Year : 2015

Cognitive anatomy of the temporal lobe: Effect of personality in population with mild cognitive impairment & Functional specialization for memory systems in healthy individuals

Zufferey Valérie

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Département des neurosciences cliniques,
Centre hospitalier universitaire Vaudois

Cognitive anatomy of the temporal lobe: Effect of personality in population with mild cognitive impairment & Functional specialization for memory systems in healthy individuals

Thèse de doctorat en Neurosciences

présentée à la

Faculté de Biologie et de Médecine
de l'Université de Lausanne

par

Valérie Zufferey

Neuroscientifique diplômée de l'Université de Genève, Suisse

Jury

Prof. Jean-Pierre Hornung, Président
Dr. Ferath Kherif, Directeur
Prof. Armin von Gunten, Co-Directeur
Prof. Jean-François Démonet, Expert
Prof. Richard Henson, Expert

Thèse n° 154

Lausanne 2015

Programme doctoral interuniversitaire en Neurosciences des Universités de Lausanne et Genève

LEMANIC NEURO SCIENCE DOCTORAL SCHOOL

UNIL | Université de Lausanne

UNIVERSITÉ DE GENÈVE

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

LEMANIC NEURO SCIENCE DOCTORAL SCHOOL

Programme doctoral interuniversitaire en Neurosciences
des Universités de Lausanne et Genève

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président	Monsieur Prof. Jean-Pierre **Hornung**
Directeur de thèse	Monsieur Dr Ferah **Kherif**
Co-directeur de thèse	Monsieur Prof. Armin **Von Gunten**
Experts	Monsieur Prof. Jean-François **Démonet**
	Monsieur Prof. Richard **Henson**

le Conseil de Faculté autorise l'impression de la thèse de

Madame Valérie Zufferey

Master en Neurosciences de l'Université de Genève

intitulée

Cognitive anatomy of the temporal lobe:
Effect of personality in population with mild cognitive impairment
&
Functional specialization for memory systems in healthy individuals

Lausanne, le 8 septembre 2015

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Jean-Pierre Hornung

Preface

Acknowledgements

I would like to express my gratitude to my supervisor Ferath Kherif for the inspiration and the help he could bring me thourough all the thesis; to my co-supervisor Armin von Gunten for his humanity in the field of old age; to Bogdan Draganski, the director of the laboratory, to give motivation and the important taste for learning; and to my colleague Alessia Donati not only for her great help in data collection on personality, but also for the very motivating discussions. Thank you all to have giving me the opportunity to work on a very interesting topic, for your advices, your support, your patience and more importantly for your human approach.

I also would like to sincerely thank all my colleagues from the Laboratoire de Recherche En Neuroimagerie (LREN) for their presence, for all the rich daily exchanges at personal and professional levels. Your encouragements were very important for me. I would like to particularly thank Leyla Loued-Khenissi, Katie Chapman, Cristina Ramponi and my supervisors for the correction of thesis and Kerstin Preuschoff for her advices in statistical models of learning. Thanks also to the Centre d'Imagerie BioMédicale (CIBM) to have helped acquiring the neuroimaging data in the project on personality.

Thanks a lot to the jurys of my thesis. I was honored that they accepted to evaluate this work.

Last, but not least, I particularly thank my family and all the friends that supported me a lot through the thesis and in the more difficult times.

Above all, my wish is to dedicate this thesis to my brother and my grand-father, who recently left this life from a brain disease, letting behind them the immortal souvenir of the kindness, humility and greatness of their souls.

Abstract

The impact of Alzheimer's disease is devastating for the daily life of the affected patients, with progressive loss of memory and other cognitive skills until dementia. We still lack disease modifying treatment and there is also a great amount of uncertainty regarding the accuracy of diagnostic classification in the early stages of AD. The anatomical signature of AD, in particular the medial temporal lobe (MTL) atrophy measured with neuroimaging, can be used as an early in vivo biomarker in early stages of AD. However, despite the evident role of MTL in memory, we know that the derived predictive anatomical model based only on measures of brain atrophy in MTL does not explain all clinical cases. Throughout my thesis, I have conducted three projects to understand the anatomy and the functioning of MTL on (1) disease's progression, (2) memory process and (3) learning process. I was interested in a population with mild cognitive impairment (MCI), at risk for AD. The objective of the first project was to test the hypothesis that factors, other than the cognitive ones, such as the personality traits, can explain inter-individual differences in the MTL. Moreover, the phenotypic diversity in the manifestations of preclinical AD arises also from the limited knowledge of memory and learning processes in healthy brain. The objective of the second project concerns the investigation of sub-regions of the MTL, and more particularly their contributions in the different components of recognition memory in healthy subjects. To study that, I have used a new multivariate method as well as MRI at high resolution to test the contribution of those sub-regions in the processes of familiarity and recollection. Finally, the objective of the third project was to test the contribution of the MTL as a memory system in learning and the dynamic interaction between memory systems during learning.

The results of the first project show that, beyond cognitive state of impairment observed in the population with MCI, the personality traits can explain the inter-individual differences in the MTL; notably with a higher contribution of neuroticism linked to proneness to stress and depression. My study has allowed identifying a pattern of anatomical abnormality in the MTL related to personality with measures of volume and mean diffusion of the tissue. That pattern is characterized by right-left asymmetry in MTL and an anterior to posterior gradient within MTL. I have interpreted that result by tissue and neurochemical properties differently sensitive to stress.

Results of my second project have contributed to the actual debate on the contribution of MTL sub-regions in the processes of familiarity and recollection. Using a new multivariate method, the results support firstly a dissociation of the subregions associated with different memory components. The hippocampus was mostly associated with recollection and the surrounding parahippocampal cortex, with familiarity type of memory. Secondly, the activation corresponding to the mensic trace for each type of memory is characterized by a distinct spatial distribution. The specific neuronal representation, "sparse-distributed", associated with recollection in the hippocampus would be the best way to rapidly encode detailed memories without overwriting previously stored memories.

In the third project, I have created a learning task with functional MRI to sudy the processes of learning of probabilistic associations based on feedback/reward. That study allowed me to highlight the role of the MTL in learning and the interaction between different memory systems such as the procedural memory, the perceptual memory or priming and the working memory. We have found activations in the MTL corresponding to a process of episodic

memory; the basal ganglia (BG), to a procedural memory and reward; the occipito-temporal (OT) cortex, to a perceptive memory or priming and the prefrontal cortex, to working memory. We have also observed that those regions can interact; the relation type between the MTL and the BG has been interpreted as a competition. In addition, with a dynamic causal model, I have demonstrated a "top-down" influence from cortical regions associated with high level cortical area such as the prefrontal cortex on lower level cortical regions such as the OT cortex. That influence decreases during learning; that could correspond to a mechanism linked to a diminution of prediction error. My interpretation is that this is at the origin of the semantic knowledge. I have also shown that the subject's choice and the associated brain activation are influenced by personality traits and negative affects.

Overall results of this thesis have brought me to propose (1) a model explaining the possible mechanism linked to the influence of personality on the MTL in a population with MCI, (2) a dissociation of MTL sub-regions in different memory types and a neuronal representation specific to each region. This could be a cue to resolve the actual debates on recognition memory. Finally, (3) the MTL is also a system involved in learning and that can interact with the BG by a competition. We have also shown a dynamic interaction of « top –down » and « bottom-up » types between the pre-frontal cortex and the OT cortex. In conclusion, the results could give cues to better understand some memory dysfunctions in aging and Alzheimer's disease and to improve development of treatment.

Résumé

L'impact de la maladie d'Alzheimer (MA) est dévastateur pour la vie quotidienne de la personne affectée, avec perte progressive de la mémoire et d'autres facultés cognitives jusqu'à la démence. Il n'existe toujours pas de traitement contre cette maladie et il y a aussi une grande incertitude sur le diagnostic des premiers stades de la MA. La signature anatomique de la MA, en particulier l'atrophie du lobe temporal moyen (LTM) mesurée avec la neuroimagerie, peut être utilisée comme un biomarqueur précoce, in vivo, des premiers stades de la MA. Toutefois, malgré le rôle évident du LMT dans les processus de la mémoire, nous savons que les modèles anatomiques prédictifs de la MA basés seulement sur des mesures d'atrophie du LTM n'expliquent pas tous les cas cliniques. Au cours de ma thèse, j'ai conduit trois projets pour comprendre l'anatomie et le fonctionnement du LMT dans (1) les processus de la maladie et dans (2) les processus de mémoire ainsi que (3) ceux de l'apprentissage. Je me suis intéressée à une population avec déficit cognitif léger (« Mild Cognitive Impairment », MCI), à risque pour la MA. Le but du premier projet était de tester l'hypothèse que des facteurs, autres que ceux cognitifs, tels que les traits de personnalité peuvent expliquer les différences interindividuelles dans le LTM. De plus, la diversité phénotypique des manifestations précliniques de la MA provient aussi d'une connaissance limitée des processus de mémoire et d'apprentissage dans le cerveau sain. L'objectif du deuxième projet porte sur l'investigation des sous-régions du LTM, et plus particulièrement de leur contribution dans différentes composantes de la mémoire de reconnaissance chez le sujet sain. Pour étudier cela, j'ai utilisé une nouvelle méthode multivariée ainsi que l'IRM à haute résolution pour tester la contribution de ces sous-régions dans les processus de familiarité (« ou Know ») et de remémoration (ou « Recollection »). Finalement, l'objectif du

troisième projet était de tester la contribution du LTM en tant que système de mémoire dans l'apprentissage et l'interaction dynamique entre différents systèmes de mémoire durant l'apprentissage.
Les résultats du premier projet montrent que, en plus du déficit cognitif observé dans une population avec MCI, les traits de personnalité peuvent expliquer les différences interindividuelles du LTM ; notamment avec une plus grande contribution du neuroticisme liée à une vulnérabilité au stress et à la dépression. Mon étude a permis d'identifier un pattern d'anormalité anatomique dans le LTM associé à la personnalité avec des mesures de volume et de diffusion moyenne du tissu. Ce pattern est caractérisé par une asymétrie droite-gauche du LTM et un gradient antéro-postérieur dans le LTM. J'ai interprété ce résultat par des propriétés tissulaires et neurochimiques différemment sensibles au stress.
Les résultats de mon deuxième projet ont contribué au débat actuel sur la contribution des sous-régions du LTM dans les processus de familiarité et de remémoration. Utilisant une nouvelle méthode multivariée, les résultats supportent premièrement une dissociation des sous-régions associées aux différentes composantes de la mémoire. L'hippocampe est le plus associé à la mémoire de type remémoration et le cortex parahippocampique, à la mémoire de type familiarité. Deuxièmement, l'activation correspondant à la trace mnésique pour chaque type de mémoire est caractérisée par une distribution spatiale distincte. La représentation neuronale spécifique, « sparse-distributed», associée à la mémoire de remémoration dans l'hippocampe serait la meilleure manière d'encoder rapidement des souvenirs détaillés sans interférer les souvenirs précédemment stockés.
Dans mon troisième projet, j'ai mis en place une tâche d'apprentissage en IRM fonctionnelle pour étudier les processus d'apprentissage d'associations probabilistes basé sur le feedback/récompense. Cette étude m'a permis de mettre en évidence le rôle du LTM dans l'apprentissage et l'interaction entre différents systèmes de mémoire comme la mémoire procédurale, perceptuelle ou d'amorçage et la mémoire de travail. Nous avons trouvé des activations dans le LTM correspondant à un processus de mémoire épisodique; les ganglions de la base (GB), à la mémoire procédurale et la récompense; le cortex occipito-temporal (OT), à la mémoire de représentation perceptive ou l'amorçage et le cortex préfrontal, à la mémoire de travail. Nous avons également observé que ces régions peuvent interagir; le type de relation entre le LTM et les GB a été interprété comme une compétition, ce qui a déjà été reporté dans des études récentes. De plus, avec un modèle dynamique causal, j'ai démontré l'existence d'une connectivité effective entre des régions. Elle se caractérise par une influence causale de type « top-down » venant de régions corticales associées avec des processus de plus haut niveau venant du cortex préfrontal sur des régions corticales plus primaires comme le OT cortex. Cette influence diminue au cours du de l'apprentissage; cela pourrait correspondre à un mécanisme de diminution de l'erreur de prédiction. Mon interprétation est que cela est à l'origine de la connaissance sémantique. J'ai également montré que les choix du sujet et l'activation cérébrale associée sont influencés par les traits de personnalité et des états affectifs négatifs.

Les résultats de cette thèse m'ont amenée à proposer (1) un modèle expliquant les mécanismes possibles liés à l'influence de la personnalité sur le LTM dans une population avec MCI, (2) une dissociation des sous-régions du LTM dans différents types de mémoire et une représentation neuronale spécifique à ces régions. Cela pourrait être une piste pour résoudre les débats actuels sur la mémoire de reconnaissance. Finalement, (3) le LTM est aussi un système de mémoire impliqué dans l'apprentissage et qui peut interagir avec les GB par une compétition. Nous avons aussi mis en évidence une interaction dynamique de type

« top –down » et « bottom-up » entre le cortex préfrontal et le cortex OT. En conclusion, les résultats peuvent donner des indices afin de mieux comprendre certains dysfonctionnements de la mémoire liés à l'âge et la maladie d'Alzheimer ainsi qu'à améliorer le développement de traitement.

List of Abbreviations

- ADC: Apparent Diffusion Coefficient
- ANVOA: ANalysis Of Variance
- BMS: Bayesian Model Selection
- BOLD: Blood Oxygenation Level Dependent
- CA: Cornu Ammonis
- CSF: Cerebrospinal Fluid
- DCM: Dynamic Causal Modeling
- DTI: Diffusion Tensor Imaging
- DWI: Diffusion Weighted Images
- EPI: Echo-Planar Imaging
- fMRI: Functional Magnetic Resonance Imaging
- FWE: Family-Wise Error
- GLM: General Linear Model
- GM: Gray Matter
- GMV: Gray Matter Volume
- GMMD: Gray Matter Mean Diffusivity
- Haemoglobin: Hb
- Hipp: Hippocampus
- HPA: Hypothalamic-Pituitary-Adrenal
- HRF: hemodynamic response function
- IOT: Inferior Occipito-Temporal cortex
- LIOT: Left Inferior Occipito-Temporal cortex
- LVOT: Left Ventral Occipito-Temporal cortex
- ML: Maximum Likelihood
- mm: millimeters
- mn: Minutes
- ms: miliseconds
- MVB: Multivariate Bayesian
- MCI: Mild Cognitive Impairment
- NCI: No Cognitive Impairment
- OT: Occipito-Temporal cortex
- PhC: Parahippocampal cortex
- PCA: Principal Component Analysis
- PhC: Perirhinal cortex
- rIFG: Right Inferior Frontal Gyrus
- s: Seconds
- sMRI: Structural Magnetic Resonance Imaging
- SNP: Single Nucleotide Polymorphism
- SPM: Statistical Parametric Map
- TE: Echo Time
- TIV: Total Intracranial Volume
- TR: Repetition Time
- VOI: Volume of Interest
- WM: White Matter

Table of Contents

List of Figures

List of Tables

INTRODUCTION

In our society, we now live longer, but as a consequence we must confront age-related diseases such as dementia in particular Alzheimer's disease (AD). Today, more than 24 million people in the word are affected by dementia and this number is going to double every 20 years. Western Europe has an overall prevalence rate of 5.4% for the over 60's, which increases exponentially with age (Hebert, Scherr, Bienias, Bennett, & Evans, 2003; Mayeux & Stern, 2012).

The impact of this disease is devastating for the affected person, with the progressive loss of memory and other cognitive faculties prior to the onset of dementia. The consequences of this disease however, are also heavily borne by family and caregivers. We lack disease modifying treatement and there is still a great amount of uncertainty regarding the accuracy of diagnostic classification in the early stages of AD. Mis-diagnosis are due to several different factors including underlying heterogeneity in etiologies and the inter-individual differences in the manifestations of the disease.

In this thesis, I investigate the use of neuroimaging to identify the anatomical signature of AD in particular the medial temporal lobe (MTL) atrophy, which can be used as an early in vivo biomarker in early stages of AD. However, we know that derived predictive anatomical model based only on measures of brain atrophy does not explain all clinically identified cases of AD (e.g. on the basis of deficits in memory function). We also need an improved knowledge of the memory associated with the MTL to better understand the mechanisms of AD. The medial temporal lobe (MTL) is composed of structures that have a central role in

declarative memory. Memory decline and brain atrophy in the MTL are hallmarks of AD (Dubois et al., 2010). It has been suggested that neurofibrillary tangles (NFT) begin in the enthorinhal/perirhinal cortex (E. J. Barbeau, Pariente, Felician, & Puel, 2010; E. Barbeau et al., 2004; H Braak & Braak, 1991; Heiko Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006) before spreading to other MTL regions. Critically, the limited knowledge of memory and learning processes in terms of brain anatomy and function in interaction with other factors in healthy brain could prevent a full understanding of AD.

In my thesis, I used structural neuroimaging to first study individuals at risk for AD with Mild Cognitive Impairment (MCI). Secondly, I used functional neuroimanging in healthy controls to study the processes related to memory and learning in the temporal cortex. I also describe how the brain regions in the MTL can be modulated by inter-individual differences such as personality, emotions and other cognitive factors. The primary goal of the thesis is to build a personalised predictive model of AD that combines the existing anatomical brain biomarkers with theoretically driven functional mapping as well as taking into account the impact of idiosyncratic factors.

The thesis is subdivided in three main parts on: (1) AD, (2) memory and (3) learning processes (Figure 1).

The first part of this thesis is on AD and its pre-clinical stage using structural neuroimaging.

- I use a voxel based morphometry analysis of structural data in the Medial Temporal Lobe (MTL), a critical region affected by AD, to study the interaction between cognitive state (i.e. Mild Cognitive Impairment vs No Cognitive Impairment) and individual difference factors such as personality traits, in an elderly population.

The second part of this thesis is on memory models using functional neuroimaging.

- I employ the well-established fMRI paradigm Remember/Know, which assumes that distinct memory functions (i.e. recollection and familiarity) can separate structures in the MTL, in particular the hippocampus, the parahippocampal cortex and the perirhinal cortex.

The third part of this thesis is on learning using functional neuroimaging.

- I use the Multiple Cue Probabilistic Learning (MCPL) fMRI paradigm to investigate large-scale memory networks and to study the functional connectivity between local (within temporal cortex) and distant cortical (frontal cortex) and subcortical nodes.
- To further understand inter-individual variability in MCPL, I also associate parameters of learning with individual factors such as personality and depressive/anxiety symptoms.

Part 1 **Personality effect in Mild Cognitive Impairement**	**Part 2** **Recollection, Familiarity**	**Part 3** **Probabilistic learning**
Structural MRI	fMRI at 7T	fMRI with virtual game environment
Classical Multivariate	Multivariate Bayes	Causal Modelling
Patients	Healthy	Healthy

Figure 1. Plan of the thesis subdivided in three main parts on (1) Mild Cognitive Impairment, Alzheimer's disease and personality effect, (2) memory and (3) learning processes.The next raws describe the neuroimaging MRI technique, the statistical method used and the population studied for each of the three parts. MRI: Magnetic Resonance Imaging.T: Tesla.

1. ALZHEIMER'S DISEASE STATE AND PERSONALITY TRAITS

1.1. Alzheimer's disease definitions

1.1.1. A Dual entity

There is a consensus in the Inernational Working Group for New Reserch Criteria for the Diagnosis of AD to define Alzheimer's disease as having a **dual entity,** with clinical and pathological features defined by (1) a broad clinical spectrum including a predominant worsening of functional episodic memory that is followed or accompanied by other cognitive, behavioral and neuropsychiatric deficits and by (2) in-vivo biomarkers of AD pathology. Those biomarkers support the presence of AD pathological changes and can be detected in the cerebro-spinal fluid (CSF) or in the brain by means of MRI and PET neuroimaging techniques. However, diagnosis of AD is only certain with histopathological post-mortem analysis

Clinical aspects: The clinical classification of AD and the early stages of the disease are still highly debated. This can be explained by the fact that various aetiologies can lead to the same phenotype of disease; that AD pathology can begin well before subjective or cognitive deficits manifest; and that a true AD diagnosis is only confirmed post-mortem. Clinical classification is further complicated by the fact that some brains containing post-mortem neuropathological changes, have been observed in people without cognitive impairment during life (Dubois et al., 2010; Hyman et al., 2012a). **Memory deficits** in AD are characterized by predominant episodic memory impairment such as forgetting meetings or recent events. Autobiographical memory impairment also appears in AD patients with the more recent memories relating to their own life more quickly forgotten than older ones.

They also recall fewer details of events (i.e. less recollection), but can still have a feeling of familiarity with that initial event. A deficit in semantic memory, evaluated for example with verbal fluency, is also detected early on in AD, although it is more age-resistant. Deficits in working memory seem inconsistent between patients in the beginning of AD. In contrast, perceptual memory, tested by the perceptual priming effect (i.e. influence of one stimulus on the response on another stimulus) (Keane, Gabrieli, Fennema, & Growdon, 1991) and the procedural memory, evaluated mainly with visuo-motor or verbal tasks, are preserved in AD. These above mentioned types of memory are investigate through the different experimental works of the thesis (Amieva, Belliard, & Salmon, 2014).

Pathological aspects: The AD pathology consists of neurofibrillary tangles (NFTs), due to intraneural abnormal phosphorylation of tau protein, and senile plaques, mainly due to extraneural amyloid beta (Aβ) deposits with some possible deposits of phosphorylated tau. AD pathology can also be manifested by synaptic loss and vascular amyloid deposits in the brain (Dubois et al., 2010). **Braak** et al. have defined stages of neurodegeneration based on the typical AD lesions found during autopsy. The density and localization of extracellular amyloid deposits are not consistent enough between patients to determine the stages of neurodegeneration, however the six stages scale is well defined by the distribution of neurofibrillary tangles (NFT) and hyper-phosphorylated Tau protein. The stages are characterized by an expansion of the presence of NFT and hyper-phosphorylated Tau protein in the following regions: 1) the transentorhinal and perirhinal cortices; 2) the entorhinal cortex; 3) the hippocampus; 4) the limbic system and insular cortex; 5) the inferior occipito-temporal cortex (or fusiform gyrus) and the Heschl's gyrus; 6) the isocortortical association cortices (Figure 2) (H Braak & Braak, 1991; Heiko Braak et al., 2006). The distribution of NFT

also correlates more with the neurodegeneration and cognitive deficits, compared to the distribution of amyloid beta (E. Barbeau et al., 2011; H Braak & Braak, 1991; Heiko Braak et al., 2006; Thal et al., 1998).

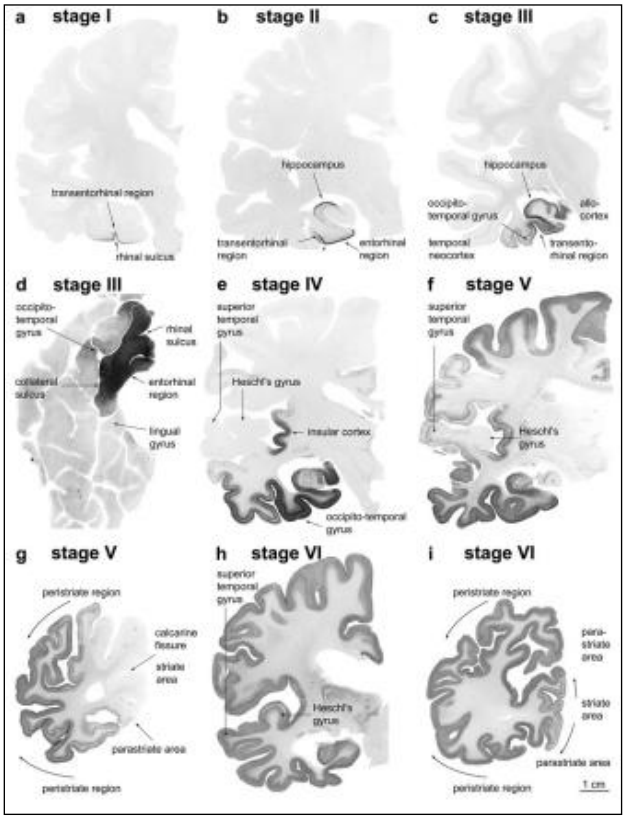


Figure 2. Schema of the main stages of the cortical neurofibrillay pathology distribution in the brain (Heiko Braak et al., 2006).

The identification of **in-vivo biological markers** of AD by means of different neuroimaging techniques such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and by means of biological sampling in the cerebro-spinal fluid (CSF) has considerably developed our knowledge of the disease. These biomarkers have mostly been used to exclude brain treatable causes, but are now recognized as promising tools to support diagnosis, to predict clinical outcome, to help the disease management and aid in new

treatment development. **High resolution structural MRI** can detect subtle brain changes considered as diagnostic markers for the identification of Mild Cognitive Impairment (MCI), for the prediction of conversion to AD and, critically, for the exclusion of a differential diagnosis (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Scheltens, Fox, Barkhof, & Carli, 2002). Measurement of hippocampal and entorhinal cortal volumes using MRI can efficiently distinguish MCI from healthy state as although hippocampal atrophy is between 15 and 48% with normal aging, it is much more pronounced in MCI and AD, with a change of 78 and 96% respectively. Structural abnormalities located in the MTL can separate MCI converters from non-converters and predict the future conversion to AD in a time of 12 to 77 months (Chételat et al., 2005). These MTL structural abnormalities observed in MCI spread to other temporo-parietal cortices such as the posterior hippocampus, the inferior, middle, superior temporal cortices, the insula, the precuneus and the posterior cingulate (Apostolova & Cummings, 2008). Changes in brain volume using MRI have even been detected 4 to 10 years before any cognitive impairment (Tondelli et al., 2011). Functional neuroimaging has also allowed investigation of synaptic activity and functional, cognitive and affective aspects of AD. PET radiological-contrast compounds are also still developed to trace brain molecules in-vivo such as inflammatory mediators and neurofibrillary tangles tracers (Johnson, Fox, Sperling, & Klunk, 2012; Perrin, Fagan, & Holtzman, 2009a; Villemagne & Okamura, 2014).

During **neurodegeneration**, there are changes in different pathological and topographical biomarkers. Despite some controversies on the sequence of biomarker change due in part to the unknown time of disease onset, a decreased concentration of Aβ42 in the CSF or Aβ42 PET tracer in the brain is usually the first detectable AD biomarker. Increased CSF levels of phosphor-tau and changes in the fluoro-deoxy-D glucose (FDG) metabolism follow the Aβ42 decrease. MRI biomarkers associated with atrophy in the MTL are closely linked to cognitive

deficit, but are the last observable marker. There are cases however, where tau pathology is present in the MTL of elderly healthy individuals and even prior to Aβ plaques in younger age. Structural MRI and tau protein levels detected in cerebro-spinal fluid (CSF) are strong predictors of the progression to Mild Cognitive Impairment (MCI) and AD (Toledo et al., 2014). However, development of an *in vivo* selective noninvasive imaging of tau proteins would aid the discovery of its role in AD and frontotemporal lobar degeneration (Villemagne & Okamura, 2014). New discoveries suggest that tau and amyloid lesions appear independently, although they can also have a common upstream and/or a synergistic toxicity depending on certain conditions such as in young, elderly people or early-, late-onset AD. Another recent study described, without taking into account any *a priori* clinical diagnostic knowledge or any biomarker cutoff, the sequence of biomarker changes with the conversion from healthy population to MCI and AD. The first change occurred in CSF markers, beginning with changes in total tau protein, then phosphorylated tau, followed by amyloid $\beta_{1\text{-}42}$, followed by changes in the rate of brain atrophy and cognitive deficits and finally a change in brain volume. However, the sequence of CSF biomarker changes is inverted for carriers of one or more APOE-4 genetic alleles or that have a certain amount of CSF amyloid markers (Young et al., 2014).

1.1.2. Mild Cognitive impairment and Subtypes of Alzheimer's disease

The exact cause of Alzheimer's disease still remains unclear, but, in addition to age, multiple other **factors** including genes and environment (Mayeux & Stern, 2012), gender and education level have been shown to influence disease onset and progression (Ganguli et al., 1991; Y. Stern, Gurland, Tatemichi, Wilder, & Mayeux, 2013; Zhang et al., 1990). Recently,

research has focused on a stage at risk for AD, called **Mild Cognitive Impairment** (MCI). It can be considered at a stage of evolving to AD, as the conversion rate of MCI to AD lies between 6 and 25% (Petersen, 2004a). There is a strong interest in finding the earliest biomarker of the MCI in order to develop therapeutic intervention and disease managment (Apostolova & Thompson, 2008). MCI defines a state of individuals who manifest cognitive decline and/or subjective cognitive complaints, but who are neither heathy aged nor demented. This is a heterogeneous clinical condition, with various possible aetiologies and cognitive profiles: with memory impairement or with single nonmemory or even with multiple cognitive domains. They refer to people suspected of having AD, but who do not fulfil all the described characteristics (Winblad et al., 2004). They can have memory symptoms not specific to prodromal AD or they can be biomarker negative (Dubois et al., 2010).

The stages of progression to AD, defined by the National Institute on Aging-Alzheimer's Association (NIA-AA) in 2012, were described as a continuum in time, from preclinical, MCI to dementia (Hyman et al., 2012). The International Working Group for New Research Criteria for the Diagnosis of AD has defined **a new lexicon for AD**: Prodromal AD is characterized by episodic memory impairment of hippocampal type (i.e. verbal free recall deficit) and CSF biomarker or imaging evidence, without any impairment in daily living; AD dementia is defined by cognitive symptoms with deficits in episodic memory impairment and at least one other cognitive domain, that interfere with social functioning and daily living activities. There are also **different variants of AD phenotypes:** Typical AD (Figure 3) is defined by progressive episodic memory impairment associated or accompanied by other cognitive impairments, neuropsychiatric changes and the presence of *in vivo* biomarkers of AD pathology; Atypical AD refers to patients showing *in vivo* biomarkers specific to AD but

with other clinical symptoms than typical AD. These cases can refer to logopenic variant of primary progressive aphasia with verbal short-term memory deficit and anomia. Frontal AD refers to individuals with deficits in executive functions and posterior cortical atrophy, to individuals with complex visuo-spatial deficits (Figure 3). The clinical features of each of these above described groups are predicted by the regional distribution of pathology in their brains as well as by genetic factors (Dubois et al., 2010; Warren, Fletcher, & Golden, 2012). In another study, AD was classified by limbic predominant and hippocampal sparing cases, characterized by the different location of neurofibrillary tangles (NFT) and atrophy in the brain. NFT are more present in the hippocampus than in cortical areas in the first case and *vice versa* in the second case. The hippocampal sparing cases had also less hippocampal atrophy, were younger and included more women than the other group (Murray et al., 2011).

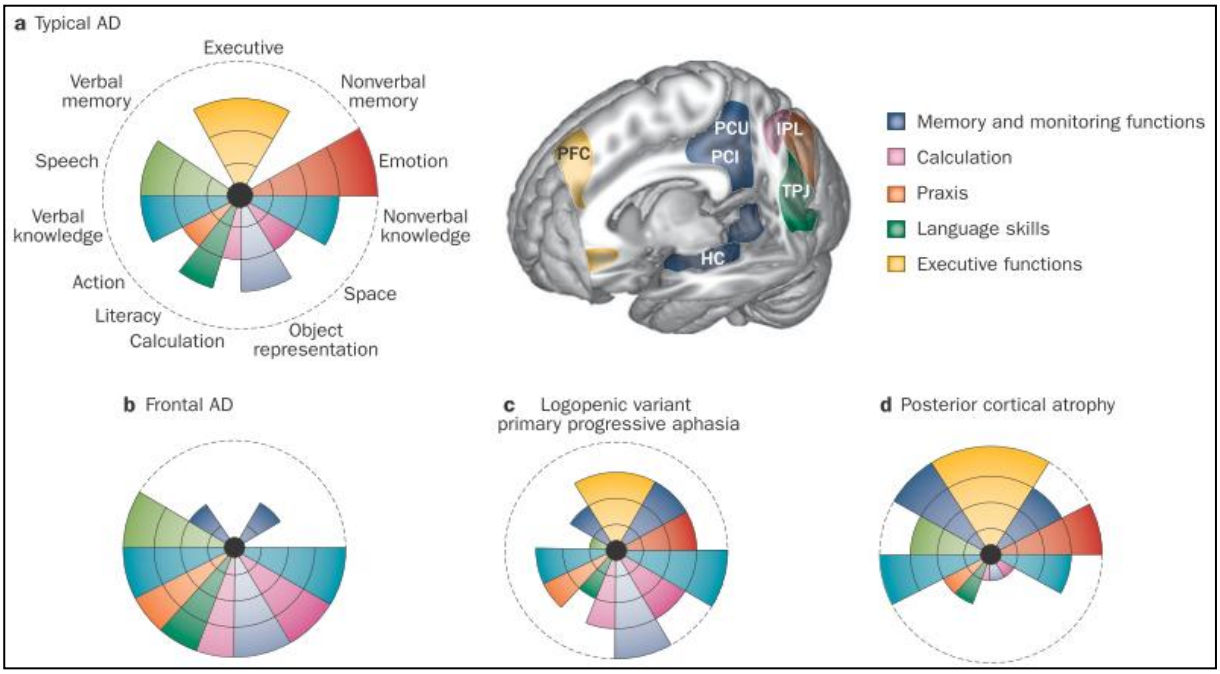


Figure 3. Schema of (a) the typical and (b-d) atypical AD (i.e. Frontal AD, logopenic variant primary progressive aphasia and posterior cortical atrophy) and the associated cognitive deficit compared with healthy age-matched controls (indicated by dotted lines). The radius (representing percentile scores) is shorter for more loss of function. Cognitive deficits are associated with specific brain regions (with the same color), but are not always related to the AD phenotype (Warren et al., 2012).

