in young adults was greater when words had been encoded using a subjective versus an objective orienting task. These results are consistent with many other studies which have found that encoding stimuli using a subjective pleasantness judgement results in better memory retrieval compared to other semantic or perceptual judgements (Grady, Bernstein, Beig, & Siegenthaler, 2002; Leshikar & Duarte, 2012; Schott et al., 2011). Neuroimaging studies have demonstrated that this mnemonic benefit is mediated by increased activation in the medial prefrontal cortex (Leshikar & Duarte, 2012; Maillet & Rajah, 2011; Shrager, Kirwan, & Squire, 2008). Activation in this region during successful encoding has also been observed during self-referential encoding tasks, such as judging whether adjectives are descriptive of oneself (Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). Relating material to oneself is thought to be an effective encoding mechanism due to the superior elaborative and organisational properties associated with the concept of self (Rogers et al., 1977; Symons & Johnson, 1997). Thus it is likely that performing a pleasantness judgement results in better memory relative to objective semantic encoding tasks because making such a subjective judgement involves greater elaboration and organisation of the encoding material through one's self schema (Leshikar & Duarte, 2012).

Studies in the MW literature have demonstrated that conditions that bias participants' attention towards themselves, such as mood induction or attention to personal goals increase rates of MW (Seibert & Ellis, 1991; Smallwood et al.,2011; Stawarczyk, Majerus, Maj, et al., 2011). In the current study we examined whether the nature of the encoding task itself (subjective versus objective) could modulate thought content in the same task. We found that this was indeed the case; young adults exhibited increased MW during the subjective versus the objective task. Thus it is possible that making pleasantness judgements, while being an effective way to encode information, also renders participants more prone to having personally salient thoughts about their past or their future. Furthermore, frequency of MW at encoding was negatively correlated with retrieval performance in the subjective task only, indicating that this increase in MW negatively affects memory. Thus, participants performing at a higher level in the subjective task may be those who are able to successfully encode words using the pleasantness judgement, without falling prey to MW that such a judgement can trigger. For example, rating the word “banana” as pleasant at encoding may trigger an internal thought that one should go to the supermarket following the experiment. While such a scenario likely results in effective memory for the word “banana”, it is likely that the subsequent word may not be properly encoded if the participant's attention is not re-focused on the task. It will be important for future studies, particularly those using neuroimaging techniques, to examine the exact mechanisms by which MW at encoding negatively affects memory performance.

On the other hand, young adults exhibited greater TRI in the objective task versus the subjective task. The objective task, in contrast to the subjective one, had a right and a wrong answer (i.e., each word was either man-made or natural). Although the man-made/natural judgement is a relatively easy task, accuracy results for this encoding task show that errors were nevertheless frequent (average of eight per participant). Thus, given that there were a greater number of errors in the objective vs subjective *encoding task* and that *retrieval* performance was lower in the objective vs subjective task, one might argue that the objective encoding task was more difficult than the subjective encoding task. It is likely that this performance component accounts for the increase in TRI and the decrease in MW in this task. It has been suggested that when an error is detected, participants may exhibit thoughts related to self-evaluation and performance, such as thinking about one's ability or the difficulty of the task (Smallwood, Davies, et al., 2004). In addition, frequency of TRI during the objective task was negatively correlated with subsequent high confidence retrieval judgements indicating that they have a detrimental effect on stimulus encoding. These results are consistent with previous studies that have found that higher levels of TRI are associated with worse performance during cognitive tasks (Coy, O'Brien, Tabaczynski, Northern, & Carels, 2011; Smallwood, Davies, et al., 2004).

For example, in one study (Smallwood, Davies, et al., 2004) young adults performed a SART task, and subsequently answered a questionnaire measuring MW and TRI. Participants were divided into low- and high-TRI groups and the high TRI group committed significantly more errors on the SART compared to the low-TRI group.

Orienting tasks at encoding such as the pleasantness judgement and the man-made/natural judgement used in the current experiment are ubiquitously used in behavioural and neuroimaging literatures of episodic memory (for reviews, see Craik, 2002; Kim, 2011; Symons & Johnson, 1997). Taken together, our results indicate that such orienting tasks affect the type of internal thoughts experienced by young adults. Furthermore, this modulation of internal thoughts is behaviourally meaningful, as demonstrated by negative associations with retrieval performance.

4.5.2. Older adults: Reduction in frequency of MW and TRI at encoding

Similar to the results obtained in young adults, older adults exhibited greater retrieval performance for words previously encoded using a subjective versus objective orienting task. As discussed above, this mnemonic benefit is thought to arise from the superior elaborative and organisational properties associated with using one's self schema during memory encoding. Our results are consistent with recent studies that have found that the self-referential effect in memory is preserved in older adults (Dulas, Newsome, & Duarte, 2011; Glisky & Marquine, 2009; Gutchess, Kensinger, & Schacter, 2010; Gutchess, Kensinger, Yoon, & Schacter, 2007; Hamami, Serbun, & Gutchess, 2011). For example, in one study (Hamami et al., 2011), older adults remembered adjectives better when they had been encoded in a self-encoding condition, versus commonness and lower/upper case encoding conditions.

One of the main goals of this study was to determine whether older adults exhibit an increase or a decrease in MW and TRI compared to young adults during memory encoding, and whether age differences in frequency of internal thoughts can account for retrieval deficits in older age. According to the inhibition deficit theory older adults are less able than young to prevent irrelevant information from entering working memory (Hasher & Zacks, 1988). Thus this theory predicts an age-related increase in internal thoughts during memory encoding which may result in a mental clutter detrimental to memory formation. On the other hand, it has been suggested that older adults exhibit reduced attentional resources at encoding (Craik, 1983); thus an alternate possibility is that older adults spend more of their resources than young adults on the encoding task, and have less resources available for MW or TRI (Smallwood & Schooler, 2006). Our results are more consistent with the latter possibility; we observed a marked age-related decrease in MW and TRI across both tasks. Furthermore, the encoding task did not modulate the frequency or type of internal thought in older adults, and frequency of MW/TRI did not correlate with retrieval performance. Note that these results are not necessarily inconsistent with the inhibition deficit theory; if older adults do not have the necessary resources available to generate internal sequences of thought during encoding, then there is no nothing to (fail to) inhibit.

Our hypothesis that the age-related decrease in MW may be replaced by TRI in older adults was not supported. Thus TRI may rely on similar cognitive/neural resources as MW, and both may be reduced in ageing during the performance of cognitively demanding tasks. For example, a recent neuroimaging study found that both TRI and MW are mediated by medial regions of the default-mode network, such as medial prefrontal cortex and posterior cingulate cortex (Stawarczyk, Majerus, Maquet, & D'Argembeau, 2011). In addition, numerous studies have demonstrated age-related changes in default-mode network during memory encoding

(Duverne et al., 2009; Duzel, Schutze, Yonelinas, & Heinze, 2011; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Leshikar, Gutchess, Hebrank, Sutton, & Park, 2010; Miller et al., 2008). Age-related changes in default-mode network may thus represent a common neural mechanism by which both TRI and MW are similarly reduced in older adults.

A limitation of the current study and of our interpretation that there is an age-related decrease in internal thoughts at encoding is that we assessed internal thoughts using a retrospective questionnaire, rather than directly probing participants for their thoughts during task performance. The main advantage of using a retrospective questionnaire is that task performance is uninterrupted; furthermore, constantly probing participants about their internal thoughts may cause them to monitor their thoughts to a greater extent (Smallwood & Schooler, 2006). Using a retrospective questionnaire also allowed us to easily compare MW and TRI rates. However, using a retrospective questionnaire also had disadvantages. First, using this method, we were unable to determine when during the encoding task MW/TRI occurred. Second, given that ageing is associated with reductions in memory retrieval, one explanation for the current findings is that older adults were less able to recall the nature of their internal thoughts compared to young adults. However, two results provide evidence against this interpretation. First, if this was the case, one would expect a *positive* relationship between MW/TRI and retrieval Pr-H, such that those adults with better memory also remember more instances of MW/TRI—this was not the case. Second, rates of MW/TRI were similarly reduced in a sub-group of high-performing older adults that performed the retrieval task as well as young adults. Finally, a recent neuroimaging study measured frequency of internal thoughts while participants were at rest, using a retrospective questionnaire (Mevel et al., 2012). This study reported no age-related differences in internal thought frequency; these results are consistent with our interpretation that reduced internal thought frequency in our study is due to reduced attentional resources during encoding, rather than due to the retrospective method of assessing MW.

Another possibility is that older adults might have been thinking about things that were not covered by the questionnaire (e.g., external distractions). Although we cannot exclude this possibility, our results are best considered along with findings from other studies using the SART or reading paradigms (Jackson & Balota, 2012; Krawietz et al.,2012). In these studies age-related changes in internal thoughts were assessed using the thought probe method; participants were randomly interrupted during task performance and asked whether they had been having thoughts unrelated to the task when they had been interrupted. The thought probe method eliminates reliance on memory, allows the localisation of internal thoughts to a particular point in a task, and is also more open-ended; participants can report any type of thought they had been experiencing. Using this method these studies have also reported an age-related decrease in internal thoughts during the SART and reading tasks (Jackson & Balota, 2012; Krawietz et al.,2012). Taken together, our results and those of others suggest that older adults exhibit a reduction in MW and TRI compared to young in different cognitive tasks, and when different thought sampling procedures are used.

Recent studies have highlighted the importance of considering task interest when examining age differences in MW frequency (Jackson & Balota, 2012; Krawietz et al., 2012). If older adults are more engaged in a task, they may be less likely to exhibit MW. For example, Jackson and colleagues (2012) reported that older adults found the SART to be more interesting than young adults, and task interest negatively correlated with self-reported MW frequency. Krawietz et al. (2012) reported that older adults exhibited less MW compared to young adults during text comprehension, but this age difference became non-significant when controlling for text interest. Consistent with these studies, in the current study older adults rated the memory tasks are significantly more interesting than young adults. However, age differences in MW and TRI frequency remained significant after accounting for this variable. Thus it is unlikely that task interest can fully account for the age-related decrease in internal thoughts observed during memory encoding. Rather, our results are more consistent with the view that the age-related decreases in MW and TRI are due to reduced attentional resources.

4.5.3. Conclusion

To summarise, our study revealed two key results. First, in young adults the orienting task affects the frequency and type of internal thoughts experienced; young exhibited more MW in the pleasantness task, and more TRI in the man-made/natural task. This modulation of internal thoughts is behaviourally relevant, as indexed by negative correlations between thought frequency and retrieval performance in both tasks. Second, older adults exhibit a marked reduction in the frequency of both MW and TRI at encoding. These results are most consistent with an account that memory encoding requires more resources in old versus young adults, leaving fewer resources available for the generation of internal thought.

4.6. References

Addis, D. R., Roberts, R. P., & Schacter, D. L. (2011). Age-related neural changes in autobiographical remembering and imagining. *Neuropsychologia, 49*(13), 3656-3669. doi: 10.1016/j.neuropsychologia.2011.09.021

Aizenstein, H. J., Nebes, R. D., Saxton, J. A., Price, J. C., Mathis, C. A., Tsopelas, N. D., . . . Klunk, W. E. (2008). Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol, 65*(11), 1509-1517. doi: 65/11/1509 [pii]

10.1001/archneur.65.11.1509

Anderson, N. D., Craik, F. I. M., & Naveh-Benjamin, M. (1998). The attentional demands of encoding and retrieval in younger and older adults: 1. Evidence from divided attention costs. *Psychol Aging, 13*(3), 405-423.

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Ann N Y Acad Sci*. doi: 10.1111/nyas.12360

Baddeley, A. (1992). Working memory. *Science, 255*(5044), 556-559.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38. doi: 1124/1/1 [pii]

10.1196/annals.1440.011

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Callard, F., Smallwood, J., & Margulies, D. S. (2012). Default Positions: How Neuroscience's Historical Legacy has Hampered Investigation of the Resting Mind. *Front Psychol, 3*, 321. doi: 10.3389/fpsyg.2012.00321

Carstensen, L. L. (1992). Motivation for social contact across the life span: a theory of socioemotional selectivity. *Nebr Symp Motiv, 40*, 209-254.

Carstensen, L. L., Fung, H. H., & Charles, S. T. (2003). Socioemotional Selectivity Theory and the Regulation of Emotion in the Second Half of Life. *Motivation and Emotion, 27*(2), 103-123.

Catrambone, R., Beike, D., & Niedenthal, P. (1996). Is the Self-Concept a Habitual Referent in Judgments of Similarity? *Psychological Science, 7*, 158-163.

Chalfonte, B. L., & Johnson, M. K. (1996). Feature memory and binding in young and older adults. *Mem Cognit, 24*(4), 403-416.

Christoff, K. (2012). Undirected thought: Neural determinants and correlates. *Brain Res, 1428*, 51-59. doi: S0006-8993(11)01807-5 [pii]

10.1016/j.brainres.2011.09.060

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc Natl Acad Sci U S A, 106*(21), 8719-8724. doi: 0900234106 [pii]

10.1073/pnas.0900234106

Clapp, W. C., & Gazzaley, A. (2012). Distinct mechanisms for the impact of distraction and interruption on working memory in aging. *Neurobiol Aging, 33*(1), 134-148. doi: S0197-4580(10)00042-4 [pii]

10.1016/j.neurobiolaging.2010.01.012

Comblain, C., D'Argembeau, A., Van der Linden, M., & Aldenhoff, L. (2004). The effect of ageing on the recollection of emotional and neutral pictures. *Memory, 12*(6), 673-684. doi: 10.1080/09658210344000477

Cook, J. L. (2014). Task-relevance dependent gradients in medial prefrontal and temporoparietal cortices suggest solutions to paradoxes concerning self/other control. *Neurosci Biobehav Rev*. doi: 10.1016/j.neubiorev.2014.02.007

Craik, F., & Tulving, E. (1975). Depth of Processing and the Retention of Words in Episodic Memory. *Journal of Experimental Psychology: General, 104*(3), 268-294.

Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. *Philosophical Transactions of the Royal Society of London, 302*(1110), 341-358.

Craik, F. I. M. (1991). Memory functions in normal aging. In T. Yanagihara & R. C. Petersen (Eds.), *Memory disorders: Research and clinical practice* New York: Dekker.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of Processing - Framework for Memory Research. *Journal of Verbal Learning and Verbal Behavior, 11*(6), 671-684.

Craik, F. I. M., & Salthouse, T. A. (2000). *The Handbook of Aging and Cognition*. Mahwah, NJ: Lawrence Erlbaum Associates.

D'Argembeau, A. (2013). On the role of the ventromedial prefrontal cortex in self-processing: the valuation hypothesis. *Front Hum Neurosci, 7*, 372. doi: 10.3389/fnhum.2013.00372

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cereb Cortex, 18*(5), 1201-1209. doi: bhm155 [pii]

10.1093/cercor/bhm155

Dennis, N. A., Daselaar, S., & Cabeza, R. (2007). Effects of aging on transient and sustained successful memory encoding activity. *Neurobiol Aging, 28*(11), 1749-1758. doi: S0197-4580(06)00239-9 [pii]

10.1016/j.neurobiolaging.2006.07.006

Diener, E., & Lucas, R. E. (1999). Personality and subjective well-being. In D. Kahneman, E. Diener & N. Schwarz (Eds.), *Well-being: The foundations of hedonic psychology*. New York: Russell Sage Foundation.

Duzel, E., Schutze, H., Yonelinas, A. P., & Heinze, H. J. (2011). Functional phenotyping of successful aging in long-term memory: Preserved performance in the absence of neural compensation. *Hippocampus, 21*(8), 803-814. doi: 10.1002/hipo.20834

Gaesser, B., Sacchetti, D. C., Addis, D. R., & Schacter, D. L. (2011). Characterizing age-related changes in remembering the past and imagining the future. *Psychol Aging, 26*(1), 80-84. doi: 10.1037/a0021054

Giambra, L. M. (1973). Daydreaming in males from seventeen to seventy-seven: A preliminary report. *Proceedings of the Annual Convention of the American Psychological Association*, 769-770.

Giambra, L. M. (1989). Task-unrelated-thought frequency as a function of age: a laboratory study. *Psychol Aging, 4*(2), 136-143.

Gould, O. N., & Dixon, R. A. (1993). How we spent our vacation: Collaborative storytelling by young and older adults. *Psychology and Aging, 6*(93-99).

Grady, C. L., Springer, M. V., Hongwanishkul, D., McIntosh, A. R., & Winocur, G. (2006). Age-related changes in brain activity across the adult lifespan. *J Cogn Neurosci, 18*(2), 227-241. doi: 10.1162/089892906775783705

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A, 100*(1), 253-258. doi: 10.1073/pnas.0135058100

0135058100 [pii]

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A, 98*(7), 4259-4264. doi: 10.1073/pnas.071043098

071043098 [pii]

Gutchess, A. H., Kensinger, E. A., & Schacter, D. L. (2010). Functional neuroimaging of self-referential encoding with age. *Neuropsychologia, 48*(1), 211-219. doi: S0028-3932(09)00360-1 [pii]

10.1016/j.neuropsychologia.2009.09.006

Gutchess, A. H., Kensinger, E. A., Yoon, C., & Schacter, D. L. (2007). Ageing and the self-reference effect in memory. *Memory, 15*(8), 822-837. doi: 783624081 [pii]

10.1080/09658210701701394

Gutchess, A. H., Welsh, R. C., Hedden, T., Bangert, A., Minear, M., Liu, L. L., & Park, D. C. (2005). Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *J Cogn Neurosci, 17*(1), 84-96. doi: 10.1162/0898929052880048

Hasher, L., & Zacks, R. T. (1988a). Working memory, comprehension, and aging: A review and a new view. *The psychology of learning and motivation, 22*, 193-225.

Hasher, L., & Zacks, R. T. (1988b). Workng memory, comprehension, and aging: a review and a new view. *The psychology of learning, 22*, 193-225.

Hashtroudi, S., Johnson, M. K., & Chrosniak, L. D. (1990). Aging and qualitative characteristics of memories for perceived and imagined complex events. *Psychol Aging, 5*(1), 119-126.

Hashtroudi, S., Johnson, M. K., Vnek, N., & Ferguson, S. A. (1994). Aging and the effects of affective and factual focus on source monitoring and recall. *Psychol Aging, 9*(1), 160-170.

Jackson, J. D., & Balota, D. A. (2012). Mind-wandering in younger and older adults: Converging evidence from the sustained attention to response task and reading for comprehension. *Psychol Aging, 27*(1), 106-119. doi: 2011-13120-001 [pii]

10.1037/a0023933

Jorm, A. F. (2000). Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. *Psychol Med, 30*(1), 11-22.

Kennedy, K. M., Rodrigue, K. M., Devous, M. D., Sr., Hebrank, A. C., Bischof, G. N., & Park, D. C. (2012). Effects of beta-amyloid accumulation on neural function during encoding across the adult lifespan. *Neuroimage, 62*(1), 1-8. doi: 10.1016/j.neuroimage.2012.03.077

Kensinger, E. A., & Schacter, D. L. (2008). Neural processes supporting young and older adults' emotional memories. *J Cogn Neurosci, 20*(7), 1161-1173. doi: 10.1162/jocn.2008.20080

Killingsworth, M. A., & Gilbert, D. T. (2010). A wandering mind is an unhappy mind. *Science, 330*(6006), 932. doi: 330/6006/932 [pii]

10.1126/science.1192439

Kim, H. (2011). Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. *Neuroimage, 54*(3), 2446-2461. doi: 10.1016/j.neuroimage.2010.09.045

Klinger, E. (2013). Goal Commitments and the content of thoughts and dreams: basic principles. *Front Psychol, 4*, 415. doi: 10.3389/fpsyg.2013.00415

Klinger, E., Gregoire, K. C., & Barta, S. G. (1973). Physiological correlates of mental activity: eye movements, alpha, and heart rate during imagining, suppression, concentration, search, and choice. *Psychophysiology, 10*(5), 471-477.

Kukolja, J., Thiel, C. M., Wilms, M., Mirzazade, S., & Fink, G. R. (2009). Ageing-related changes of neural activity associated with spatial contextual memory. *Neurobiol Aging, 30*(4), 630-645. doi: S0197-4580(07)00336-3 [pii]

10.1016/j.neurobiolaging.2007.08.015

Legrand, D., & Ruby, P. (2009). What is self-specific? Theoretical investigation and critical review of neuroimaging results. *Psychol Rev, 116*(1), 252-282. doi: 2009-00258-009 [pii]

10.1037/a0014172

Leshikar, E. D., & Duarte, A. (2012). Medial prefrontal cortex supports source memory accuracy for self-referenced items. *Soc Neurosci, 7*(2), 126-145. doi: 10.1080/17470919.2011.585242

Leshikar, E. D., Gutchess, A. H., Hebrank, A. C., Sutton, B. P., & Park, D. C. (2010). The impact of increased relational encoding demands on frontal and hippocampal function in older adults. *Cortex, 46*(4), 507-521. doi: S0010-9452(09)00225-1 [pii]

10.1016/j.cortex.2009.07.011

Liu, P., Hebrank, A. C., Rodrigue, K. M., Kennedy, K. M., Section, J., Park, D. C., & Lu, H. (2013). Age-related differences in memory-encoding fMRI responses after accounting for decline in vascular reactivity. *Neuroimage, 78*, 415-425. doi: 10.1016/j.neuroimage.2013.04.053

Macrae, C. N., Moran, J. M., Heatherton, T. F., Banfield, J. F., & Kelley, W. M. (2004). Medial prefrontal activity predicts memory for self. *Cereb Cortex, 14*(6), 647-654. doi: 10.1093/cercor/bhh025

bhh025 [pii]

Maillet, D., & Rajah, M. N. (2013). Association between prefrontal activity and volume change in prefrontal and medial temporal lobes in aging and dementia: a review. *Ageing Res Rev, 12*(2), 479-489. doi: 10.1016/j.arr.2012.11.001

Malinowski, P. (2013). Neural mechanisms of attentional control in mindfulness meditation. *Front Neurosci, 7*, 8. doi: 10.3389/fnins.2013.00008

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science, 315*(5810), 393-395. doi: 315/5810/393 [pii]

10.1126/science.1131295

Mather, M. (2012). The emotion paradox in the aging brain. *Ann N Y Acad Sci, 1251*, 33-49. doi: 10.1111/j.1749-6632.2012.06471.x

Mather, M., & Carstensen, L. L. (2005). Aging and motivated cognition: the positivity effect in attention and memory. *Trends Cogn Sci, 9*(10), 496-502. doi: S1364-6613(05)00237-8 [pii]

10.1016/j.tics.2005.08.005

Mather, M., & Knight, M. (2005). Goal-directed memory: the role of cognitive control in older adults' emotional memory. *Psychol Aging, 20*(4), 554-570. doi: 2006-00628-003 [pii]

10.1037/0882-7974.20.4.554

McVay, J. C., & Kane, M. J. (2009). Conducting the train of thought: working memory capacity, goal neglect, and mind wandering in an executive-control task. *J Exp Psychol Learn Mem Cogn, 35*(1), 196-204. doi: 10.1037/a0014104

McVay, J. C., & Kane, M. J. (2010). Does mind wandering reflect executive function or executive failure? Comment on Smallwood and Schooler (2006) and Watkins (2008). *Psychol Bull, 136*(2), 188-197; discussion 198-207. doi: 10.1037/a0018298

McVay, J. C., & Kane, M. J. (2012). Why does working memory capacity predict variation in reading comprehension? On the influence of mind wandering and executive attention. *J Exp Psychol Gen, 141*(2), 302-320. doi: 10.1037/a0025250

Mol, M., Carpay, M., Ramakers, I., Rozendaal, N., Verhey, F., & Jolles, J. (2007). The effect of perceived forgetfulness on quality of life in older adults; a qualitative review. *Int J Geriatr Psychiatry, 22*(5), 393-400. doi: 10.1002/gps.1686

Mormino, E. C., Brandel, M. G., Madison, C. M., Marks, S., Baker, S. L., & Jagust, W. J. (2011). A{beta} Deposition in Aging Is Associated with Increases in Brain Activation during Successful Memory Encoding. *Cereb Cortex*. doi: bhr255 [pii]

10.1093/cercor/bhr255

Naveh-Benjamin, M. (2000). Adult age differences in memory performance: tests of an associative deficit hypothesis. *J Exp Psychol Learn Mem Cogn, 26*(5), 1170-1187.

Northoff, G. (2011). Self and brain: what is self-related processing? *Trends Cogn Sci, 15*(5), 186-187; author reply 187-188. doi: S1364-6613(11)00036-2 [pii]

10.1016/j.tics.2011.03.001

Northoff, G., Qin, P., & Feinberg, T. E. (2011). Brain imaging of the self--conceptual, anatomical and methodological issues. *Conscious Cogn, 20*(1), 52-63. doi: S1053-8100(10)00177-7 [pii]

10.1016/j.concog.2010.09.011

Northoff, G., Qin, P., & Nakao, T. (2010). Rest-stimulus interaction in the brain: a review. *Trends Neurosci, 33*(6), 277-284. doi: S0166-2236(10)00031-7 [pii]

10.1016/j.tins.2010.02.006

Oh, H., & Jagust, W. J. (2013). Frontotemporal Network Connectivity during Memory Encoding Is Increased with Aging and Disrupted by Beta-Amyloid. *J Neurosci, 33*(47), 18425-18437. doi: 10.1523/JNEUROSCI.2775-13.2013

Park, D. C., & Gutchess, A. H. (2005). Long-term Memory and Aging: A Cognitive Neuroscience Perspective. In R. Cabeza (Ed.), *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. NY: Oxford Press.

Park, H., Kennedy, K. M., Rodrigue, K. M., Hebrank, A., & Park, D. C. (2013). An fMRI study of episodic encoding across the lifespan: changes in subsequent memory effects are evident by middle-age. *Neuropsychologia, 51*(3), 448-456. doi: 10.1016/j.neuropsychologia.2012.11.025

Pihlajamaki, M., & Sperling, R. A. (2009). Functional MRI assessment of task-induced deactivation of the default mode network in Alzheimer's disease and at-risk older individuals. *Behav Neurol, 21*(1), 77-91. doi: R6331X54T779523W [pii]

10.3233/BEN-2009-0231

Pike, K. E., Savage, G., Villemagne, V. L., Ng, S., Moss, S. A., Maruff, P., . . . Rowe, C. C. (2007). Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain, 130*(Pt 11), 2837-2844. doi: 10.1093/brain/awm238

Powers, C. B., Wisocki, P. A., & Whitbourne, S. K. (1992). Age differences and correlates of worrying in youth and elderly adults. *The Gerontologist, 32*, 82-88.

Qin, P., & Northoff, G. (2011). How is our self related to midline regions and the default-mode network? *Neuroimage, 57*(3), 1221-1233. doi: S1053-8119(11)00516-7 [pii]

10.1016/j.neuroimage.2011.05.028

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682. doi: 10.1073/pnas.98.2.676

98/2/676 [pii]

Rajah, M. N., Ames, B., & D'Esposito, M. (2008). Prefrontal contributions to domain-general executive control processes during temporal context retrieval. *Neuropsychologia, 46*(4), 1088-1103. doi: S0028-3932(07)00370-3 [pii]

10.1016/j.neuropsychologia.2007.10.023

Rajah, M. N., & D'Esposito, M. (2005). Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain, 128*(Pt 9), 1964-1983. doi: awh608 [pii]

10.1093/brain/awh608

Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., . . . Villemagne, V. L. (2007). Imaging beta-amyloid burden in aging and dementia. *Neurology, 68*(20), 1718-1725. doi: 10.1212/01.wnl.0000261919.22630.ea

Roy, M., Shohamy, D., & Wager, T. D. (2012). Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn Sci, 16*(3), 147-156. doi: 10.1016/j.tics.2012.01.005

Schooler, J. W., Smallwood, J., Christoff, K., Handy, T. C., Reichle, E. D., & Sayette, M. A. (2011). Meta-awareness, perceptual decoupling and the wandering mind. *Trends Cogn Sci, 15*(7), 319-326. doi: 10.1016/j.tics.2011.05.006

Schott, B. H., Wustenberg, T., Wimber, M., Fenker, D. B., Zierhut, K. C., Seidenbecher, C. I., . . . Richardson-Klavehn, A. (2011). The relationship between level of processing and hippocampal-cortical functional connectivity during episodic memory formation in humans. *Hum Brain Mapp, 34*(2), 407-424. doi: 10.1002/hbm.21435

Seibert, P. S., & Ellis, H. C. (1991). Irrelevant thoughts, emotional mood states, and cognitive task performance. *Mem Cognit, 19*(5), 507-513.