Mixed AD refers to a full typical AD diagnosis, but with other in vivo evidence of comorbid disorders such as cerebrovascular or Lewy Body diseases. Preclinical states of AD refer to stages of AD pathology, with brain lesions, but without any cognitive changes. These are often defined post-mortem but can also refer to living patients: notably those with presymptomatic AD that include individuals with AD monogenic mutations or asymptomatic at-risk for AD, and those with in-vivo biomarkers of AD, but with no evidence that predicts AD development.

1.1.3. Inter-individual differences in Mild Cognitive Impairment and Alzheimer's disease

There are a lot of debates on classifications of individuals with MCI because of the heterogeneity of this population. Indeed, persons with MCI can convert to AD, can stay stable or can recover (Winblad et al., 2004).

In addition, beyond the brain decline commonly described in AD, clinical evidence shows inter-individual differences between observed brain pathology and cognition. Different patients with the same level of AD brain pathology can be at high or low risk of MCI depending on genotype, cognitive reserve or life style (Jack et al., 2013).

The multifaceted nature of AD can lead to wide inter-individual differences in disease manifestation. The lack of understanding of phenotypic diversity in AD also arises from the limited knowledge of the anatomo-functional network of memory and learning in the healthy brain, but also from the difficulty in understanding the integration of different levels of network organization (i.e. genes, neurons, synapses, anatomical regions, functions, and physiology) and in inclusion of other information such as neuropsychiatric characteristics (e.g. depression, apathy, anxiety and sleep disturbance), personal history, information about general health or subjective cognitive complaints in a coherent model (Belleville, Fouquet, Duchesne, Collins, & Hudon, 2014; Lebedeva et al., 2014; Winblad et al., 2004). Diagnostic error can also come from the main emphasis on memory to assess the onset of dementia (Warren et al., 2012).

In this context, other factors, such as personality traits, can be very informative markers of early disease stage. It is known that personality can affect cognition, behavioral and

psychiatric symptoms and ways to cope with difficulty, which could help to manage the disease manifestations and to alleviate the related burden (Donati et al., 2013; von Gunten, Pocnet, & Rossier, 2009). The concept of personality will be explained in more detail in the next chapters.

1.2. Personality and depression/anxiety effects on cognition

1.2.1. Personality definition and measure

Personality is defined as a long-tem, stable, individual characteristic resulting from the co-adaptation between emotion and cognitive information processing. To investigate personality using objective measure, different models exist, but here I focused on a model that has been constructed based on a factorial analysis of language samples and psychological tests. It is structured in five orthogonal personality dimensions and is called the "**Big Five**" model. The dimensions of that model are well concordant with other existing models of personality, for example with the P-E-N three factors model from Eysenck, and have a robust stability in time in adults. They also remain stable between self and external rating. The labels of these dimensions or domains can differ, but they generally refer to traits of Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness. To better explain inter-individual variability, 6 facets subdivide each of those five dimensions (Goldberg & Rosolack, 1994). Neuroticism is related to the general tendency to feel distress or a negative affect such as anger, anxiety, envy, guilt and a depressed mood. The level of neuroticism is based on a continuous scale. The two extremes of this scale represent emotional stability against a low control of impulse in stressful situations and may also be linked to risks of psychiatric problems. The depression facet of neuroticism measures the tendency to feel sadness, guilt, despondency and loneliness. Extraversion refers to a tendency towards sociability and liveliness, openness, to a tendency to be open to new experiences, agreeableness, to be cooperative, altruistic and trusting, and conscientiousness, to be careful, dutiful and responsible () (P. Costa & MacCrae, 1992).

The five personality traits can be measured with the Revised NEO Personality inventory (Neo-Pi-R). They are hierarchically organized in five domains containing six facets (Figure 4) (Bienvenu et al., 2004a). This questionnaire contains 240 items and is assessed by a five-level scale from “strong disagreement” to “strong agreement”. This is used as a hetero-evaluation by close proxy. A high score on one domain means a higher probability of expressing that trait relative to a normal distribution. This test is known to have a very good test-retest reliability, and internal/external validity for long periods and with age (P. Costa & MacCrae, 1992; Roepke, McAdams, Lindamer, Patterson, & Jeste, 2001).

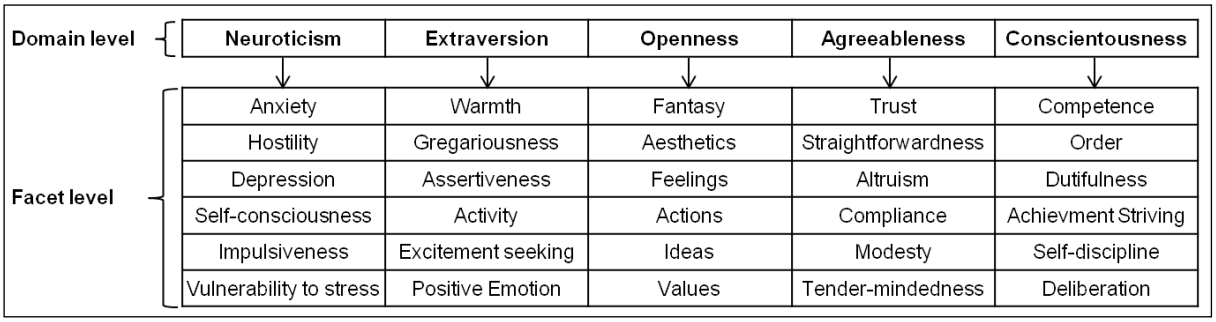


Figure 4. NEO Personality inventory (NEO-Pi-R) is hierarchical construct composed of 5 domains and 6 facets in each domain.

1.2.2. Personality and cognition/memory

A personality trait or temperament generally refers to **non-cognitive** component (or “what we generally do”) and can be measured with self-report inventories whereas intelligence is mainly measured with objective tests (or “what we can do”). However, some psychologists such as Cattell and Eysenck have tried to assess intelligence as a **cognitive** component of personality. Further, in a meta-analysis, crystallized intelligence, or acquired knowledge, was correlated with neuroticism, extraversion and openness, but cognitive speed related to fluid

intelligence was only correlated with extraversion (Ackerman & Heggestad, 1997). In a study by Chamorro et al., 2006 (Chamorro-premuzic & Furnham, 2006), “measured intelligence” and “actual intelligence” slightly differed with the former referring to effects of personality on cognitive test performance; for example anxiety could impair cognitive performance. The latter referred not only to the effect of personality on intelligence, but also to the inverse relation. For example, the positive link between openness and crystallized intelligence can be explained by the fact that more intellectual curiosity is associated with higher cognitive experience and the acquisition of more knowledge. However, it is not clear which is the cause and the consequence, as it could be the acquisition of more knowledge that has an impact on openness.

Personality has also been related to choice of **learning strategy** such as task or effort/ego-orientated-learning and to **cognitive styles** such as rumination (i.e. thinking about an idea such as causes, meanings and consequences of symptoms in a sustained and repetitive way) (E. Roberts, Gilboa, & Gotlib, 1998; Vermetten, Lodewijks, & Vermunt, 2001)**.** Personality has been shown to affect efficacy of working memory training (Chamorro-premuzic & Furnham, 2006b , Studer-Luethi, Jaeggi, Buschkuehl, & Perrig, 2012), emotional memory (Richards & Gross, 2006), prospective memory (Uttl, White, Wong Gonzalez, McDouall, & Leonard, 2013) and subjective complaints of memory in elderly subjects (Merema, Speelman, Foster, & Kaczmarek, 2012; Naghavi, Lind, Nilsson, Adolfsson, & Nyberg, 2009a).

1.2.3. Neurobiology of personality

The five dimensions of personality have been studied as biological substrates at different levels, from molecular genetics to psychophysiology and brain systems (Deyoung, Hirsh, Shane, & Papademetris, 2010). Personality is thought to be around 50% determined by genetics with gene-environment interaction or individual temporal environment having equal influence (Loehlin, McCrae, Costa, & John, 1998). Heritability of the anxious trait is between 40 and 50% (Montag, Reuter, Jurkiewicz, Markett, & Panksepp, 2013).

A **neuroimaging** study (Deyoung et al., 2010) correlated the five domains of personality with Gray Matter Volume (GMV) in 116 healthy adults. As personality reveals frequent behavioral tendencies that could be related to the regular functioning of specific brain systems, personality could be anatomically associated with those systems. They found that neuroticism was associated with volumes of frontal and temporal brain regions (i.e the right dorsomedial pre-frontal cortex, the left mid temporal lobe, the posterior hippocampus, the globus pallidus and the bilateral subthalamic nuclei) regions involved in processing of negative and threatening information. Extraversion was associated with the medial orbitofrontal cortex, which is involved in reward processing and agreeableness, along with the posterior cingulate cortex and superior temporal cortex, which are concerned with the processing of mental states of others. Finally, conscientiousness was positively associated with the lateral pre-frontal cortex and negatively with inferior occipito-temporal cortex and the lateral prefrontal cortex, involved in control of behavior (Deyoung et al., 2010).

In another study, **neuroticism** was also associated with the volume of frontal and temporal brain regions (Montag et al., 2013). The prefrontal cortex is related to top-down regulation of anxiety and rumination, meaning related to high-level cognitive interpretation or

reappraisal of an anxious stimulus. In contrast, perception of anxiety and emotional affects is associated with low-level processes that generate quick, bottom-up affective analysis of the stimulus in the amygdale or the hippocampus (Ochsner et al., 2010). The orbitofrontal cortex is relatd to reward hedonic processing. In addition, a negative association has been found between neuroticism and fractional anisotropy (measuring fiber density using Diffusion Tensor Imaging (DTI), cf. more details in the appendix, chapter 6.3. “Neuroimaging”) in white matter fibre tracts of the uncinante fasciculus, which connects the ventral medial prefrontal cortex and the amygdale. It is speculated that this connection is involved in top down processes for emotion regulation (Montag et al., 2013; Ochsner et al., 2004; Zuurbier, Nikolova, Åhs, & Hariri, 2013). In the review of Montag et al., 2013 (Montag et al., 2013), it is highlighted that the associations between brain regions and personality are only correlations. In general, it is not clear which factor is the cause and which is the consequence and not all brain changes are related to personality. In addition, in a study, a distinction was also made between the trait of anxiety, related to neuroticism, and the state or behaviour of anxiety. Anxiety is a response to an uncertain environment related to self-safety. State and trait differ in the fact that the first is more transient than the second, though an overlap can exist. Indeed, repetition of the same state over time correlates with trait, indicating that a transient state can become a trait if it is maintainated over time. It is also argued that anatomical brain measures may be better suited to testing the effect of personality trait, whereas functional brain measure may be better to test the effect of states (Montag et al., 2013).

Openness, associated with intellectual engagement and imagination, was shown to be related to a decreased annual rate of GMV over the course 6 years, in the right inferior parietal lobules, regions involved in working memory and creativity (Taki et al., 2013).

In Gray's theory, introverts are more sensitive to punishment and to the frustration coming from no reward than extraverts (Gray, 1970). In Eyeseck's model, introverts, who experience lower arousal, are more efficient than extraverts in an environment with low arousal potential (Eysenck HJ, 1967). In the brain, introversion is thought to involve inhibitory systems called the "Ascending Reticular Activating System" that includes the orbital frontal cortex, the medial septal area and the hippocampus (Gray, 1970). A recent study confirmed that a high extraversion score was associated with a greater change in BOLD MRI signal, or greater cortical arousal, in the dorsolateral prefrontal cortex and the anterior cingulate cortex in a task demanding attention (Kumari, Ffytche, Williams, & Gray, 2004). Inter-individual differences in extraversion are explained by the sensitivity to positive incentive and by motivation for behavioural approach. Processing of the saliency of incentive information depends on the medial prefrontal cortex, the amygdala and the hippocampus, whereas the processing of stimuli intensity promoting motivation would depend on dopaminergic structures such as the nucleus accumbens, the ventral pallidum and the ventral tegmental area. Finally, the generation of motivation to move is associated with the motor system (Depue & Collins, 1999). In a recent study, the magnitude of brain activation related to the reward system in the left medial orbitofrontal cortex and the right nucleus accumbens was predicted by both extraversion and presence of a specific allele on a dopaminergic receptor gene (M. Cohen, Young, Baek, Kessler, & Ranganath, 2005).

It has also been shown that the revised 7 factors measuring personality temperaments and characters by Cloninger's Tridimensional Personality Questionnaire (TPQ) were independently heritable and dependant on monoaminergic pathways (Cloninger, 1986; Gillespie, Cloninger, Heath, & Martin, 2003). For example, novelty-seeking, a tendency to be explorative and more sensitive to novel and rewarded stimuli, is linked to dopaminergic

neurotransmission and dopaminergic genes (Benjamin et al., 1996). People with a high **novelty seeking** trait and low harm avoidance traits, as measured by the Clooniger's temperament test, showed a greater sensitivity in the hippocampal region upon the presentation of novel stimuli, which is the inverse for the opposite personality profile (Naghavi et al., 2009).

Personality trait related to anxiety has also been associated with **genetics.** For example, genetic marker of serotonin neurotransmitter could contribute to explain 3 to 4% of the anxiety-related personality trait (K. Lesch et al., 1996; Sen, Burmeister, & Ghosh, 2004).

1.2.4. Depressive/anxiety symptoms related to learning and memory

Some aspects of memory and leaning are affected by a subset of depressive patients (Burt, Zembar, & Niederehe, 1995), showing the diversity of mechanisms that can appear. However, in different studies, depressed patients improved in learning and memory performance after drug treatment (Weingartner HG, 1981).

Depressive symptoms are associated with less efficient processing in effortful learning tasks. This can be explained by a diminished level of arousal and concentration, by negative ruminative thoughts, by deficit of control and maintenance of attention on relevant aspects and by a deficit to remove irrelevant information from their working memory (Channon, 1996; R. Cohen, Ph, Lohr, Paul, & Boland, 2001; Hammar et al., 2011). Depression also leads to an impairment in autobiographical memory, more particularly for positive memories (Brittlebank et al., 1993). Depression symptoms also have an impact on cognitive emotion regulation strategy such as rumination, positive reappraisal, self-blame or catastrophizing

(Garnefski & Kraaij, 2006). In the elderly, the level of depression is correlated with memory complaints but not with performance (Robert L. Kahn, PhD; Steven H. Zarit, PhD; Nancy M. Hilbert, MA; George Niederehe, 1975). Stress has also been associated with increased learning of stimuli with positive valence (Lighthall, Gorlick, Schoeke, Frank, & Mather, 2013).

1.2.5. Personality and non-cognitive factors related to Mild Cognitive Impairment and Alzheimer's disease

The actual debate on **personality** and AD is on whether personality change represents a loss or accentuation of traits or whether a "universal Alzheimer personality" exists. Personality is defined as a stable characteristic of a person when reacting to different situations, such as how they cope with adversities. However, high score of neuroticism is associated with higher risk of experiencing stressful and negative events, the occurrence of psychiatric problems such as depression and anxiety disorders, comorbidity with other mental disorders, a lower quality of life, less social support and a shorter life expectancy (Lahey, 2009). Even if a personality represents a more stable concept than a state, which is temporary and fluctuating, there is still controversy over their relation with psychopathologies. A decreasing enthusiasm and energy are consistently found in AD (Montag et al., 2013; Robins Wahlin & Byrne, 2011; von Gunten et al., 2009). It has also been shown that personality, more particularly an increase in neuroticism and a decrease in conscientiousness, can discriminate between healthy individuals and those with a very mild AD dementia (Robins Wahlin & Byrne, 2011). Low level of conscientiousness can also predict MCI and AD (R S Wilson, Schneider, & Boyle, 2007). In other studies, neuroticism has also been shown to be

predictive of cognitive impairment and AD (Balsis et al., 2005; Duchek et al., 2007; Wilson et al., 2004; 2006b; 2011; 2012). A 12 years follow-up study (Kuzma et al. (2011) showed that a high score of neuroticism increased the probability of cognitive decline more than two-fold. Semantic memory or the feeling of self-identity may be impaired between mild and severe AD, because past personality profile seems to be more reported by patients when asked to describe their current one (Donati et al., 2013). Investigation of personality by the surrounding of the patient seems thus a more objective measure.

Other non-cognitive factors such as **behavioral and psychological symptoms (BPS)** referring to affective, behavioural or psychotic disorders can also be part of some personality dimensions, but the relation between them is not fully established. However, a change of personality and BPS are co-determinants in the prediction of a future decline in MCI (Rouch et al., 2014; von Gunten et al., 2009). In addition, the inclusion of neuropsychiatric symptoms such as depression, apathy, anxiety, irritability and sleep disturbance can also increase the prediction of conversion from MCI to AD (Belleville et al., 2014) and could represent a higher risk for rapid cognitive deterioration and institutionalization. Some studies have also shown associations between depression and a higher risk of developing cognitive impairment and AD (Chung & Cummings, 2000; Jones, Fitzpatrick, Breitner, & Dekosky, 2012; Vicini Chilovi et al., 2009; von Gunten et al., 2009). For example, 85% of amnesic MCI and 43% of persons with MCI or dementia manifest neuropsychiatric symptoms with depression and then apathy or anxiety (Jones et al., 2012a; Rozzini et al., 2008). Other studies suggest that in late-life, depression may be an early manifestation of dementia rather than increasing risk for dementia (Scale, National, & Discharge, 2011). However, it is not clear whether BPS are persistent changes of personality or ephemeral manifestations. One study suggested the existence of a spectrum between personality and psychopathology

in which all phenotypes/behaviours could be explained by external factors such as genes and environment (Krueger et al., 2002).

1.3. Open questions

Personality traits are clinical predictors of Alzheimer's disease in the same way as cognitive impairment. The identification of biological markers associated with personality in Mild Cognitive Impairment (MCI) would advance the early detection and understanding of AD mechanisms. The aim of the first project (Figure 5) is to quantify the interaction between personality traits, state of cognitive impairment and MRI-based anatomical biomarkers within the Medial Temporal Lobe (MTL). State refers to temporary feelings, but trait, to more stable characteristic. This will be investigated in chapter 1.4 entitled "Experiment 1 - Traits of neuroticism, depression and anxiety exacerbate state of cognitive impairment and hippocampal vulnerability to Alzheimer's disease**"**.

Part 1 **Personality effect in Mild Cognitive Impairement**
Structural MRI
Classical Multivariate
Patients

Figure 5. Plan of the first part of the thesis. The raws describe the research topic, the neuroimaging MRI technique, the statistical method used and the population studied. MRI: Magnetic Resonance Imaging.

1.4. Experiment 1 - Traits of neuroticism, depression and anxiety exacerbate state of cognitive impairment and hippocampal vulnerability to Alzheimer's disease

1.4.1. Objective

Translational research in Alzheimer's disease (AD) relied mostly on tests based on assessment of cognitive state for the identification of individuals at risk - Mild Cognitive Impairments (MCI) - and for the detection of biomarkers - Medial temporal Lobe (MTL) atrophy (Apostolova & Thompson, 2008b; Dubois et al., 2010; Perrin, Fagan, & Holtzman, 2009b; Petersen, 2004b; Scheltens et al., 2002; Winblad et al., 2004). Looking beyond the unidimensional concept of MCI, current research aims to identify other important factors (genetic, environmental…) and to model their interactions for explaining disease progression. The main key challenge for improving the prognostic accuracy of the current tests is explaining the high degree of individual variability in MTL atrophy not associated with cognitive decline. Considering that in AD, personality changes, perhaps more than cognitive decline, are also salient feature of the disease (Donati et al., 2013; Dubois et al., 2010; Petersen, 2004b; Robins Wahlin & Byrne, 2011; Terracciano et al., 2013; von Gunten et al., 2009; R S Wilson et al., 2007; Robert S Wilson et al., 2006; Winblad et al., 2004), our study aims to test whether pre-clinical and normal facets of personality might explain individual differences within MTL. Interest in personality traits and AD in previous studies (Kuzma, Sattler, Toro, Schönknecht, & Schröder, 2011b; R S Wilson et al., 2004; Robert S Wilson et al., 2011) were motivated by the fact that personality traits are stable in adulthood (Hampson & Goldberg, 2006; B. W. Roberts & DelVecchio, 2000) with genetic underpinnings (Jönsson et al., 2003; K.-P. Lesch et al., 1996; Van Gestel & Van Broeckhoven, 2003) and predictive of

late life events such as cognitive dysfunction (R S Wilson et al., 2007), psychiatric symptoms (Lahey, 2009). However, the influence of personality traits on disease causation and biological manifestations still remains unclear (Apostolova & Thompson, 2008; Duron et al., 2014; Terracciano et al., 2013; Robert S Wilson et al., 2006, 2011). To quantify MTL atrophy, we used structural magnetic resonance imaging (sMRI) and the derived measure of gray matter volume (GMV) and gray matter mean diffusivity (GMMD). GMMD is considered as more subtle markers of brain tissue properties related mainly to water diffusivity in MCI (Matthias et al., 2007).

We used a multivariate strategy (Kawasaki et al., 2007; Kherif et al., 2002) to provide a comprehensive explanation of the association between personality traits (P. Costa & MacCrae, 1992), cognitive state and brain anatomy. The method (Figure 6C) is data-driven, unbiased, take into accounts the multidimensional and hierarchical nature of personality traits at domain level (neuroticism, extraversion, openness, agreeableness and conscientiousness) and facet level (P. Costa & MacCrae, 1992) (Figure 6A) and used anatomical constraint to decompose the different sources of variability (Figure 6B).

We hypothesized first that cognitive state (i.e. Mild Cognitive Impairment (MCI) vs No Cognitive impairment (NCI)) would explain differences in the MTL for both GMV and GMMD. Our main hypothesis is that reduced set of personality traits with a precise spatial effect along known functional organization within the MTL (e.g. gradient along the longitudinal axis) (Bryan a. Strange, Witter, Lein, & Moser, 2014) would explain the anatomical inter-individual variance between the two groups not already explained by cognitive state. We predict that neuroticism and the underlying facets -anxiety, depression and stress- have the most contributive effect in the disease progression models.

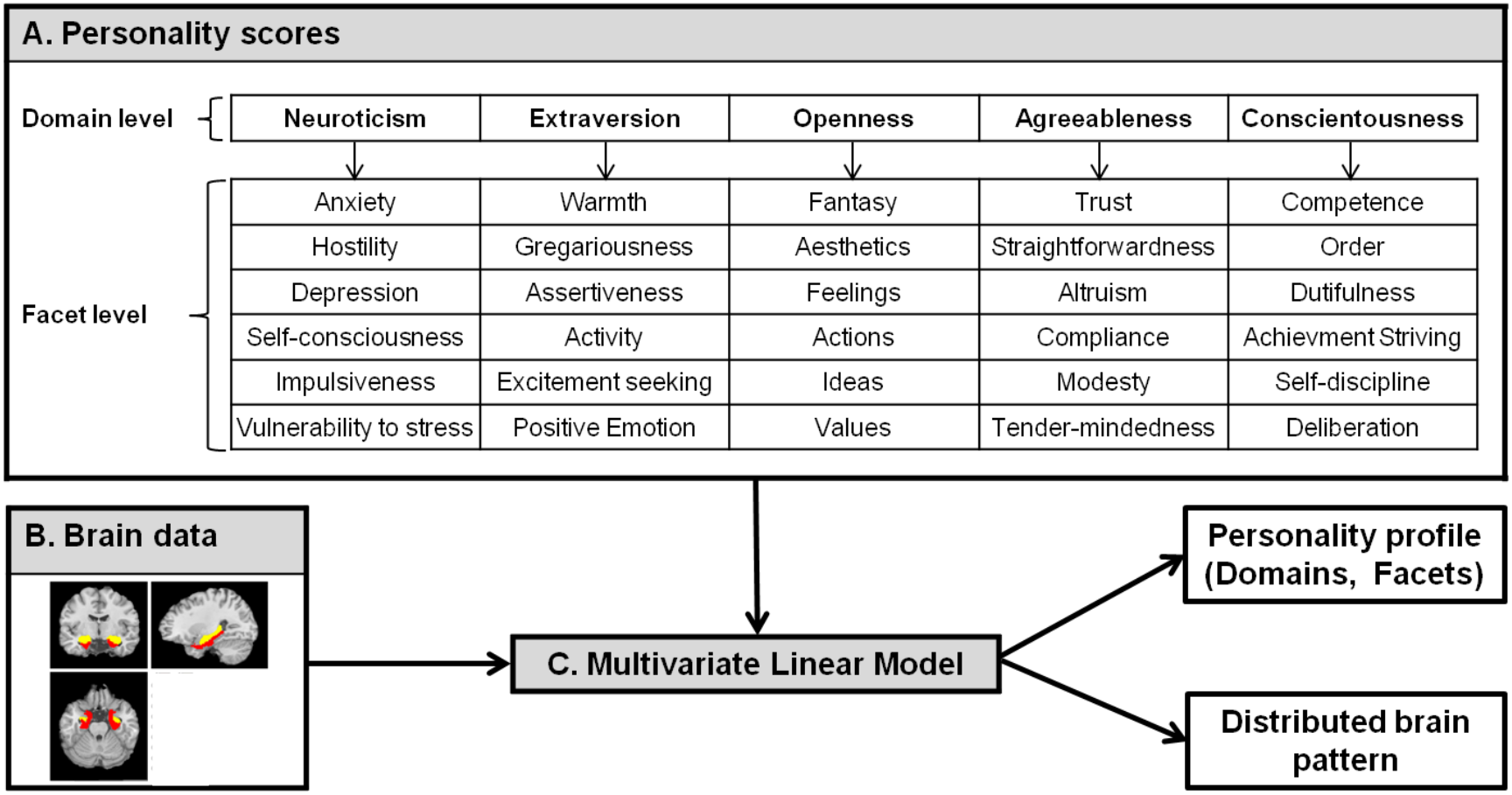


Figure 6. Multivariate association between NEO Personality inventory (NEO-Pi-R) and MTL anatomical differences. (A) NEO-Pi-R is a hierarchical construct of 5 domains containing 6 facets. (B) Search volume of interest with the hippocampus in yellow and parahippocampal cortex in red. (C) Multivariate Linear Model (MLM) identified the personality profile and the brain distributed pattern that best explain the covariance between them.

1.4.2. Materials and methods

Neuropsychological, psychological and psychiatric measures

Participants. The study included older adults selected from a longitudinal cohort recruited from the psychogeriatric and geriatric memory clinics of the Lausanne University hospital. The local ethics committee gave permission for the research protocol and all participants gave written informed consent before taking part in the study. All participants completed comprehensive clinical, psychiatric and cognitive assessments with a psychologist or neuropsychologist before a session of MRI scanning. Participants with psychiatric or neurological CNS disorders (stroke, tumor), dementia and alcohol or drug abuse were excluded. The 97 participants included in the study were divided in two groups, MCI and NCI, according to the conventional Winblad's criteria (Winblad et al., 2004), in which MCI is defined as not normal and do not fulfill the diagnostic criteria for dementia with Clinical Dementia Rating scale (CDR) (Morris, 1993) score being 0.5. 29 participants were MCI (age mean: 68 years, SD: 8 years, Male:Female (8:21), MMSE: 27.7±1/ range [25-29], CDR=0.5) of whom 23 were MCI with amnesic syndrome (Winblad et al., 2004), and 68 were NCI (age mean: 66 years, SD: 6 years, Male:Female (18:50), MMSE: 29.1±1/range [26-30], CDR=0). MMSE measures the cognitive state (Folstein, 1983)**.** The cued-recall RI-48-item task was also used to test episodic memory (Buschke H, Sliwinski MJ, Kulansky G, 1997).

Personality and neuropsychological/psychiatric assessments. Aiming to obtain reliable measures of current personality profile, the relatives of participants we asked to complete the 240-items Neo-Pi-R personality questionnaire (P. Costa & MacCrae, 1992). This

questionnaire, rated on a 5-point agreement scale, is based on the Five-Factor Model of personality derived from statistical factorial analysis of various personality inventories. It is hierarchically divided into five broad domains: neuroticism (a tendency to feel negative affects and to be susceptible to psychological distress), extraversion (a tendency to be sociable and lively), openness (a tendency to be open to new experiences), agreeableness (a tendency to be cooperative, altruistic and trusting), and conscientiousness, (a tendency to be careful, dutiful and responsible). Each domain contains six facets (Figure 6A). The facets of the neuroticism domain are anxiety, angry hostility, depression, self-consciousness, impulsiveness, and vulnerability to stress. The test NEO-PI-R has a high test-retest reliability in the elderly (P. Costa & MacCrae, 1992), and high inter-rater reliability in patients with AD (Strauss M, Pasupathi M, 1993).

Internal reliability of the NEO-PI-R scores was estimated with Cronbach's alpha. In our sample the values ranged from 0.63 to 0.68 for the NEO-PI-R domains and from 0.79 to 0.87 for the facets of neuroticism (a nominal value of 0.7 denotes internal consistency (Boyle J Gregory, Matthews Gerald, 2008)). TPQ-Novelty Seeking score was also calculated with a weighted combination of NEO-FFI-R five personality traits. The scale is -0.09*neuroticism + 0.32*extraversion + 0.17*openness - 0.1*agreeableness - 0.6*conscientiousness. High score of novelty-seeking mean high excitement by novel stimuli (P. Costa & MacCrae, 1992; Jonathan Benjamin, Lin Li, Chavis Patterson, Benjamin D. Greenberg, Dennis L. Murphy, 1996). To measure anxiety and depressive symptoms, the Hospital Anxiety and Depression Scale (HADS-A and HADS-D respectively) was used (Zigmond, AS, Snaith, 1983) .

MRI sequences

Data was acquired using whole-brain MRI T1-weighted (T1w) structural images (sMRI protocol-1mm isotropic resolution with a matrix of 256*256 voxels, TR 2.3s, TE 2.91s) and diffusion weighted MR images (DWI) (1.8x1.8x2 mm^3 resolution, with a matrix of 128x128 voxels, 30 directions, high b of 1000s/mm^2) on a 3T MRI scanner (Siemens Trio).

Univariate statistical analysis: Voxel-based Quantification

We first conducted an univariate regression analysis to test for differences in the brain measures (GMV and GMMD) between MCI and NCI groups. The model included the cognitive state stratification factor and age and total intracranial volume (TIV) as confound variables. In a second model, the personality scores were included as parametric modulators of each group to test the interaction of cognitive state with personality traits (Figure 7).