Shrager, Y., Kirwan, C. B., & Squire, L. R. (2008). Activity in both hippocampus and perirhinal cortex predicts the memory strength of subsequently remembered information. *Neuron, 59*(4), 547-553.

Shulman, G. L., Fiez, J. A., Buckner, R. L., Miezin, F. M., Raichle, M. E., & Peterson, S. E. (1997). Common blood flow changes across visual tasks: II.: decreases in cerebral cortex. *Journal of Cognitive Neuroscience, 9*, 648-663.

Smallwood, J. (2013). Distinguishing how from why the mind wanders: a process-occurrence framework for self-generated mental activity. *Psychol Bull, 139*(3), 519-535. doi: 10.1037/a0030010

Smallwood, J., & Andrews-Hanna, J. (2013). Not all minds that wander are lost: the importance of a balanced perspective on the mind-wandering state. *Front Psychol, 4*, 441. doi: 10.3389/fpsyg.2013.00441

Smallwood, J., Baracaia, S. F., Lowe, M., & Obonsawin, M. (2003). Task unrelated thought whilst encoding information. *Conscious Cogn, 12*(3), 452-484. doi: S1053810003000187 [pii]

Smallwood, J., Brown, K., Baird, B., & Schooler, J. W. (2011). Cooperation between the default mode network and the frontal-parietal network in the production of an internal train of thought. *Brain Res*. doi: S0006-8993(11)00667-6 [pii]

10.1016/j.brainres.2011.03.072

Smallwood, J., & Schooler, J. W. (2006). The restless mind. *Psychol Bull, 132*(6), 946-958. doi: 2006-20202-006 [pii]

10.1037/0033-2909.132.6.946

Spencer, W. D., & Raz, N. (1995). Differential effects of aging on memory for content and context: a meta-analysis. *Psychol Aging, 10*(4), 527-539.

Sperling, R. A., Laviolette, P. S., O'Keefe, K., O'Brien, J., Rentz, D. M., Pihlajamaki, M., . . . Johnson, K. A. (2009). Amyloid deposition is associated with impaired default network function in older persons without dementia. *Neuron, 63*(2), 178-188. doi: S0896-6273(09)00505-4 [pii]

10.1016/j.neuron.2009.07.003

Stawarczyk, D., Majerus, S., Maj, M., Van der Linden, M., & D'Argembeau, A. (2011). Mind-wandering: phenomenology and function as assessed with a novel experience sampling method. *Acta Psychol (Amst), 136*(3), 370-381. doi: S0001-6918(11)00003-5 [pii]

10.1016/j.actpsy.2011.01.002

Stawarczyk, D., Majerus, S., Maquet, P., & D'Argembeau, A. (2011). Neural correlates of ongoing conscious experience: both task-unrelatedness and stimulus-independence are related to default network activity. *PLoS One, 6*(2), e16997. doi: 10.1371/journal.pone.0016997

Symons, C. S., & Johnson, B. T. (1997). The self-reference effect in memory: a meta-analysis. *Psychol Bull, 121*(3), 371-394.

Szpunar, K. K., Moulton, S. T., & Schacter, D. L. (2013). Mind wandering and education: from the classroom to online learning. *Front Psychol, 4*, 495. doi: 10.3389/fpsyg.2013.00495

Todd, R. M., Cunningham, W. A., Anderson, A. K., & Thompson, E. (2012). Affect-biased attention as emotion regulation. *Trends Cogn Sci, 16*(7), 365-372. doi: 10.1016/j.tics.2012.06.003

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of memory* (pp. 381-403). New York: Academic Press.

Tulving, E. (2002). Episodic memory: from mind to brain. *Annu Rev Psychol, 53*, 1-25. doi: 10.1146/annurev.psych.53.100901.135114

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., . . . Buckner, R. L. (1998). Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*(5380), 1188-1191.

Zierhut, K., Bogerts, B., Schott, B., Fenker, D., Walter, M., Albrecht, D., . . . Schiltz, K. (2010). The role of hippocampus dysfunction in deficient memory encoding and positive symptoms in schizophrenia. *Psychiatry Res, 183*(3), 187-194. doi: S0925-4927(10)00108-3 [pii]

10.1016/j.pscychresns.2010.03.007

4.7. Suffix

The finding of an age-related decrease in TUT frequency during episodic encoding provides evidence against one of the most common interpretations of age-related increases in mFC during in the fMRI literature: that it reflects an age-related increases in TUT, or a reduction in concentration. This suggested to me that there was a need to revisit these earlier findings, and look for alternate interpretations. I thought that the best way to systematically review earlier findings was through a quantitative meta-analysis, which is what I did in the next study.

5. Study 4: Age-related differences in brain activity during the subsequent memory paradigm: a meta-analysis

5.1. Abstract

Healthy aging is associated with declines in episodic memory. This reduction is thought to be due in part to age-related differences in encoding-related processes. In the current study, we performed an activation likelihood estimation meta-analysis of functional magnetic resonance imaging (fMRI) studies assessing age-related changes in the neural correlates of episodic encoding. Only studies using the subsequent memory paradigm were included. We found age-related under-recruitment of occipital and fusiform cortex, but over-recruitment in a set of regions including bilateral middle/superior frontal gyri, anterior medial frontal gyrus, precuneus and left inferior parietal lobe. We demonstrate that all of the regions consistently over-recruited by older adults during successful encoding exhibit either direct overlap, or occur in close vicinity to regions consistently involved in encoding failure in young adults. We discuss the possibility that this overall pattern of age-related differences represent an age-related shift in focus: away from perceptual details, and towards evaluative and personal thoughts and feelings during memory tasks. We discuss whether these age-related differences benefit performance in older adults, and additional considerations.

5.2. Introduction

Healthy aging is associated with declines in episodic memory (Craik and Salthouse, 2000). Furthermore, memory difficulties represent the most common cognitive complaint in older adults and can diminish their quality of life (Mol et al., 2007). In recent years, many studies have used functional magnetic resonance imaging (fMRI) to examine the neural correlates of episodic memory decline in healthy aging. These studies have typically focused on two stages: encoding and retrieval. In the current study, we focus exclusively on age-related changes in episodic encoding.

Studies assessing age-related changes in fMRI activation have mostly used the subsequent memory paradigm, in which activity related to subsequently remembered events is contrasted against activity related to subsequently forgotten ones. Many of these studies have reported that older adults exhibit reduced activation in various brain regions during successful encoding compared to young adults (age-related under-recruitment). For example, in a study of age-related differences in encoding of pictures of outdoor scenes, Gutchess et al. (2005) reported under-recruitment of bilateral lateral occipital cortex and bilateral parahippocampal gyrus in older versus young adults. Age-related decreases in activity are often observed when older adults perform significantly worse than young adults on memory tasks and is thus thought to reflect older adults' deficit in utilizing some cognitive process to the same extent as young adults.

An equally consistent finding in prior fMRI studies of episodic memory is that older adults activate some brain regions to a greater degree than young adult during encoding (age-related over-recruitment). For example, in addition to reporting age-related under-recruitment in occipital and medial temporal lobes, Gutchess et al. (2005) also reported greater activity in bilateral middle/superior frontal gyri (MFG/SFG) and anterior medial FG in older vs. younger adults. In contrast with under-recruitment, there is no straightforward explanation for why older adults would over-recruit some brain regions to perform a task that they do not perform as well as young adults. In their paper, Gutchess et al. (2005) suggested that at least some of the age-related over-recruitment in prefrontal cortex (PFC) may reflect attempted compensation for reduced activation in parahippocampal gyrus.

A variety of theoretical models have been put forward to explain age-related over-recruitment (Cabeza, 2002; Davis et al., 2008; Dennis and Cabeza, 2012; Greenwood, 2007; Maillet and Rajah, 2013b; Park and Reuter-Lorenz, 2009; Rajah and D'Esposito, 2005; Reuter-Lorenz and Cappell, 2008). In general, these models are not specific to episodic memory encoding, but rather attempt to explain this phenomenon across a range of distinct cognitive tasks. In addition, the majority of these models have focused on the PFC as the primary site of age-related over-recruitment, and have suggested that over-recruitment may reflect attempted compensation for declines in other brain regions in the aging brain. For example, the posterior-anterior shift in aging (PASA) model suggests that across different cognitive tasks, PFC over-recruitment may compensate for declines in posterior brain regions, such as occipital cortex (Davis et al., 2008), a proposal similar to the one by Gutchess et al. (2005) in their study of episodic encoding. Another model, the scaffolding theory of aging and cognition, suggests that over-recruitment in older adults represent neural scaffolds, "additional circuitry that shores up declining structures whose functioning has be-come noisy, inefficient, or both" (p. 183; Park and Reuter-Lorenz, 2009). The PFC is thought to be the primary site of scaffolds, due its versatile and flexible nature. Specifically, the PFC is thought to compensate for declines in functioning in the hippocampus, visual processing regions and the default-mode network (Park and Reuter-Lorenz, 2009).

Although these models provide a useful starting point to understanding age-related over-recruitment, a number of outstanding questions remain within the domain of episodic encoding. First, it remains unclear if specific sub-regions of PFC are consistently over-activated by older adults, or if this over-recruitment is observed throughout the PFC. Some studies suggest that age-related over-recruitment is observed in a specific subset of PFC regions. For example, Gutchess et al. (2005) reported age-equivalent activation in IFG; and over-recruitment in bilateral MFG/SFG and medial FG. Morcom et al. (2003) reported age-equivalent activation in left IFG and MFG, but age-related over-recruitment in bilateral anterior SFG. These findings indicate that only a subset of PFC regions may be over-activated by older adults; yet theoretical models of age-related over-recruitment generally do not make predictions regarding specific regions of PFC. Second, although the PFC has been the main focus of theories of age-related over-recruitment and of individual studies of episodic memory encoding, it remains unclear if PFC is the only region in which older adults consistently exhibit over-recruitment. For example, in

Morcom et al. (2003), older adults over-recruited not only bilateral anterior SFG, but also left inferior parietal lobe and medial occipital cortex. In Gutchess et al. (2005), in addition to bilateral MFG/SFG and medial FG, older adults also over-recruited bilateral inferior parietal lobes.

Identifying which brain regions, both in PFC and outside PFC are consistently over-recruited by older adults may be important for understanding which specific component cognitive processes older adults may be utilizing to a greater degree than young adults during episodic encoding. In young adults, different brain regions are thought to be involved in different component processes during episodic encoding. For example, in a recent meta-analysis of studies using the subsequent memory paradigm in young adults, it was reported that bilateral IFG/MFG, bilateral medial temporal lobes (MTL), bilateral occipital/fusiform gyri and bilateral superior parietal cortex are involved in successful encoding (Kim, 2011b). The left IFG was primarily engaged in studies using verbal materials, prompting the author to suggest this region may be involved in controlled semantic/phonological analysis. A posterior region of the IFG was recruited to a greater extent when encoding was associative (e.g. item-context or item-item associations), prompting the author to suggest that this region may be involved in organizational processes. On the other hand, a distinct set of regions including the medial FG, bilateral SFG, posterior cingulate/precuneus, inferior parietal lobes and lingual gyrus were recruited to a greater extent in subsequently forgotten vs. remembered events. The author suggested that these regions may be involved in internally-directed attention detrimental to encoding processes. Consistent with this proposal, we found in a recent study that many of these regions including bilateral MFG/SFG, posterior cingulate and lingual gyrus were activated during encoding events directly preceding reports of task-unrelated thoughts (TUT) such as mind-wandering in young adults

(Maillet and Rajah, 2013c). Therefore, assuming that distinct brain regions are involved in specific component processes during episodic encoding in young adults, and assuming relative preservation of the relationship between a brain region and its role in cognition with aging, identifying precisely which brain regions are consistently over-recruited by older adults may yield insight into which cognitive processes are up-regulated in older age.

In the current study, we performed a quantitative activation likelihood estimation (ALE) meta-analysis of age-related differences in brain activation to identify consistent differences in brain activation during successful encoding. One previous quantitative meta-analysis of age-related changes in brain activation at encoding was conducted by Spreng et al. (2010). In this meta-analysis, it was reported that older adults under-recruited left posterior MFG, putamen, and right medial temporal lobe (MTL), but over-recruited right postcentral gyrus compared to young adults. In addition to including new studies that have been published since this prior work, our meta-analysis differs in another, critical aspect: while the previous meta-analysis included coordinates from all encoding studies regardless of which contrast was used in these studies, we only included studies that have used the subsequent memory paradigm. This is important, since the different contrasts used in distinct studies are sensitive to different aspects of cognitive processing. For example, contrasting the brain activity observed during subsequently remembered vs. forgotten events does not target the same cognitive processes as contrasting the brain activity observed during encoding using a perceptual vs. a semantic encoding task, or contrasting brain activity during relational vs. non-relational encoding. This could potentially have diluted the effects found in (Spreng et al., 2010). Enough studies using the subsequent memory paradigm have now been published to restrict the meta-analysis to these studies. Therefore, it is now possible to specifically identify neural activation differentiating subsequently remembered vs. forgotten encoding events in older versus younger adults using a quantitative meta-analysis.

Given our specific focus on age-related differences in brain activation during successful vs. unsuccessful encoding, we predict our results will differ from those previously reported by Spreng et al. (2010). Based on the findings of studies discussed earlier (Gutchess et al., 2005; Morcom et al., 2003), as well as others (e.g., de Chastelaine et al., 2011; Duzel et al., 2011), we predicted that older adults would exhibit over-activation in only a subset of PFC regions, including SFG and anterior medial FG. Secondly, we predicted that older adults would also over-recruit regions outside of PFC, including medial and lateral parietal cortex. Finally, to better understand the cognitive processes subserved by the brain regions over-recruited by older adults, we examined the overlap between the regions over-recruited by older adults and those recruited by young adults in subsequent memory studies.

5.3. Methods

5.3.1. Study selection

We performed a literature search using Pubmed to find fMRI papers published before January 1st 2014 that had examined age-related differences in activation at encoding with the subsequent memory paradigm. The following keywords were used in the literature review: aging/age, fMRI, encoding, subsequent memory. The following inclusion criteria were employed in selecting papers for this meta-analysis: 1) The paper had to report whole-brain activation data comparing brain activation between young and older adults. Papers reporting activation data on only one part of the brain or on specific regions of interest (ROIs) were excluded. Additionally, papers reporting only within-group results were excluded. 2) The paper had to use a subsequent memory contrast, that is, a contrast comparing successful vs. unsuccessful encoding events. Coordinates from ROI analyses (typically conducted at lower thresholds in either MTL or right inferior/middle FG) were excluded, even if they displayed a subsequent memory effect, since these introduce a bias in the meta-analysis.

Three studies using the subsequent paradigm were excluded for the following reasons. The studies of (Fischer et al., 2010) and (Morcom et al., 2010) were excluded because of the use of ROIs. The study by (Gutchess et al., 2010) was excluded because this study reported subsequent memory effects that were reversed across tasks and age groups, and although interesting, it was unclear to us how to meaningfully enter this data in the meta-analysis. To limit the contribution of any particular study, we only included one contrast per study. When an arbitrary decision had to be made regarding which contrast to include, the first contrast reported in the paper was used. We converted peaks reported in Talairach to MNI space using the conversion tools implemented in GingerALE. Specifically, papers that had normalised their data to an MNI template and converted their stereotaxic coordinates using the Brett (mni2tal) transform were re-converted to MNI space using the inverse algorithm. The coordinates from studies that normalised their data to a Talairach template (e.g. those using AFNI) were converted to MNI space using the Lancaster (icbm2tal) transform (Laird et al., 2010; Lancaster et al., 2007). When there was uncertainty regarding the stereotaxic space in which coordinates were reported for a particular study, we contacted the authors for clarification. In total, we found 18 studies that met our inclusion criteria (Table 1).

5.3.2. ALE analyses

We used the software GingerALE (version 2.3.1) to perform a quantitative meta-analysis of activation foci (Eickhoff et al., 2009; Laird et al., 2009). ALE allows the identification of regions consistently activated across distinct experiments. In ALE, individual activation foci in a study are treated as spatial probability distributions centered around the peak coordinate. The FHWM of the probability distribution is calculated automatically according to each study's sample size so that more weight is given to studies with higher sample sizes. Each experiment's probability distributions are combined to form a "modeled activation" map for each study (Eickhoff et al., 2009). The combination of these modeled activation maps across all studies on a voxel-wise basis generates ALE scores. In the current meta-analysis, we thresholded all ALE analyses at a false-discovery rate (FDR) of $p<0.01$. This threshold is as conservative (Spreng et al., 2010) or more conservative (Kim, 2011a, b; Schwindt and Black, 2009; Spaniol et al., 2009; Turner and Spreng, 2011) than the thresholds used in previous ALE meta-analyses in the field of aging and/or episodic memory. Additionally, the "pN" option for FDR was chosen, which makes no assumptions about how the data is correlated (more conservative option). We initially set the cluster threshold for all ALE analyses at 50mm3. After each ALE is run, GingerALE recommends a minimum threshold to be used based on the false discovery rate and the total volume above threshold. The resulting minimum volume is calculated so as to remove any cluster smaller than the allowed false positives, leaving only activations that should be true positives. We report the recommended minimum cluster threshold for all analyses, and only report results above this threshold.

Three ALE analyses were performed. First, we assessed brain regions which were commonly recruited during successful>unsuccessful encoding in young and older adults by including coordinates from all studies reporting between-group similarities in brain activity. Second, we assessed brain regions exhibiting an age-related reduction in activation by examining the coordinates from all studies reporting between-group young > old adult contrasts. Finally, we assessed regions exhibiting an age-related increase in activation by examining the coordinates from all studies reporting between-group old>young adult contrasts.

One of the objectives of the current meta-analysis was to determine whether old>young effects overlap with regions commonly recruited by young adults during episodic encoding tasks. After performing the old>young adult ALE, we noticed a similarity between the effects observed and regions recruited by young adults during unsuccessful>successful encoding in the meta-analysis of Kim (2011b) (see results). To determine the extent of this similarity, we performed an additional ALE analysis of unsuccessful>successful encoding effects in young adults. All the 17 studies included in the original meta-analysis by Kim were included. The details of these studies can be found in the original paper. In addition, we included coordinates from four additional studies included in the between-group ALE analysis that also reported unsuccessful vs. successful encoding effects in young adults (de Chastelaine et al., 2011; Duzel et al., 2011; Kukolja et al., 2009; Park et al., 2013). Thus, in total, 21 studies were included in this additional ALE analysis. GingerALE 2.3.1 offers a new feature which allows the calculation of conjunctions among two different ALE maps. Thus, as a final step, we calculated the conjunction between the old>young adults ALE results from the current meta-analysis and the unsuccessful>successful ALE in young adults reported by Kim et al., and in the aforementioned additional papers. That is, we calculated the overlap between regions over-activated by older adults during successful encoding and the regions activated to a greater extent during unsuccessful>successful encoding in young adults.

5.4. Results

5.4.1. Study characteristics

On average, the studies included in this meta-analysis had a sample size of 18.17 young adults and 19.56 older adults, t(1,34)=0.333, p=0.74. The average age of young and older adults of the studies reporting this value was 22.8 and 69.5, respectively (t(1,32)=39, p<0.001. The encoding stimuli used in the contrasts included from these studies were: words in 5 studies (de Chastelaine et al., 2011; Dennis et al., 2007; Duverne et al., 2009; Kim and Giovanello, 2011; Morcom et al., 2003), pictures of objects in 4 studies (Kensinger and Schacter, 2008; Kukolja et al., 2009; Leshikar and Duarte, 2013; St Jacques et al., 2009), scenes in 4 studies (Duzel et al., 2011; Gutchess et al., 2005; Oh and Jagust, 2013; Park et al., 2013) faces in 2 studies (Dennis et al., 2008; Stevens et al., 2008), face-name pairs in 2 studies (Bangen et al., 2012; Miller et al., 2008), or both words and pictures of objects in 1 study (Dulas and Duarte, 2011). In 11 studies, participants encoded only single items (Dennis et al., 2007; Dennis et al., 2008; Duverne et al., 2009; Duzel et al., 2011; Gutchess et al., 2005; Kensinger and Schacter, 2008; Morcom et al., 2003; Oh and Jagust, 2013; Park et al., 2013; St Jacques et al., 2009; Stevens et al., 2008), in 3 studies they encoded item-context associations (Dulas and Duarte, 2011; Kukolja et al., 2009; Leshikar and Duarte, 2013), and in 4 studies, they encoded item-item associations (Bangen et al., 2012; de Chastelaine et al., 2011; Kim and Giovanello, 2011; Miller et al., 2008). The encoding task used in each experiment is listed in Table 1.

Table 1: Details of studies included in the meta-analysis

Study	Subjects	Age	FMRI Encoding Task	FMRI Contrast
Bangen, 2012	9YA, 10OA	26.89, 75.6	Determine if face-name pairs are old or new	Events given 'Remember' judgement vs. all others
de Chastela	18YA, 36OA	21, 70	Determine which word of a word-pair is more likely to	Study pairs endorsed as intact (hit) vs. study pairs identified as rearranged (miss)

ine, 2011			fit into the other	
Dennis, 2007	12YA, 12OA	22.2, 67.4	Determine which semantic category a word fits into	Parametric modulation of subsequent memory (high confidence hit > low confidence hit > forgotten)
Dennis, 2008	14YA, 14OA	19.4, 68.4	Determine if current face stimulus is the same as the one presented 2 stimuli ago	High confidence hits vs. low-confidence hits and misses
Dulas, 2011	16YA, 14OA	24.13, 65.86	Determine whether object or word stimuli would fit into a shoebox, or whether they are living/non-living	Source hits vs. incorrect source and don't know source trials
Duverne, 2009	16YA, 32OA	22, 69	Animate/inanimate judgement on word stimuli	Confident Hit vs. misses
Duzel, 2011	24YA, 13OA High FADE	23, 65	Indoor/outdoor judgement on image stimuli	Hits vs. misses
Gutchess, 2005	14 YA, 13OA	21, 70	Determine whether picture stimuli contained water	High confidence hits vs. misses
Kensinger, 2008	17YA, 17OA	21.6, 73.3	Determine whether positive, negative or neutral object stimuli would fit inside a filing cabinet drawer	Hits ("Same" or "similar" judgement) vs. misses
Kim, 2011	13YA, 12OA	20.9, 74.8	Intentional encoding of word pairs under full attention	Hits ("together" responses) vs. misses ("separate" responses)
Kukolja, 2009	18YA, 17OA	23.9, 59	Natural/artificial judgement	Spatial context hit vs. miss
Leshikar, 2013	19YA, 19OA	22.4, 64.5	Pleasantness judgement (self or other)	Source hit vs. source miss
Miller, 2008	17YA, 17OA	23.9, 74.9	Determine whether the name is a good "fit" for the face	High confidence hits vs. misses
Morcom, 2003	14YA, 14OA	21, 68	Animate/inanimate judgement on word stimuli	High confidence hits vs. low confidence hits and misses
Oh, 2013	15YA, 23 PIB -	23.2, 75.6	Determine whether picture stimuli contained water	High confidence hits vs. misses

	OA			
Park, 2013	64 YA, 64 MA, 64 OA	20-39, 40-59, 60-79	Determine whether picture stimuli contained water	High confidence hits vs. misses
St Jacques, 2009	15YA, 15OA	24.8, 70.2	Negative/neutral/positive judgement on picture stimuli	Greater subsequent memory effects for negative vs. neutral pictures
Stevens, 2008	12YA, 10 OA	26.4, 70.3	Determine if face stimuli are old/high confidence, old/low confidence or new	High confidence hits vs. low confidence hits and misses

Note. Listing of the 18 fMRI studies on age-related changes in subsequent memory included in the meta-analysis. The first column lists the first author and year of publication. Column 2 lists the sample size used in the study (YA = young adults; MA= middle-age adults; OA = older adults). The third column presents the mean age of the YA sample (listed first) and the OA sample. Column 4 lists the encoding task employed in the study and the last column lists the fMRI contrast in each study.

5.4.2. ALE of age-invariant effects

Eleven experiments reported between-group similarity contrasts for a total of 142 activation peaks. The ALE indicated that young and older adults exhibited common subsequent memory effects in several regions including left fusiform gyrus, occipital cortex, bilateral MTL (hippocampus, parahippocampal gyrus, amygdala), bilateral IFG/MFG, bilateral precentral gyrus and left middle temporal gyrus. A complete list of regions identified in this ALE analysis, and in all subsequent between-group ALE analyses, is presented in Table 2, and Figure 1.

Table 2: Between-group ALE results

Hemishere	Gyral location	Brodmann	MNI coordinates	Cluster

		area	x	y	z	size (mm^3)
Age-invariant subsequent memory effects						
Left	Fusiform gyrus	37/20	-50	-51	-16	1880
Right	Parrahippocampal gyrus/ Hippocamus	34/28	25	-13	-21	432
Left	Cerebellum/retrosplenial cortex	30	-8	-58	5	408
Right	Inferior/middle FG	46	51	39	15	376
Left	Inferior/middle FG	9/46	-45	19	22	352
Left	Inferior FG	47/45	-41	28	-5	328
Left	Parahippocampal gyrus	36/20	-38	-33	-18	272
Left	Occipital gyrus	18/19	-36	-85	-1	224
Left	Lingual gyrus	17	-20	-64	6	216
Left	Middle temporal gyrus	21/20	-51	-34	-8	144
Left	Inferior FG	45	-53	28	10	144
Right	Precentral gyrus	6/9	48	6	29	128
Left	Precentral gyrus	6/9	-46	4	30	128
Left	Medial superior FG	8	-6	53	44	88
Left	Occipital gyrus	19	-36	-85	21	80
Left	Parahippocampal gyrus/amygdala		-28	-11	-15	64
Young>old subsequent memory effects						
Right	Occipital gyrus	19	39	-78	23	600
Right	Fusiform gyrus	37	45	-53	-12	584
Right	Precentral gyrus	6	36	7	41	208
Left	Lingual gyrus / cuneus	18/23	-10	-76	9	168

Right	Posterior superior FG	6	17	-5	63	88
Left	Fusiform gyrus	37	-33	-51	-15	64
Left	Superior parietal lobe	7	-21	-63	51	56

Old>young subsequent memory effects

Left	Middle/superior FG	8/6/9	-41	31	39	792
Left	Inferior parietal lobe	39/40	-47	-53	27	400
Medial	Anterior medial FG	10	7	57	6	352
Medial	Anterior medial FG	10	-1	65	20	168
Left	Anterior middle/superior FG	9	-40	46	26	144
Right	Superior FG	10	26	56	2	104
Medial	Precuneus	7	5	-77	47	88
Right	Middle/superior FG	8	21	45	38	56

Note: ALE of age-invariant, young>old and old>young subsequent memory effects. A false discovery rate of $p<0.01$ was used for all analyses. The minimum cluster size recommended by GingerALE was $53mm^3$, $19mm^3$ and $22mm^3$ for the age-invariant, young>old, and old> young analyses, respectively. FG = frontal gyrus