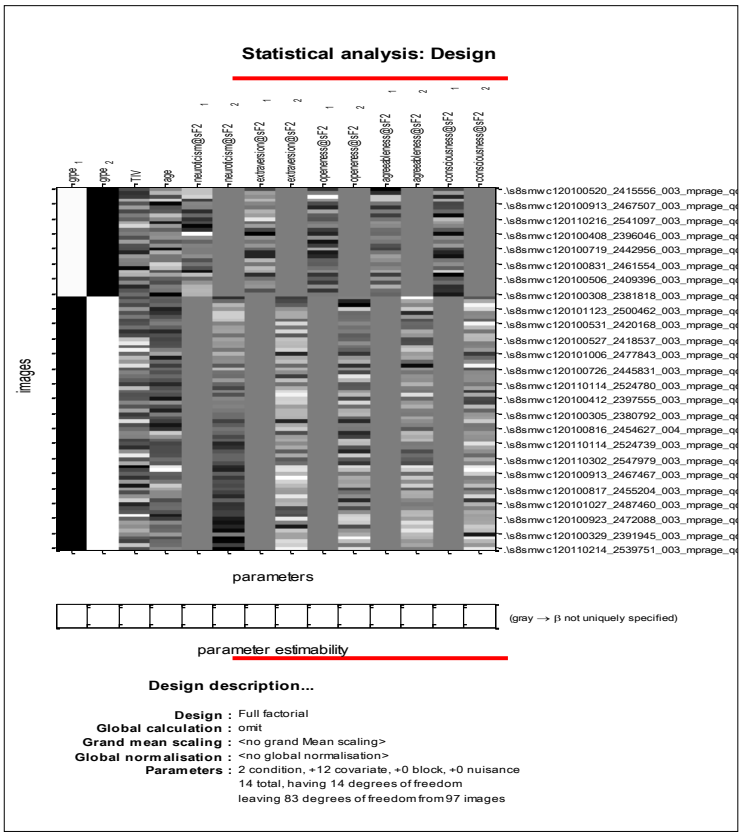


Figure 7. Design matrix including the factor of cognitive state (MCI/NCI), the confounding factors age and Total Intracranial Volume (TIV) and the five personality trait scores as regressors for each group. The first two columns represent subject's scans.

Multivariate Linear analysis of Medial Temporal Lobe abnormality associated with personality

Secondly, we used a multivariate model (Kherif et al., 2002) to address the question whether, beyond cognitive factors, there are specific personality profiles that can explain anatomical differences between MCI and NCI in the MTL. In the literature, multivariate factorial analysis (MFA) has often been used in studies of personality to extract significant factorial structures (P. Costa & MacCrae, 1992; Goldberg, 1990; Roepke et al., 2001). We used a variant, the multivariate linear method (MLM), which is similar to standard MFA, but it additionally integrates anatomical information together with the cognitive variables and confounds. The MLM procedure is based on singular value decomposition (SVD) which summarizes covariance between the anatomical data and personality scores. The output of the MLM is pairs of spatially distributed brain patterns associated with a set of linear combinations of personality traits that are maximally correlated with brain patterns. The significance of the personality profiles is assessed with a multivariate F-test (based on partial averages of the eigenvalues) that defines the spaces of interest for the five personality domains, beyond those of the cognitive and other confounding factors. Post-hoc univariate analyses were then performed with identified profiles to determine their mapping at the voxel level. Note that the proper test is based on multivariate analysis (Kherif et al., 2002). In addition, we performed a MLM analyses at the facet level within the whole search volume of interest.

The detailed mathematical formula of MLM method can be found in articles from Kherif et al. (Kherif et al., 2002, and Worsley et al., 1997) and in appendix in the chapter “6.5. Multivariate Linear Method”. The number of significant personality profiles is assessed with a multivariate F-test (based on partial average of the eigenvalues).

In our case of multi-dimensional predictors (with many personality traits and many voxels in the MTL), the usage of MLM is particularly suited, not only because of the high-dimensional data, but also because the analysis is performed on effect of interest only (i.e. personality model) and the interpretation is easier. It is also faster to build a concise model that includes the most contributive predictors than doing multiple univariate analysis. As a post-hoc test, there is the possibility to apply a standard univariate, voxel-wise, statistical analysis of the effect of the extracted particular personality profile in the MTL. Here, instead of only testing where MCI shows more atrophy associated with each personality scores compared to NCI (e.g. with contrast 1 for NCI and -1 for MCI for neuroticism score), we inserted the weight extracted from the MLM.

1.4.3. Results

Demographic, personality traits and neuropsychological/psychiatric results

In summary (see details in table 1), there were no statistical differences between MCI and NCI groups for all demographic variables (age, gender). As expected, the MMSE and CDR scores were significantly different between the two groups although the mean MMSE score was high in the MCI group. There were also no statistical differences in HADS-D for depressive symptom and HADS-A for anxiety symptom scores. The memory scores measured with the RI-48 memory item task were significantly lower in the MCI group. Neuroticism trait scores were also significantly higher in MCI patients (Table 1).

Instead of testing each personality trait separately, we did a multiple regression analysis with all traits scores in one model to take into account correlation between traot scores. In this case, the analysis revealed that personality could significantly explain 27.8% of the

variability (R^2=0.278) in cognitive state (p<0.001, F=7.02, df=5, n=97). The significant domains were agreeableness (p=0.04, Beta=-0.21, T=-2.06), conscientiousness (p<0.001, Beta=-0.43, T=-4.1), but not neuroticism (p=0.19, Beta=-0.14, T0-1.32), extraversion (p=0.28, Beta=-0.11, T=-1.08) or openness (p=0.065, Beta=-0.05, T=-0.44).

Table 1. Demographic variables and neuropsychological scores

	NCI (mean±SD)	**MCI (mean±SD)**	**T- or χ^2-statistic (df)**	***P* Value**
Demographic variables				
n	68	29		
CDR	0	0.5		
MMSE	29.1±1	27.7±1	5.4 (95)	<0.001
Age	66±6	68 ±8	-1.6 (95)	0.1
Gender (F/M)	0.7	0.7	0.01 (95)	0.9
Education level	2	2	0.4 (2)	0.8
Personality: Domain scores (NEO PI-R)				
Neuroticism	77.6±23	88.8±27	-2 (95)	0.04
Extraversion	105.7±18	94.72±17	2.7 (95)	0.007
Openness	109.9±19	98.9±16	2.6 (95)	0.01
Agreeableness	135.2±17	123.2±17	3 (95)	0.003
Conscientiousness	134.5±19	111.5±22	5 (95)	<0.001
Other neuropsychological scores				
Cued recall (RI-48)	29.2±4	27.27	-40.83	<0.001
Depression score (HADS-D)	2.1±2	3.3±3	-1.8 (95)	0.07
Anxiety score (HADS-A)	4.7±3	5±3	-0.3 (95)	0.7

Table 1. Demographic characteristics and neuropsychological score for MCI and NCI. Score differences between groups were tested with an independent Student T-test. Differences in gender and education level were tested a Pearson Chi-square test. Level 1, 2 and 3 of education corresponds to 11, 12-13 and > 13 years of education. Df: Degree of freedom.

Univariate analysis of brain abnormality associated with MCI

Using a whole-brain family-wise error correction, we found no significant differences in GMV. However, with the same stringent level of correction for multiple comparisons, GMMD was significantly different between the two groups in several regions. In the MTL, local maxima for these differences (Table 2A, Figure 8) were located in both parahippocampal and hippocampal sub-regions (cornu ammoni, dentate gyrus and subiculum, according to probabilistic cytoarchitectonic map (Eickhoff et al., 2005). At whole brain level, GMMD differences were significant in the left middle temporal cortex (Z=5.06, xyz = [-57,-13.5,-3]), right superior temporal cortex (Z=4.74, xyz = [54,0,-3], Z=3.83, xyz = [-32, -23, -5]), left insula (Z=4.84, xyz = [-41,12,-14]; Z=4.83, xyz = [-41,3,-9]), left lingual cortex (Z=4.65, xyz = [-12,-36,0]) and right postcentral gyrus (Z=4.79, xyz = [53,-24,56]). Inclusion of education level and gender did not add contributive information from the brain measures.

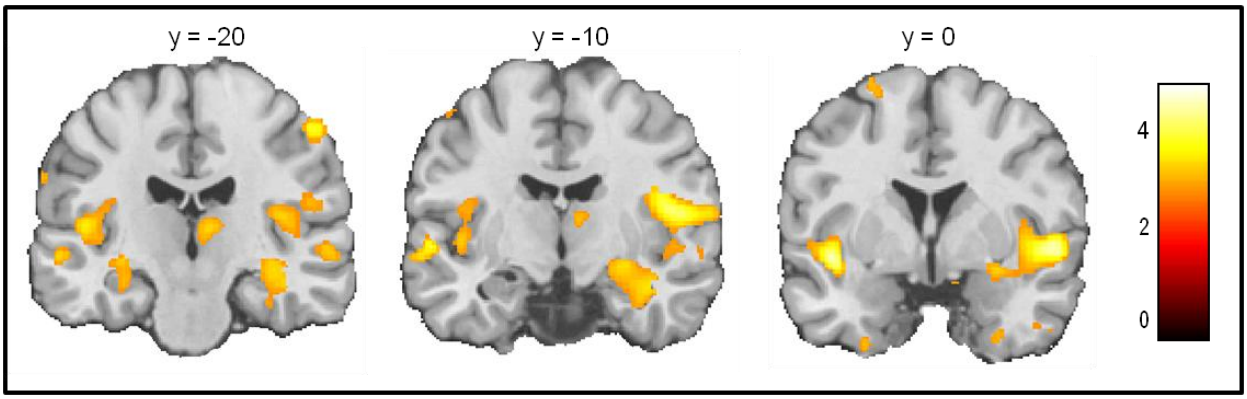


Figure 8. Statistical parametric map for the comparison between MCI and NCI groups for GMMD, with a statistical threshold of p<0.05 corrected. GMMD = Gray Matter Mean Diffusivity.

Multivariate analysis of Medial Temporal Lobe abnormality associated with personality profile at domain level in MCI

The multivariate analysis of GMV showed that there was a significant contribution of personality domains to alterations of brain structure. The first component identified, related to personality traits (Figure 9A), was significant ($F=3.77$, $p<e-5$) and explained 54.39% of the between group covariance in the MTL (Figure 9B). Neuroticism and agreeableness were identified as the main domains contributing to this component. No other regions showed significant differences between the two groups.

Post-hoc univariate regression analyses of GMV were performed with the first component of the MLM analysis at the domain level as predictor. This revealed significant structural differences located in both parahippocampal cortices (in entorhinal cortex and subiculum) (Table 2B).

MLM analysis of GMMD also showed a significant contribution of personality traits (Figure 9C) in the first component ($F=5.32$, $p<e-1$), which explained 69.24% of the between group covariance in the search volume of interest (Figure 9D). The domains neuroticism and agreeableness had more weight than the three other and a distributed spatial pattern of brain differences was revealed in the right hippocampal and parahippocampal cortices (Figure 9D).

Post-hoc univariate analyses of GMMD with the first component of the MLM analysis revealed significant brain differences between MCI and NCI in the right subiculum, cornu ammonis, dentate gyrus and in a part of the right hippocampal-amygdala transition area (Table 2B). Outside this region, GMMD was also significantly higher in MCI compared to NCI in the right inferior temporal cortex (at 2 significant sites: $Z=5.77$, $xyz = [39,9,-43.5]$); $Z=4.54$,

xyz = [61.5,-31.5,-16.5]), the right temporal pole (Z=4.23, xyz = [36,18,-33]), the right temporal cortex (at 2 significant sites: Z=4.21, xyz = [46.5,-51,-4.5]; Z=4.12, xyz = [58.5,-9,-19.5]) and in the right rolandic operculum (Z=4.52, xyz = [52.5,10, 3]).

Multivariate analsis of Medial Temporal Lobe abnormality associated with neuroticism profile at facet level in MCI

The multivariate MLM analysis of GMV showed contributions from the neuroticism facets profile (Figure 9E) in the MTL region, mainly in the right hemisphere (Figure 9F). The first component was significant (F=8.84, p=0) and explained 72.71% of the covariance.

MLM analysis of GMMD again revealed a significant contribution of personality facets profile (Figure 9G) with the first component significant (F=3.52, p<0.0005) explaining 46.72% of the variance in the MTL, mainly in the anterior part (Figure 9H).

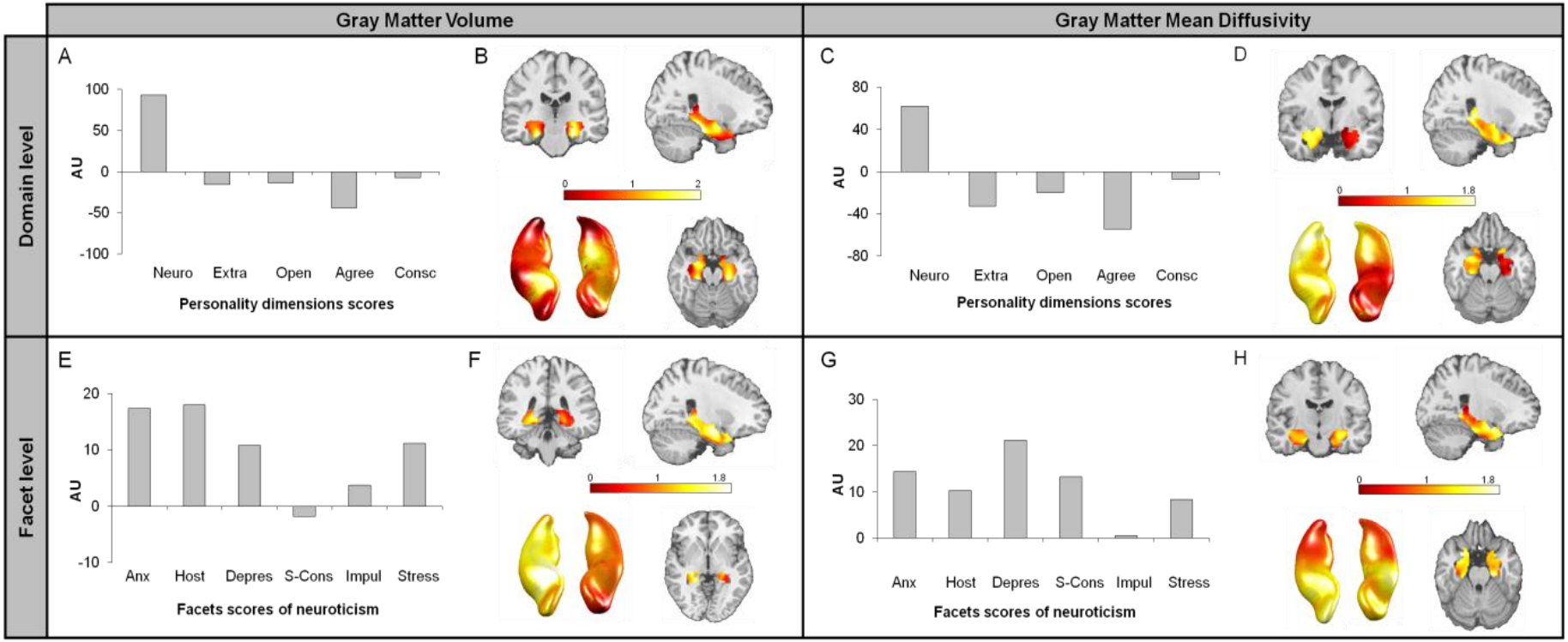


Figure 9. MLM analysis of personality profile at domain level. MLM analysis of personality profile at domain level (A-B) in GMMD and (C-D) in GMV and at facet level of neuroticism (E-F) in GMMD and (G-H) in GMV. Neuro=Neuroticism, Extra=Extraversion, Open=Openness, Agree=Agreeableness, Consc=Conscientiousness. Anx=Anxiety, Host=Hostility, Depress=Depression, S-Cons=Self-Consciousness, Impuls=Impulsiveness, Stress=Vulnerability to stress. Y axis is an arbitrary unit (AU).

Table 2. Neuroimaging results

A. Summary of VBM results					
GMMD: MCI>NCI					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**Z statistic**
621	Left hippocampus	-14	-35	2	4.57
		-29	-27	-11	4.27
		-15	-39	5	4.17
		-17	-33	-1	4.07
	Left parahippocampal	-23	-36	-6	3.72
96	Left parahippocampal	-23	7	-23	4.26
		-18	4	-20	4.08
1645	Right hippocampus	38	-24	-7	3.94
		30	-6	-14	3.93
		38	-8	-20	3.85
		27	-32	-3	3.84
		17	-33	3	3.77
	Right parahippocampal cortex	17	-35	-4	3.31
		33	-21	-24	3.25
112	Right parahippocampal cortex	27	11	-23	3.77
B. Post hoc MLM analysis on the five domains of personality					
GMV: Interaction with disease: MCI<NCI					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**Z statistic**
209	Left parahippocampal	-24	-22.5	-22.5	3.98
77	Right parahippocampal	24	-27	-19.5	3.91
		24	-31.5	-13.5	3.74
(GMMD) Interaction with disease: MCI>NCI					
905	Right hippocampus	15	-30	-3	4.1
	Right parahippocampal	22.5	-39	-3	4.02
		28.5	-31.5	-13.5	3.78
96	Right parahippocampal	30	10.5	-31.5	4.07
	Right hippocampus	16.5	-31.5	1.5	3.86
		36	-22.5	-9	3.8
		22.5	-31.5	3	3.71
		28.5	-30	-3	3.69
		15	-27	-6	3.5
		13.5	-34.5	6	3.35
90	Right hippocampus	18	-9	-13.5	3.79
154	Right hippocampus	30	-7.5	-12	3.35
		28.5	-6	-21	3.33

Table 2. (A) Significant regions showing greater GMMD in MCI compared to NCI (P_{FWE}<0.05). (B) Post-hoc univariate analyses of GMMD and GMV with the first component of the MLM analysis (P_{FWE}<0.05, with SVC). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute (MNI) space.

In post-hoc analysis at facet level with GMV, the maximal difference in brain structure was identified by domain analysis in the left parahippocampal cortex (xyz = [-24, -22.5,-22.5]) (Figure 10B) and was dominated by the depression facet (Figure 10A). With GMMD, the maximal difference in brain structure was found in the right parahippocampal cortex (xyz = [15,-30,-3]) (Figure 10D). The depression facet was the dominant contributor (Figure 10C).

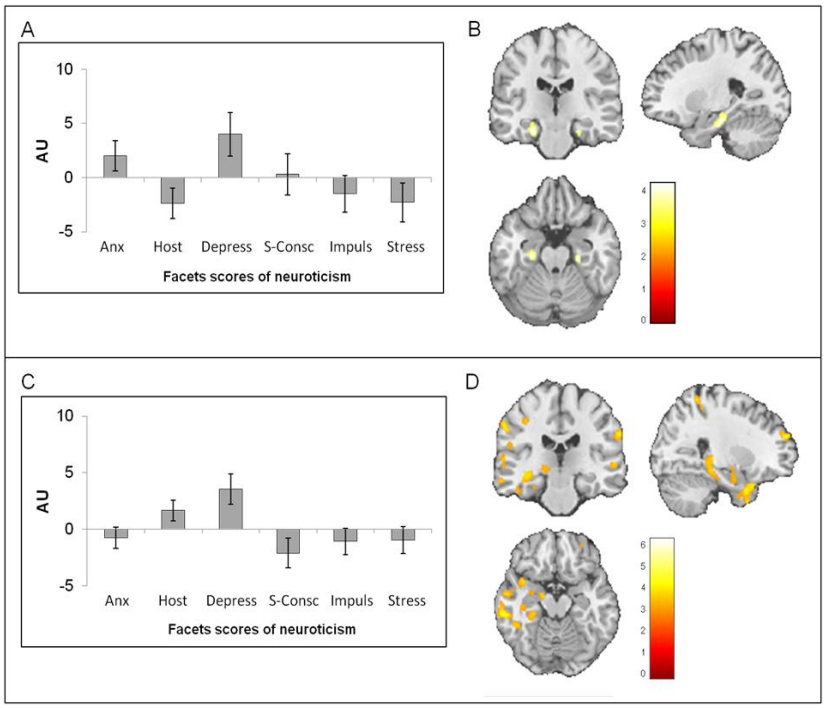


Figure 10. (A) Contrast estimate of the 6 facets of neuroticism associated with (B) the peak maxima of the first MLM eigencomponent located in the left parahippocampal cortex (xyz=[-20, -24, -27]) (statistical threshold of p<0.05 corrected), for the comparison between MCI and NCI groups in GMV. (C) Contrast estimate of the 6 facets of neuroticism associated with (D) the peak maxima for GMMD located in the right parahippocampal cortex (xyz=[6, -27, -6]) and the associated contrast. Abbrev: Anx=Anxiety, Host= Hostility, Depress= Depression, S-Consc= Self-Conscientiousness, Impuls= Impulsiveness, Self-Consciousness, Stress= Vulnerability to stress. Y axis is an arbitrary unit (AU).

Personality profile modulates structural brain whithin MCI subtypes

Our MCI sample is heterogeneous and is composed of 12 individuals with amnesic MCI – single domain (1D) (i.e. with memory deficit only), 11 with amnesic MCI - multiple domains (MD) (i.e. with memory and another cognitive deficit) and 6 with non-amnesic MCI (without memory deficits).

Post-hoc univariate analyses of GMV with the first component of the MLM analysis revealed significant brain differences between MCI amnesic (1D and MD) and MCI non-amnesic in the right hippocampus (Z=5.41, xyz = [37,-5,-25]) and the in left anterior cingulate gyrus (xyz = [Z=5.09, xyz = [-12,39,12]). The same brain regions were found for the comparisons between MCI amnesic 1D and non-amnesic MCI (Right hippocampus: Z=5.41, xyz = [37,-5,-25], left cingulate gyrus: Z=5.06, xyz = [-12,39,12]) and also between MCI amnesic MD and non-amnesic MCI (Right hippocampus: Z=5.42, xyz = [37,-5,-25], left cingulate gyrus: Z=5.08, xyz = [-12,39,12]).

Post-hoc univariate analyses of GMMD with the first component of the MLM analysis revealed significant brain differences between MCI amnesic (1D and MD) and MCI non-amnesic in the right parahippocampal cortex (Z=4.37, xyz = [30,-11.-31]). The same brain regions were found for the comparisons between MCI amnesic 1D and non-amnesic MCI (Z=4.19, xyz = [31,-11,-31]) and also between MCI amnesic MD and non-amnesic MCI (Z=4.23, xyz = [28,-9,-31]).

1.4.4. Discussion

Neuropsychological, psychiatric and personality measures

In our study, patients with MCI were comparable to those with No Cognitive Impairment (NCI) in terms of demographic information such as age, gender and education level. If those factors were significantly different, they could have a confounding effect on cognition (Crum, 1993) and dementia (Hebert et al., 2003; Mayeux & Stern, 2012; Stern et al., 2013; Zhang et al., 1990). MCI differed from NCI in MMSE score and in memory task RI-48.

All personality traits differed in MCI compared with NCI group. MCI have higher neuroticism score, lower extraversion, lower openness, lower agreeableness and lower conscientiousness scores. This is in accordance with the view that personality change can appear well before cognitive and emotional alteration of dementia (Wahlin et al., 2011). In addition, difference in neuroticism trait cannot be confounded with depressive states and anxiety symptoms because MCI does not manifest more of those symptoms than the NCI group on HADS test. This is in line with a study showing that, after adjusting for depressive symptoms, stress proneness related to chronic tendency to feel negative emotions as anxiety and depression was associated with 40% higher risk of higher risk of MCI and also with a more rapid cognitive decline (R S Wilson et al., 2007). High score of neuroticism is often reported to be predictive of cognitive impairment in AD (Kuzma et al., 2011a; R S Wilson et al., 2007; Robert S Wilson et al., 2006, 2011) and is related to the occurrence of neuropsychiatric problems (e.g. depression and anxiety symptoms) in persons with MCI and NCI, higher comorbidity of mental disorders, lower quality of life and shorter life expectancy (Lahey, 2009; Mendez Rubio, Antonietti, Donati, Rossier, & Gunten, 2013). Premorbid

agreeableness is linked to agitation and irritability in AD (Archer et al., 2007; von Gunten et al., 2009). Low levels of conscientiousness also predict conversion of MCI to AD (Robert S Wilson, Schneider, Arnold, Bienias, & Bennett, 2007). Personality alteration in openness and extraversion (Robins Wahlin & Byrne, 2011; von Gunten et al., 2009) have also been associated with early AD and MCI.

Univariate analysis of brain abnormality associated with MCI

We identified a spatial pattern of anatomical alteration in MCI that extended beyond the temporal cortex to the left insula, the left lingual cortex and the right postcentral gyrus in GMMD. We also observed that diffusion-based measures are more sensitive than volumetric ones for detecting brain abnormality in MCI in line with recent findings (Fellgiebel & Yakushev, 2011; Kantarci et al., 2005; Matthias et al., 2007; Scola et al., 2010; van Norden et al., 2012). GMMD differences might be caused by modifications of intra/extracellular space due to pre-atrophic changes (Fellgiebel & Yakushev, 2011; Fellgiebel et al., 2004). Indeed, changes in the neuronal, axonal, synaptic and glial compartments or in intra-cortical white matter may reflect the earliest effects of underlying pathophysiological mechanisms e.g. amyloid and/or tau deposition (Fellgiebel & Yakushev, 2011; Fellgiebel et al., 2004).

In addition, alterations in GMMD could reflect the regional progression of atrophy in MCI patients who convert to AD (Bakkour, Morris, & Dickerson, 2009; Chételat et al., 2005; B. C. Dickerson et al., 2009; Hämäläinen et al., 2007). This could also indicate the existence of a "specific cortical large-scale signature" in MCI and/or in the early phase of AD, not only focalized in the temporal cortex (Bakkour et al., 2009; B. C. Dickerson et al., 2009).

Multivariate analysis of Medial Temporal Lobe abnormality associated with personality profile at domain and facet level in MCI

Our multifactorial and multivariate analysis decomposes the complex relationship between three risk markers of Alzheimer's disease, namely the two state makers of (1) anatomical atrophy, (2) cognitive decline and (3) personality traits and revealed clinical and topographical signature in MCI and have direct implications for refining current models of AD.

Our findings highlight neuroticism, agreeableness and facets of anxiety, stress, hostility and depression as key explanatory variables of anatomical changes in MTL. Our results are important because with a few exceptions, there is a paucity of data linking personality to neurobiological mechanisms of disease. A few neuropathological studies (Rapp et al., 2006; Terracciano et al., 2013; Robert S Wilson et al., 2011, 2007) of confirmed AD cases have provided evidence of a role for neuroticism, and depression in relation to disease symptoms, but provide ambiguous evidence for any direct link with lesions observed at autopsy (neurofibrillary tangles and neuritic plaques).

In detail, a study has shown that patients with AD and a major depression in their life had more pronounced AD neuropathologic lesion such as plaques and neurofibrillary tangles in hippocampus compared to those without depression (Rapp et al., 2006). In contrast, Wilson et al., 2007 (Robert S Wilson et al., 2011, 2007) did not find link between neuroticism, conscientiousness and postmortem AD lesions. However, high conscientiousness was associated with the negative interaction between pathological tangles changes and global cognition (Robert S Wilson et al., 2007). With the same AD neuropathology, a resillient

personality profile, with lower neuroticism and higher conscientiousness, was associated with delayed clinical dementia (Terracciano et al., 2013).

Neuroimaging studies of personality have been mainly conducted in healthy adults and have found significant associations between neuroticism and structural differences in frontal and temporal regions (Bienvenu et al., 2004b; Deyoung et al., 2010). A recent study showed that, in MCI, the severity of white matter lesions in the MTL, and not the atrophy, was associated with higher neuroticism and lower conscientiousness (Duron et al., 2014). Critically, our study investigates the multivariate relationship between personality and MTL and provides a link with a vast majority of neuroimaging studies in AD that report consistent effects of stress and depressive symptoms, or AD state on the hippocampus (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006; Egger et al., 2008; Gianaros et al., 2007; Lee et al., 2011; Videbech, Ravnkilde, & Ph, 2004).

The link between depression and AD has been reported clinically (Andersen, Lolk, Kragh-Sørensen, Petersen, & Green, 2005; Chung & Cummings, 2000; Jones et al., 2012; Rozzini et al., 2008; R S Wilson et al., 2007). Biologically, our results, supported by these studies, converge to suggest that depression and AD share biological substrates in the hippocampus that are stress-related (Rothman & Mattson, 2010; Sotiropoulos et al., 2008). Indeed, depression can be strongly linked to neuroticism's facets, because they share some genetic risk factors and some items of neuroticism scale overlap with symptoms of depression and anxiety (Bienvenu et al., 2004b; Geda, 2006; Kendler, 1993; Lahey, 2009). Moreover, a high score of neuroticism can show great health significance in the risk and prediction of psychiatric problems such as depression and anxiety disorder (Lahey, 2009). In animal's studies, stress and depression have a well established impact on hippocampus vulnerability.

The mechanisms described at the cellular level can be linked to glucocorticoids effects (Sapolsky, 2000) or mineralocorticoid receptors, those last receptors being more present in humans than in rats. Effects of glucocorticoids may lead to cell death, atrophy and/or hypometabolism (Davidson, Pizzagalli, Nitschke, & Putnam, 2002a; Bruce S McEwen, 2005a; Sagi et al., 2012), making the hippocampal formation and its associated cognitive/memory performance more vulnerable to injuries. Other mediators such as neurotrophic factors downregulation, vascular or cell deterioration due to toxic substances related to stress could be involved. It is also possible that early pre- or post- natal stressful life events would make the hippocampus more vulnerable to some diseases. In animal models, proneness to distress or chronic stress can affect the hippocampal formation by decreasing dendritic branching, spines, neurogenesis (Bruce S McEwen, 2005a) or LTP (Davidson, Pizzagalli, Nitschke, & Putnam, 2002b; Frodl et al., 2002; Gianaros et al., 2007; Gross & Hen, 2004; Lucassen et al., 2013; B S McEwen, 2000; Bruce S McEwen, 2005b; Montag et al., 2013; Müller et al., 2003; Sagi et al., 2012; Sapolsky, 2000; Videbech et al., 2004; R S Wilson et al., 2007). It is however unclear whether specific disease mechanisms such as ischemia, long-term inflammation, epigenetic factors related to genetic makeup such as Apo-lipoprotein e4 homozygosity lead to different types of disease (AD or depression), or whether it is their precise anatomical distribution that determines which clinical features are manifested (Andersen et al., 2005).

Topographical signature of personality traits. We identified a specific anatomical pattern associated with the personality traits. The MLM analysis of GMMD revealed an asymmetry between right and left MTL at domain level, and a gradient from the anterior to posterior

parts of the MTL at facet level of neuroticism. For GMV, the asymmetry was also observed at facet level of neuroticism.

The antero-posterior gradient has been related to the specific role of the anterior hippocampus in stress and emotion-related behavior and in genes expression related to regions involved in stress. NMDA receptors related to hypoxic excitotoxicity are also differently distributy along the anterior to posterior gradient (Fanselow & Hong-Wei, 2010; Sahay & Hen, 2007; Bryan a. Strange et al., 2014; Szeszko et al., 2006; Willard, Friedman, Henkel, & Shively, 2009). In contrast, the posterior part would be more related to cognitive, memory retrieval processes (Fanselow & Hong-Wei, 2010; Sahay & Hen, 2007; Szeszko et al., 2006; Willard et al., 2009)**.**

Other studies on stress effect also reported differences between left and right hippocampus that can be explain by neurochemical and brain tissue property differences (Bremner et al., 2000; Frodl et al., 2002; Madsen et al., 2012; Spasojevic, Jovanovic, & Dronjak, 2013). An animal study showed for example that stress, induced by isolation, was associated with decreased noradrenaline content in the right hippocampus and this did not affect spatial learning and memory (Spasojevic et al., 2013). In human, higher level of basal cortisol was found in the left compared with the right hippocampus mean diffusion (MD), but not in the volume. As they did not observe any correlation between MD and volume in the hippocampus, they concluded for different biological properties of MD and volume measures. They also explained the asymmetry by a different hypothalamic-pituitary-adrenal axis (HPA) regulation or individual differences in cortisol level between right and left hippocampus. The role of HPA axis is to control stress reaction or other processes such as immune system or digestion (Madsen et al., 2012). This is supported by studies showing a

smaller left than right hippocampus volume in depressive patients or in males with first episode of depression (Bremner et al., 2000; Frodl et al., 2002).

Implication for refining current models of AD. Our data suggest that personality is a critical feature that needs to be taken into account when defining temporal biomarkers or models of the pathophysiological processes leading to AD (Jack et al., 2013; R S Wilson et al., 2007). Recently, a new model has been proposed by Jack et al. (Jack et al., 2013) in which different state biomarkers of AD (e.g., brain atrophy, tau, abeta, memory, clinical function) follow each a sigmoid shaped curve (Figure 11). The authors argue that for AD the most informative parameters in this model are the onset of curves on the horizontal time axis, their slopes and their temporal ordering. We suggest a model, based on the psychopathology literature, in which a specific personality trait, such as proneness to stress or depression, can affect the shape and the temporal ordering of state biomarker curves by two main mechanisms. The first mechanism is predisposition/vulnerability, where a personality trait profile increases the risk of disease and impacts the onset of biomarker curves. The second exacerbating mechanism is pathoplasticity, where a personality trait has an additive or multiplicative effect on the course of disease and hence impacts the slopes of the temporal curves (Figure 12). We believe that modeling the interaction between state and trait will capture the causes of inter-individual variability in disease trajectories.