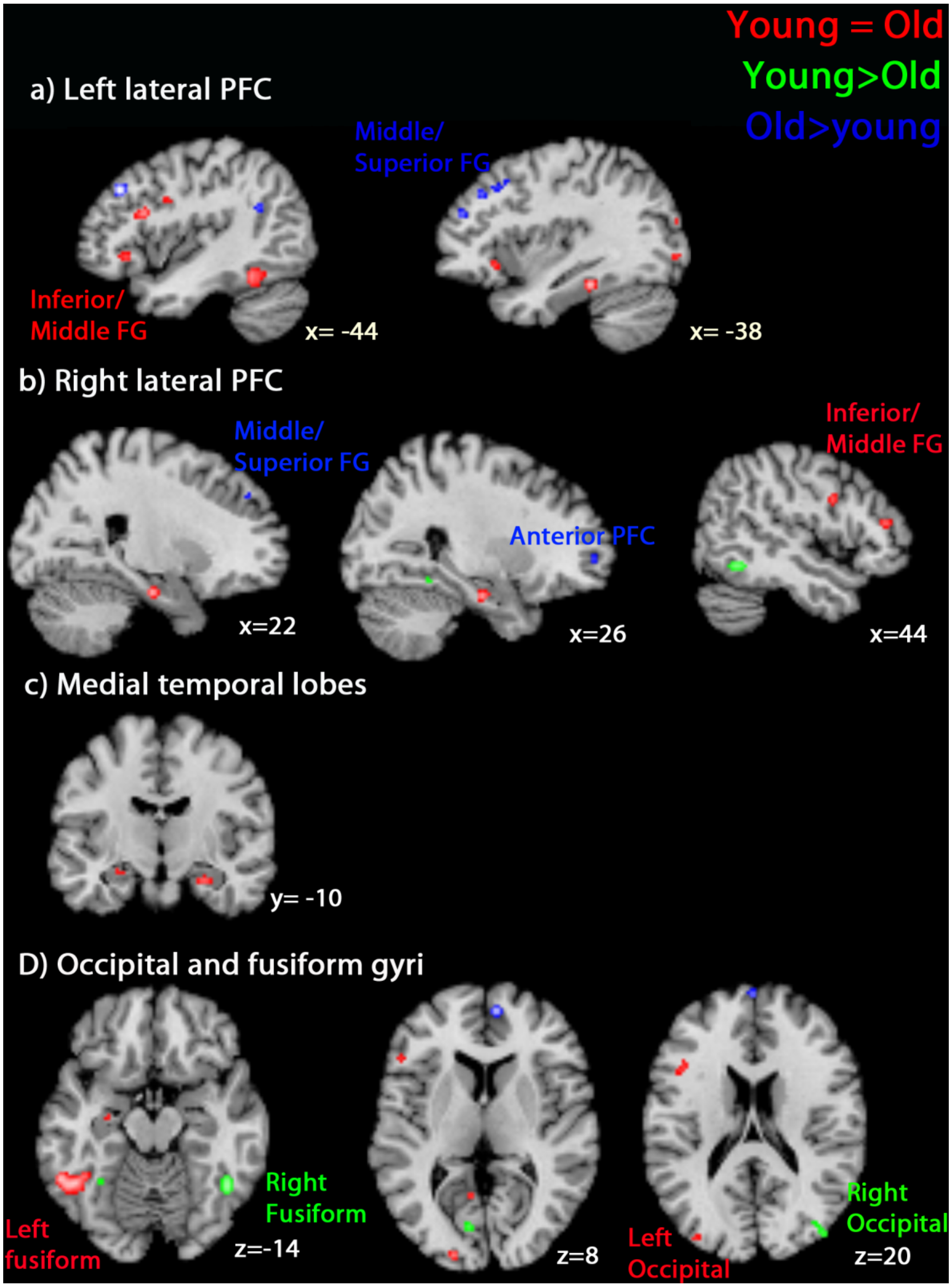

Figure 1: Summary of the age-invariant (red), young>old (green) and old>young (blue) activation likelihood estimation (ALE) analyses. Results are show for a) left lateral prefrontal cortex (PFC), b) right lateral PFC, c) medial temporal lobes d) occipital and fusiform gyri.

5.4.3. ALE of young>old effects

Thirteen experiments reported young>old contrasts, for a total of 96 activation peaks. The ALE identified young > older adult effects in occipital cortex, right fusiform gyrus, right precentral gyrus and left superior parietal lobe.

5.4.4. ALE of old>young effects

Sixteen experiments reported old>young effects for a total of 115 activation peaks. The ALE identified old>young effects in bilateral posterior and anterior MFG/SFG, anterior medial FG, precuneus/lingual gyrus, and left inferior parietal lobe. This set of regions were similar to regions that exhibit unsuccessful>successful encoding effects in young adults (Kim, 2011b). To objectively measure this similarity, we performed an additional ALE analysis of 22 studies reporting unsuccessful>successful encoding effects in young adults and calculated the conjunction between this ALE and the old>young ALE (see methods). Unsuccessful>successful encoding effects in young adults were observed in precuneus, posterior cingulate, anterior cingulate, anterior medial FG, bilateral MFG/SFG, bilateral IPL and left insula (Table 3). We observed a conjunction between the unsuccessful>successful ALE in young adults and the old>young between-group ALE in left MFG/SFG ([-40 35 35], cluster size= 112 mm^3), right MFG/SFG ([21 45 38], cluster size= 56 mm^3 and anterior medial FG ([6 56 5], cluster size= 112 mm^3). Moreover, even in regions where no direct overlap was observed, all of the regions exhibiting old>young effects were in very close proximity to regions involved in encoding failure in young adults (Figure 2).

Table 3: Unsuccessful>successful encoding in young

Hemisphere	Gyral location	Brodmann area	MNI coordinates			Cluster size (mm^3)
			x	y	z	
Unsuccessful>successful encoding in young adults						
Medial	Precuneus	7/31	4	-62	40	2064
Right	Middle/superior FG	9/8	26	45	34	1176
Right	Inferior parietal lobe	40/39	60	-44	31	1152
Left	Middle/superior FG	9/8	-38	38	33	800
Medial	Cingulate gyrus	24/31	1	-19	39	664
Left	Superior FG	9/8	-22	46	34	584
Left	Posterior cingulate cortex	31	6	-43	39	456
Right	Inferior parietal lobe	40	51	-51	38	344
Left	Inferior parietal lobe	40	-54	-52	36	304
Right	Middle/superior FG	8	38	32	41	272
Right	Posterior cingulate cortex	31	-12	-50	36	256
Medial	Anterior cingulate cortex	24/32	5	37	-3	248
Left	Precuneus	7	-13	-57	45	216
Right	Right Premotor cortex	6	42	20	55	168
Medial	Anterior medial FG	10	5	56	5	136
Left	Insula	13	-44	7	9	120

Note: ALE of unsuccessful>successful encoding in young adults, false discovery rate $p<0.01$, cluster size threshold = 100mm^3

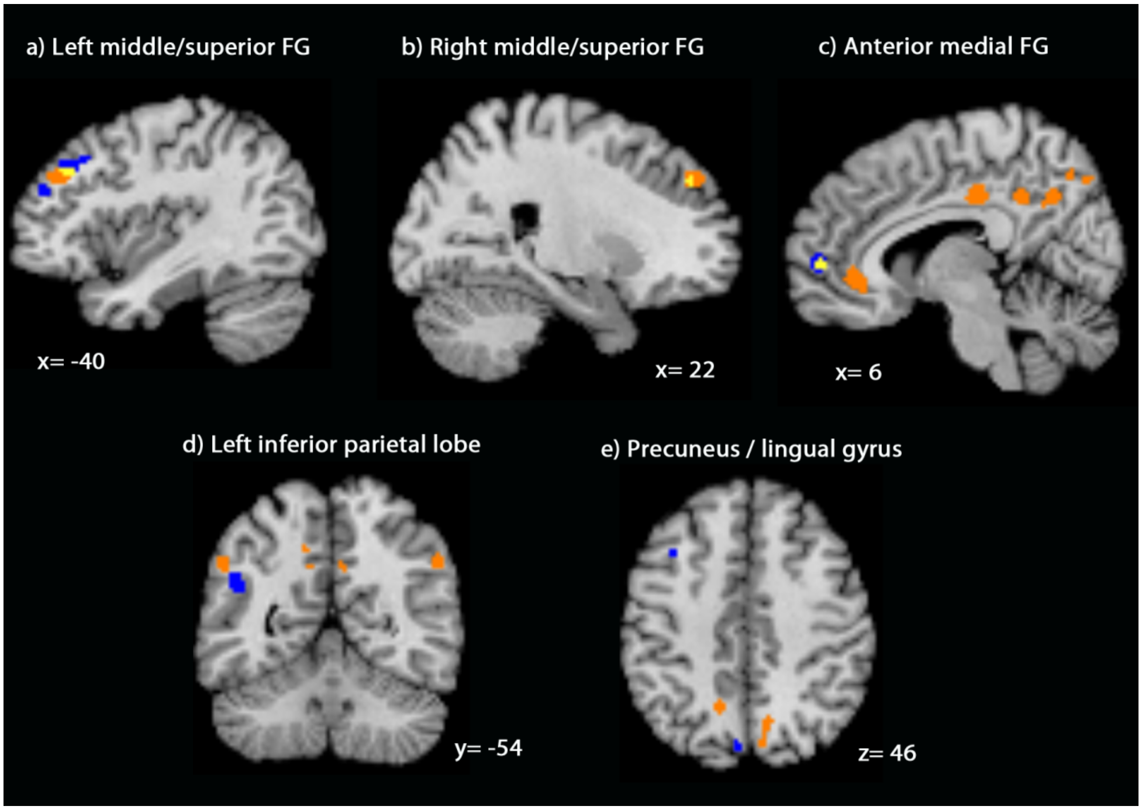

Figure 2: Similarity in ALE results for brain regions over-recruited by older adults during successful encoding (blue), and regions recruited by young adults during unsuccessful> successful encoding (orange). The conjunction between these two effects is illustrated in yellow. These effects are illustrated for the a) left middle/superior frontal gyrus (FG), b) right middle/superior FG, c) medial anterior FG, d) left inferior parietal lobe and e) precuneus/lingual gyrus.

5.5. Discussion

We performed a quantitative meta-analysis of studies that have examined age-related differences in the subsequent memory contrast. The main objective of this meta-analysis was to determine which specific regions both in the PFC and outside PFC are consistently over-recruited by older adults during successful encoding. Furthermore, to better understand the cognitive processes subserved by over-activated regions in older adults, we examined whether the regions over-recruited by older adults overlap with regions commonly recruited by young adults during episodic encoding, and if so, what cognitive processes these regions are thought to mediate in young adults.

Before turning to old>young subsequent memory effects, we briefly discuss the age-invariant and young>old effects found in this meta-analysis. First, age-invariant effects were found in bilateral MTL indicating that increased recruitment of these regions contributes to subsequent memory in both age groups. The age-invariant effect in right MTL is particularly interesting, given that a previous meta-analysis indicated that this region was under-recruited in older adults during episodic encoding (Spreng et al., 2010). As mentioned in the Introduction, the main difference between the meta-analysis by Spreng et al. and the current one is that we only included studies using the subsequent memory contrast, while Spreng et al. included all encoding studies, regardless of the contrast used. Thus one possibility is that age-related reductions in activation in right MTL are observed primarily in studies that do not separate encoding events according to whether they were successfully encoded or not. Since young adults generally perform better than older adults on episodic memory tasks, this could indicate that age-related differences in these studies reflects a greater amount of successfully encoded items in young vs. older adults, rather than actual differences in the recruitment of this region during successful episodic encoding. However, we emphasize that age-related reductions in MTL activation have been reported in a few studies using the subsequent memory paradigm (Dennis et al., 2007; Gutchess et al., 2005; Kensinger and Schacter, 2008; St Jacques et al., 2009). Subsequent memory effects unique to older adults have also been reported (Dulas and Duarte, 2011; Stevens et al., 2008). Thus, although the current meta-analysis indicates that overall, young and older exhibit similar subsequent memory effects in bilateral MTL, an important area of future research is to investigate why this is not always so.

Age-invariant subsequent memory effects were also observed in bilateral IFG/MFG. In young adults, during episodic encoding, the left IFG is thought to be involved in controlled semantic elaboration (Kim, 2011b; Wagner et al., 1998), a process which may be largely preserved in older adults. Right IFG/MFG was also commonly recruited by young and older adults, particularly in studies including pictorial encoding items (e.g., Gutchess et al., 2005; Park et al., 2013). Bilateral IFG/MFG are amongst the most commonly reported brain regions implicated in subsequent memory in young adults (Kim, 2011b); the current meta-analysis reveals that these effects are largely preserved in older adults.

Findings regarding occipital and fusiform gyri were mixed. Age-invariant subsequent memory effects were observed in the left hemisphere while age-related under-recruitment tended to occur in similar regions in the right hemisphere (Figure 1d). Age-related under-recruitment of visual cortex has been reported across a variety of cognitive domains and is thought to reflect impaired visual processing in older vs. young adults (Davis et al., 2008). However, the finding of a hemispheric asymmetry in the recruitment of occipital and fusiform gyri during successful episodic encoding was unexpected. One possibility is that this finding partially reflects the fact that a greater number of studies in the current meta-analysis used pictorial (13 studies) instead of verbal (5 studies) materials, rather than a disproportionate reduction in activation of right vs. left visual processing regions during successful episodic encoding. However, even when we restricted the ALE analyses to the 13 studies using pictorial items, similar hemispheric effects were observed (data not shown). Thus, the present results may indicate that older adults disproportionately recruit left vs. right visual cortex during successful encoding, although further studies are required to confirm this association and whether it generalizes across multiple types of stimuli.