In addition, other features, such as behavioral and psychological symptoms (Apostolova & Thompson, 2008b; Archer et al., 2007; Chung & Cummings, 2000), genetic susceptibility factors such as serotonin (Assal & Alarcón, 2004; Beaumont, Fiocco, Quesnel, Lupien, & Poirier, 2013; Gross & Hen, 2004; Meltzer CC, Smith G, DeKosky ST, Pollock BG, Mathis CA, Moore RY, Kupfer DJ, 1998; O'Hara et al., 2007), and personality, as demonstrated here and

elsewhere (Donati et al., 2013; Mendez Rubio et al., 2013; Robins Wahlin & Byrne, 2011) may help better clarify mechanisms more than at present explaining the association between cognitive decline and hippocampus in ageing.

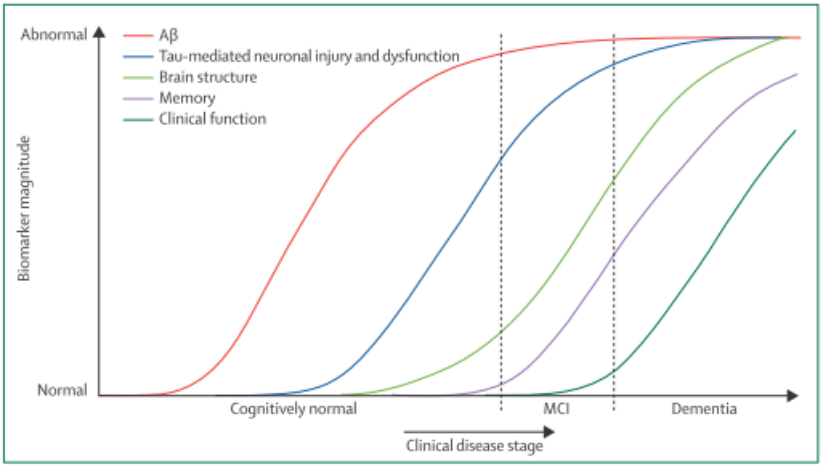


Figure 11. Model of biomarkers change from cognitively normal to MCI and then dementia state. MCI (Mild Cognitive Impairment, Aβ: Amyloid β) (Jack et al., 2008).

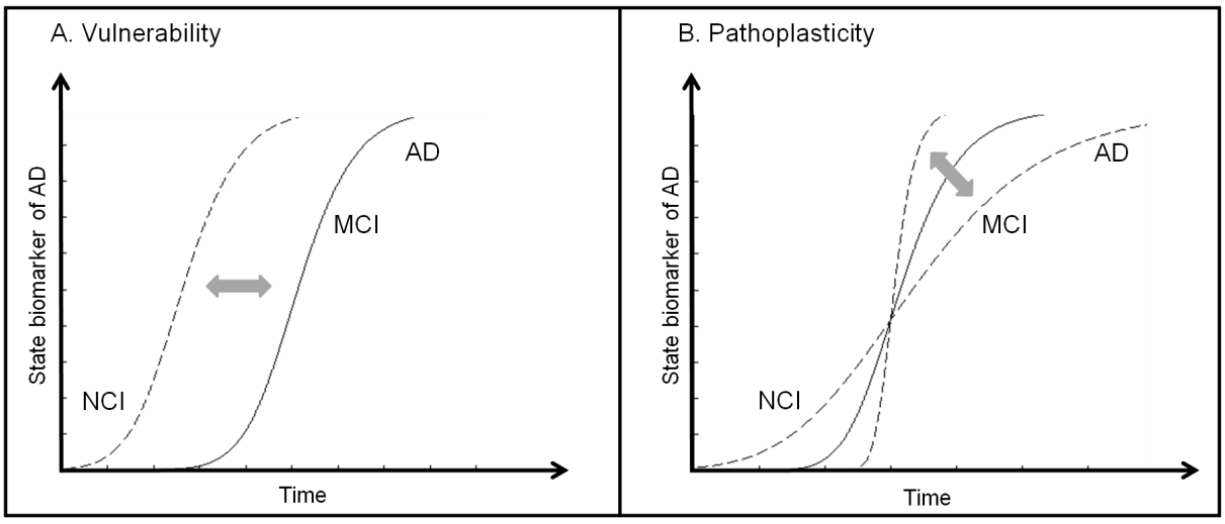


Figure 12. Hypothetical model of state marker in Alzheimer's disease (AD) influenced by personality profile. The curves show the time evolution of state marker abnormality of AD. X axis represents the time, and Y axis, the state biomarker abnormality of AD such as cognitive or brain decline. Individuals characterized with a different personality profile (e.g. with lower neuroticism score) can show different onset (A, vulnerability) or rate (B, pathoplasticity) of decline.

1.4.5 Limitations and perspectives

Limitations. There are still many unknowns in the understanding of the transition from normal cognitive function to symptomatic manifestations of AD. MCI as a concept is highly debated (Dubois et al., 2010). Even if MCI represents a greater risk of conversion to AD, more particularly for the amnesic MCI, as a clinical category it is very heterogeneous. In our results, there is even a differential impact of personality in MTL abnormality depending on the type of cognitive deficit (MCI vs NCI, MCI amnestic vs MCI non-amnestic) (Cf. results in chapter "Personality profile modulates structural brain in MCI subtypes").

Beside personality, behavioral and psychological symptoms (BPS) of anxiety and depression are also found to be critical factors that accompany MCI and worsen the risk of AD and institutionalization (Apostolova & Thompson, 2008a; Jones et al., 2012; Mendez Rubio et al., 2013; von Gunten et al., 2009). Those features and others such as genes (Beaumont et al., 2013) or life events (Johansson et al., 2013; Lahey, 2009) as demonstrated here and elsewhere (Donati et al., 2013; Mendez Rubio et al., 2013; Robins Wahlin & Byrne, 2011) may help clarify mechanisms more than at present.

In other limitations, we can also highlight that the sample is less representative than the whole population knowing that recruitment is not community-based. Moreover, neuroticism personality trait and the corresponding depression, anxiety and stress facets could reflect depression and anxiety symptoms themselves instead of stable traits; however this potential bias was attenuated by the fact that MCI was not different from NCI group in depressive or anxiety symptoms revealed by scores in the HADS test. On the neuroimaging side, it could be possible that the difference in Gray Matter Mean Diffusivity (GMMD) detected in the hippocampus and parahippocampal cortex is contaminated by the proximity of the signal

coming from the CSF in the lateral ventricles or by presence of potential WM lesions (Matthias et al., 2006b). Nevertheless, theses limitations have been minimized by imposing an a priori mask allowing constraining analysis only in the GM tissue of hippocampus and parahippocampal regions. In a future study, WM lesion measure could provide more information on the impact of such lesions on AD progression as it has been shown that periventricular WM lesions were correlated with lower cognitive score in MCI (Defrancesco et al., 2013), and that the severity of white matter lesions in the MTL was associated with higher neuroticism and lower conscientiousness (Duron et al., 2014).

Perspectives. Regarding the limitations of our study, a model including a combination of multiple factors, and their interactions, more specifically those which are the most sensitive predictors of AD could help refine MCI model and increase prediction to AD conversion or other age-related diseases. For example, it has recently been shown that the severity of white matter lesion, and not MTL atrophy, was associated with lower conscientiousness and higher levels of neuroticism in MCI subjects (Duron et al., 2014). In addition, as MCI represents a very heterogeneous group in composition and in evolution, a longer follow-up than 2 years with larger sample size could give much more information on disease progression and on identification of different subpopulations at risk for the disease. On top of that, studies on earlier stage of MCI, more specifically on individuals with subjective cognitive impairment (SCI), could reveal important cues on progression to age-related diseases. For example, it has been shown that increased SCI was correlated with higher rate of objective memory decline and with higher risk of dementia when additional factors such as worries about decline are included in the model (Belleville et al., 2014).

2. MEMORY

2.1. Memory and learning processes and models

The main models of memory and learning throughout history. They are presented in figure 13. The details of this schema are described below.

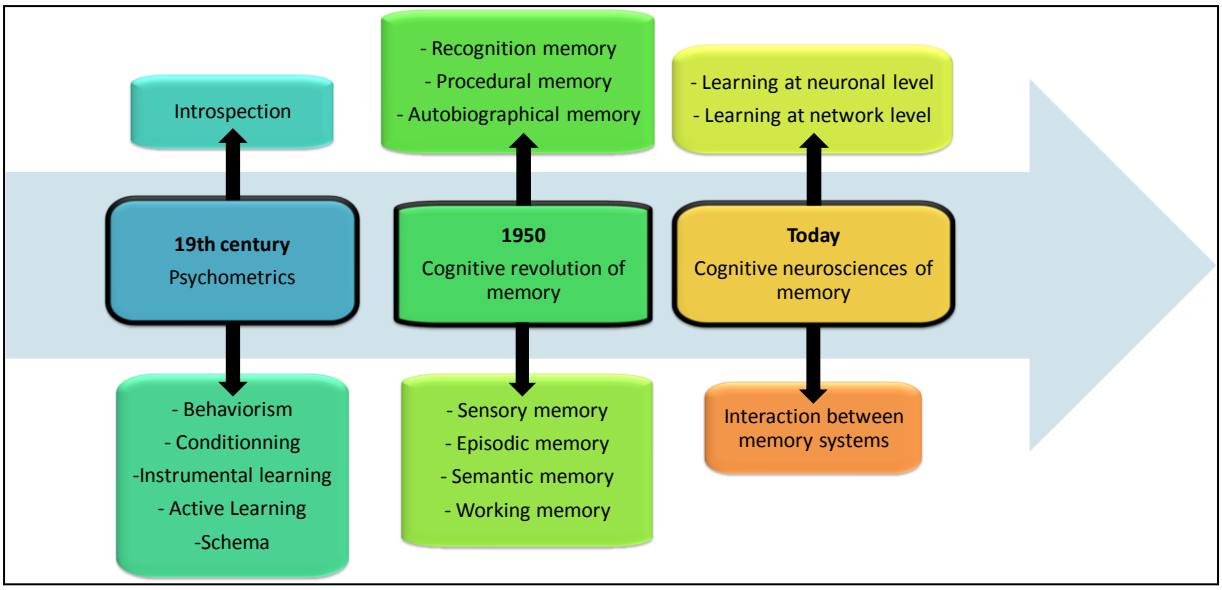


Figure 13 Schema of the main memory and learning models throughout history.

2.1.1. Psychometrics and behaviorism

Mental faculties such as memory have been investigated since the ancient times by philosophers and physicists. They tried to explain the functioning of the soul or the spirit and its interaction with the body and the universe. However, it is only in the nineteenth century that psychometrics first appeared, a field in which objective measures of mental activity, such as the test of free association by F. **Galton,** were developed. Introspection was then used by W. **Wundt** to allow measuring conscious auto-observation of thoughts, emotions and desires (Boring, 1953). However, this was refuted by J.B. **Watson** who declared that only

observable behavior is science, leading to the field of behaviorism. I.P. **Pavlov** discovered that all complex behaviors can be broken down into simple reflexes. Behaviors are learned according to classical conditioning, in which a neutral stimulus can provoke a conditioned response, when it is repeatedly followed by an unconditioned stimulus that naturally causes an unconditioned response.

For E.L. **Thorndike**, conditioning was not sufficient to explain the learning of all complex behaviors. He affirmed that behaviors are also reinforced or weakened by consequences, both positive and negative. This is also known as trial-and-error learning, which is incremental and not consciously processed. This train of thought influenced B.F. **Skinner** who defined instrumental conditioning. This is learning dependent on the association between the response and the consequence/reinforcement (i.e. the unconditioned stimulus), in contrast to the conditioning described by Pavlov in which the consequence was received independently of whether the response was learned or not. The frequency of a particular behavior can be modulated by this reinforcement.

Later on, E.C. **Tolman** stated that learning is not only influenced by stimulus-response, but also by expectations, attitudes and objectives of the individual. At the end of the nineteenth century, H. **Ebbinghaus** was the first to describe learning and forgetting rates by means of repeated syllables lists. F. **Bartlett** introduced schema, which are organized patterns of thought and behavior to perceive and organize the world. Here, memory is not only a repetition, but also a transformation of the perceived world (M. A. Gluck & Myers, 2008).

2.1.2. Cognitive revolution and models of memory

In 1950, the **cognitive revolution** appeared with the aim of understanding the transformation between stimulus and response, with the help of computers as models of the human brain and with more and more specific measures in some tests. G.A. **Miller** measured human capacities of information processing and the natural limit of seven digits span in short term memory.

Later on, new paradigms of memory appeared such as free and cued recall. There is increasing evidence showing that a person is active while learning to organize information or using pre-existing knowledge for example. Numerous other paradigms of contextual memory, recognition and priming also appeared (M. A. Gluck & Myers, 2008). W. **James** dissociated memory into primary and secondary forms of memory corresponding to short and long term memory as described in today's terms (Nadel & Hardt, 2011). In the **modal model of memory by Atkinson and Schifrin,** there are three types of memory that work in serial. First, information is processed in the **sensory or iconic memory,** which retains all sensory information after presentation, but information is lost after a delay. Then the information is transmitted to short-term, temporary, memory before passing to long term, permanent, memory after repetition of the same information (Atkinson & Shiffrin, 1968). In the level of processing model of memory, stronger and longer term memory is promoted by a deeper level of processing such as the semantic one compared with a more superficial, perceptual, one (Craik & Lockhart, 1972).

Later on, **Tulving** dissociated functionally independent memories: **episodic memory,** the processing of specific events with awareness of the spatial and temporal context in which

the event has been encountered, and **semantic memory**, the processing of general knowledge without contextual information (Tulving, 1972).

A. Baddeley then developed a three component model of **working memory** that allows the simultaneous maintainence and manipulation of information. This model contains a phonological loop and visuo-spatial sketchpad, two independent short-term memory buffers, and a central executive that distributes resources/attention to pertinent information between the two aforementionned components. In that model, there is also an episodic buffer, with limited storage capacity, that links to long term memory and can bind information coming from different modalities to form integrated episodes. This buffer is able to group items into meaningful classes (also called “chunking”) and to expand the memory span. In the model proposed by **Norman and Shallice**, schema control units allow the representation of routines or usual activities. When a schema is no longer adaptive, e.g. in a new situation, a contention scheduling system resolves the conflict (Norman & Shallice, 1986). In **P. Barouillet** model, the capacity of the central administrator is shared between the processing and the maintenance of information by a switching mechanism (Barrouillet, Bernardin, & Camos, 2004).

2.1.3. Cognitive neuroscience of memory

Cognitive neuroscience of memory aims to understand memory from psychological and neurobiological views. Memory is characterized by the combined use of experimental analysis in healthy or brain-damaged individuals, animal models and more recently computational models. Jerry Fodor, an influent researcher in the cognitive sciences, suggests a theory of modularity of mind affirming that each mental faculty is partly

structured in modular and non-modular ways. A module is characterized by its specificity in one domain of information; its independence from the other modules; and its unconscious or fast way of processing information. The functioning of these modules would also be innate (Fodor, 1983).

At the neuronal level, the **Hebbian theory** describes the association of two neuronal cells that fire nearly at the same time. The weight or synaptic strength between these neurons will increase with the activity of one cell facilitating the other. This weight can also decrease if they do not fire together. The repetition of the same activity, also called reverberatory activity or trace, will induce cellular and structural changes. The same mechanism happens at the cell assembly or system level. Hebbian learning explains that the repetition of an input, which causes the same pattern of activity in a system, will tend to strengthen the association of each element of this pattern, but to weaken the association of elements that are not active upon the presentation of the same input.

This allows the formation of engrams, which represent ways that memory traces are stored in the brain. Reverberatory activity supports short term memory, and with enough repetition, this creates structural change and allows consolidation and formation of long term memory (M. A. Gluck & Myers, 2008; Nadel & Hardt, 2011).

At the system or neural network level, literature in the cognitive neuroscience of memory has mainly focused on dissociation of memory systems in different brain regions. In the **serial-parallel-independent (SPI) model by Tulving and Gazzaniga** (1995), the three main memory systems, related to encoding, storage and retrieval, work in a serial, parallel and independent fashion respectively. This means that each system has a different memory trace and retrieval can occur independently of the information in the other systems.

Tulving defines **recognition memory** as two types of subjective memory judgments, recollection and familiarity, that are associated with specific brain regions, i.e. the hippocampus and the parahippocampal cortex respectively. The first is related to event retrieval with the context in which it has been firstly encountered, whereas the second is related to the feeling that an event has been met in the past without retrieval of any contextual detail related to it. In the SPI model, recognition memory includes recollection, which is the retrieval form of episodic memory, and familiarity which the retrieval form of semantic memory. Priming is the process in which a preceding stimulus influences the response to a subsequent stimulus. It is defined as a retrieval form of perceptual memory. The episodic memory, mainly dependent on the hippocampus, binds items with context into a single event, whereas semantic memory, mainly dependent on the anterior temporal cortex, extracts combinations of perceptual features with repeated events. Modality-specific perceptual memory, mainly supported by higher sensory cortices, processes sensory information into more abstract representations (Richard N Henson & Gagnepain, 2010). In studies on **amnesic** patients, information was shown to be transiently stored in the hippocampus and then, with consolidation, stored elsewhere in the neocortex. **Animal** models have allowed the exploration of how different processes of memory, such as storage, consolidation and retrieval can be differentially affected by the type of learning involved (Nadel & Hardt, 2011).

The dissociation between recollection and familiarity is not always clear or a one-to-one mapping, meaning that one process maps only one brain region. Recently, some authors suggest that most of the time there is a **dynamic interaction between memory systems** (Richard N Henson & Gagnepain, 2010). A pathway between perceptual and episodic

systems has even been shown to explain that the semantic system (or familiarity) can be impaired, but not the episodic memory (or recollection). This also shows that information does not need always to be processed in semantic memory to create episodic memory (Graham, Simons, Pratt, Patterson, & Hodges, 2000).

In the **Multiple Inputs Model (MIM),** other memory systems are described such as **procedural memory** related to motor skill learning **and autobiographical memory** related to episodes from an individual's life. In this later memory, there would be episodic and semantic memory components related to the self (Eustache & Desgranges, 2008). In the **predictive interactive multiple memory systems (PIMMS)** framework of Henson and Gagnepain, there are at least three different memory systems of episodic, semantic and modality-specific perceptual systems that can interact through forward and backward flows of information. In this model, memory encoding and retrieval are mainly influenced by the difference between predictions coming from backward connections and forward sensory information, also called **Prediction Error (PE).** Reducing PE also refers to maximizing "free energy" according to the "predictive coding" (K. Friston, 2010; Richard N Henson & Gagnepain, 2010). Recent neurimaging studies also show that learning and memory are dependent on multiple brain memory systems, associated with episodic and procedural memories, and that they can interact in parallel or competitive manner under neuromodulatory influences (Russell a Poldrack & Packard, 2003)**.** Since 1950, those types of observations were mainly studied in humans and animals with a paradigm called probabilistics classification learning which consist of learning probabilistic associations between cues and outcome (Foerde, Race, Verfaellie, & Shohamy, 2013; Hopkins, 2004; Knowlton, Squire, & Gluck, 1994; Russell a Poldrack & Packard, 2003; Daphna Shohamy, Myers, Hopkins, Sage, & Gluck, 2008).

2.2. Role of the Medial Temporal Lobe in memory

The medial temporal lobe (MTL) is composed of structures that have a central role in declarative memory. Understanding the segregation of the MTL could help define the mechanisms behind brain diseases.

Anatomy. The hippocampal formation includes the **hippocampus proper** and the surrounding cortex, **the parahippocampal gyrus**. The regions located along this gyrus are named the parahippocampal cortex, and the most anterior and inferior part, the perirhinal cortex (Figure 14). The enthorinal cortex is part of both the parahippocampal cortex and the perirhinal cortex.

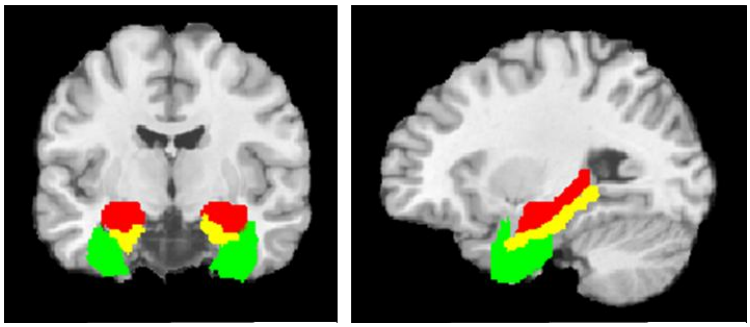


Figure 14. Figure of the three subregions of the medial temporal lobe in MNI standard space: the hippocampus (in red), the parahippocampal cortex (in yellow) and the perirhinal cortex (in green).

The enthorinal cortex is directly connected to different hippocampal subregions of the hippocampus such as the granule cells of the dentate gyrus (DG) through the perforant pathway. The hippocampus proper includes the CA3, CA1 and the subiculum (Figure 15). The DG projects to the pyramidal neurons of the cornus ammonis CA3 through the mossy fibres. The CA3 and DG have a function in pattern separation to differentiate memories or representation (or outputs) from similar events (or inputs), allowing less interference between memories. The DG has sparse coding, meaning that an "event is encoded with

strong activation of a small set of neurons" (Deng, Aimone, & Gage, 2010). The CA3 is an auto-associative network that contains pattern separated representations and is also associated with pattern completion. The CA3 is able to retrieve memories from partial cues, e.g. in a context of perceptual uncertainty, by activation of a set of neurons related to a memory that will activate neurons that store that specific memory. This would be possible by means of connection within the CA3 network. This region also has a role in integration of spatial and non-spatial information. The CA3 projects to the CA1 through the Schaffer collateral. The role of the CA1 is to compare sensory inputs with internal representations and reactivate the distributed cortical memory trace (Bonnici et al., 2012; Deng et al., 2010; Hasselmo, 2005). The CA1 in turn projects to the subiculum. From the subiculum, the connection goes back to the entorhinal cortex and then to the neocortex. Another connection, through the fornix, goes from the subiculum to the mammillary body and the "Papez circuit" (Figure 15) (Henke, 2010). This circuit is a pathway that includes the limbic system, including the hippocampal formation, the amygdala, the hypothalamus, the cingulum, the mammilo-thalamic tracts and the prefrontal cortex. This was originally thought to be involved in the emotional system, but is now also now considered as a memory system (Rajmohan & Mohandas, 2007).

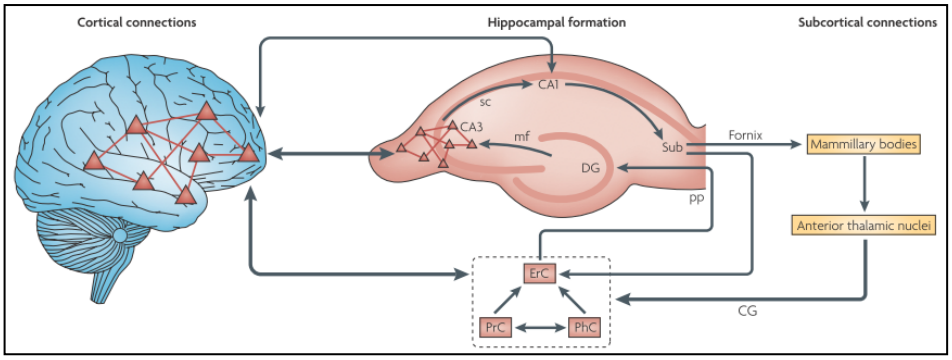


Figure 15.Schema of hippocampal formation (source (Henke, 2010)).

Functions. The **main function of the MTL system** is to encode new information and to rapidly store it temporarily as a "trace" in the hippocampus and cortical network. The hippocampus and the neocortex, important for the **episodic memory**, have a role in the rapid encoding of events, in associations and in binding an item with a context in a single trial. Then, with repetition of multiple learning trials, there is the reinstatement of hippocampal neural replay related to the encoded information. This information is then transferred and stored long term in the neocortex. The hippocampus can also transiently retrieve information in multiple ways, e.g. by association or binding of this information with other aspects of the episode such as sensory, conceptual informations or spatial and temporal context of the episode and by activation of different brain regions. This flexibility for integration of multiple informations ("what-where-when") in one unique episode allows using that knowledge to travel back in time, to make inferences, to adapt in novel situation, to plan or even to create. In addition, the MTL can support a slower process for the consolidation of information in **semantic memory** by the extraction of regularities of multiple episodic memories accompanied by abstraction and loss of details of those memories. This new emerging information leads to neorcorticalization; the recall of a trace in the neocortex, which then becomes independent of the MTL. However, the neocorex is not involved in the recall of details surrounding the encountered event; the hippocampus is required for the retrieval of episodic memories that preserve details of the context and stay flexible or adaptable to new knowledge after the time of encoding. The hippocampus can then encode new information **in an interleaved manner,** allowing the storage of new information into pre-existing network without damaging existing structures of memory in the neocortex. This would be possible with development of schema (e.g. learning of association between two items that allow inference and novel judgment about items that

are not directly related to the schema structure learned) and a process of update of this schema with integration of new information. This interleaved encoding facilitates then consolidation of schema (Frankland & Bontempi, 2005; Henke, 2010; McClelland, McNaughton, Bruce, & O'Reilly, 1994; L R Squire & Zola-Morgan, 1991). The update of schema also depends on the interaction of the hippocampus with the prefrontal cortex which would accumulates informations such as location in which an event was encountered and accommodate pre-existing schema (Preston & Eichenbaum, 2013).

In the context of a subtype of declarative memory called **recognition memory**, a prominent, yet debated, view is that the hippocampus is mainly involved in the binding of items with episodic contexts and recollection, a type of subjective memory judgment consisting of the retrieval of an event and the precise context in which it was first encountered. In contrast, the extrahippocampal region of the MTL is more involved in familiarity, another type of subjective memory judgment, which requires the awareness of the previous occurrence of an event and a feeling of familiaritiy with that event, but without retrieval of the contextual details it was encoutered. The perirhinal cortex would also be associated with familiarity with its role in processing unitized item. The hippocampus and the extrahippocampal region would also have a role in the qualitative and quantitative processing of information respectively (J P Aggleton & Brown, 1999; Bowles et al., 2007; Diana, Yonelinas, & Ranganath, 2007; Eichenbaum H. Yonelinas A.R., 2007; Richard N Henson & Gagnepain, 2010; Wolk, L., Dickerson, Aizenstein, & Dekosky, 2011; Yonelinas, Aly, Wang, & Koen, 2010). In addition, the actvation of some regions of the parahippocampal cortex (i.e. in the occipito-temporal cortex) depends on the type of stimulus. For example, the fusiform face area (FFA) is specifically activated for human face perception and expertise (Gauthier, Tarr, Anderson,

Skudlarski, & Gore, 1999) and the parahippocampal place are (PPA), for recognition of stimuli of scenes (Köhler, Crane, & Milner, 2002). The hippocampus also works with other brain regions during memory and learning, as described previously with updating of schema. For example, the activation of both the hippocampus and the prefrontal cortex at encoding is correlated with recall success (Grön et al., 2001; Kirchhoff, Wagner, Maril, & Stern, 2000). Recent studies investigate the neural signature of recognition memory traces though multivariate and predictive analysis from distributed brain activity patterns. This approach explores the process and the encoding type of information rather than the content itself. For example, MTL would process enough distributed pattern of activity to decode rich episodic memories. The hippocampus would have less episodic information than the cortex surrounding the hippocampus (Rissman, Greely, & Wagner, 2010; Rissman & Wagner, 2012) and would contain a distributed pattern of localized neural activity associated with episodic memory (Wixted et al., 2014).

Another form of memory, called **priming/perceptual memory**, is described as the rapid encoding of a single and unitized item. Priming and the feeling of familiarity can share mechanisms, but can also be distinct. Priming means the facilitation, repetition suppression and neural adaptation related to the repeated exposure to information and mainly depends on low level sensory cortices and then high level brain cortical regions surrounding the hippocampus. In contrast, familiarity depends only upon the higher level of information processing in the perirhinal cortex, a cortical region surrounding the hippocampus (Henke, 2010). An interaction between the two mechanisms has also been found in a study showing that repetition suppression was greater with familiar face stimuli compared to unfamiliar face stimuli of face in the left inferior occipito-temporal (LIOT) cortex. Multiple repetitions of

the same stimulus could initiate the familiarization of a face, but additional semantic information stored in other brain regions are needed to identify the face. As explained in the article Henke et al. (Henke, 2010), the activation of the LIOT cortex is also task dependent, as its activation was only present during the implicit fame-judgment task, irrelevant to repetition, and not in an explicit task of episodic recognition (R N Henson, Shallice, Gorno-Tempini, & Dolan, 2002). In another study, the activation of the LIOT cortex was also reduced when the preceding stimulus, the prime, was identical in terms of concept compared to an unrelated stimulus, and this was independent of the visual form of the stimuli (written words or objects). This supports the possibility of common top-down influences from high level amodal brain regions. In other terms, those regions can process conceptual knowledge not related to a specific sensory modality such as attention, task demand or prime and they can also integrate bottom-up perceptual information, in line with the predictive coding account theory. That theory assumes that learning depends on the minimization of free energy, which represents the difference between bottom-up information and predictions coming from top-down higher level brain (K. Friston & Kiebel, 2009; Kherif, Josse, & Price, 2011).

Connectivity. According to the "Binding of Item and Context" (BIC) model , MTL subregions process different types of information depending on the task demand (Diana et al., 2007). This model is based upon a three-component model observed behaviorally, both from lesion studies and by neuroimaging in both human patients and animal models (Eichenbaum H. Yonelinas A.R., 2007). The medial **entorhinal cortex** mainly receives inputs from the parahippocampal gyrus and the lateral entorhinal cortex receives inputs primarily from the perirhinal cortex. These two main regions projecting to the entorhinal cortex consist of

different anatomical pathways associated with spatial processing ("where") and nonspatial ("what") aspects of sensory inputs respectively. The **parahippocampal cortex**, specific to spatial processing, receives projections from the parietal cortex and other regions such as the superior temporal cortex, retrosplenial cortex and visual association areas. In contrast, the **perirhinal cortex** processes nonspatial information and receives projections mainly from the ventral, superior temporal cortices and visual areas. The item specific information of the perirhinal cortex ("what stream") and the item-context information of the parahippocampal cortex ("where stream") then converge in the hippocampus for the binding of different information (Diana et al., 2007) (Figure 16).

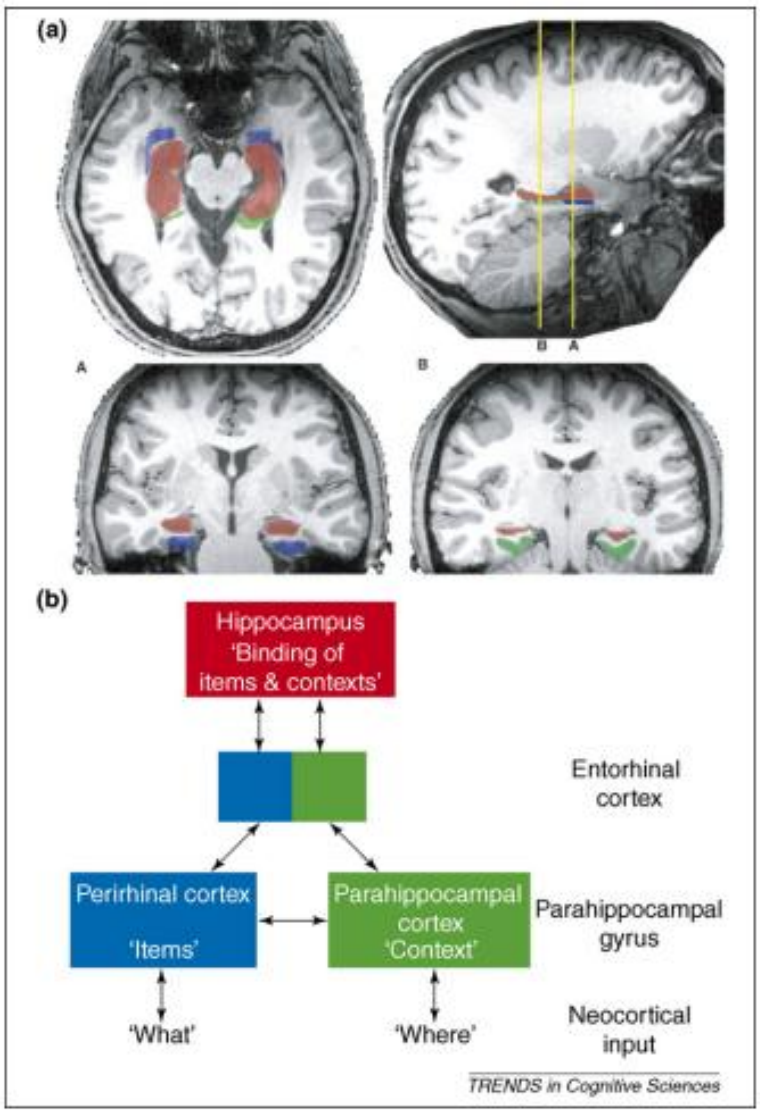


Figure 16. BIC model assuming that (a) hippocampus (red), parahippocampal cortex (green) and perirhinal cortex (blue) have (b) different roles in recognition memory. Arrows indicate anatomical connections between them (Source (Diana et al., 2007)).