5.5.1. Old vs. young subsequent memory effects

The ALE for old>young subsequent memory effects identified bilateral MFG/SFG, anterior medial FG, precuneus/lingual gyrus and left inferior parietal lobes. There are several interesting aspects about the precise regions identified. First, as we had hypothesized, older > young effects were found not only in the PFC, but also in parietal lobes. Second, none of the regions identified in the older > young ALE contrast overlapped with regions that were recruited by young adults during successful encoding such as IFG and MTL. In other words, it is not simply the case that older adults over-recruited brain regions used by young adults during successful encoding (e.g. because of neural inefficiency). Instead, old>young effects during successful vs. unsuccessful encoding tended to occur in very specific brain regions: those in which young adults exhibited unsuccessful>successful effects (see Figure 2).

It is important to note not all regions that are identified in a contrast targeting age-related over-recruitment during successful vs. unsuccessful encoding reflect the fact that older adults exhibit greater activity in these regions during successful encoding in old vs. young adults. Although this is generally the case (e.g., de Chastelaine et al., 2011; Duverne et al., 2009; Duzel et al., 2011; Kukolja et al., 2009; Miller et al., 2008; Morcom et al., 2003), other old>young subsequent memory effects arise because young adults exhibit less activity in these regions during successful vs. unsuccessful encoding, while older adults exhibit no difference in activation between these conditions (e.g., medial PFC in Gutchess et al., 2005). The difference in activation between unsuccessful>successful encoding events that is present in young adults in these regions seems to decrease and eventually reverse as a function of increasing age and decreasing memory performance (de Chastelaine et al., 2011; Park et al., 2013). For example, Park et al. (2013) reported that the difference in activation between unsuccessful>successful events in medial FG, bilateral SFG, precuneus and left inferior parietal lobe in young adults was reduced in middle-aged adults, and further reduced in older adults. Miller et al. (2008) reported that low-performing older adults exhibited larger subsequent memory effects in precuneus and right dorsolateral PFC compared to high performers. Duverne et al. (2009) reported an age group-by subsequent memory interaction in precuneus in which young adults exhibited greater activation in unsuccessful>successful events, but older adults had greater activation in successful>unsuccessful events. Further analyses revealed that this effect was driven by low-performing older adults. de Chastelaine et al. (2011) similarly reported reversed effects in young and older adults in posterior cingulate, bilateral dorsolateral PFC and right inferior parietal lobe, and that the tendency for activation to be higher in successful>unsuccessful encoding events in older adults was negatively related to performance on the task. Duzel et al. (2011) reported that while both high- and low-performing older adults over-activated bilateral inferior parietal lobe compared to young, low-performers additionally recruited regions including anterior cingulate cortex, precuneus and bilateral MFG/SFG.

In summary, an adequate explanation for the old> young effects identified in this meta-analysis must account for the findings that 1) these regions are consistently involved in encoding failure in young adults, 2) these regions can be activated to a greater extent in unsuccessful> successful encoding events in young adults and in successful>unsuccessful encoding events in older adults 3) those individuals with the highest activation in these regions tend to perform worst. We discuss each of these points in turn.

5.5.2. Old vs. young effects occur in regions involved in encoding failure in young adults

A useful starting point for interpreting old>young effects in subsequent memory studies may be to understand why these regions are involved in unsuccessful>successful encoding in young adults. Several interpretations have been proposed in the literature, including attentional lapses, a “diversion of neurocognitive resources away from processes that yield effective encoding” (p. R966; Wagner and Davachi, 2001), exhibiting an internally vs. externally processing mode (Kim, 2011b), and exhibiting task-unrelated thoughts (TUT) such as mind-wandering (Shrager et al., 2008). These suggestions are not mutually exclusive. Attentional lapses have been associated with the occurrence of TUT (for reviews, see Smallwood, 2013; Smallwood and Schooler, 2006). Moreover, a “diversion of neurocognitive processes away from processes that yield effective encoding” could simply indicate processing of internally generated thoughts, rather than processing important for encoding externally presented events.

TUT are frequent during episodic memory encoding tasks in young adults: according to one of our recent studies, they occur approximately 50% of the time in which subjects are probed for their occurrence (Maillet and Rajah, 2013c). Moreover, several studies have demonstrated a negative association between frequency of TUT and memory performance in young adults, both in laboratory settings (Maillet and Rajah, 2013a, c; Seibert and Ellis, 1991; Smallwood et al., 2003) and in natural settings such as classroom learning (for review, see Szpunar et al., 2013). In a recent study, we reported that exhibiting TUT during episodic encoding was associated with increased activation in posterior cingulate, lingual gyrus and bilateral MFG/SFG (Maillet and Rajah, 2013c). Other studies using sustained attention tasks have also reported greater activation in regions including bilateral middle and superior FG, precuneus, medial anterior FG and inferior parietal lobe when subjects exhibit TUT vs. when they are concentrated on the task (Christoff et al., 2009; Stawarczyk et al., 2011). Taken together, these results suggest that at least part of the regions recruited during unsuccessful>successful encoding events in young adults may be involved in exhibiting TUT.

5.5.3. Young and older adults often exhibit reversed effects in these regions

If regions involved in unsuccessful>successful encoding in young adults are involved in TUT, then one possibility is that old>young effects in these regions are related to an age-related change in the frequency, type or content of subjective/personal thoughts experienced during encoding tasks. Interestingly, studies to date suggest that older adults do not exhibit an increased frequency of TUT compared to young adults. Rather, although the results sometimes differ based on which specific thought type is being probed, studies to date have reported an overall decrease in TUT frequency during episodic encoding (Maillet and Rajah, 2013a), sustained attention tasks, and reading comprehension tasks (Giambra, 1989; Jackson and Balota, 2012; Jackson et al., 2013; Krawietz et al., 2012; McVay et al., 2013; Staub et al., 2013). However, to our knowledge no study to date has examined age-related changes in type/frequency of TUT during performance of a cognitive task in an fMRI study; thus these findings from behavioural studies await confirmatory evidence from the neuroimaging literature. More importantly, even if it were present, an age-related increase in frequency of TUT/attentional lapses is not a plausible mechanism for explaining the old>young effects found in this meta-analysis. This is because in the subsequent memory paradigm, encoding events are separated into those successfully vs. unsuccessfully retrieved. Thus while it could be argued that age-related differences in frequency of TUT may partially account for age-related differences in the frequency of incorrect encoding trials, it cannot account for 1) increased magnitude of activation in these regions during correct vs. incorrect trials in older adults, since presumably, TUTs occur to a greater extent during unsuccessful > successful encoding events, or 2) increased activation in these regions during successful encoding in older vs. young adults (unless one argues that older adults successfully encode information while exhibiting more TUT/lapses in attention compared to young adults, which seems unlikely).

Rather, although the evidence to date suggests that older adults do not exhibit an increase in frequency of task-unrelated thoughts compared to young adults, one possibility is that there are age-related differences in the frequency of thoughts related to the encoding stimuli themselves (i.e. spontaneous reactions to the encoding stimuli) and/or in the extent to which these thoughts serve as cues when making retrieval judgements in older vs. young adults (Hashtroudi et al., 1990). That is, a distinction should be made between TUTs (thoughts that truly have nothing to do with an ongoing task, e.g. thinking of something one has to do following the experiment) and spontaneous reactions (e.g. evaluative thoughts, feelings) about the encoding events themselves. It may be that older adults exhibit an increased reliance of this latter type of thought vs. young adults during memory tasks. In our opinion, this latter form of thought should not be labeled as task-unrelated, since it can serve as a potential retrieval cue.

For example, Hashtroudi et al. (1990) measured young and older adults' memory for different types of details regarding perceived and imagined events including contextual details, sensory details, clarity, intensity and thoughts/feelings. Young adults produced more perceptual and spatial information, while older adults produced more thoughts, feelings and evaluative statements. The authors give the example of an older adult reporting having thought "I would never have packed such a sparse picnic basket" when remembering an event involving a picnic basket. The authors suggested that with age, there may be an increase in the importance of personal values and information, and that older adults may be more likely to interpret presented information in relation to their value system and feelings. In another study, young and older adults were asked to justify their "remember" responses in a memory test using the remember/know paradigm for pictures encoded two weeks earlier (Comblain et al., 2004). Older adults attributed more of their “remember” responses to a recollection of their initial emotional reaction/feelings to the stimulus, compared to young. However, there was a trend for young adults to remember more of the associations they had made with the stimuli vs. older adults. The authors suggested that as a result of emotional self-focus, older adults may focus on emotional aspects of events, such as their own emotional reaction, at the expense of perceptual and contextual details. Both of these studies suggest that older adults may exhibit more affective thoughts and feelings related to the encoding events during episodic memory tasks compared to young adults, and that these thoughts may serve as cues in retrieval tasks. Other studies suggest that while older adults exhibit substantial impairments in recalling perceptual information, they exhibit little to no impairment in memory tasks for more meaningful and affective information (May et al., 2005; Rahhal et al., 2002). Another closely related line of research suggests that older adults are oriented more towards interpretation and integration of past and present as opposed to veridical reproduction (e.g., Adams et al., 1990; Gaesser et al., 2011; Hess, 2005). More generally, several investigators have emphasized the tendency of older adults to focus more on more personal, affective, elaborative and/or emotional aspects of ongoing events compared to young adults (for reviews, see Carstensen, 1992; Carstensen et al., 2003; Hess, 2005; Kensinger, 2009).

Age-related increases in frequency of evaluative thoughts and feelings related to the encoding events themselves, or in the extent to which such thoughts are used as retrieval cues may thus represent one possible mechanism for the consistent, old>young subsequent memory effects observed here. In fact, when interpreting the findings from this meta-analysis as a whole, it is tempting to conclude that age-related decreases in activation in occipital and fusiform gyri along with increases in medial FG, precuneus, IPL and bilateral MFG/SFG represent an age-related shift in focus away from specific perceptual and contextual details, and towards evaluative thoughts and feelings about the encoding stimuli with age (Hashtroudi et al., 1990). However, we emphasize the speculative nature of this proposal. A more complete understanding of the old>young effects observed here may require a better understanding of 1) the cognitive processes involved not only in successful, but also in unsuccessful encoding in both age groups (e.g., Maillet and Rajah, 2013c; Mattson et al., 2013) and 2) a better understanding of differences in the specific qualitative details encoded and retrieved in young vs. older adults during memory tasks.

5.5.4. Old vs. young subsequent memory effects are associated with worse performance

Another interesting aspect of old>young subsequent memory effects reported in this meta-analysis is that some studies have simultaneously reported that older adults exhibit subsequent memory effects in these regions, but that these subsequent memory effects are either only present in lower performing individuals, or present in these individuals to a greater extent (de Chastelaine et al., 2011; Duverne et al., 2009; Duzel et al., 2011; Miller et al., 2008). These findings may appear contradictory; however, as discussed by several other investigators in different contexts (Daselaar et al., 2013; Dennis and Cabeza, 2012; Duzel et al., 2011), this may indicate that these regions are compensatory only in low-performing older adults. For example, one could postulate that these regions are involved in cognitive processes that can support successful encoding (accounting for higher activation in remembered vs. forgotten events), but that the use of these cognitive processes is not the most efficient way to encode information (explaining the negative correlation with performance across individuals). For example, in a study described earlier, (Hashtroudi et al., 1990) suggested that a focus on personal thoughts/feelings may be detrimental to performance on memory tasks, since thoughts/feelings may not be as reliable an indicator as perceptual and contextual details that an event occurred (see also Hashtroudi et al., 1994; Kensinger, 2009). Thus, while thoughts/feelings may serve as a cue for successful retrieval, individuals who rely on these types of cues to a greater extent (rather than relying on perceptual and contextual details) may perform the worse overall in memory tasks.

5.5.5. Additional factors of consideration and limitations

In previous sections, we have provided a cognitive interpretation for the age-related differences in subsequent memory effects observed in the ALE analysis. However, it is likely that other non-cognitive factors at least partly explain age-related differences in the fMRI signal observed during episodic encoding. For example, Liu et al. (2013) recently measured cerebrovascular reactivity in participants aged in their 20s-80s using a CO_2-inhalation task and also had the same participants perform a picture encoding task. Using a picture viewing (independently of subsequent memory) > baseline contrast, they observed age-related reductions in activation in MTL and occipital cortex, but age-related increases in right IFG. However, after correcting for cerebrovascular reactivity, the age-related decreases in MTL and occipital cortex were no longer observed, while the age-related increase in PFC was still observed. Since this analysis was performed using a picture viewing vs. baseline contrast, it is unclear whether a similar association would have been found using a subsequent memory contrast. Nevertheless, it is possible that the age-related decreases in activation in subsequent memory effects in occipital cortex in this meta-analysis can be accounted for by differences in vascular properties with increasing age.

Other work suggests that the magnitude of the fMRI signal during episodic encoding may be altered by Alzheimer's disease (AD)-related pathology (Kennedy et al., 2012; Mormino et al., 2011; Oh & Jagust, 2013; Pihlajamaki & Sperling, 2009; Sperling et al., 2009). For example, Sperling et al. (2009) found that otherwise healthy older adults with amyloid-B deposition in the posterior cingulate cortex, as measured by Pittsburgh Compound B (PiB) positron emission tomography (PET) imaging, exhibited greater activation in several regions including the posterior cingulate, medial PFC and lateral parietal regions in a successful encoding vs. baseline contrast compared with PIB-negative older adults. Across all older participants, there was a positive correlation between increasing amyloid and fMRI signal in the posterior cingulate cortex. Pihlajamaki and Sperling (2009) asked healthy older adults, mild-cognitive impairment (MCI) patients, and AD patients to encode novel and repeated face-name pairs and contrasted activation in both of these conditions vs. baseline. Healthy older adults exhibited greater deactivation of the precuneus during encoding of face-name pairs compared to MCI patients, who in turn exhibited greater deactivation relative to AD patients. In addition, within both the healthy older adult and AD patient sub-groups, individuals without the apolipoprotein E (APOE) e4 allele exhibited greater deactivation of precuneus relative to APOE e4 carriers. Although the current meta-analysis only included studies from healthy older adults that did not meet diagnostic criteria for MCI or AD, the majority of studies did not report information regarding APOE status, or presence of beta amyloid deposition. Recent studies suggest that approximately 20-30% of cognitively normal older adults may harbour beta-amyloid levels associated with AD (Aizenstein et al., 2008; Oh & Jagust, 2013; Pike et al., 2007; Rowe et al., 2007), and that even sub-threshold levels of beta-amyloid deposition are associated with altered fMRI signal

(Kennedy et al., 2012). Thus, it is unclear to what extent these factors affected the magnitude of the fMRI response in the healthy older adult samples included in the current meta-analysis.