A study on functional connectivity has shown that the perirhinal/entorhinal cortices activation were correlated with the activation of the head of the hippocampus whereas the activation in the posterior parahippocampal cortex was correlated with the activation of the body of the hippocampus (Kahn, Andrews-hanna, Vincent, Snyder, & Buckner, 2008). This suggests that the different functions of MTL subregions and their roles in memory could be explained by integrative, parallel and hierarchical model that include the surrounding brain rgions. This can be linked to the fact that the hippocampus subfields are also functionally dissociated along the **anterior-posterior axis.** The anterior hippocampus, which sends projections to the prefrontal cortex and is directly connected to the amygdala, nucleus accumbens and other regions related to the Hypothalamic-Pituitary-Adrenal (HPA) axis for stress regulation, is involved in emotion, stress, sensory-motor integration and goal-driven activity. The posterior hippocampus is in contrast more connected to the visual cortex for visuo-spatial sensory information processing through the perirhinal and parahippocampal cortices and is thought to be involved in memory and cognitive activities. The functional specificity of those anterior-posterior parts of the hippocampus is also supported by lesions and electrophysiological studies. Contrary to the dorsal hippocampus, the ventral hippocampus seems to modulate dopamine projections to the prefrontal cortex and nucleus accumbens. The anterior hippocampus is also specific to the encoding of new information and to neural adaptation whereas the posterior part would be more specific to the degree of familiarity of behaviorally relevant stimuli (B a Strange, Fletcher, Henson, Friston, & Dolan, 1999).

One recent view (Bryan a. Strange et al., 2014) highlights the functional organization of the hippocampus as a gradient in the longitudinal axis which is superimposed by a discrete dichotomy between the ventral/anterior part, involved in stress related affects, and the

dorsal/posterior part, involved in memory and spatial navigation. The gradient is supported by smooth and symmetrical transitions of input and output projections between anterior-posterior MTL and cortical and subcortical regions. There are similarly oriented gradients in genes, receptor expression as well as vulnerability to ischaemia. The size of place fields is also larger in the ventral part, which could be linked to more potential for flexibility and for semantic memory (Figure 17) (Bryan a. Strange et al., 2014).

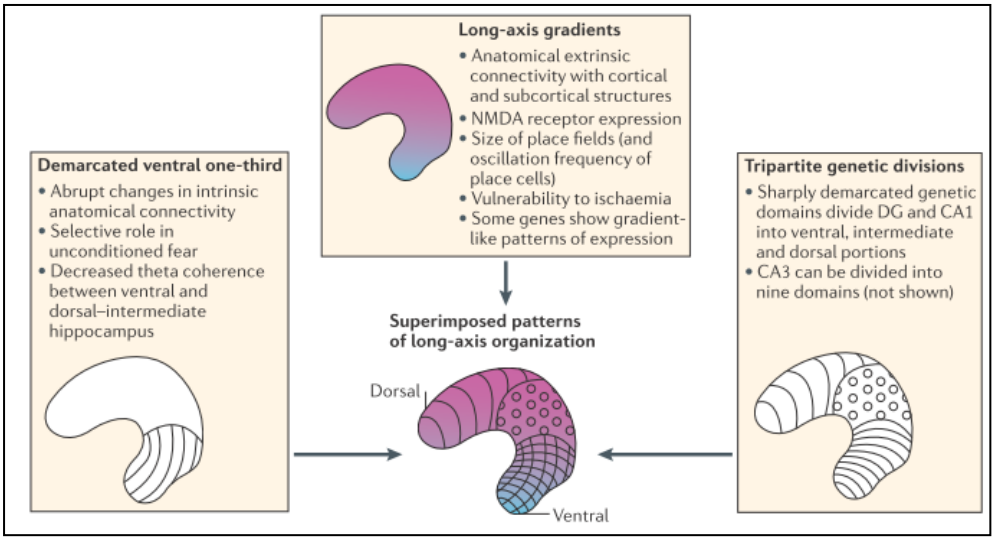


Figure 17. Schema of long-axis organization in the hippocampus (Bryan a. Strange et al., 2014).

2.3. Open questions

Based on the literature on the anatomo-functional mapping of the MTL, we aim to test whether different memory processes can be associated with different representations in MLT subregions such as the hippocampus, the parahippocampal cortex and the perirhinal cortex (Figure 18). This is investigated in the chapter 2.4 on "Experiment 2 - A predictive anatomo-functional mapping of the medial temporal lobe subregions in recognition memory".

Part 2 **Recollection, Familiarity**
fMRI at 7T
Multivariate Bayes
Healthy

Figure 18.. *Plan of the second part of the thesis. The raws describe the research topic, the neuroimaging MRI technique, the statistical method used and the population studied. MRI: Magnetic Resonance Imaging.*

2.4. Experiment 2 - A predictive anatomo-functional mapping of the Medial temporal lobe subregions in recognition memory

2.4.1. Objective

When we recognize a person, we can have different subjective experiences. We can either recollect that the person has been met somewhere or we can just feel that the person is simply familiar. In the literature, there is a long standing debate on whether these two types of declarative recognition memory, recollection and familiarity, correspond to two different processes or to a single continuous process that differ only on the strength of memory (Slotnick, 2013; Larry R Squire, Stark, & Clark, 2004; Yonelinas, 2002).

Neuroimaging studies that attempt to associate these two types of memory to different MTL substructures, i.e. hippocampus (Hipp) and the surrounding parahippocampal cortex (PhC) and perirhinal cortex (PrC) (Figure 19), did not provide strong or conclusive results for a double dissociation/exclusivity or the unitary view of the role of MTL structures (Song, Jeneson, & Squire, 2011). However, a dominant view is that hippocampal activation is most of the time associated with recollection-based memory, while activation in the surrounding cortex, mainly in the anterior part, the PrC, is associated with familiarity. The contribution of the PhC to those memories is mixed. Neuroimaging studies have shown that the PhC contributes to recollection (Brown & Aggleton, 2001; Eichenbaum H. Yonelinas A.R., 2007; Slotnick, 2013; Yonelinas, 2002) but seems necessary for familiarity in models derived from lesion and volumetric studies (Bowles et al., 2007; Wolk, L., Dickerson, Aizenstein, & Dekosky, 2011; Yonelinas, 2002). In addition, others studies found that there is not a simple mapping between MTL regions and recognition memory components. For example, the

hippocampus is thought to be involved in binding item with context, the PrC in individual item processing and PhC in binding item with specific spatial context (Diana, Yonelinas, & Ranganath, 2007).

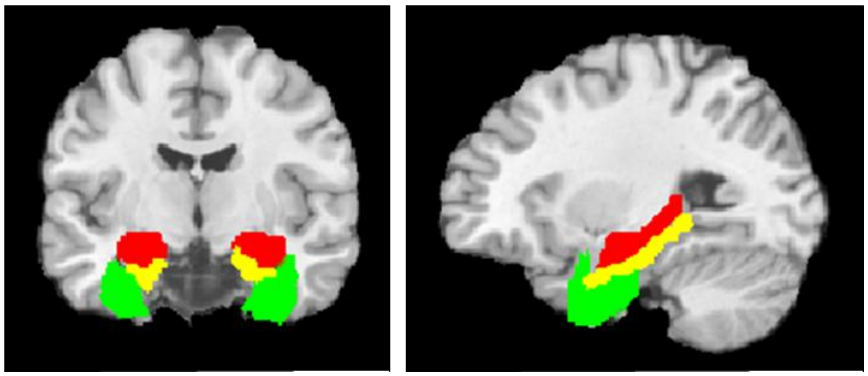


Figure 19. Figure of the three subregions of the medial temporal lobe in the MNI space: the hippocampus (in red), the parahippocampal cortex (in yellow) and the perirhinal cortex (in green).

We aimed to test the different models that have been proposed in previous studies in one single experiment. Theoretical cognitive models of the contribution of the two memory components (Figure 20A) are represented on a continuum from unique process view (unitary strength view) to partially shared processes (redundancy or independency theory) and then to complete dissociation of processes (exclusivity theory) (Mayes, Montaldi, & Migo, 2007; Skinner & Fernandes, 2007). Based on these cognitive models, we aimed to test the corresponding neurocognitive models by measuring the contribution of each sub-region of the MTL for explaining recollection or familiarity (Figure 20B).

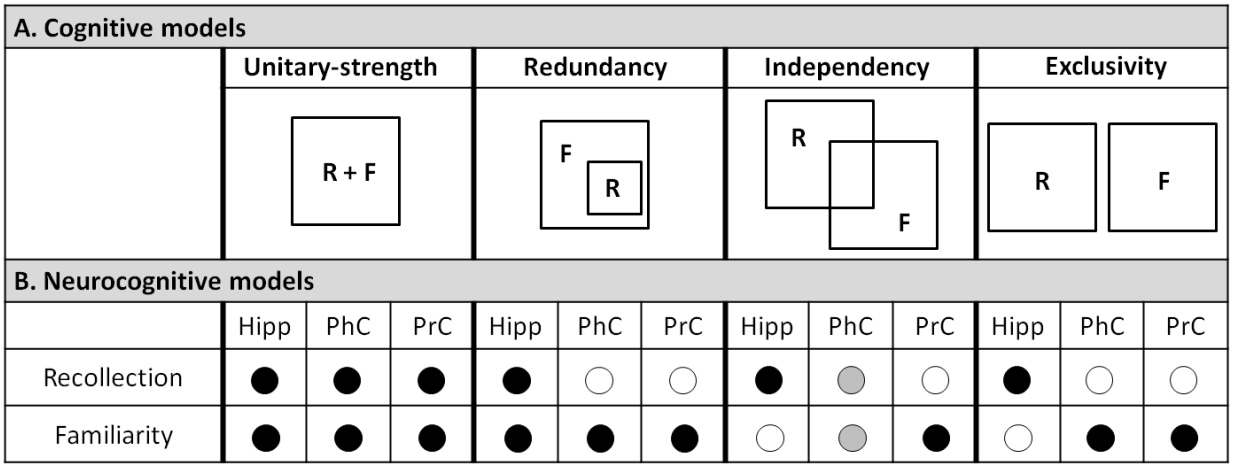


Figure 20. (A) Cognitive models of recollection and familiarity (from left to right) according to the unitary-strength theory, the exclusivity theory, the redundancy theory and the independence theory. (B) Neurocognitive models proposed for recollection and familiarity according to each cognitive theory and for each of the three regions of the medial temporal lobe, i.e. the hippocampus (Hipp), the parahippocampal cortex (PhC) and the perirhinal cortex (PrC). Black sphere indicates strongest contribution, white sphere indicates weakest contribution and grey sphere indicates intermediate contribution of one region compared to the other regions for recollection or familiarity.

Most of the current statistical methods in neuroimaging based on mass univariate statistical inferences cannot address questions related to the comparisons between brain regions or questions about the spatial distribution of activation. In this study we used a hierarchical Multivariate Bayesian (MVB) approach and Bayesian selection (BMS) methods which provide the valid statistical framework to address questions related to structure-to-function mapping (Chadwick, Bonnici, & Maguire, 2012; R. Henson, 2005; Morcom & Friston, 2012). In addition, we used high-resolution 7Tesla Magnetic Resonance Imaging (fMRI), which increases signal to noise ratio, thus improving sensitivity for detecting medial temporal activation in the memory task (Carr, Rissman, & Wagner, 2010; Yassa & Stark, 2009).

MVB and BMS allow to identify the best model for the different regions in MTL using different models of structure-function mapping called spatial priors. The spatial priors are

described in term of sparseness and smoothness of activation and include sparse, sparse-distributed (i.e. compact) and distributed (i.e. smooth) priors (Figure 21). Those three priors reflect a continuum (Figure 21 from left to right) between the types of activation: from few neurons (or voxels) responding strongly to few specific stimuli (i.e. as described in the grandmother cell theory), to distributed response of multiple neurons (or voxels) responding to many stimuli or even class of stimuli (Rolls & Treves, 1990).

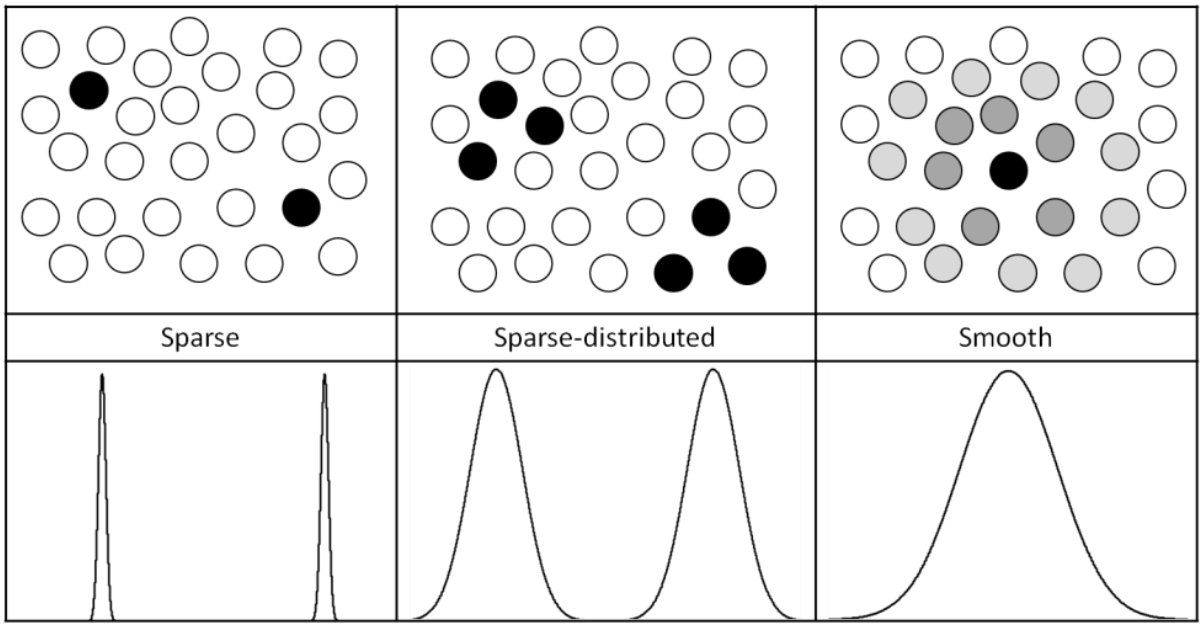


Figure 21. The different models of spatial priors are shown from left to right. They differ in term of spatial distribution: They are sparse, sparse-distributed or smooth. At the top, models are represented from the z axis view of a three dimensional space and in the bottom, they are represented from the x and y views.

In this way, we can probe further the neural coding and spatial distribution of memory traces created at encoding. Most studies have investigated the neuronal representation of semantic memory in the human hippocampus, however in a recent study (Wixted, Squire, Jang, Papesh, Goldinger, Kuhn, et al., 2014), it was found that activation of the Hipp associated with episodic memory followed a sparse distributed code. It was assumed that there is a bimodal distribution of activity in the MTL, with distributed clusters of localized neurons. The sparse mapping allows a efficient selective coding of memory by minimising the overlap between the rapidly encoded new episodes and those that are already stored (Olshausen & Field, 2004; Waydo, Kraskov, Quian Quiroga, Fried, & Koch, 2006).

In contrast, the distributed mapping allows the coding of multiple memories or class of stimuli by multiple neurons (or voxels), with the disadvantage to lose details of those memories and to increase the interference between them (Rolls & Treves, 1990). Sparse-distributed mapping in the hippocampus can also be realated to the sparse and distributed neural representation of episodic and semantic memory respectively (Wixted, Squire, Jang, Papesh, Goldinger, Kuhn, et al., 2014).

We predict first that recollection and familiarity will be associated with distinct regions and second with different neuronal representations in each of those regions.

In this study, participants underwent a study phase in the scanner in which they were instructed to read words on the screen. This was followed by an incidental recognition test outside the scanner. For each recognized word participants made a remember or know judgement to tap recollection and familiarity. As emotional items have been associated in recognition memory with richer recollective experience (Sharot, Delgado, & Phelps, 2004; Sharot, Verfaellie, & Yonelinas, 2007) the to-be-remembered stimuli included words with emotional content and comparison neutral words.

2.4.2. Materials and methods

Behavioral task

Recognition memory was tested with Remember/Know paradigm (J.M. Gardiner, 1988; Tulving, 1999). Thirteen healthy participants (age mean: 24.53, SD: 2.72, Male:Female (8:5)) were tested individually over two sessions comprising a study phase in the scanner, followed by an incidental recognition test phase, outside the scanner. The stimuli consisted of 200 French words divided equally neutral words and emotional words. Half of the words were used for the study phase and the other half, for the recognition test (Figure 22). The randomization of emotional (positive and negative) and neutral words in the study and test lists was performed with a 3 by 3 Latin square. This consists of 3 lists of positive, negative and neutral words that were matched for frequency and imagery and then spit in 2 parts for the emotional words and in 3 parts for the neutral words. Each part was then pseudo-randomly assigned to a study and test list for each subject. In the study phase, participants were instructed to read, aloud (to check that they really read) but with the least possible movement of the jaw, the words that appeared on the screen for 500 ms with an inter-stimulus interval of 1400 ms. A short time of 5 minutes for that study phase favoured spontaneous encoding by decreasing usage of specific goal-directed strategies (Kafkas & Montaldi, 2011). After approximately 10 and 15 minutes after the study phase, the test phase took place. The participant was then given extensive instructions and training on how to make remember and know judgements following a positive recognition. Words were presented in the middle of the screen and two options, old or new, were presented the right and left, respectively, in the bottom part of the screen. Participants had to choose “old” for

positive recognition and “new” for negative recognition. Participants were discouraged from guessing: if they were unsure, they were asked to choose the option of “new” word. In case of a positive recognition, two other options appeared in the bottom of the screen and participants had to choose whether they remembered or whether they knew the word with the left and right button respectively. They were told to take their time to decide, but they could also trust their feeling, reducing the possible bias on differential effort provided in the different judgements (Kafkas & Montaldi, 2012).

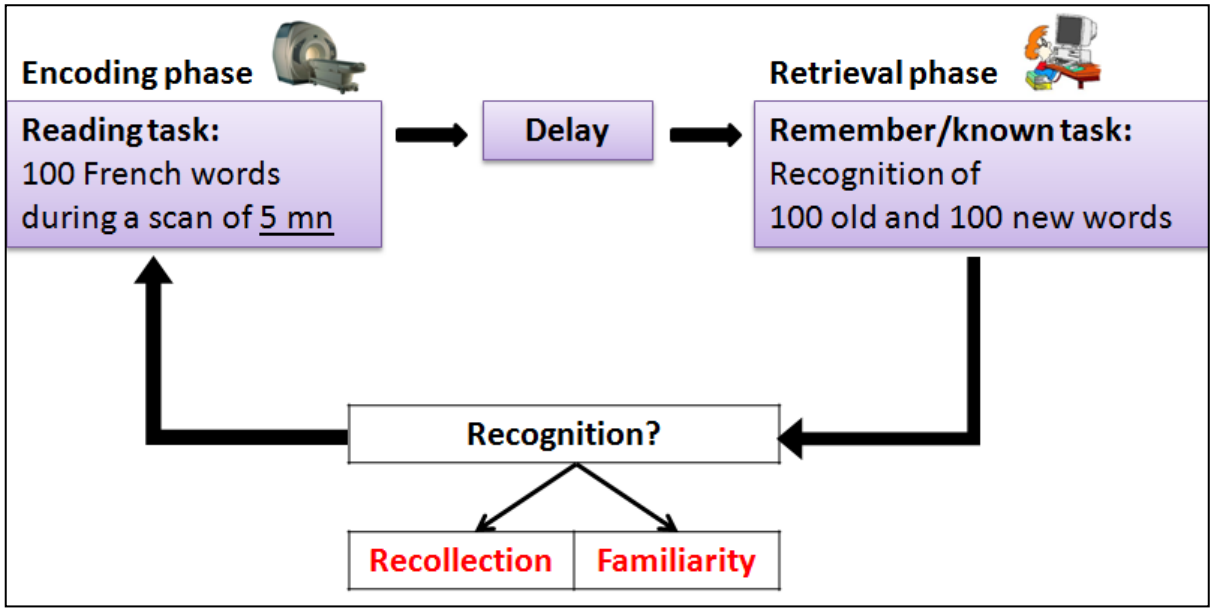


Figure 22. Remember/Know paradigm consists of two sessions comprising a study/encoding phase in the scanner, followed by an incidental recognition/retrieval test phase, outside the scanner. In case of positive recognition, they had to choose between remembered (i.e. recollection) or known (i.e. familiarity) judgment.

The instruction (in French) given to the participant includes three phases (task, explication and example) and are described below.

TASK

(For the study phase)

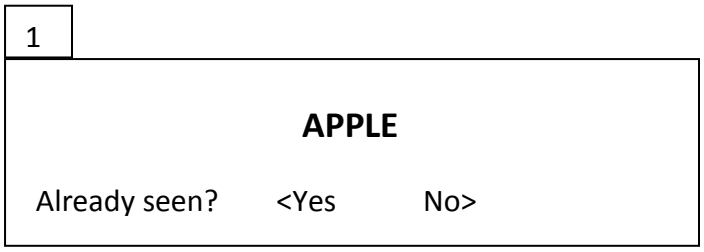
“In this task, you will see a serie of words appearing successively on the screen. For each word, you will have to read it aloud while trying not to move the jaw. Try to imagine what this word evokes for you.

(For the test phase)

In this task, you will see a serie of words appearing successively on the screen. For each word, you will have to answer 2 successive questions which will appear on the screen:

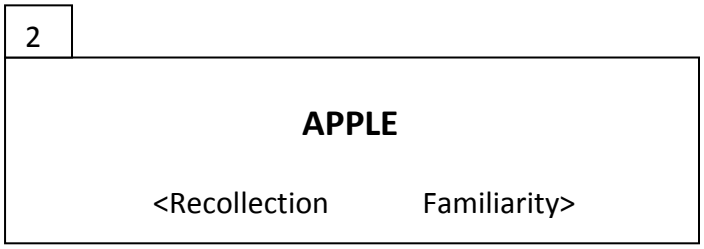
1. Firstly, you will have to decide if the word that you see is a word you have already read previously in the list of words presented in the scanner, or not. The question " already seen?" will appear on the screen. You will have to choose if the word that you see is a word already seen (old) or not (new). If you are sure that you have already seen the word, click on the left button for "yes" or on the right button for "no". If you are not sure that the word was read before, select also "no.”

Here is the example with the word “apple”.



2. Then, for the words that you recognized as "already seen" (in the first question), you can choose between 2 categories of EXPERIENCE OF RECOGNITION. Select one of the 2 options

appearing on the screen: either "Recollection" with the left arrow, or "Familiarity" with the right arrow.



There is no time pressure, but trust also your instinct to answer.

EXPLANATION

"Recollection" means that you can travel back in time and remember something associated with the recognized word, such as the context or the moment when you met this word. For example, you recognize a face and you remember having spoken to this person during a party the last night. Here, you remember the context that allowed you the recognition of the face.

In the other category corresponding to the option "Familiarity", you have no recollection of what allowed you this experience recognition. In this case, you are sure you recognize this face, and you know that you recognize this person because you have a strong feeling of familiarity, but you do not have more precise recollection that indicates you have already seen this person previously.

EXAMPLE

Now, an additional example is described below and will help you to better understand the different categories of recognition experience: imagine you are watching a movie at the TV and that a new actor appears on the scene. You think that you have already seen this actor previously, but only one time. Now you can have two categories of recognition experience.

In the first category (that we call "recollection"), when you see the face, you can almost immediately travel back in time and remember the moment or another cue related to the first time you saw this actor. You can thus situate him in the time or the context in which you saw him for the first time.

There is also a second category of recognition experience (that we call "Familiarity") that you can have when you see the actor at the TV. You notice that you know who is the actor, you recognize him, you are sure that you have already met him by chance previously, but you have no recollection of the moment or any cue related to this first meeting. However, there is something in you that tells you have already seen this actor before. He is familiar to you, but you cannot travel back in time, and situate the actor in the context of the first meeting, but you have a strong feeling you have already seen this actor previously."

MRI sequences

Previous studies in animals and patients with lesions have considerably improved our understanding of mechanisms in the MTL, however, considering the size of the human hippocampus, from 4 to 4.5 cm in the longitudinal axis, and its subregions, the in-vivo

investigation of human's MTL, specifically the Cornu Ammon (CA) 2 subfield and the Dentate Gyrus (DG), is still limited by the resolution of **neuroimaging** techniques (Tamminga, 2013) or by strong artifact such as signal dropouts coming from higher field strength in the inferior and anterior parts of the temporal cortex. Nevertheless, it has recently been shown that with imaging techniques at high magnetic field, memory encoding is associated with stronger BOLD dependent signal in the MTL. Neuroimaging studies using higher resolution, up to 1 or 1.5 mm^3 resolution, would considerably improve the understanding of functional anatomy in MTL, in part due to decreased partial volume effects associated with a smaller voxel's volume (Theysohn et al., 2013). Partial volume loss can occur in regions that contain a mixture of tissue types (J Ashburner & Friston, 2003). The aim of this study is to explore the different functions of the MTL taking part of the advantage of higher magnetic field, at 7 Tesla that leads to greater sensitivity of memory-related processes and greater spatial resolution.

We conducted high-resolution event-related fMRI BOLD sensitive experiment to probe neural activation associated with recollection and familiarity using the Remember and Know paradigm. Data were acquired at 7T Siemens MAGNETOM scanner with shielded activity (Siemens Medical Solutions) located at the Centre d'Imagerie BioMedicale (CIBM) in Lausanne, Switzerland. EPI sequence were acquired with a 8-channel head volume RF-coil (RAPID Biomedical GmbH) and with sinusoidal readout gradients, specially developed for 7T and with the following settings: TR 3000ms, TE 27ms, flip angle 69 degrees (SAR limited), FOV 200*200 mm, matrix size 132*132 *45 (1.5*1.5 mm resolution in-plane), 6/8 partial Fourier acquisition, bandwidth 1722 Hz/pixel. 100 volumes containing 43 1.5 mm axial-oblique slices with the phase-encoding direction anterior-posterior located in the MTL were acquired in a single run with a total scanning time of 5 minutes.

An anatomical T1-weighted high-resolution 3D image was acquired using the MP2RAGE pulse sequence optimized for 7T MRI (Marques et al., 2010) with these parameters: resolution $1mm^3$, TR 5500ms, TE 28.2ms, flip angle of 5 degrees, matrix size 340*256*176.

The 7T procedure used in our study has already been successfully performed with fMRI task investigating the motor cortex (van der Zwaag et al., 2009) and the auditory cortex (S. Da Costa et al., 2011). That technique allows increased signal-to-noise ratio, smaller voxel size, reduced signal of venous signal with shortened relaxation time, improving the spatial BOLD signal specificity (van der Zwaag et al., 2009, 2011).

It is possible to compare the proportion of Hits and FA to measure sensitivity (Table 3). There are other corrected scores of recognition that can be calculated with a sensitivity index d' with hit rate, the proportion of Hit, substracted by the proportion of false alarm (FA) rate (i.e. Hits rate - False Alarms rate). The higher is this index, the more distance there is between signal and noise in subject's response.

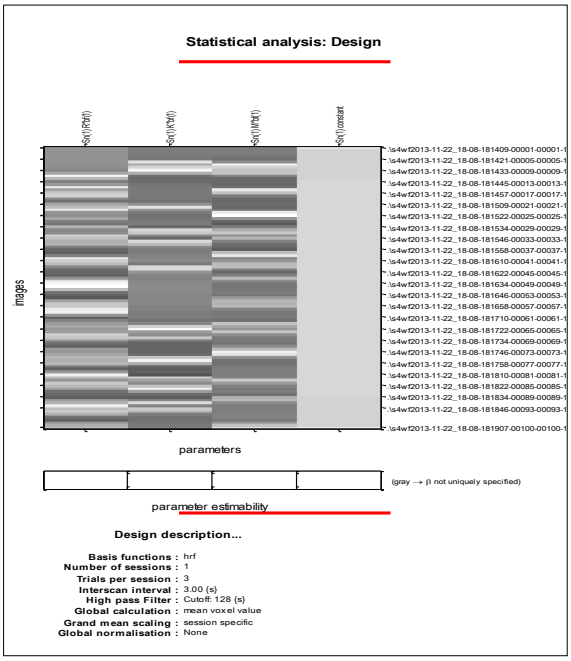
	Response "Old"	Response "New"
True "Old"	Hit	Miss
True "New"	False Alarm	Correct Rejection

Table 3. Table of signal detection theory applied to recognition memory task in which words in a studied list have to be recognized later in a testing list containing new words compared with the studied list. Items are classified as Old or New depending on whether they are recognized as part of the studied list or not (i.e. Response "Old" or "New") and whether they belong to those lists in reality (i.e. True "Old" or "New") .

Univariate statistical analysis

Data were analysed using Statistical Parametric Mapping (SPM8-Matlab toolbox, http://www.fil.ion.ucl.ac.uk/spm). Pre-processing consisted of spatial transformations with realignment (for correcting movement artefacts), segmentation, normalization to the MNI space, and spatial smoothing (with isotropic 4-mm full-width at half-maximum kernel) and finally, temporal high-pass filtering (1/128 Hz cutoff) was applied. Based on the subsequent recognition test responses of each subject, old items were classified into 3 categories: Missed (or forgotten) items (neutral and emotional), remembered items (neutral and emotional) know items (neutral and emotional) (Figure 23A). For the fMRI data analysis, we constructed a design matrix for the General linear model (GLM) that contained regressors for these 3 conditions corresponding to a nested factorial design (Figure 23B). The regressors were built by convolving the canonical hemodynamic BOLD response function with each condition. The subject's effect was not included in the design, because it was assumed that between-subject variability was low.

A



B

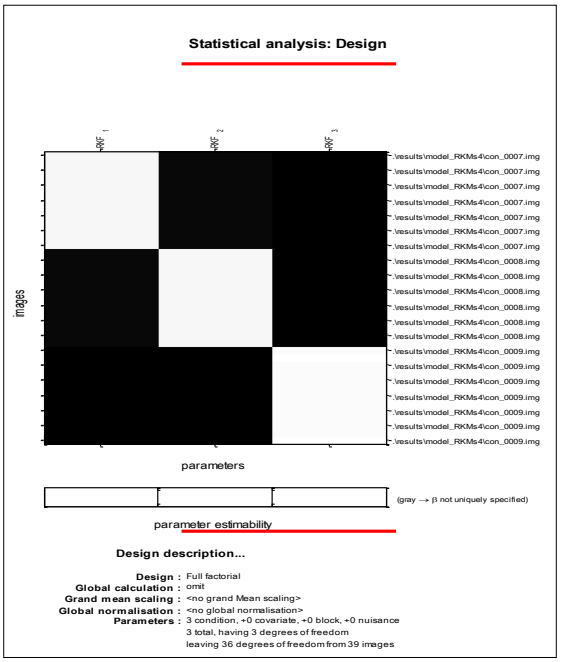


Figure 23. (A) Design matrix at subject's level containing three regressors for remember, know and forgotten conditions. The rows represent the scans and the columns, the explanatory variables/regressor. (B) Design matrix at group level corresponding to a full factorial design including the three same conditions as subject's level. The rows represent the contrasts estimated at subject's level and the columns, the explanatory variables/regressors.

Multivariate analysis of spatial distribution: MVB, BMS

We used multivariate Bayesian method (MVB) and Bayesian Model Selection (BMS) with SPM12 software to extract and identify the best model in term of multivariate spatial contribution of activity in MTL subregion, namely the hippocampus, the parahippocampal cortex and the perirhinal cortex, for encoding words that were subsequently recognized and classified as remember or know judgments.

BMS. Bayesian Model Selection (BMS) allows comparing directly multiple models by comparing log-model evidences between different models. An exceedance probability is a measure of probability that one model exceeds all the others in term of ranking. For the inference method, "Random effects" (RFX) option was selected in order to take into account inter-individual differences in the task at group-level. Bayesian method affords a predictive validity and generalizaility of the model tested (Stephan et al., 2009).

MVB. Withing each MTL subregions, the Multivariate Bayesian Method (MVB) was used to explain the link between multivariate distributed data (or target) X and predictors Y (K. Friston et al., 2008). MVB generates a decoding model in which some priors about the pattern weights over data features (i.e. voxels) are assigned. This pattern called partition is first assumed to have similar variance in the pattern weights and then, with a greedy search, this partition is optimized, using variational scheme under Laplace assumption, to obtain the subset of largest pattern weights. The search will finish with a high number of subsets, with higher covariance and weights, if the distribution is sparse. In other terms, MVB output can be related to the type of neuronal representation in a region (K. Friston et al., 2008; Karl J Friston & Stephan, 2007). Sparse distribution means that few voxels have large variance and most of them have small variance. Smooth prior represents clusters of voxels or spatially

coherent distribution over anatomy with local Gaussian kernels. Sparse-distributed (or compact) prior is a reduced (with singular value decomposition, SVD) local compact model of support prior. Support models mean large number of distributed patterns (K. Friston et al., 2008; Morcom & Friston, 2012). These priors could be related to a continuum between "grand-mother cell" to "mass action" distribution (Quiroga, Kreiman, Koch, & Fried, 2008) as described in the **Error! Reference source not found.** from left to the right.

Concerning MTL subregions anatomical mapping, the Hipp and PhC cortex were defined with AAL atlas (Tzourio-Mazoyer et al., 2002). The PrC map, based on macro-anatomic landmarks (Insausti et al., 1998), was created with group-based probabilistic map in the MNI-152 space and comes from a published work on perceptual information integration fMRI paradigm (Holdstock, Hocking, Notley, Devlin, & Price, 2009). In order to compare MTL subregions, the part of the PrC that overlaps the PhC was excluded of the perirhinal mask for the analysis and vice versa for the PhC. Those anatomical maps were fitted to the participant's native space and they were visually inspected. We suspected a signal dropout in the PcR due to MR artefacts of fMRI echo-planar in the anterior part of the temporal cortex (Olman et al., 2009). Percentages of voxels with non-zero values in the PrC were 100% (n=2), 99% (n=2), 94% (n=1), 93% (n=1), 92% (n=1), 83% (n=1), 70% (n=2), 67% (n=1), 57% (n=1), and 55% (n=1). In the Hipp and PhC, all voxels are preserved, except in one participant with 97% of non-zeros value in the Hipp. In addition, no bias was observed in the model evidence due to the different volume in each of the MTL subregions.

2.4.3. Results

Emotional effect in recollection and familiarity

The participants were tested individually over two phases: a study phase that took place in the scanner and an incidental recognition phase outside the scanner. In table 4, we report the mean proportions of emotional and neutral studied words recognized as old words (hits) and unstudied words recognized as old (false alarm) for remember and know judgments. Participants could discriminate between the old words and the new words: overall hits (M=.65, SD=.17) were significantly higher than the false alarms (M=14, SD=.12; $t(12)=10.36$, $p<0.05$). Analyses on accurate recognition (hits minus false alarms) showed, as predicted, that more emotional words were remembered (M=.44, SD=.19) than neutral words (M=.37, SD=.15; $t(12)=2.66$, $p<0.05$), but not known (known emotional words, M=.09, SD=.12., known neutral words: M=11, SD=.11; $t(12)=.62$, $p>0.05$).

Table 4

	Hits		False Alarms	
	Remember	**Know**	**Remember**	**Know**
Emotional	.47 (.06)	.20 (.02)	.03 (.01)	.11 (.03)
Neutral	.40 (.04)	.22 (.03)	.03 (.01)	.11 (.03)

Table 4. Mean proportion and standard errors (in brackets) of correctly recognized (Hits) and incorrectly recognized (FA) emotional and neutral words judged as remembered or known.

Univariate analysis of brain activation associated with recollection and familiarity

Using a whole-brain family-wise error corrected threshold of p-value 0.05, we report in table 5 the significant brain regions associated with main effect of each of these conditions: Reading (including all read words), recognition (including all correctly recognized words), recollection including all correctly recognized words judged as recollected) and familiarity (including all correctly recognized words judged as known, familiar).

Reading condition was associated with regions in the in bilateral occipito-temporal cortices (Table 5A). Recognition was not only associated with regions in bilateral occipito-temporal cortices, but also in the left cerebellum and left inferior frontal cortex (Table 5B).

Recollection was associated with regions in bilateral occipito-temporal cortices, but also in the left cerebelum and in the inferior frontal cortex (Table 5C, Figure 24A), whereas familiarity was only associated with regions in bilateral occipito-temporal cortex (Table 5D, Figure 24B).

Using the same statistical threshold, no significant voxels were for the negative association with recollection and familiarity even when they are subtracted by the miss condition (meaning incorrectly unrecognized, or forgotten words); idem for the positive association substracted by the miss condition. However, the effect of miss condition was included in the design to control for it.

Table 5

A. Reading					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**T statistic**
1036	Right inferior occipito-temporal cortex	32	-76	-21	7.87
	Right lingual cortex	21	-84	-11	6.82
		24	-84	-18	5.84
3077	Left occipital cortex	-44	-76	-14	7.72
	Left cerebelum	-45	-70	-27	6.94
	Left inferior occipito-temporal cortex	-30	-81	-20	6.93
928	Left superior temporal cortex	-54	9	-9	5.65
		-48	3	-11	4.99
		-53	12	-17	4.9
B. Recognition					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**T statistic**
882	Right inferior occipito-temporal cortex	32	-76	-21	7.84
	Right lingual cortex	23	-81	-12	6.34
	Right inferior occipital cortex	33	-87	-9	5.48
2799	Left inferior occipital cortex	-45	-75	-14	7.51
	Left cerebelum	-44	-67	-24	6.96
	Left inferior occipital cortex	-42	-55	-15	6.8
765	Left superior temporal cortex	-54	9	-9	5.73
		-48	2	-9	5.13
	Left inferior frontal cortex (pars opercularis)	-48	8	6	4.99
255	Left cerebellum	-11	-61	-20	4.87
		-12	-72	-20	3.58
C. Recollection					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**T statistic**
1792	Left inferior occipito-temporal cortex	-41	-76	-18	6.32
	Left inferior occipital cortex	-42	-55	-15	6.4
	Left cerebellum	-45	-70	-27	5.39
637	Right inferior occipito-temporal cortex	32	-76	-21	7.61
	Right inferior occipital cortex	33	-87	-9	5.17
	Right lingual cortex	23	-81	-12	5.5
534	Left superior temporal pole	-51	15	-12	5.2
	Left inferior frontal cortex (pars opercularis)	50	15	-3	4.78

107	Left inferior frontal cortex (pars triangularis)	-56	30	-2	4.41
		-48	23	7	4.2
D. Familiarity					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**T statistic**
1580	Left inferior occipito-temporal cortex	-26	-81	-20	6.63
	Left inferior occippital cortex	-44	-76	-14	6.63
	Left lingual cortex	-20	-91	-11	5.46
	Right lingual cortex	21	-84	-11	5.55
	Right occipito-temporal cortex	32	-76	-21	5.44
	Right calcarine gyrus	11	-90	-8	3.63

Table 5. (A) Significant regions showing average activation for reading (P_{FWE}<0.05) (B), for recognition, (C) for recollection and (D) for familiarity. Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute space.

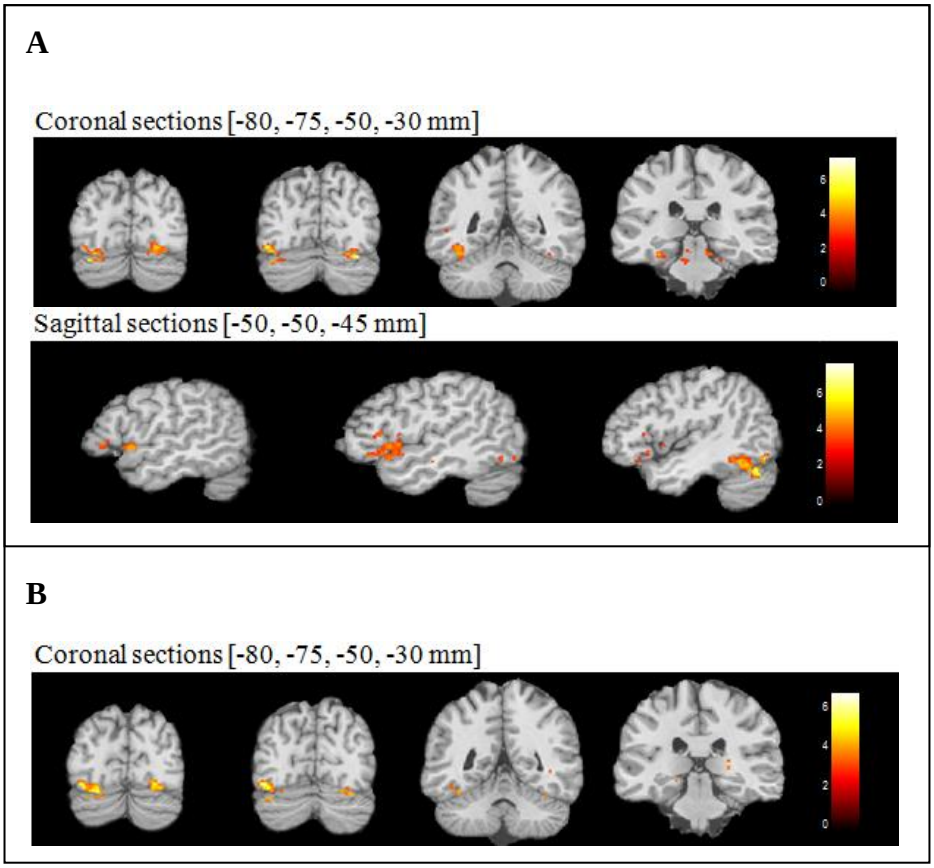


Figure 24. Statistical parametric map of (A) recollection associated with left occipito-temporal cortex (top figure) and inferior frontal cortex (bottom) and (B) familiarity associated only with left inferior occipito-temporal cortex. Results are based on threshold of p<0.05 FWE corrected, and figure with a statistical threshold of p<0.001 uncorrected.

Multivariate analysis of spatial distribution of activation in the Medial Temporal Lobe associated with recollection and familiarity

For each model of MTL subregion, Hipp, PhC and PrH activity (Figure 25), we report the parameters of exceedance probabilities to predict remember and know judgments (Figure 26). There was greater evidence for the Hipp activity than the other MTL subregions to predict all recognized words (Figure 26A) and remember judgments (Figure 26B). The PhC predicted also more remember judgments compared with the PrC (Figure 26B). In contrast, for know judgments, the PhC is a better model than the other MTL subregions (Figure 26C).

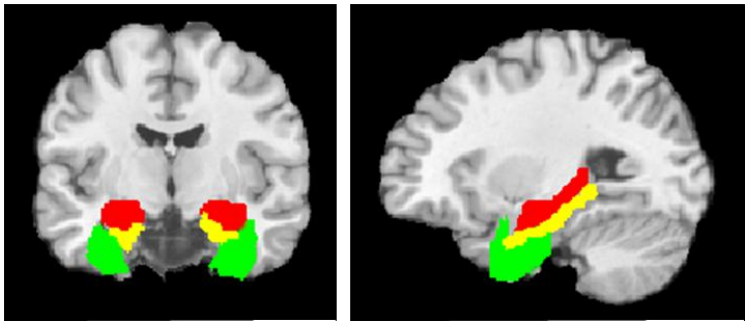


Figure 25. Figure of the three subregions of the medial temporal lobe in the MNI space: the hippocampus (in red), the parahippocampal cortex (in yellow) and the perirhinal cortex (in green).

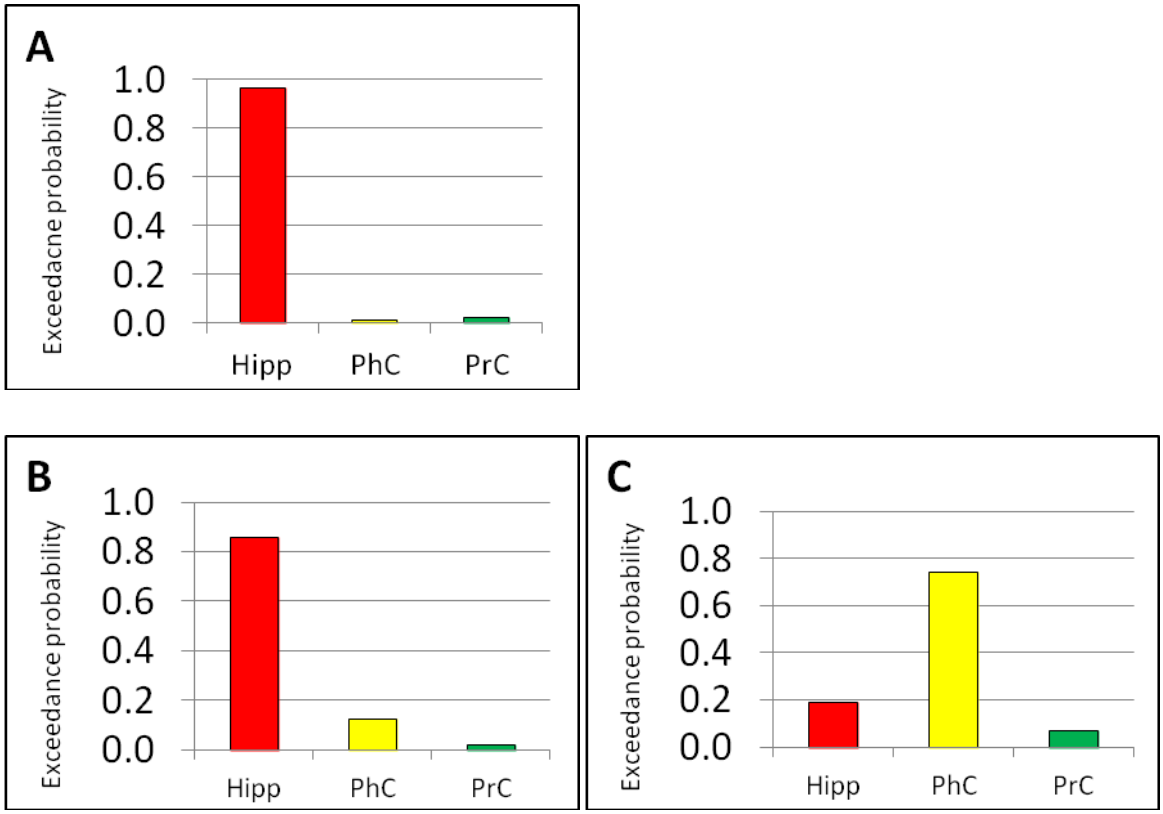


Figure 26. Comparison of MTL subregions models, namely the Hipp, the parahippocampal cortex and the perirhinal cortex models for (A) recognition, (B) remember and (C) know judgments using the Bayesian Model Selection (BMS) with the best spatial prior model. Y axis: Exceedance probability of each model to outperform the others.

Within the Hipp, the best model, in terms of spatial distribution of activity predicting all recognized words, was sparse-distributed and smooth within the PhC compared to the two other models (i.e. the three models are sparse, sparse-distributed or smooth). No model outperformed clearly the others within the PrC (Figure 27A). For remember judgments, we observed that the Hipp was best predicted by a sparse-distributed model, whereas the two other cortical regions of the MTL were best predicted by sparse model compared to two other models (Figure 27B). In contrast, for know judgments there was no clear pattern: no one model outperformed the others, but within the PrC, there was slightly more evidence for a sparse model (Figure 27C).

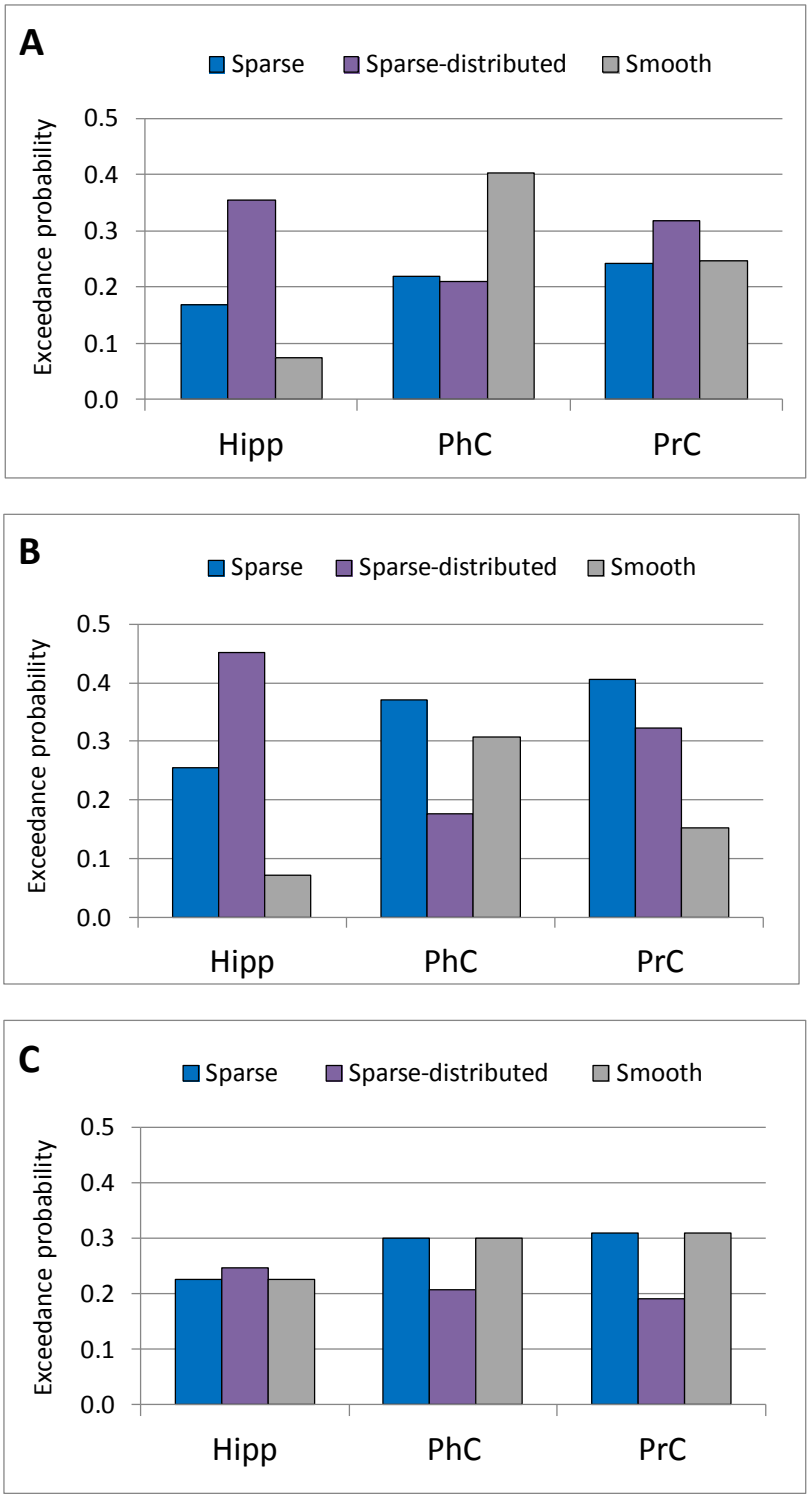


Figure 27. Comparison of spatial priors models, namely sparse, sparse-distributed and distributed models (represented in blue, purple and gray colours respectively) within each region of the MTL, namely the Hipp, the parahippocampal cortex (PhC) and the perirhinal cortex (PrC). Y axis: Exceedance probability of each model to outperform the others are reported for (A) recognition, (B) recollection and (C) familiarity condition.

In addition, there was no bias due to the complexity of penalty (i.e. number of voxels in each region) in the variational approximation of the model evidence used with MVB, because we report no significant effect of the volume of MTL subregions in the individual native space on the log-model evidence (i.e. F value) associated with recognition (p=0.065,F=2.447,df=38), remember (p=0.602,F=0.693,df=38) and know (p=0.28,F=1.304,df=38) judgments. In addition, knowing that the anterior part of the temporal cortex, i.e. in the PrC, could be biased by MR artifact (Olman et al., 2009), we tested whether the small contribution of the PrC in remember and know judgments is driven by a lower regional size. However this hypothesis was rejected, because we found that the size of the PrC (34886±2901 mm^3) is higher than the PhC (21535±1417 mm^3) and this last is higher than the Hipp size (24509±1612 mm^3) (p=0.00, F=147.08,df=38).

2.4.4. Discussion

Our results reveal a dissociation and specific mapping, at the level of neuronal representation, between MTL subregions and recognition memory components. This is a new finding that has direct implication for the on-going debate on neurocognitive models in recognition memory.

Emotional effect in recollection and familiarity

The experience of recollection was associated more with the recognized emotional words than the neutral words, thus replicating the advantage that emotional items have in recollection over neutral ones. By contrast, familiarity appears not affected by the emotional valence associated with the recognized items. One hypothesis is that, due to the Hipp specificity to process associations, emotional stimuli will enhance recollection. It is also possible that emotional remembered stimuli recruit more the amygdala to enhance the feeling of arousal and perceptual fluency (Sharot et al., 2004, 2007).

Univariate analysis of brain activation associated with recollection and familiarity

In the univariate analysis, we observe that brain activation associated with recollection and familiarity is mainly located in the inferior occipito-temporal cortex. We report that there is an additional activation associated with recollection in the inferior frontal cortex (i.e. operculum and triangularis parts).

The inferior temporal cortex, the medial temporal lobe (MTL) and left frontal cortex are commonly found to be associated with encoding of items that are subsequently recognized and associated with recollection and/or high confidence experience. The inferior frontal cortex associated with recollection could reflect a controlled effortful engagement allowing retrieval of source information (Skinner & Fernandes, 2007) or to the encoding of elaborate and organized episodic memory, in addition to the temporal cortex that would have a role in memory storage (Andrew P. Yonelinas, 2002).

We also report that brain activation associated with recollection is localized in the anterior part of the left occipito-temporal region. In contrast, brain activation associated with familiarity is also localized in the same regions, but in the posterior part, including the calcarine gyrus. This could be explained by the fact that the MTL, and more particularly the hippocampus, has the function to store information in memory by a transformation of visual stimuli coming from inferior temporal (IT) cortex to more abstract, sparse, invariant representations, possibly with less detail than the variant dependent neurons in IT cortex (Quiroga et al., 2008; Quiroga, Reddy, Kreiman, Koch, & Fried, 2005).

Recollection would involve mainly the hippocampus and anterior part of the MTL to store information coming from the ventral stream of the temporal cortex. In contrast, according to the representational-hierarchical view, familiarity would involve more the posterior part of the visual ventral stream in order to process visual features. The next steps involve complex conjunctions of features in the aim of representing them as a whole, fine-grained representation of object in the more anterior part of the temporal cortex (McTighe, Cowell, Winters, Bussey, & Saksida, 2010) with a semantic meaning (Tyler, Chiu, Zhuang, Randall, & Devereux, 2014).

Multivariate analysis of spatial distribution of activation in the Medial Temporal Lobe associated with recollection and familiarity

Dissociation between hippocampus and parahippocampal cortex for recollection and familiarity. Our results highlight the dissociation between Hipp and PhC for remember and know judgments respectively. This is in accordance with the exclusivity model or also the independency model if both processes are dependent on another common region in the MTL such as the PrC (Figure 20, right). Mainly, our results indicate that there is evidence for Hipp activity model to predict **remember** judgments compared with the surrounding cortical region. The PhC predicted also more remember judgments compared with the PrC. There was also a positive evidence for the PhC compared with the other MTL subregions to predict **know** judgments.

We also observed that Hipp activity model during encoding predicts strongly **all recognized words** compared to the other MTL subregions, This confirms that, within the MTL, the Hipp contains the largest amount of information related to memory compared with the other MTL subregions. This is in accordance with studies showing high sensitivity of hippocampal activity during fMRI memory task at high resolution (Carr et al., 2010; Yassa & Stark, 2009). We also confirm that, in MTL regions, a multivariate approach adds information compared to the univariate one in a memory paradigm (Chadwick et al., 2012). In addition, the advantage of MVB is that it can simulate a virtual lesion, by measuring the contribution of each region if they were absent (K. Friston et al., 2008), avoiding also collateral effects of lesions (e.g. compensation, presence of a "hidden" pathology) (J P Aggleton & Brown, 1999; Chadwick et al., 2012; Richard Henson, 2005; Morcom & Friston, 2012; Andrew P Yonelinas et al., 2010) that could bias the results.

Our observation of **dissociation between the hipp and PhC to predict recollection and familiarity** respectively is in line with models derived from lesion and volumetric studies. They found that the PhC, including perirhinal and entorhinal cortices, is necessary for familiarity (Bowles et al., 2007; Wolk et al., 2011; Yonelinas, 2002). These models are consistent with our results knowing that the entorhinal cortex is part of both the PrC and PhC. The majority of studies on amnesic patients showed that atrophied Hipp, but spared immediate surrounding cortical region, was associated with deficits only in recall, but not in recognition-related to spared familiarity processes (John P Aggleton et al., 2005; John M Gardiner, Brandt, Vargha-Khadem, Baddeley, & Mishkin, 2006; Yonelinas, 2002). The selective pattern of brain abnormality in the Hipp and in the enthorinal/perirhinal cortices was also correlated with recollection and familiarity deficit respectively (Eichenbaum H. Yonelinas A.R., 2007; Wolk et al., 2011). In addition, in a single case study, the resection of perirhinal and enthorinal cortices, with spared other parts of the PhC, impaired familiarity but not recollection (Bowles et al., 2007). The PhC can thus be associated with familiarity, probably with involvement of entorhinal cortex that is also part of the PhC in our study.

In most neuroimaging studies, they found similar results for the association between recollection and the Hipp, but not for familiarity and the PhC. They observed that the Hipp and the PhC, mostly in the posterior part of the MTL, are both associated with recollection and that the more anterior part of the PhC, i.e. the PrC, is associated with familiarity (Diana et al., 2007; Eichenbaum H. Yonelinas A.R., 2007; Slotnick, 2013; Yonelinas, 2002). In our results, we found that the PrC is less predictive of familiarity than the PhC, which seems contradictory with the majority of studies showing that the PrC is critical for familiarity (Diana et al., 2007; Eichenbaum H. Yonelinas A.R., 2007; Slotnick, 2013; Yonelinas, 2002).

However, a recent study found a triple dissociation between regions in the MTL. Recollection was associated with the posterior half of the Hipp, familiarity with the posterior PhC and novelty with the anterior half of the Hipp (Daselaar, Fleck, & Cabeza, 2006). Numerous other studies suggest a role of the anterior part of MTL, such as the PrC, in novelty detection (Rissman & Wagner, 2012; Yonelinas et al., 2010).

We notice that the difficulty in providing conclusive results in lesion and neuroimaging studies lies in the various **definitions** of the surrounding cortex of the Hipp between studies and in the fact that this region is sensitive to MRI susceptibility-distortion effects (Eichenbaum H. Yonelinas A.R., 2007; R. Henson, 2005b). In our study we observed that the PrC is not only the less involved in familiarity, but also in recollection and overall recognition. This could raise the question of whether results on anterior region could be biased by MR artifact (Olman et al., 2009) and by the small region size. Nevertheless, we did not report any significant effect of the volume of MTL subregions on the log-model evidence (i.e. F value) for each condition (i.e. recognition, remember and know judgments) (Hulme, Skov, Chadwick, Siebner, & Ramsøy, 2014). In addition, we observed that the size of the PrC was higher than the two other regions of the MTL. It could also be possible that the difference in our results from other studies could be driven by the different method, here MVB, used.

In addition, even if our results show specificity for each MTL subregion in remember and know judgments, other studies found that there is **not a simple mapping** (Larry R Squire et al., 2004). Those regions are associated differently with remember and know, depending on specific demands of the task and the type of information or domain involved: The Hipp has a role in binding item with context; the PrC in individual item, complex visual objects processes and the PhC in binding item with spatial context and scene and in categories

distinction (Diana et al., 2007; Rissman & Wagner, 2012; Staresina, Duncan, & Davachi, 2011). The PrC and entorinal cortex are also associated with semantic, but not episodic memory (Davies, Graham, Xuereb, Williams, & Hodges, 2004), whereas the Hipp predicts more episodic memory than the surrounding cortex (i.e. the PhC and the entorhinal cortex) (Chadwick, Hassabis, Weiskopf, & Maguire, 2010). Likewise, the PrC projects to the lateral part of the entorhinal cortex for "what"/item specific information processing, whereas the PhC projects to the medial entorhinal cortex for "where"/location-specific information processing (Alvarado & Bachevalier, 2005; Eichenbaum H. Yonelinas A.R., 2007).

In our study, we went also further in the investigation of the complex mapping, in term of spatial distribution of coding, between recognition memory components and MTL subregions by using MVB.

Neuronal coding of MTL subregions predicting recollection and familiarity. For the first time in our knowledge, we found that for recognition and recollection, the associated Hipp spatial distribution activity was best predicted by sparse-distributed model compared to all the other models (i.e. smooth and sparse). In contrast, there was a positive evidence for the sparse model compared with the other models to predict the activity in the surrounding cortical subregions of the MTL, i.e. the PhC and the PrC, for recollection. But for familiarity, none of the models clearly outperform the other within the PhC.

The emerging literature has investigated the neural representation/distributed pattern and its function for memory in the MTL, but was mainly focused on semantic rather than episodic memory. However, our result on recognition memory is highly consistent with a recent study (Wixted, Squire, Jang, Papesh, Goldinger, & Kuhn, 2014) that found that Hipp activation was associated with episodic memory and followed a **sparse distributed** coding

with distributed pattern of localized neural activity. This was described as the best way to rapidly encode memories without overwriting previously stored memories. Sparse-distributed mapping in the hippocampus is in line with the fact that episodic memory involves both retrieval of details related to one single episode (i.e. in favor of sparse representation) and to semantic knowledge arising from exposure of multiple episodes and extraction of regularities, explaining that many neurons or voxels are activated by many stimuli from the same class (i.e. in favor of more distributed representation) (Wixted, Squire, Jang, Papesh, Goldinger, Kuhn, et al., 2014).

Some studies explain the **sparsity** of the Hipp with its role in binding or association of information coming from different cortical regions outside the Hipp to form a single, complex and nonoverlapping episode in the Hipp (Chadwick et al., 2010; Diana et al., 2007; O'Reilly & Rudy, 2001; Quiroga et al., 2008; Rissman & Wagner, 2012; Rolls & Treves, 1990; Staresina et al., 2011). In a study (Quiroga, Kreiman, Koch, & Fried, 2008b), the Hipp representation was defined as sparse, however, the sparsity corresponds to neurons that fire to very few stimui such as abstract concepts, but not to single individual which was suggested in the Grandmother-cell theory (Quiroga et al., 2008, 2005). In a neural network learning context, the coding of several conjunctions (e.g. object and context) allows to process in parallel many solutions and find an optimal one, allowing generalization to novel inputs and avoiding exhaustive search through all possible combinations (e.g. each object and context) (Reilly & Busby, 2002)**.** In most previous studies on the neuronal representation of declarative memory, mainly semantic memory, they found sparse representation in the Hipp. In addition, there would be less than 1% of neurons related to this memory in the Hipp (Wixted et al., 2014). In a recent study, they found that the Hipp subfield Cornu Ammonis has an increased sparsity compared to the surrounding entorhinal cortex. This sparsity

would arise from the dentate gyrus, another Hipp subregion, involved in pattern separation (i.e. the process of generating different neural codes from highly similar stimuli) (Deng et al., 2010; Hulme et al., 2014). The Hipp would quickly bind together pattern separated representations and would favor recollection. In contrast, the cortical part of the MTL would be more poor in term of pattern separation and would be more specific to familiarity (Montaldi & Mayes, 2010).