In the present meta-analysis, we only included studies that had used the subsequent memory procedure so that the contrasts used in distinct studies targeted similar cognitive processes. However, a limitation of the current meta-analysis is that we did not separate studies according to stimulus type, whether encoding was associative/non-associative, or the encoding instructions, so as to identify effects unique to these conditions. Many more studies will be needed before such analyses are feasible.

5.6. Conclusions

In summary, our meta-analysis reveals that older adults consistently under-recruit occipital and fusiform gyri, but over-recruit bilateral MFG/SFG, medial anterior FG, precuneus and left inferior parietal lobes compared to young adults in studies using the subsequent memory contrast. Moreover, the regions over-recruited by older adults exhibit either direct overlap or occur in close vicinity to regions involved in encoding failure in young adults. Based on behavioural findings, we have suggested that one possible interpretation of these results is that it reflects an increased focus on evaluative thoughts and feelings about encoding events during successful encoding in older adults vs. young adults. This proposal is speculative, and as such, we hope that these ideas will stimulate future research that will either confirm, refine or disprove this proposal.

5.7.References

Adams, C., Labouvie-Vief, G., Hobart, C.J., Dorosz, M., 1990. Adult age group differences in story recall style. J Gerontol 45, P17-27.

Bangen, K.J., Kaup, A.R., Mirzakhanian, H., Wierenga, C.E., Jeste, D.V., Eyler, L.T., 2012. Compensatory Brain Activity during Encoding among Older Adults with Better Recognition Memory for Face-Name Pairs: An Integrative Functional, Structural, and Perfusion Imaging Study. J Int Neuropsychol Soc, 1-19.

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging 17, 85-100.

Carstensen, L.L., 1992. Motivation for social contact across the life span: a theory of socioemotional selectivity. Nebraska Symposium on Motivation. Nebraska Symposium on Motivation 40, 209-254.

Carstensen, L.L., Fung, H.H., Charles, S.T., 2003. Socioemotional Selectivity Theory and the Regulation of Emotion in the Second Half of Life. Motivation and Emotion 27, 103-123.

Christoff, K., Gordon, A.M., Smallwood, J., Smith, R., Schooler, J.W., 2009. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. Proc Natl Acad Sci U S A 106, 8719-8724.

Comblain, C., D'Argembeau, A., Van der Linden, M., Aldenhoff, L., 2004. The effect of ageing on the recollection of emotional and neutral pictures. Memory 12, 673-684.

Craik, F.I.M., Salthouse, T.A., 2000. The Handbook of Aging and Cognition. Lawrence Erlbaum Associates, Mahwah, NJ.

Daselaar, S.M., Iyengar, V., Davis, S.W., Eklund, K., Hayes, S.M., Cabeza, R.E., 2013. Less Wiring, More Firing: Low-Performing Older Adults Compensate for Impaired White Matter with Greater Neural Activity. Cereb Cortex.

Davis, S.W., Dennis, N.A., Daselaar, S.M., Fleck, M.S., Cabeza, R., 2008. Que PASA? The posterior-anterior shift in aging. Cereb Cortex 18, 1201-1209.

de Chastelaine, M., Wang, T.H., Minton, B., Muftuler, L.T., Rugg, M.D., 2011. The effects of age, memory performance, and callosal integrity on the neural correlates of successful associative encoding. Cereb Cortex 21, 2166-2176.

Dennis, N.A., Cabeza, R., 2012. Frontal lobes and aging: deterioration and compensation, in: Stuss, D., Knight, R. (Eds.), Principles of frontal lobe function, 2nd ed. ed. Oxford University Press, New York.

Dennis, N.A., Daselaar, S., Cabeza, R., 2007. Effects of aging on transient and sustained successful memory encoding activity. Neurobiol Aging 28, 1749-1758.

Dennis, N.A., Hayes, S.M., Prince, S.E., Madden, D.J., Huettel, S.A., Cabeza, R., 2008. Effects of aging on the neural correlates of successful item and source memory encoding. J Exp Psychol Learn Mem Cogn 34, 791-808.

Dulas, M.R., Duarte, A., 2011. The effects of aging on material-independent and material-dependent neural correlates of contextual binding. Neuroimage 57, 1192-1204.

Duverne, S., Motamedinia, S., Rugg, M.D., 2009. The relationship between aging, performance, and the neural correlates of successful memory encoding. Cereb Cortex 19, 733-744.

Duzel, E., Schutze, H., Yonelinas, A.P., Heinze, H.J., 2011. Functional phenotyping of successful aging in long-term memory: Preserved performance in the absence of neural compensation. Hippocampus 21, 803-814.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 30, 2907-2926.

Fischer, H., Nyberg, L., Backman, L., 2010. Age-related differences in brain regions supporting successful encoding of emotional faces. Cortex 46, 490-497.

Gaesser, B., Sacchetti, D.C., Addis, D.R., Schacter, D.L., 2011. Characterizing age-related changes in remembering the past and imagining the future. Psychol Aging 26, 80-84.

Giambra, L.M., 1989. Task-unrelated-thought frequency as a function of age: a laboratory study. Psychol Aging 4, 136-143.

Greenwood, P.M., 2007. Functional plasticity in cognitive aging: review and hypothesis. Neuropsychology 21, 657-673.

Gutchess, A.H., Kensinger, E.A., Schacter, D.L., 2010. Functional neuroimaging of self-referential encoding with age. Neuropsychologia 48, 211-219.

Gutchess, A.H., Welsh, R.C., Hedden, T., Bangert, A., Minear, M., Liu, L.L., Park, D.C., 2005. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. J Cogn Neurosci 17, 84-96.

Hashtroudi, S., Johnson, M.K., Chrosniak, L.D., 1990. Aging and qualitative characteristics of memories for perceived and imagined complex events. Psychol Aging 5, 119-126.

Hashtroudi, S., Johnson, M.K., Vnek, N., Ferguson, S.A., 1994. Aging and the effects of affective and factual focus on source monitoring and recall. Psychol Aging 9, 160-170.

Hess, T.M., 2005. Memory and aging in context. Psychol Bull 131, 383-406.

Jackson, J.D., Balota, D.A., 2012. Mind-wandering in younger and older adults: Converging evidence from the sustained attention to response task and reading for comprehension. Psychol Aging 27, 106-119.

Jackson, J.D., Weinstein, Y., Balota, D.A., 2013. Can mind-wandering be timeless? Atemporal focus and aging in mind-wandering paradigms. Frontiers in psychology 4, 742.

Kensinger, E.A., 2009. How emotion affects older adults' memories for event details. Memory 17, 208-219.

Kensinger, E.A., Schacter, D.L., 2008. Neural processes supporting young and older adults' emotional memories. J Cogn Neurosci 20, 1161-1173.

Kim, H., 2011a. Differential neural activity in the recognition of old versus new events: An Activation Likelihood Estimation Meta-Analysis. Hum Brain Mapp.

Kim, H., 2011b. Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. Neuroimage 54, 2446-2461.

Kim, S.Y., Giovanello, K.S., 2011. The Effects of Attention on Age-related Relational Memory Deficits: fMRI Evidence from a Novel Attentional Manipulation. J Cogn Neurosci.

Krawietz, S.A., Tamplin, A.K., Radvansky, G.A., 2012. Aging and mind wandering during text comprehension. Psychol Aging 27, 951-958.

Kukolja, J., Thiel, C.M., Wilms, M., Mirzazade, S., Fink, G.R., 2009. Ageing-related changes of neural activity associated with spatial contextual memory. Neurobiol Aging 30, 630-645.

Laird, A.R., Eickhoff, S.B., Kurth, F., Fox, P.M., Uecker, A.M., Turner, J.A., Robinson, J.L., Lancaster, J.L., Fox, P.T., 2009. ALE Meta-Analysis Workflows Via the Brainmap Database: Progress Towards A Probabilistic Functional Brain Atlas. Front Neuroinform 3, 23.

Laird, A.R., Robinson, J.L., McMillan, K.M., Tordesillas-Gutierrez, D., Moran, S.T., Gonzales, S.M., Ray, K.L., Franklin, C., Glahn, D.C., Fox, P.T., Lancaster, J.L., 2010. Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: validation of the Lancaster transform. Neuroimage 51, 677-683.

Lancaster, J.L., Tordesillas-Gutierrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., Mazziotta, J.C., Fox, P.T., 2007. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum Brain Mapp 28, 1194-1205.

Leshikar, E.D., Duarte, A., 2013. Medial prefrontal cortex supports source memory for self-referenced materials in young and older adults. Cogn Affect Behav Neurosci.

Maillet, D., Rajah, M.N., 2013a. Age-related changes in frequency of mind-wandering and task-related interferences during memory encoding and their impact on retrieval. Memory 21, 818-831.

Maillet, D., Rajah, M.N., 2013b. Association between prefrontal activity and volume change in prefrontal and medial temporal lobes in aging and dementia: a review. Ageing Res Rev 12, 479-489.

Maillet, D., Rajah, M.N., 2013c. Dissociable roles of default-mode regions during episodic encoding. Neuroimage.

Mattson, J.T., Wang, T.H., de Chastelaine, M., Rugg, M.D., 2013. Effects of Age on Negative Subsequent Memory Effects Associated with the Encoding of Item and Item-Context Information. Cereb Cortex.

May, C.P., Rahhal, T., Berry, E.M., Leighton, E.A., 2005. Aging, source memory, and emotion. Psychol Aging 20, 571-578.

McVay, J.C., Meier, M.E., Touron, D.R., Kane, M.J., 2013. Aging ebbs the flow of thought: adult age differences in mind wandering, executive control, and self-evaluation. Acta Psychol (Amst) 142, 136-147.

Miller, S.L., Celone, K., DePeau, K., Diamond, E., Dickerson, B.C., Rentz, D., Pihlajamaki, M., Sperling, R.A., 2008. Age-related memory impairment associated with loss of parietal deactivation but preserved hippocampal activation. Proc Natl Acad Sci U S A 105, 2181-2186.

Mol, M., Carpay, M., Ramakers, I., Rozendaal, N., Verhey, F., Jolles, J., 2007. The effect of perceived forgetfulness on quality of life in older adults; a qualitative review. Int J Geriatr Psychiatry 22, 393-400.

Morcom, A.M., Bullmore, E.T., Huppert, F.A., Lennox, B., Praseedom, A., Linnington, H., Fletcher, P.C., 2010. Memory encoding and dopamine in the aging brain: a psychopharmacological neuroimaging study. Cereb Cortex 20, 743-757.

Morcom, A.M., Good, C.D., Frackowiak, R.S., Rugg, M.D., 2003. Age effects on the neural correlates of successful memory encoding. Brain 126, 213-229.

Oh, H., Jagust, W.J., 2013. Frontotemporal Network Connectivity during Memory Encoding Is Increased with Aging and Disrupted by Beta-Amyloid. J Neurosci 33, 18425-18437.

Park, D.C., Reuter-Lorenz, P., 2009. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol 60, 173-196.

Park, H., Kennedy, K.M., Rodrigue, K.M., Hebrank, A., Park, D.C., 2013. An fMRI study of episodic encoding across the lifespan: changes in subsequent memory effects are evident by middle-age. Neuropsychologia 51, 448-456.

Rahhal, T.A., May, C.P., Hasher, L., 2002. Truth and character: sources that older adults can remember. Psychol Sci 13, 101-105.

Rajah, M.N., D'Esposito, M., 2005. Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. Brain 128, 1964-1983.

Reuter-Lorenz, P., Cappell, K.A., 2008. Neurocognitive Aging and the Compensation Hypothesis. Current Directions in Psychological Science 17, 177-182.

Schwindt, G.C., Black, S.E., 2009. Functional imaging studies of episodic memory in Alzheimer's disease: a quantitative meta-analysis. Neuroimage 45, 181-190.

Seibert, P.S., Ellis, H.C., 1991. Irrelevant thoughts, emotional mood states, and cognitive task performance. Mem Cognit 19, 507-513.

Shrager, Y., Kirwan, C.B., Squire, L.R., 2008. Activity in both hippocampus and perirhinal cortex predicts the memory strength of subsequently remembered information. Neuron 59, 547-553.

Smallwood, J., 2013. Distinguishing how from why the mind wanders: a process-occurrence framework for self-generated mental activity. Psychol Bull 139, 519-535.

Smallwood, J., Baracaia, S.F., Lowe, M., Obonsawin, M., 2003. Task unrelated thought whilst encoding information. Conscious Cogn 12, 452-484.

Smallwood, J., Schooler, J.W., 2006. The restless mind. Psychol Bull 132, 946-958.

Spaniol, J., Davidson, P.S., Kim, A.S., Han, H., Moscovitch, M., Grady, C.L., 2009. Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. Neuropsychologia 47, 1765-1779.

Spreng, R.N., Wojtowicz, M., Grady, C.L., 2010. Reliable differences in brain activity between young and old adults: a quantitative meta-analysis across multiple cognitive domains. Neurosci Biobehav Rev 34, 1178-1194.

St Jacques, P.L., Dolcos, F., Cabeza, R., 2009. Effects of aging on functional connectivity of the amygdala for subsequent memory of negative pictures: a network analysis of functional magnetic resonance imaging data. Psychol Sci 20, 74-84.

Staub, B., Doignon-Camus, N., Bacon, E., Bonnefond, A., 2013. Investigating sustained attention ability in the elderly by using two different approaches: Inhibiting ongoing behavior versus responding on rare occasions. Acta Psychol (Amst) 146C, 51-57.

Stawarczyk, D., Majerus, S., Maquet, P., D'Argembeau, A., 2011. Neural correlates of ongoing conscious experience: both task-unrelatedness and stimulus-independence are related to default network activity. PLoS One 6, e16997.

Stevens, W.D., Hasher, L., Chiew, K.S., Grady, C.L., 2008. A neural mechanism underlying memory failure in older adults. J Neurosci 28, 12820-12824.

Szpunar, K.K., Moulton, S.T., Schacter, D.L., 2013. Mind wandering and education: from the classroom to online learning. Frontiers in psychology 4, 495.

Turner, G.R., Spreng, R.N., 2011. Executive functions and neurocognitive aging: dissociable patterns of brain activity. Neurobiol Aging.

Wagner, A.D., Davachi, L., 2001. Cognitive neuroscience: forgetting of things past. Curr Biol 11, R964-967.

Wagner, A.D., Schacter, D.L., Rotte, M., Koutstaal, W., Maril, A., Dale, A.M., Rosen, B.R., Buckner, R.L., 1998. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science 281, 1188-1191.

6. General Discussion

The goal of the current thesis was to investigate the role of mFC in young and older adults during episodic encoding. Previous studies have provided contradictory findings regarding the role of mFC during episodic encoding in young adults. On one hand, a recent meta-analysis found that increased activation in mFC, along with other regions including posterior cingulate and bilateral dorsolateral PFC is greater during unsuccessful vs. successful encoding (Kim, 2011). These data suggest that mFC is detrimental to memory formation, perhaps because this region is involved in exhibiting TUT. On the other hand, studies that have used self-referential encoding tasks (e.g. pleasantness judgements) have reported that mFC activation is greater for successful vs. unsuccessful encoding (Leshikar & Duarte, 2012; Macrae et al., 2004). Moreover, self-referential encoding tasks result in optimal performance in memory tasks: subjects using such tasks perform much better than when they make semantic, perceptual or other-reference encoding tasks (Symons & Johnson, 1997).

Studies assessing age-related changes in activation during episodic encoding have reported that older adults often over-activate mFC compared to young adults during episodic encoding (e.g., Gutchess et al., 2005). In agreement with the literature in young adults, two main interpretations have been used to explain this finding. First, the majority of studies have interpreted age-related increases in mFC as reflecting reduced concentration, and/or increases in TUT in older adults (e.g., Grady et al., 2006; Leshikar et al., 2010), which is detrimental to their performance. A related interpretation often provided in the literature is that older adults "fail to deactivate this region" (e.g., H. Park et al., 2013). However, another interpretation is that older adults over-activate mFC during episodic encoding because of an increased tendency to process information in a self-referential manner compared to young adults (Kensinger & Schacter, 2008).

The central framework proposed in the introduction of this thesis is that mFC reflects self-referential evaluation processes that can either benefit encoding (if directed towards the encoding events themselves) or be detrimental to encoding (if directed to TUT). In Figure 2 of the Introduction, I suggested that mFC may be highest during successful self-referential encoding, because this task explicitly requires self-referential evaluation. Activation in mFC may be intermediate during unsuccessful encoding, irrespective of encoding tasks, since TUT occur to a greatest extent during encoding events, and TUT tend to be highly self-referential. Finally, mFC activation may be lowest during successful semantic encoding, since this task does not involved self-referential evaluation.

In Study 1, this framework was directly tested. We found that ventral mFC exhibited highest activation during successful self-referential encoding, intermediate activation during unsuccessful encoding, and the lowest amount of activation during successful semantic (man-made/natural) encoding. Unfortunately, because our study contained few TUT trials, we had to collapse TUT trials across encoding tasks, and it was impossible to test the hypothesis that this region was involved in TUT vs. on-task trials in the man-made encoding task only. In the manuscript, we suggested an alternate possibility: that if this region is involved in self-referential evaluation, then the extent to which this process was used in the man-made natural task would have been associated with worst performance on the subsequent retrieval task since it could have led to a source misattribution (falsely responding that a word was studied in the pleasantness task). That is, increased activation in this region in the man-made task could be associated with worst performance because it is associated with 1) TUT, or 2), self-referential evaluation of the encoding stimuli, leading to source misattribution. Future studies will be needed to test these possibilities. Interestingly, we also found a more dorsal region of mPFC that was involved in encoding success across tasks. We suggested that this more dorsal region of mPFC may have been involved in internally directed attention to task-relevant thoughts (i.e. to which of the two encoding judgements was being performed), which was a requirement for the subsequent source retrieval task.

In study 2, we assessed the relationship between self-referential encoding activation in mFC and retrieval accuracy in young and older adults. One suggestion regarding age-related over-recruitment of mFC in older adults is that it reflects an increased tendency to process encoding information in a self-referential manner (Kensinger & Schacter, 2008). That is, irrespective of the encoding task that is provided (e.g. semantic, perceptual), older adults tend to process this information in a self-referential manner, while young adults encode the information using the judgement provided. I reasoned that if this was the case, age-related differences in mFC would disappear when both age groups are asked to encode events using a pleasantness judgement (since in this case, both groups encode in a self-referential manner). This hypothesis was not supported. We found that that increased activation in a network of brain regions including mFC, ventrolateral PFC and hippocampus was associated with higher retrieval accuracy (and higher hippocampus volume) only in young adults, but not in older adults. These results are hard to reconcile with the position that increased mFC activation in older adults reflects an increase in self-referential processing. However, one possibility that was suggested earlier is that self-referential evaluation of encoding stimuli only benefited retrieval performance in young adults because they additionally encoded the spatial/temporal context, while older adults did not do so as efficiently.

In study 3, we conducted the first behavioural study to assess age-related differences in frequency of TUT during episodic encoding. If, as has been suggested in the fMRI literature, older adults exhibit increased mFC activation because of an age-related increase in frequency of TUT, then one would expect that older adults would in fact exhibit an increase, rather than a decrease in TUT frequency, compared to young adults. This hypothesis was not supported. We found that across two distinct encoding tasks, older adults exhibited reduced frequency of both mind-wandering and task-related interferences compared to young.

In Study 4, we performed a quantitative meta-analysis of all studies that have investigated age-related differences in activation using the subsequent memory paradigm. We found age-related under-recruitment of occipital and fusiform cortex, but over-recruitment in a set of regions including bilateral middle/superior frontal gyri, anterior mFC, precuneus and left inferior parietal lobe. We also demonstrated that all over-activated brain regions in older adults occur in regions that are involved in encoding failure in young adults. Thus, a critical insight that was gained from this meta-analysis is that age-related over-activation in mFC does not occur in isolation; the exact same phenomenon of reversal of subsequent memory effects (higher activation in unsuccessful vs. successful encoding in young, but higher activation in successful vs. unsuccessful encoding in older adults) occurs in lateral PFC and parietal regions. Moreover, increased activation in these regions during successful vs. unsuccessful encoding in older adults is often found to *negatively* correlate with overall performance on the task.

We proposed a novel model in Study 4 to explain this age-related reversal. We suggested that in young adults, these brain regions are involved in encoding failure because of their involvement in TUT. Older adults exhibit a reduction in TUT (e.g. Study 3), making it unlikely that age-related over-recruitment of these regions represents an age-related increase in TUT.

Rather, we proposed, based on behavioural findings, that activation in these brain regions during successful encoding reflects task-related evaluative thoughts and feelings in older adults. The mFC specifically may be recruited due to the self-referential nature of these thoughts, or due to the introspective attention needed to experience these thoughts. Furthermore, we proposed that the more older adults rely on these evaluative thoughts during memory tasks, rather than relying on perceptual and contextual information, the worst they perform on episodic memory tasks.

6.1. Future directions

We emphasized in Study 4 that this proposal was speculative. Thus an important area of future investigation will be to conduct research that validates or refutes this proposal. Two elements of this proposal require further investigation. First, there is very little evidence to support our proposal that with age there is a change in focus away from perceptual details, and towards evaluative thoughts and feelings. That is, there exists very little information regarding the specific qualitative details that young and older adults attend to during memory tasks. Another open question is whether this proposed age-related shift in attention occurs at encoding, retrieval or both. For example, one possibility is that older adults initially focus on distinct aspects of events at encoding, and that their memory is therefore skewed towards these aspects. However, another possibility is that young and older adults attend to exactly the same information at encoding, but that older adults base their retrieval judgements on distinct criteria versus young adults, perhaps because some information is easier to retrieve than others (e.g. remembering the thoughts one had may be easier than remembering specific perceptual details). The subsequent memory paradigm cannot differentiate between these possibilities. Future experiments will need to specifically probe young adults for the types of details they attend to at both encoding and retrieval to distinguish between these possibilities.

Second, a key component of this model is that older adults exhibit reduced frequency of TUT compared to young adults (e.g. Study 3). However, we cannot at this point provide any mechanistic account as to why older adults would exhibit a reduction in TUT compared to young adults. In study 3, this result was interpreted as reflecting decreased attentional resources in older vs. young adults. This proposal remains to be confirmed, perhaps by correlating TUT frequency with working memory capacity. However, it is interesting to note that one study has reported that older adults also exhibit reduced TUT in their everyday life compared to young adults (Giambra, 1973). Although it is still possible to argue that this reflects decreased attentional resources in older vs. young adults in daily activities, it is more of a stretch. For example, do older adults exhibit fewer TUT than young while washing the dishes, and if so, can this truly be attributed to the fact that older adults spend more of their attentional resource on dish washing vs. young? Perhaps another possibility is that it is not "attentional ressources" per se, but rather a diminished ability in older adults to engage in "mental time travel". It is widely accepted that older adults exhibit reductions in not only memory retrieval but also thinking about the future (Addis, Roberts, & Schacter, 2011). Mind-wandering is just that: thinking about one's past or future. An association between reduced TUT, reduced episodic memory, and reduced prospection, perhaps all of which are associated with decreased integrity of the hippocampus, remains to be demonstrated. Finally, motivational and lifestyle factors should not be overlooked. Perhaps older adults simply have less to think about than young since their life is more "calm" (i.e. because of retirement). Or perhaps older adults simply like to focus more on the present than young adults, because they have less to look forward to.

A question of special interest and importance is whether the findings in this thesis could be used to improve young and older adults' memories. Studies 1, 3 and 4 suggest that in young adults, the occurrence of TUT during episodic encoding tasks is negatively related to later memory performance. Thus, it may be the case that engaging in activities that have been associated with reductions in TUT, such as meditation (Malinowski, 2013), could improve memory performance in young adults. Since older adults seem to naturally exhibit less TUT than young, it is not clear whether such an intervention would be as effective with age. It was suggested in Study 4 that one of the main reasons that older adults perform at a lower level than young during episodic encoding tasks is that they focus less on perceptual and contextual details, and more on thoughts and feelings. Thus, it is possible that encouraging older adults to focus on the former types of details could improve their performance on traditional memory tasks. For example, Hashtroudi, Johnson, Vnek, and Ferguson (1994) had pairs of young and older adults participate in a play in which they were asked to say specific lines. Following the play, they were asked to reflect back on the play using one of three focus: 1) a factual focus (think about what had been said), 2) an affective focus (think about how you felt) or 3) control condition (think about anything regarding the play). A memory test for specific lines in the play followed. Young adults performed equally well on the memory test, independently of the focus group. On the other hand, older adults performed better in the factual condition relative to the other 2 conditions. Moreover, older adults performed equally well in the affective and control conditions, suggesting that their natural focus may be an affective one. This study suggests that asking older adults to focus on perceptual and factual details may improve their memory for these events.

6.2. Limitations

The limitations of each individual study were discussed within the manuscripts themselves. However, some other general limitations should be emphasized. First, studies 2 and 3 used a cross-sectional design to assess the effects of aging on episodic memory. Additionally, Study 4 is a meta-analysis of studies that have also exclusively used cross-sectional designs. Thus, it is possible that the age differences reported in this thesis may not have been due to age per se, but instead to developmental, historical or other cohort effects. Additional studies using longitudinal designs would be useful in this regard.

Second, studies 2 and 4 examined age-related differences in brain activation using fMRI. fMRI is an indirect measure of neural activity based on the properties of the hemodynamic response function. Care should be taken when interpreting age-related differences in the BOLD signal, as it could potentially be affected by non-neural factors (D'Esposito et al., 2003; Rajah et al., 2005).

6.3. References

D'Esposito, M., L. Y. Deouell and A. Gazzaley (2003). "Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging." Nat Rev Neurosci 4(11): 863-872.

Giambra, L. M. (1973). "Daydreaming in males from seventeen to seventy-seven: A preliminary report." Proceedings of the Annual Convention of the American Psychological Association: 769-770.

Grady, C. L., M. V. Springer, D. Hongwanishkul, A. R. McIntosh and G. Winocur (2006). "Age-related changes in brain activity across the adult lifespan." J Cogn Neurosci 18(2): 227-241.

Hashtroudi, S., Johnson, M. K., Vnek, N., & Ferguson, S. A. (1994). Aging and the effects of affective and factual focus on source monitoring and recall. *Psychol Aging, 9*(1), 160-170.

Kensinger, E. A. and D. L. Schacter (2008). "Neural processes supporting young and older adults' emotional memories." J Cogn Neurosci 20(7): 1161-1173.

Leshikar, E. D. and A. Duarte (2012). "Medial prefrontal cortex supports source memory accuracy for self-referenced items." Soc Neurosci 7(2): 126-145.

Leshikar, E. D., A. H. Gutchess, A. C. Hebrank, B. P. Sutton and D. C. Park (2010). "The impact of increased relational encoding demands on frontal and hippocampal function in older adults." Cortex 46(4): 507-521.

Malinowski, P. (2013). Neural mechanisms of attentional control in mindfulness meditation. *Front Neurosci, 7*, 8.

Macrae, C. N., J. M. Moran, T. F. Heatherton, J. F. Banfield and W. M. Kelley (2004). "Medial prefrontal activity predicts memory for self." Cereb Cortex 14(6): 647-654.

Rajah, M. N. and M. D'Esposito (2005). "Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory." Brain 128(Pt 9): 1964-1983.