Numerous other studies suggest that activation of the **PhC** (i.e. mostly in the inferior part of the temporal cortex) is sparse, in line with our results. The representational-hierarchical view of the ventral visual stream, including regions from the visual cortex to the inferior temporal cortex and then to the perirhinal cortex, assumes that the representation of an object is increasing in complexity of conjunction of features along the stream. The posterior part of the temporal cortex processes visual detailed features and the more anterior part processes complex conjunctions of those features to obtain a whole representation of object, or categories, invariant to object metrics, with less details and with a semantic meaning (Baddeley et al., 1997; McTighe et al., 2010; Rolls & Treves, 1990; Tyler et al., 2014). Those regions are mainly involved in perceptual functions; they can also generate representations of objects useful for other functions such as memory. The role of the MTL, mainly the Hipp, would be to store complex visual precepts in long-term memory in a less detailed, but more abstract way, allowing then generalization and learning processes (Quiroga et al., 2008; Reilly & Busby, 2002).

In addition, as shown in our results, the **PrC** is different in the type of neuronal representation, with sparse coding. This is in accordance with the fact that this region processes mainly unitized object and item information and is more selective to some specific perceptive information (Malcolm W Brown & Aggleton, 2001; Diana et al., 2007;

Duff, Hengst, Tranel, & Cohen, 2005; Henke, 2010; Kafkas & Montaldi, 2011a; Montaldi & Mayes, 2010; Quiroga et al., 2005; Slotnick, 2013; Yonelinas et al., 2010; Yonelinas, 2002).

However, the different **scales** or sampling of analysis used between studies makes difficult the description of coarse or fine-scale distribution of activation (Rissman & Wagner, 2012; Waydo et al., 2006). Kurtosis is also a measure of sparsity in biological studies. Higher degree of sparsity allows more selectivity to specific pattern of input, increasing the efficiency of storing memories with less energy and less confusion. One study reported that sparse coding in the MTL would allow less cost to recall the input already encoded (Olshausen & Field, 2004) and, in animals, the Hipp would contain place cells sensitive to specific locations and that are uniformly distributed or coarsely-distributed in human (Rissman & Wagner, 2012). The definition of sparsity should be adapted to the level of brain unit (e.g. neuron or voxel) and should correspond to units that contain enough information to distinguish between representations by taking into account human brain constraint (i.e. size) (Quiroga et al., 2008).

In conclusion, our results support a hierarchical organization of the Hipp and PhC, not exclusively based on memory function, but also on the spatial representation of the encoded information. This hierarchical representation of information could serve to multiple cognitive functions related to those types of representation (McTighe et al., 2010), such as familiarity and recollection. Our contribution on previous debates on recognition memory highlights the dissociation between regions of the MTL characterized by specific multivariate anatomical and functional profiles associated with recollection and familiarity. In the perspective to better understand the roles of MTL subregions, we could also investigate

their interaction with other cortical content-specific brain regions (Richard N Henson & Gagnepain, 2010; Skinner & Fernandes, 2007; Yonelinas et al., 2010; Yonelinas, Otten, Shaw, & Rugg, 2005) and how they can be affected by different types of stimuli (Sharot et al., 2004).

2.4.5. Limitations and perspectives

Limitations. In our study, we cannot be certain that difference between recollection and familiarity does not involve other possible non-mnemonic processes (Richard Henson, 2005). Indeed, recollection and familiarity are not matched in term of confidence of memory and in accuracy (Kafkas & Montaldi, 2012). However, we limited those problems by carefully asking the participants to choose a positive answer only if they were sure they remembered the word from the study list, making recollection and familiarity more comparable in term of confidence. The answer "No" allowed disregarding guessing and no confident answering.

In addition, there is no objective control to ensure that recollection and familiarity definitions were correctly understood. In some studies, the experimenter adds a contextual detail (e.g. color) with the item (i.e. source recollection) to check whether recollection is based on qualitative retrieval of contextual information. However, the disadvantage of that strategy is that it adds associative information and could bias the process of familiarity based on item processing only (Davachi, Mitchell, & Wagner, 2003; Rugg et al., 2012). However, in our study, we checked the instruction understanding by carefully asking the subject to explain the way they recognized the first six words of the test list. However, because recollection and familiarity represent subjective memories, it is difficult to assess them objectively. For example, a subject could associate a word with personal information, such as

an event in his life or an emotion (e.g. the word “ski” was remembered because the participant plans to ski the next week-end or because he likes skiing). Some studies used pupillary response (Kafkas & Montaldi, 2011) and reaction time (R N Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Yonelinas et al., 2005) to dissociate them. In our study, no time constraint was given to judge the memory, avoiding an additional bias to potential answers.

Perspectives. In perspective, we could test whether the pattern of activation found in encoding can predict subsequent memory judgment in new participants. To have higher prediction accuracy, we should also replicate the results with more participants. The ultimate goal would be to investigate MTL subregion contribution and spatial distribution associated with recognition memory components in individuals with MTL abnormality such as patients with AD, amnesia or depression. This could help identify abnormal memory trace and would represent individual biological markers of brain disease related to memory. This could also be useful to find ways to improve memory or depression and to understand the effect of some therapies at the brain level. For example, some studies report positive effect of therapies in AD and depression, but they do not report the effect at the brain level. For example, it has been shown that recollection in AD patients would be less impaired in events that contain an emotional valence and are self-related (Amieva et al., 2014; Kalenzaga & Clarys, 2013). In another study, a training of recalling more detailed and specific events has been shown to decrease depressive symptom (Watkins et al., 2009). In addition, knowing that removal of visual interference between the study and test phase could rescue recognition memory impairment, more particularly the ability to distinguish novel from repeated stimulus (McTighe et al., 2010), it could be interesting to understand how this intereference modulates the task performance and the neural code in healthy controls, AD and depressive patients.

3. LEARNING

3.1. Multiple cues learning and memory systems interactions

Recent models of memory systems highlight that in order to understand the functions of the temporal cortex in guiding behaviors it is necessary to identify its interaction with other memory systems in the brain (Gagnepain et al., 2011; Richard N Henson & Gagnepain, 2010). It has been proposed that memory systems (Figure 28) could be a result of the specialization of specific regions in processing different information and whose response will thus depend on the task demand (Henke, 2010). The multiple cue probabilistic learning (MCPL) task (described in section "Behavioral task" of chapter "3.3.2. Materials and methods ") offers a way to probe different memory systems, their interaction, and their specific components related to trial-and-error learning based on feedback. MCPL is also a cognitive process constantly encountered in daily life in order to adapt to our environment. The task has been mainly used to test procedural memory and declarative-episodic memory in patients with brain lesions in specific regions such as the basal ganglia (BG) and the MTL (Foerde et al., 2013; Hopkins, 2004; Knowlton et al., 1994; Daphna Shohamy et al., 2008). Recent neuroimaging studies have confirmed that in classification/categorization learning, the MTL and BG memory systems, in addition to the pre-frontal cortex, are involved and can interact through cooperation and/or competition depending on the learning situation. For example, when a memory system is altered, another system can show up to enhance learning or when a system is increasing, the other is decreasing for the same task. The MTL is active early for generation of new stimuli representation and for declarative memory of past experience. It becomes then deactivated through learning trials. In contrast, the BG is related to non-declarative/procedural memory and gradual learning with feedback and increases over time

(R a Poldrack et al., 2001; Russell a Poldrack & Packard, 2003; D Shohamy, Myers, Kalanithi, & Gluck, 2008).

According to the literature, different brain regions have different functions during MCPL. As this type of learning involves visual categorization, the **visual cortex** processes first the sensory information of the environment and then detailed representations with bottom-up influences, meaning from basic, detailed elements to linked elements that are larger and more complex in the level of organisation. In the **"ventral stream"** composed of the visual areas V1, V2, V4 and the inferior temporal cortex (Ungerleider & Haxby, 1994), there is not only the perceptual processes and image segmentation of image, but a transformation of visual percepts in brain's internal view of objects (Sheinberg & Logothetis, 1997). With repeated exposure or attention to a stimulus, the neurons of this area can adapt and become specific to this stimulus with a certain degree of tolerance. This repetition can improve the perceptual processing of relevant information, but it is not sufficient for some decision-making and the generalization of information. In the accumulator model (Seger & Peterson, 2013), emerging from mathematical psychology, the information needs to be accumulated and summed up until a decision can be made. The accumulation of evidence (or information) can also recruit regions in the inferior temporal lobe or the dorsolateral prefrontal cortex. It is known that the inferior temporal and the occipito-temporal (OT) cortices contain neurons that respond selectively to the shape of stimuli and can categorize them based on their perceptual properties and similarities. This involves perceptual memory and pattern recognition (Seger & Peterson, 2013). The OT cortex can thus processes complex visual forms and integrate top-down influences, i.e. high to low level of information processing (Kherif et al., 2011)..

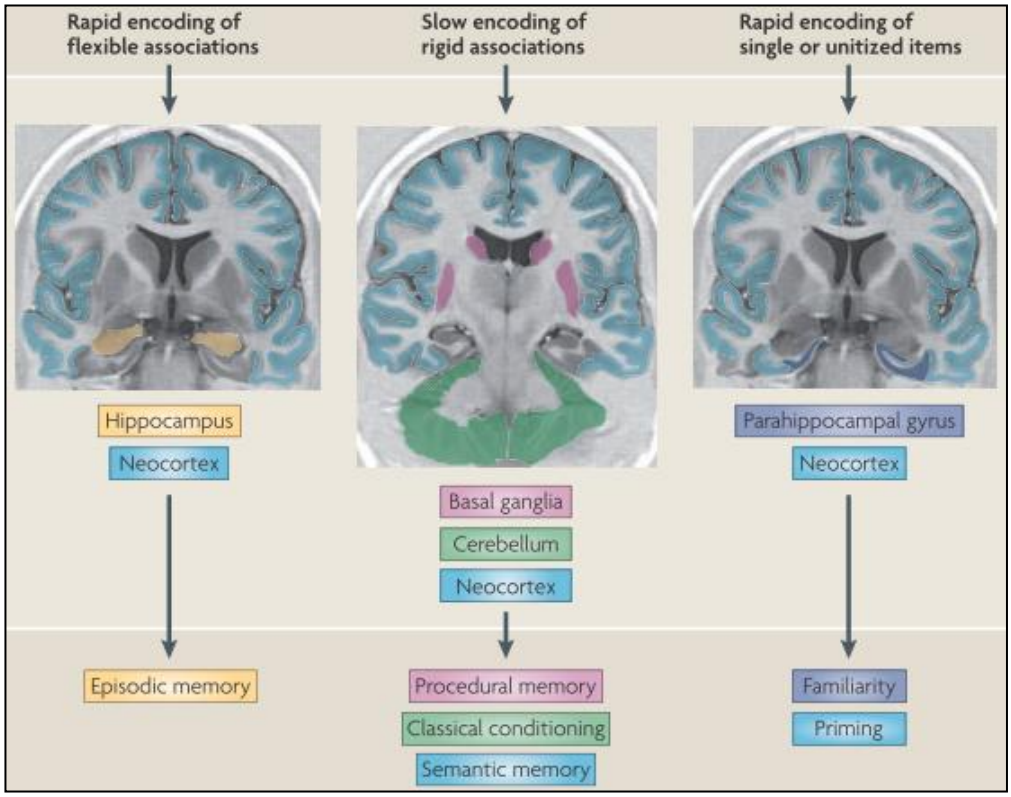


Figure 28. Schema of different memory systems (i.e. episodic memory, procedural memory and priming/semantic memory) with the associated brain regions and the cognitive process related to them (Henke, 2010).

In categorization tasks, the **MTL** is involved in remembering individual examples and instances or exceptions to rules and error corrections (M. a Gluck, Myers, & Meeter, 2005; Henke, 2010; Seger & Miller, 2010; Seger & Peterson, 2013). In a study on animals performing a spatial trial-and-error learning, the ventral hippocampus was shown to be related to early learning local search strategies whereas the dorsal hippocampus was involved in late learning and was associated with more proficient learning strategies (Ruediger, Spirig, Donato, & Caroni, 2012). Both the MTL and the pre-frontal cortex also crucially contribute to making stored information accessible to other systems such as the neocortex and the striatum through dopamine projections (Foerde, Knowlton, & Poldrack, 2006). In addition, the MTL is also involved in generalization of stored information to new situations, which can make learning more flexible (Seger & E. K. Miller, 2010). Flexibility

means that the storage of information occurs in different brain regions allowing recall to be done in many different ways (Henke, 2010). Other studies have investigated MCPL in amnesic patients and have shown that they were less able to use a more complex and optimal strategy that combines multiple information, probably due to their incapacity to remember strategies or feedback (M. a Gluck et al., 2005; Hopkins, 2004; M Meeter, Radics, Myers, Gluck, & Hopkins, 2008; Martijn Meeter, Myers, Shohamy, Hopkins, & Gluck, 2006). They also exhibited late learning deficits in the task (Knowlton et al., 1994), but also early on (Hopkins, 2004). In contrast, fMRI studies show that hippocampal activation is more involved early on and decreases and even becomes deactivated as the learning proceeds, which is the opposite case for the basal ganglia. There is an initial process in the MTL to acquire appropriate stimuli representation and that normally facilitates subsequent learning and makes that initial representation accessible to other brain regions. This mechanism is absent in patients with MTL lesions, explaining their deficits in MCPL (M. a Gluck et al., 2005; R a Poldrack et al., 2001).

Hippocampal and striatal activations have been shown to work in coupled, complementary or competitive manners depending on the task demand. The competition between MTL and BG is likely to be to enhance learning by balancing access to flexible knowledge against an automatic, fast learning (Packard, White, & Ha, 1989; R a Poldrack et al., 2001; D Shohamy et al., 2008). It has also been shown that these two regions can act in parallel and complementary manners to facilitate learning (K. C. Dickerson, Li, & Delgado, 2011; Foerde et al., 2006). Their interaction would be for example supported by their functional neuroconnectivity through a dopaminergic loop in situation of novelty-detection (Lisman & Grace, 2005).

The **basal ganglia (BG),** mostly involved in "know how" or procedural memory, contributes in the MPCL, but mainly in the late stage of learning. This region is associated with gradual incremental aspects of learning based on feedback, with the integration of multiple information and with a shift from simple to more complex strategies (D Shohamy et al., 2008). Procedural memory is a main part of implicit memory, acquired slowly as a skill learning to extract common elements from a serie of separate events. BG activation is involved in learning specific to one skill and in the slow encoding of rigid associations, in contrast to the hippocampus, which is more involved in the generalization and flexibility of learning (Henke, 2010). Recent computational models have predominantly associated the activation of the caudate nucleus, part of the BG, with dopamine and reward/feedback related learning (Delgado, Miller, Inati, & Phelps, 2005; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). In a study on patients with pallidotomy, meaning with neurochirugical destoyement of a part of the BG called globus pallidus that is overactive in Parkinson's disease, the learning of weakly predictive cues, a more implicit learning than for strong predictive cues, was impaired (Sage et al., 2003). In the BG, the ventral striatum was also shown to be positively modulated by subject's performance in MCPL (Vink et al. , 2013). The ventral striatum, connected to the orbitofrontal cortex, is associated with prediction error (PE) and reward-learning associations, whereas the dorsal striatum is more sensitive to the predicted value of the reward. The BG also contributes, as part of the cortico-thalamo-striatal loop, to decision thresholding and response criterion setting. Anatomically, the caudate nucleus projects from the cortex to the striatum, then to the thalamus and back into the cortex. The response selection is supported by the inhibition of the thalamus through a direct pathway (Seger & Peterson, 2013).

The **Pre-Frontal Cortex (PFC)** contains neurons sensitive to the boundaries of category representations and to abstract rule-based categorization (Seger & Miller, 2010). The PFC maintains recent information in working memory to reach a goal. The PFC would also be connected to the BG via dopaminergic pathways, which filter non pertinent information and allow attentional learning for stimulus selection, motor learning or process of shifting between rules (Moustafa & Gluck, 2011; D Shohamy et al., 2008). The PFC could also be implicated, with the parietal cortex, in top-down attention processes (Buschman & Miller, 2007) and can also be recruited for decision making, to choose a high value option or to switch from one strategy to another to maximize reward (Seger & Miller, 2010). In a study using repetitive transcranial magnetic stimulation (rTMS), which produces electrical currents with magnetic field generation, on the dorsal PFC early in a probabilistic task, there was a disruption of subsequent learning strategies (Rushby et al., 2011). In addition, the PFC can interact with the hippocampus to process associations (Seger & Peterson, 2013), to consolidate memory or to recall information through strategic control on retrieval. This allows the selection of more pertinent memories linked to a context and the suppression of other less relevant memories (Preston & Eichenbaum, 2013).

The orbitofrontal cortex, also called the ventral PFC, is also involved in coding the value of a stimulus and is crucial for learning and decision-making by taking into account emotional and motivational experience associated with the stimulus. This is in line with neuroeconomic theories which affirm that in learning based on reward, the expected computed value does not always predict a rational decision, particularly in the case of uncertainty, which is present in situations of categorization. Indeed, a decision also integrates other factors such as **motivation and affects** and is often called “choice”. For example, impulsivity can explain

the preferential choice for an immediate reward and the involvement of the PFC. In addition, the uncertainty of a reward induces risk and ambiguity that depends on the prediction of a reward and involves dopaminergic systems of the BG and dorsolateral PFC. The anterior prefrontal cortex is also associated with choice making in the future (Seger & Peterson, 2013). In addition, other individual factors such as the presence of depression symptoms decreases the response to reward and increases the sensitivity to punishment in learning probabilistic associations (Brinkmann, Franzen, Rossier, & Gendolla, 2014; Whitmer, Frank, & Gotlib, 2012). Individuals with depressive symptoms without a depression diagnosis, also called dysphoric individuals, are more sensitive to change of contingences to learn (Msetfi, Murphy, & Kornbrot, 2012). Beyond this, stress can also favor striatal activation in categorization learning rather than the MTL system (Schwabe & Wolf, 2012). These observations highlight the fact that, in a categorization task such as MCPL, different individualized factors can influence learning and interact to make choices. Those systems could also be modulated by personality, affective and motivation states.

3.2. Open questions

The aim is to investigate the role of the MTL and the temporal lobe during learning, by exploring their interactions with other memory systems (Figure 29). This is investigated in chapter 3.3 entitled “Experiment 3 - The interactive role of the occipito-temporal cortex with frontal cortex during probabilistic learning and uncertainty”. The effect of reward and prediction error in learning was investigated in the chaper 3.4 on “Experiment 4 – Neural substrate associated with reward and prediction error in probabilistic learning”. Individual factors such as personality and negative affects will also be related to learning. This is investigated in the chapter 3.5 entitled “Experiment 5 – Neural substrate associated with personality and depressive/anxiety symptoms in probabilistic learning”.

Part 3 **Probabilistic learning**
fMRI with virtual game environment
Causal Modelling
Healthy

Figure 29. Plan of the third part of the thesis. The raws describe the research topic, the neuroimaging MRI technique, the statistical method used and the population studied. MRI: Magnetic Resonance Imaging.

3.3. Experiment 3 - Uncertainty and the interaction between the occipito-temporal cortex and frontal cortex during probabilistic learning.

3.3.1. Objective

Learning is an adaptative process allowing predicting the future based on the past experience. In reality, the context is often uncertain and humans have still the capacity to learn but in probabilistic and individual ways (M. a Gluck et al., 2002). Well-adapted behavior and optimal decision making require the extraction of relevant information from noisy sensory inputs, as well as weighting of evidences from multiple sources of information (Behrens, Woolrich, Walton, & Rushworth, 2007). Recent studies aim to understand neuronal mechanisms in such environment (Huettel, Song, & Mccarthy, 2005). To capture those mechanisms of learning, we used a paradigm called multiple-cue probability learning (MCPL). We adapted the Weather prediction task (Knowlton et al., 1994) to a virtual game environment and used pseudo-letters to render the cue integration task similar to a pseudo-word learning paradigm. In the MCPL task, subjects have to predict a criterion/outcome based on some cues presented at each trial. In order to learn the probabilistic association between the cues and the outcome, they have to combine cues to extract relevant information. The probabilistic nature of the task and the combination of cues generates random errors and uncertainty. Multiple studies on neuroimaging (R a Poldrack et al., 2001; D Shohamy et al., 2008) and on patients with brain lesions (Foerde et al., 2013; Hopkins, 2004; Knowlton et al., 1994; Daphna Shohamy et al., 2008) have shown the implication of different memory networks localized in the medial temporal lobe (MTL) and the basal

ganglia (BG) associated with episodic and procedural memory (Figure 30) respectively. However, far less is known about the regions associated with within subject learning and about the role of the occipito-temporal (OT) cortex in priming memory or semantic memory and the functional connectivity with higher order cortical areas such as the frontal cortex involved in working memory and attention processes (Figure 30). We want to test whether the activation of these regions can explain some aspects of the MCPL task. We hypothesize that those nodes are segregated but interacting systems that underlie individual learning and memory components. The MTL would also have a dynamic or flexible role in that dynamic learning.

In addition, a lot of studies have focused on behavioral learning in MCPL, but few of them have linked this learning with brain activity. Regarding the high inter-individual variability in learning strategies (Gluck et al., 2002), we will use a neurocomputational model of learning that is weights of cues (Kelley & Friedman, 2002; D. A. Lagnado, Newell, Kahan, & Shanks, 2006; Speekenbrink, Channon, & Shanks, 2008; Zeithamova, Schlichting, & Preston, 2012). We expect this will help understanding the dynamic role of different memory systems and their interaction during learning by capturing the inter-individual variability of subject's learning (K. C. Dickerson et al., 2011; M. a Gluck et al., 2002). Regarding the lack of investigation of the dynamic neural mechanism underlying interaction of memory networks during MCPL, we investigated the directionality, in terms of "forward" and "backward" flows, between brain memory networks associated with models learning and whether this can be explained by the predictive coding account theory. In this theory, the OT is described as having a central role in integration of visual forms and in comparison of them with conceptual knowledge (or expectation) under top-down influences (K. Friston & Kiebel, 2009; Kherif et al., 2011).

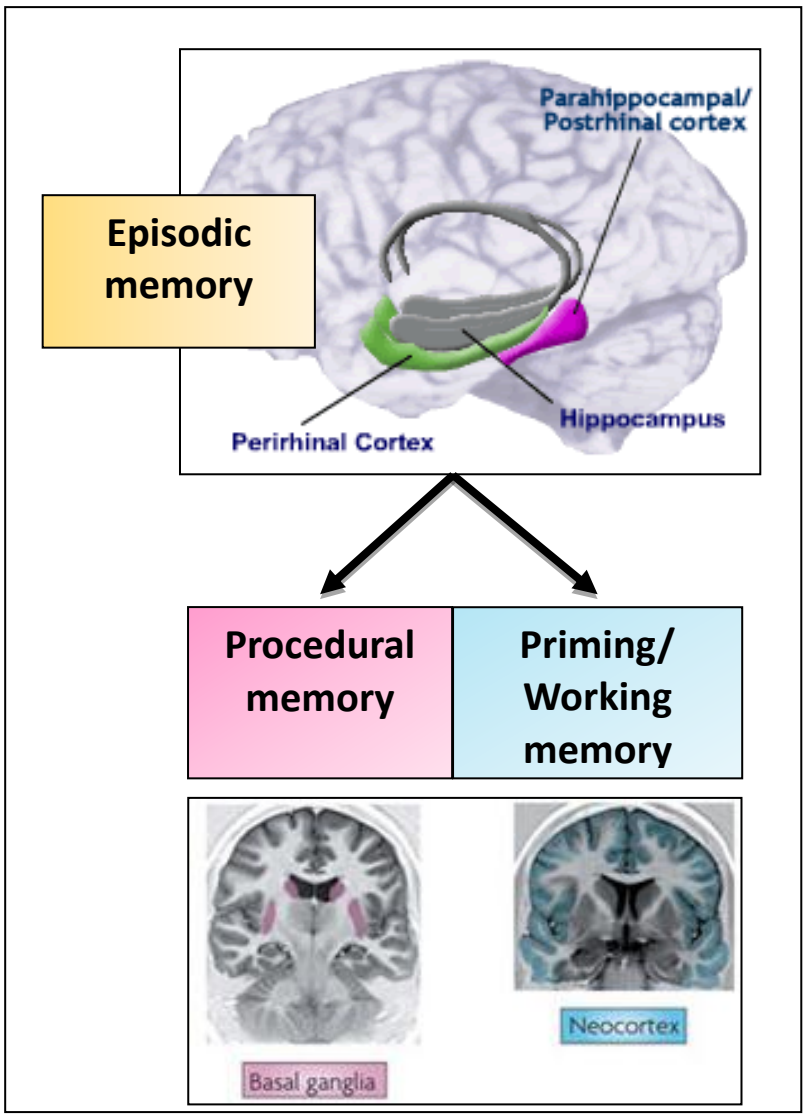


Figure Figure 28. Schema of different memory systems (i.e. episodic memory, procedural memory and priming/working memory) and the associated brain regions hypothesized to be involved in MCPL (Modified source: (Henke, 2010), http://www.bristol.ac.uk/synaptic/pathways/).

3.3.2. Materials and methods

Participants

27 participants that took part on the experiment. Four of them were removed for the brain imaging analysis, because of MR artifacts and excessive movements in the scanner. The 23 remaining subjects were about 26 years old (age mean: 26.2 years, SD: 4.6 years), with 11 men and 12 women and 91% of them were right-handed.

Behavioral task

1-back task

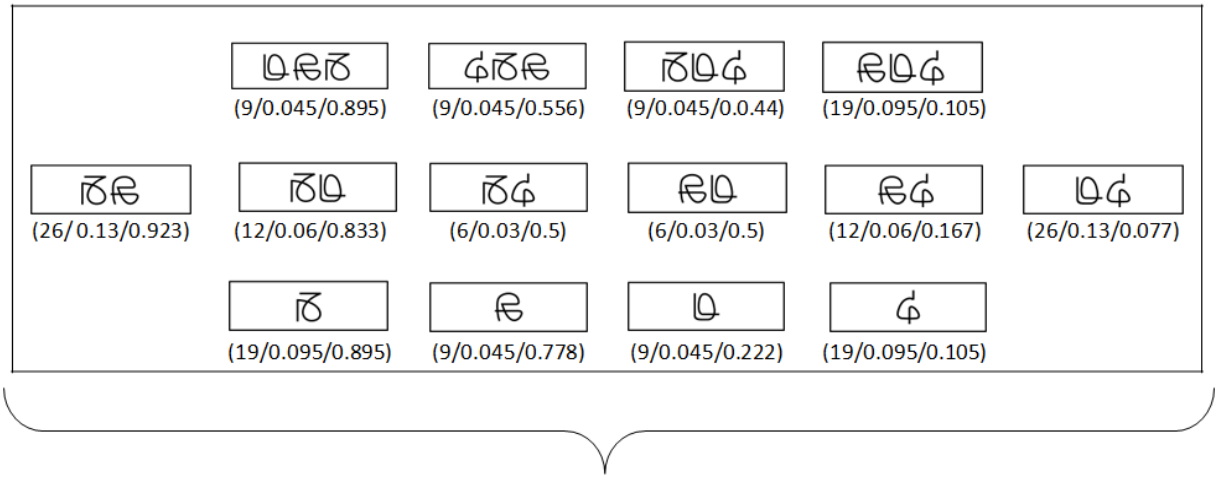
Before training and test phases of the MPCL task, participants underwent a discrimination task called 1-back task (Kirchner, 1958). That test allowed testing whether the four symbols used in the MCPL task were not different in terms of accuracy and reaction time. Three additional symbols were included to increase the subject's engagement in the task. Each symbol was presented successively on a computer's screen. Participants had to answer whether the previous symbol was similar or different than the present one. This task requires discriminating symbols and maintaining attention. N-back task is also known to test working memory. In total, there are 207 trials presenting 7 different symbols whose 4 are the same than in the MCPL task. The frequency of appearance of each symbol was nearly similar (29 times for 5 symbols, 28 and 34 times for the two last symbols).

MCPL task

Training of MCPL task. To familiarize the participants with the gaming context of the MCPL task and to ensure that the instructions were well understood, they were trained with a shorter version of the MCPL task outside the scanner. In total, there are 36 trials which present symbols different than the ones in the MCPL task.

MCPL task. A 3D gaming version of the MCPL task (M. a Gluck et al., 2002; David A Lagnado & Newell, 2006a; Speekenbrink et al., 2008) was performed in the scanner. On each trial, the participants had to predict the correct outcome, symbol A or B, presented on a door based on the presentation of a card containing a combination of one, two or three pseudo-letters sequence. Symbols A and B have a shape of trapeze or hexagon respectively. If the participants made the correct choice they received a positive feedback (coin) allowing them to learn the association. There are learning trials in which the cards illustrate pseudo-letters and non-learning trials where cards illustrate the outcome A or B (Figure 31). Pseudo-letters, also called cues, are selected among four different pseudo-letters. They are combined in 14 patterns (or cards). The association between each card with outcome is probabilistic (Figure 32, top part). This allows generating probabilities of association between each cue and outcome with the following probability: 20%, 40%, 60% and 80% (Figure 32, below part). The overall occurrence of symbol A and B is identical. The pattern frequency, the probability of association and the conditional probability of association between the pattern and the outcome A knowing the frequency of the pattern are described in article of Gluck et al. (Gluck et al., 2002). In each of the two sessions, each of the 4 cues appear 50 times and the non-learning trials, 80 times. The cards are presented in an identical order through the two sessions, but the order of combination of cues on a card is randomized between subjects.

A feedback phase was also planned at the end of the first and the second session. The subjects were asked to estimate the probabilistic association between each cue and the outcome. At the end of the second session, they also had to choose which strategies they thought they used during MCPL among a list of different strategies. They are based on presence of one cue; on cards containing only one cue or multiple cues; on number of cues, on the most frequent cards, on memorization of each card, on geometric shape of the symbols, on localization of symbols, on hazard, on intuition or on other strategies. This was mainly used to check whether the subjects understood the task and to have an insight of the variability in the way they performed the task.



%		Symbol A	Symbol B
Cue			
1		20	80
2		40	60
3		60	40
4		80	20

Figure 30. Figure of cues and cards with their pattern frequencies. From the 4 symbols/cues (below) and their conditional probability of association with the outcome (symbol A or B), 14 patterns/cards are generated (top) with indication of pattern frequency, probability of association and conditional probability of association between the pattern and the outcome A knowing the frequency of the pattern written below each card.

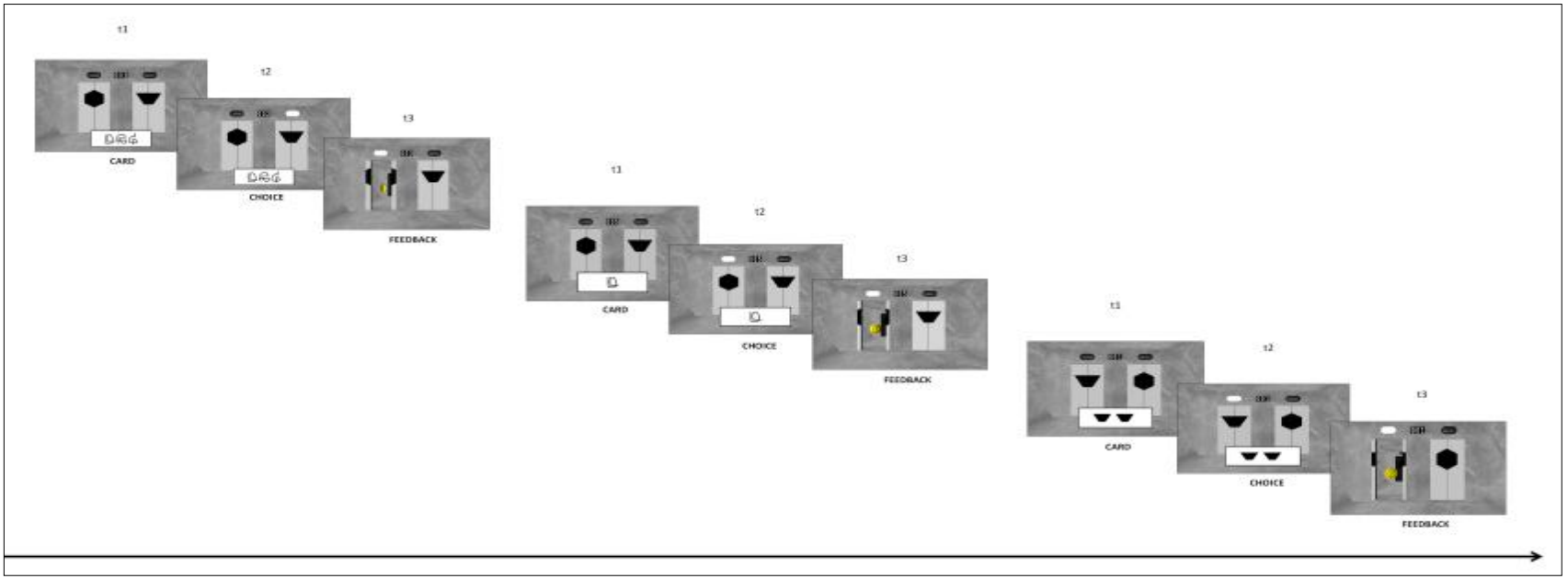


Figure 31. Task/game description of two learning trials and one non-learning trial (from left to right).. At time 1 (t1), the card is presented. At time 2 (t2), the subject has to choose between 2 outcomes: symbol A or B and, in case of correct prediction, the subject receives a feedback represented with a coin (t3).

The instruction (in French) given to the participant is described below.

(For the training phase)

"Imagine that you are on another planet and that you enter in building containing a multitude of doors leading to rooms. Before entering in a room, there will be a card presented in front of you that is composed of a serie of 1, 2 or 3 alien letters (Figure 33A). You will have to predict which door (i.e. symbol drawn on it) is the most associated with this combination of letters. After having chosen a door, a light switches on and the door opens. If you make the correct choice, you will be rewarded by a precious coin. Your purpose is to collect the most possible of coins to reach the final destination. (The position of the symbols on the cards and of the doors is not an informative cue).

In addition, some cards are bonus: they contain the same symbol than the one on the doors. You will just have to indicate which door contains the same symbol than on the card. Each time you collect a coin, one point will be added on the clock over the door (Figure 33B).

A **B**

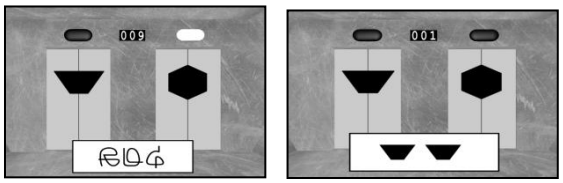


Figure 32. Figure of the task. Illustration of (A) the alien letters in learning trials and (B) symbols similar as on the doors in non-learning trials.

Your task will be to click on the left button to choose the left door or on the right button for the right door. After having chosen a door, a light switches on and the door opens. You will see that it is a trial-and-error learning. To be prepared with this mission, you will now train with some cards. After this first session, the real mission in the MRI will begin.

Last message: Be the most correct and fast possible.

(For the test phase)

Now, your real mission in the MRI is going to begin. You will see other symbols on cards and on doors (look well at them on the illustrations, Figure 34). Be the most correct and fast possible. Good luck! "

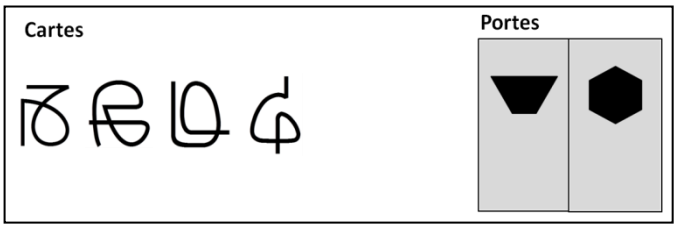


Figure 33. Figure of the task. Illustration of the alien letters in learning trials (left) and symbols similar as on the doors in non-learning trials (right).

MRI sequences

We acquired EPI images in a 3-Tesla Siemens scanner located at the Centre d'Imagerie BioMedicale (CIBM) in Lausanne, Switzerland. EPI sequences were acquired with a 32-channel head volume RF-coil. In total, there were 482 acquisitions of $3mm^3$ resolution with the following settings: TR 2000ms, TE 30ms, flip angle 90 degrees, FOV read 216 mm, 32 slices per volume, FOV phase 100%, bandwidth 2480 Hz/pixel, echo spacing 0.47ms, interleaved multi-slice mode, long term average mode). Each trial lasted 3.5 s. with card presentation lasting 2 s, feedback 0.5 s and inter-stimulus interval 1 s. There were 2 sessions of 280 trials that included series of 9±1 learning trials interspersed with 4±1 non-learning trials. Frequency of each cue was randomized within and balanced between each block of learning trials.

Statistical analysis

SPM8 was used for data pre-processing and statistical analyses. Pre-processing consisted of spatial transformations with realignment (for correcting movement artefacts), segmentation, normalization to the MNI space, and spatial smoothing (with isotropic 8-mm full-width at half-maximum kernel) and finally, temporal high-pass filtering (1/128 Hz cutoff) was applied. For the fMRI data analysis, we aim to compare learning trials compared with non-learning trials and the modulation of behavioral model of learning. For this purpose, we constructed a mixed parametric design matrix with the General linear model (GLM) that contained for each session: 4 conditions of learning trials related to each cue, 4 parametric modulators corresponding for each of the last conditions and that represent parameters (weights) of behavioural learning‘s model. Additional conditions corresponding to non-learning trials and to timeout trials were added. In the first session, the first 30 trials were also included as covariate as they do not allow modelling a stable regression. The regressors were built by convolving the canonical hemodynamic BOLD response function with each condition. Onsets of each condition were defined as events of 0 s.

Behavioral model of learning: cue utilization weight

We used the cue utilization weights to estimate the internal model of individual’s judgment policy to capture the dynamic probabilistic structure of the environment. This model comes from the Brunswik’s Lens model framework (D. A. Lagnado et al., 2006) and is also an extension of the “rolling regression” technique to take into account the dynamic of learning

(Kelley & Friedman, 2002). At each learning trial, a window of the last 50 consecutive trials allows computing a weight for each cue in each trial using a rolling multiple logistic regression. Based on binary response, this method produces a weight for each cue and can account for the learning of other cues even if they are absent. The size of the window takes also into account human memory constraint (D. A. Lagnado et al., 2006; Speekenbrink et al., 2008; Zeithamova, Schlichting, et al., 2012).

From binary response, i.e. choice of outcome (Symbol A) and presence or absence of cues at time t, the regression computes thus weights (β) for each cue given the weight of the other cues using a multiple logistic regression (1). Each weight represents also the log-likelihood ratio for the choice of the outcome (Symb A) given the presence of a specific cue (2). Weights are also transformed in odds (3) by a logistic function in order to compute probability values between 0 and 1 (Speekenbrink et al., 2008). When weights are inserted in the fMRI design, the learning curves of cues associated with probability lower than 50% are also reversed in order to test the effect of increasing learning curve.

$$\text{Choice } A_t = (\beta 1_t * \text{cue } 1_t) + (\beta 2_t * \text{cue} 2_t) + (\beta 3_t * \text{cue} 3_t) + (\beta 4_t * \text{cue} 4_t) \quad (1)$$

$$\beta 1_t = \ln(P(\text{choice } A_t) | \text{cue } 1_t) / P(\text{choice } B_t | \text{ cue } 1_t)) \quad (2)$$

$$\text{Odd } \beta 1_t = \exp(\beta 1_t) / (\exp(\beta 1_t) + 1)) \quad (3)$$

Univariate statistical analysis

After pre-processing and smoothing of the data with isotropic 8 mm full-width at half-maximum Kernel, we tested the effect of learning trials in MCPL. We built a design matrix at subject's level composed of two conditions including learning trials and non-learning trials for each of the two sessions (Figure 35). Non-learning trials represent the baseline condition. T-contrast was then performed to test the effect of learning trials compared with non-learning trials at subject level. This contrast was then brought in the second level analysis to perform a one-sample t-test at group-level. This tests whether the effect size or the average of the contrast images of each suject is different from zero at group-level. The same statistic was performed for the effect of reward compared with non-reward condition, except that the presence/absence of reward was inserted as parametric modulator of the learning trials condition.

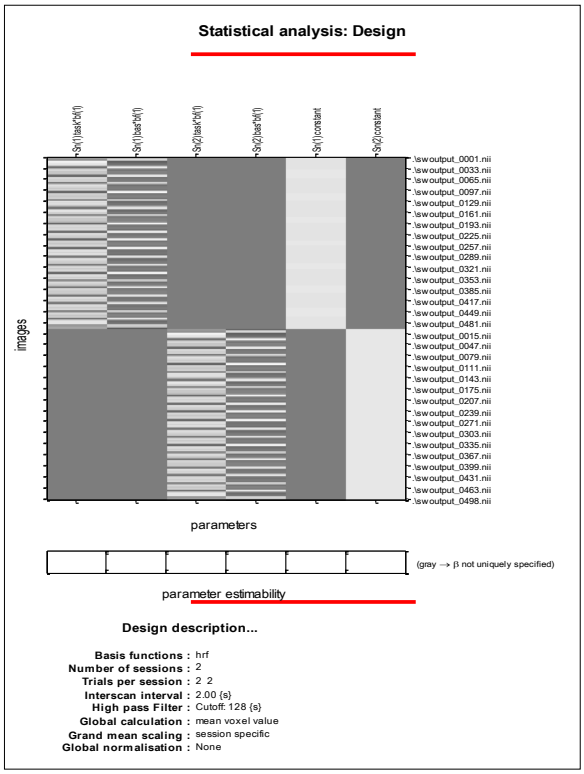
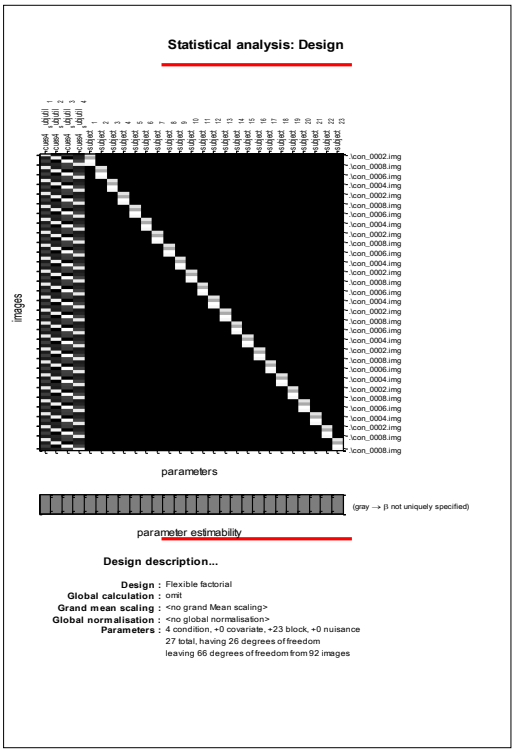


Figure 34. Design matrix containing two regressors for learning and non-learning condition in each of the two sessions. The design matrix includes scans in rows and explanatory variables/regressors in columns for each of the two sessions.

Then, to identify brain activations associated with subject's learning, parametric modulators of cues were included in the design matrix. In each session, there were four conditions, one for each cue. For each condition, we added a parametric modulator corresponding to learning measure (Figure 36A). The timeout, non-learning trials of the two sessions and the 30 first trials of the first session were included as regressors of no interest. The thirty first trials were removed due to instability of subject's utilization weights of multiple logistic regressions. However, they were not removed in the model of PE. At group level, an ANOVA test with repeated measures (i.e. flexible factorial design) was performed (Figure 36B). This statistical design is used when there are multiple measures/contrasts by subject and can test the effect of repeated measures while removing the subject's effect. It is also possible to add parameters of subject's movements to remove their possible confounding effect in the effect of interest.

A



B

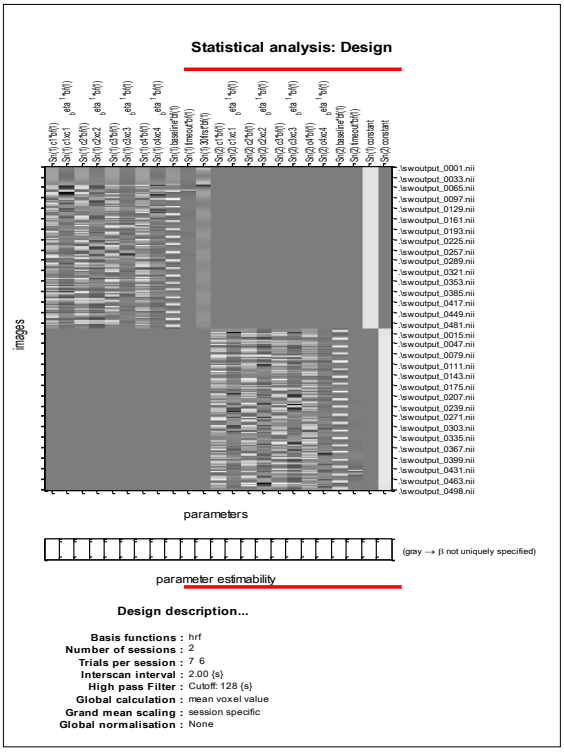


Figure 35. (A) Design matrix at subject's level containing 10 regressors for each of the two sessions. They are four conditions for each cue, four parametric modulators of learning for each cue and two other conditions for non-learning trials and timeout. The first session contains an additional condition with the thirty first trials. The rows represent the scans and the columns, the explanatory variables/regressors. (B) Design matrix at group level which corresponds to a flexible factorial design including four parametric modulators of learning for each cue and for each subject and a subject's condition. The rows represent the contrasts estimated at subject's level and the columns, the explanatory variables/regressors.

Multivariate analysis of effective connectivity between regions: VOI, DCM and BMS

We used Volume of Interest (VOI), Dynamical Causal Modeling (DCM) and Bayesian Model Selection (BMS) with SPM8 software to extract time series activation from the left occipito-temporal cortex (LOT) and the right mid frontal cortex and to identify the best model in term of effective connectivity, namely bottom-up, top-down or both directionalities, between the two regions. The selection of those two regions is based on previous results associated with behavioral learning and on the fact that those regions work together for the acquisition of new conceptual knowledge during decision making (Kumaran, Summerfield, Hassabis, & Maguire, 2009).

VOI. VOI coordinates in LOT (XYZ(-39,-48, -10.5)) and in right mid frontal cortex (XYZ(-39,-48, -10.5)) correspond to the most significant voxels associated with the behavioral model of learning with threshold $p<0.001$ whole brain FWE corrected for multiple comparisons. VOI computes the first principal component of the time series from all voxels included in a sphere of 6 mm around each coordinate defined as a starting point to search the nearby local maximum.

DCM. VOI's are then used in DCM to measures the functional, effective (i.e. causal) connectivity between those brain nodes using temporal information of neuronal activity. DCM models not only the coupling between those nodes (i.e. functional connectivity), but also estimates the causal directed influences of changes in experimental context between the nodes (i.e. effective connectivity). The model of neuronal dynamic is calculated by a transformation of BOLD signal in neuronal and synaptic activity using a forward

hemodynamic model. The parameters that allow inferring the BOLD signal to neuronal inputs are described in the "Balloon" model. This includes effects of blood volume, deoxyhemoglobin, flow induction and vasodilatory signal of the vessels (Klaas Enno et al., 2008; Stephan et al., 2010). To test the causal change in connectivity, the model space includes parameters that can perturb the system. In our study, we tested a system constituted of two current states Z or nodes that are the LOT cortex and the right mid frontal cortex that can interact spatially and temporally. We used the classical DCM which is deterministic, bilinear and includes one-state for each node. The external inputs u, the learning trials, drives direct influence on the LOT and a second type of input, the behavioral model of learning, modulates the coupling between nodes and the nodes themselves. The model encompasses also the nonlinear and dynamic nature of neuronal responses in the interaction between nodes. This critically allows inferring a causal mechanism of neuronal responses (K J Friston, Harrison, & Penny, 2003).

BMS. BMS allows identifying the best predictive model of connectivity among the bottom-up, top-down and both directionalities models. Based on F values accounting for parameter interdependencies, an exceedance probability was calculated for each model and each subject. This probability is computed by optimizing the balance between accuracy/fit and complexity (i.e. with less parameter used) of the model. The model with the higher posterior probability relatively to the others corresponds to the best model in terms of predictive validity and generalizability, knowing some constraints (priors) and parameters that govern the hemodynamic and the neuronal states in a region.

Six subjects were removed from the DCM analysis, because their VOI's were too far from the original coordinates (i.e. two times more than the FWMH of the smoothing kernel, here

16mm) and did not correspond to the anatomical region of interest defined with the atlas automated anatomical labeling (AAL) defined in MNI space.

3.3.3. Results

Discrimination of stimuli

In the 1-back task, the 4 symbols shown later in the MPCL task were not different in terms of mean of correct answer (p=0.34, F=1.143, df=181), reaction time for correct trials (p=0.1,F=1.79,df=181) and reaction time for all trials (p=0.48, F=1.69, df=181) , avoiding a perceptual advantage for some symbols (Twomey, Kawabata Duncan, Price, & Devlin, 2011). The means of accuracy and reaction time for correct trials were: 89±8 % and 543±0.7ms respectively.

Performance by block of trials and by cues

Over the 400 learning trials, the number of reward collected (or correct prediction) was 251±34 (i.e. 62.7%) for the whole group. The best and worst score were 307 (i.e. 76%) and 173 (i.e. 43%). To assess whether subjects have learned during the MCPL task, we tested whether the correct predictions, meaning the number of rewards collected, was increasing between the 4 blocks of 100 trials and we tested whether the learning was different for each of the 4 cues using a two-way repeated measures ANOVA 4 (block) X 4 (cue) (Figure 37). We report a main effect of block (p=0.00, F=8.27, df=3), a main effect of cue (p=0.003, F=6.68, df=3), but no interaction between cue and block (p=0.19, F=0.19, df=9). In post-hoc analysis,

we see that the performance in block 1 is not different from block 2 (p=0.29, F=1.15, df=1), but then block 2 is different from block 3 (p=0.002, F=12.2, df=1) and finally block 3 is not different from block 4 (p=0.85, F=0.035, df=1). Two subjects (num. 6 and 19) were consistently under 50% chance of correct prediction in the fourth block for each cue (Figure 38). However, they were not removed of the analysis, because their performances (i.e. score of 291 for subject num. 4 and score of 224 for subject num. 19 respectively) were in the average margin (i.e. 251±34), and not the worst, of the whole group.

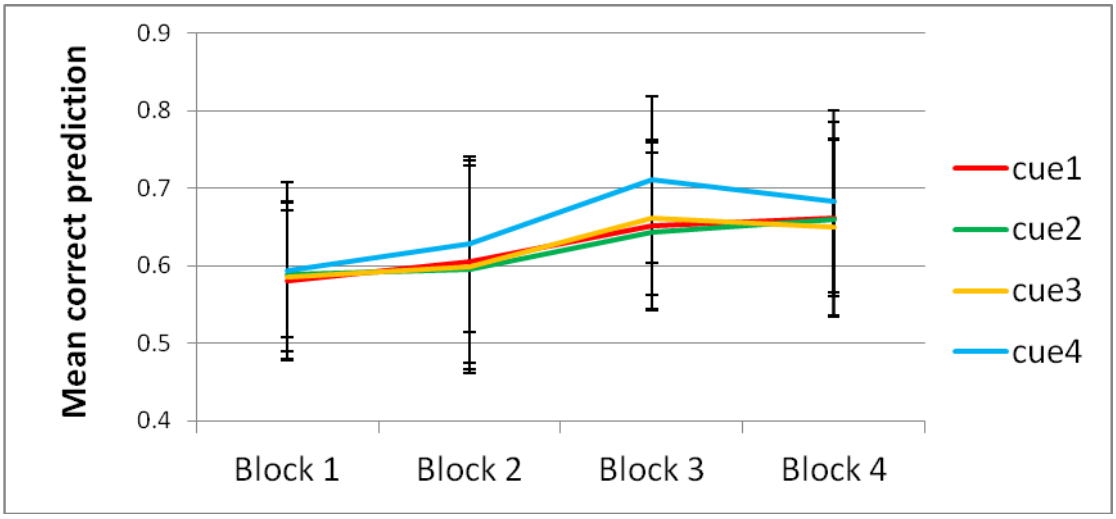


Figure 36. Correct prediction. Effect of block on subject's performance, measured by the number of reward obtained.. Vertical bars indicate standard-deviation.

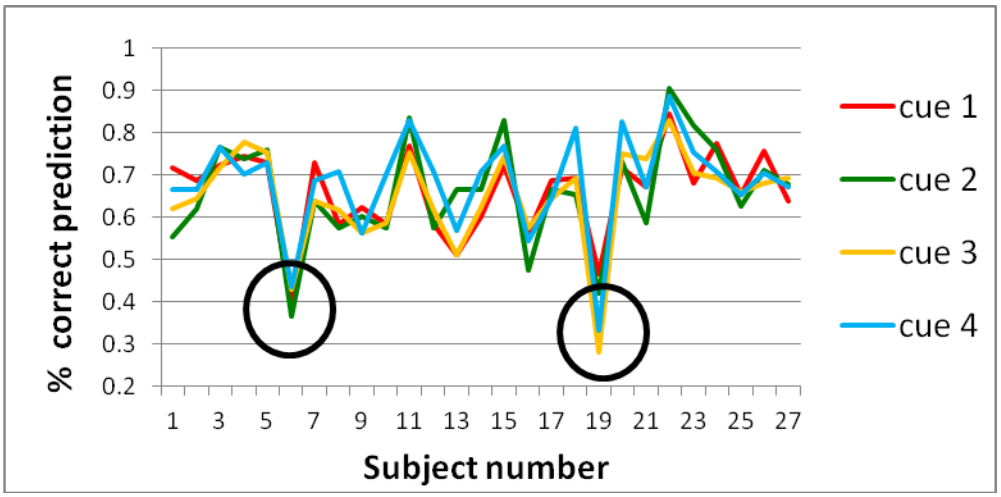


Figure 37. Correct prediction. All participants have a performance higher than 50% for each cue within the fourth block of 100 trials, except for two subjects (number 6 and 19 within black circle.)

Performance (probabilistic reward) by block of trials and cues. In addition, we used another measure to test performance. Instead of scoring the number of reward obtained, we measured the number of rewards weighted by the probability of association of the pattern with outcome at each trial. This allows measuring the probabilistic reward, which is more reliable in the way that it distinguishes between strong and weak predictive cues (Speekenbrink et al., 2008). Performance scores for cue 1 and 2 were reversed in order to test the increase of performance. Here, using a two-way repeated measures ANOVA 4 (block) X 4 (cue), we report a main effect of cue ($p<0.001$, $F=29,11$, $df=2.47$), an effect of block ($p<0.001$, $F=13.82$, $df=3$) and an effect of interaction between cue and block ($p=0.025$, $F=3.22$, $df=3.14$) (Figure 39).

In post-hoc analysis for the effect of block, we observed that the performance in block1 is not different from block 2 ($p=0.17$, $F=1.97$, $df=1$), block 2 is different from block 3 ($p=0.001$, $F=15.11$, $df=1$) and block 3 is different from block 4 ($p=0.59$, $F=0.28$, $df=1$). For the effect of cue, we observed that the performance with cue 1 is different from cue 2 ($p<0.001$, $F=68.2$, $df=1$), cue 2 is different from cue 3 ($p<0.001$, $F=9.07$, $df=1$) and cue 3 is different from cue 4 ($p<0.001$, $F=37.5$, $df=1$). In the interaction between block and cues, we reported a significant effect of block 1 and 2 with cue 3 and 4 ($p<0.001$, $F=26.33$, $df=1$), with cue 2 and 3 ($p=0.04$, $F=4.7$, $df=1$), but not with cue 1 and 2 ($p=0.62$, $F=0.24$, $df=1$). There is an interaction between block 2 and 3 with cue 1 and cue 2 ($p=0.03$, $F=5.27$, $df=1$), with cue 2 and 3 ($p=0.01$, $F=7.46$, $df=1$) but not with cue 3 and 4 ($p=0.19$, $F=1.79$, $df=1$). There is also an interaction between block 3 and 4 with cue 3 and 4 ($p=0.03$, $F=5.24$, $df=1$), but not with cue 1 and cue 2 ($p=0.47$, $F=0.52$, $df=1$) and with cue 2 and 3 ($p=0.06$, $F=3.62$, $df=1$).

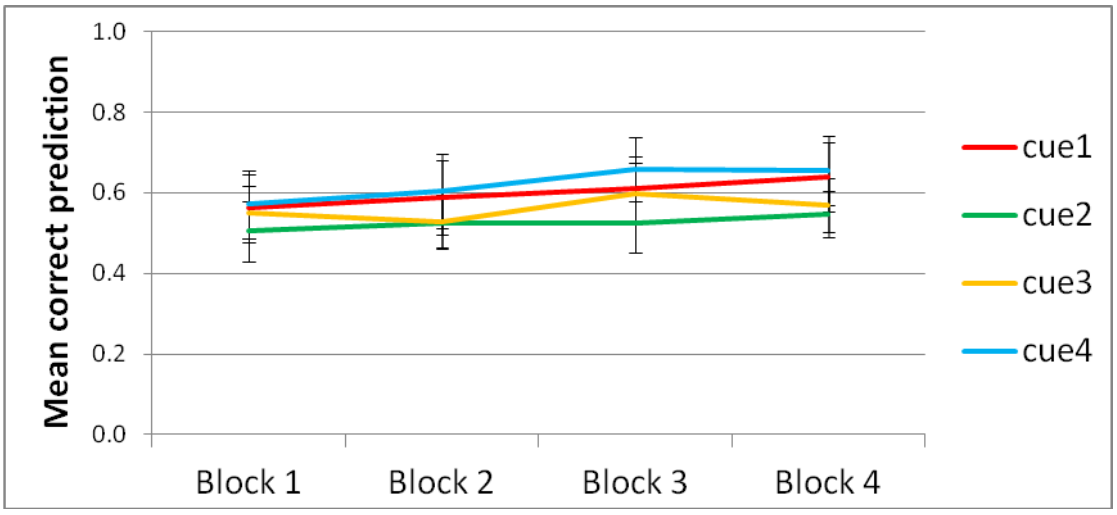


Figure 38. Correct prediction. Effects of block, cue and interaction between block and cues on subject's performance, measured by the number of probabilistic reward obtained. Vertical bars indicate standard-deviation.

Cue utilization weight

To test whether subjects followed the probabilistic nature of the task, we measured the subject's choice of outcome (symbol A) by means of the transformed subject's utilization weight in odd for each of the 4 cues along the 4 blocks of 100 trials. Results show significant effect of cue ($p<0.001$, $F=64.2$, $df=3$), effect of interaction between cue and block ($p<0.001$, $F=14.48$, $df=9$), but no effect of block ($p=0.2$, $F=1.563$, $df=3$) (Figure 40). We see that the subject's utilization weight is only different between block 3 and 4 ($p=0.041$, $F=4.6$, $df=1$), but not between block 1 and block 2 ($p=0.1$, $F=2.86$, $df=1$) and block 2 and 3 ($p=0.148$, $F=2.22$, $df=1$). In the interaction effect of block with cue, there is a significant different between block 1 and 2 for the difference between cue 3 and 4 ($p=0.00$, $F=26.9$ $df=1$), and between block 2 and 3 for cues 2 and 3 ($p=0.00$, $F=25$, $df=1$), and between block 3 and 4 for cues 1 and 2 ($p=0.048$, $F=4.3$ $df=1$) and for cues 3 and 4 ($p=0.018$, $F=6.3$ $df=1$). At the end, in

the last block of 100 trials, the probability of subject's choice for symbol A (with cue 1: 26±13% , cue 2: 42±12%, cue 3: 60±10%, cue 4: 74±12%) is very close to the probabilities defined in the task for each cue (cue 1: 20%, cue 2: 40%, cue 3: 60%, cue 4: 80%). Two subjects did not learn the correct probability in the fourth block for each cue (Figure 41).

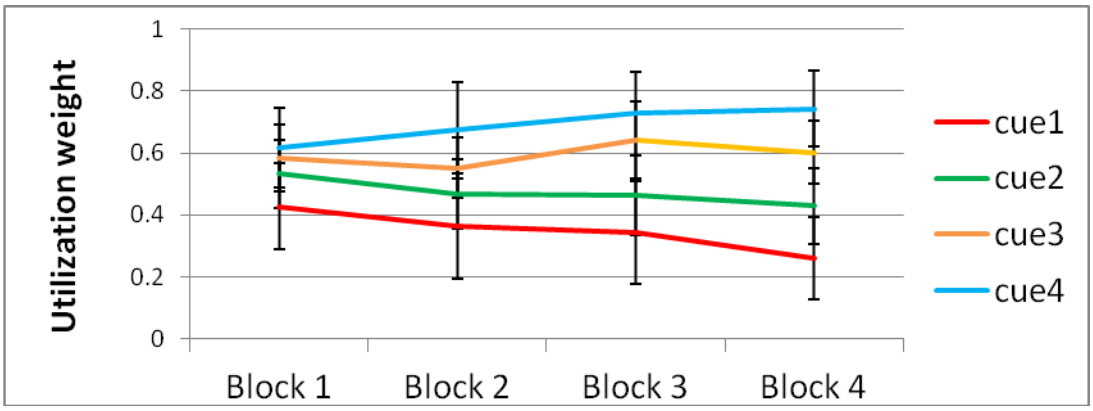


Figure 39. Utilization weights (odds). Effects of cue and interaction between cue and block on the utilization weights of the 4 cues. At the end of the fourth block, the weights approach the correct probability: 80% for cue 4 (in blue), 60% for cue 3 (in orange), 40% for the cue 2 (in green), 20% for cue 1 (in red). Vertical bars indicate standard-deviation.

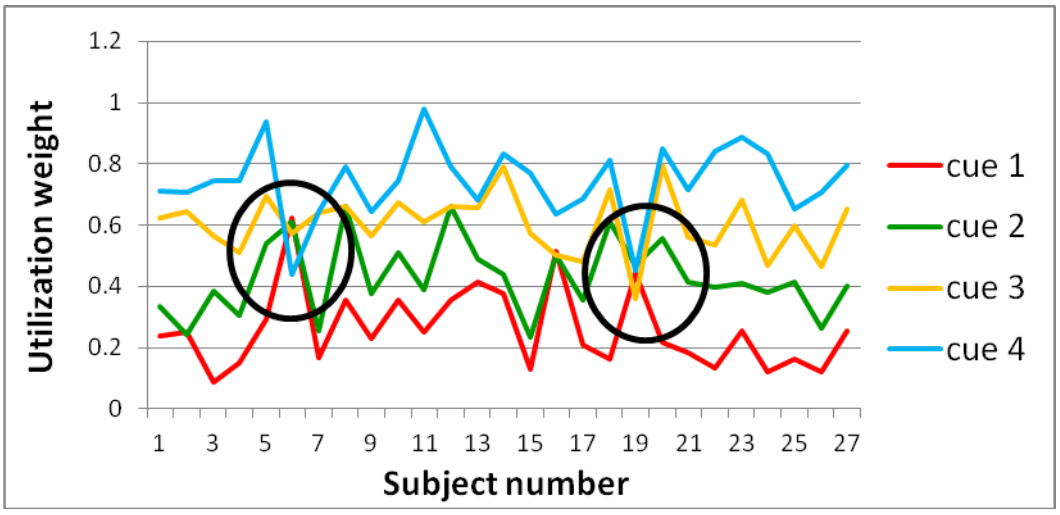


Figure 40. Utilization weights. All participants follow the probability of association between each cue and symbol A (i.e. 80-60-40-20%), within the fourth block of 100 trials, except for two subjects (number 6 and 19 within black circle).

Univariate analysis of brain activation associated with learning trials

Brain regions significantly more activated in learning trials compared with non-learning trials (i.e. baseline condition) include the bilateral caudate nuclei (Figure 42A), the bilateral mid frontal cortices, the right superior orbital frontal cortex, the right inferior frontal cortex, the bilateral insula, the left inferior and superior parietal cortex, the right angular cortex, the right inferior temporal cortex, the left inferior occipital cortex, the right mid occipital cortex, the bilateral cerebellum, the left precentral cortex, the right superior motor cortex, the right occipital inferior cortex (Table 6A). In contrast, the brain regions less activated in learning trials compared with non-learning trials are the bilateral hippocampi, the bilateral parahippocampal cortices (Figure 42B), the left mid temporal cortex, the left anterior cingulum, the right superior temporal pole, the left superior medial frontal cortex, the bilateral mid orbital frontal cortices, the left inferior orbital frontal cortex, the right mid frontal cortex, the bilateral mid frontal cortex, the left inferior orbital frontal cortex, the right mid frontal cortex, the bilateral anterior cingulum, the bilateral mid cingulum, the right posterior cingulum, the left cingulum, the left mid occipital cortex, the left calcarine cortex, the bilateral cerebellum (Table 6B).

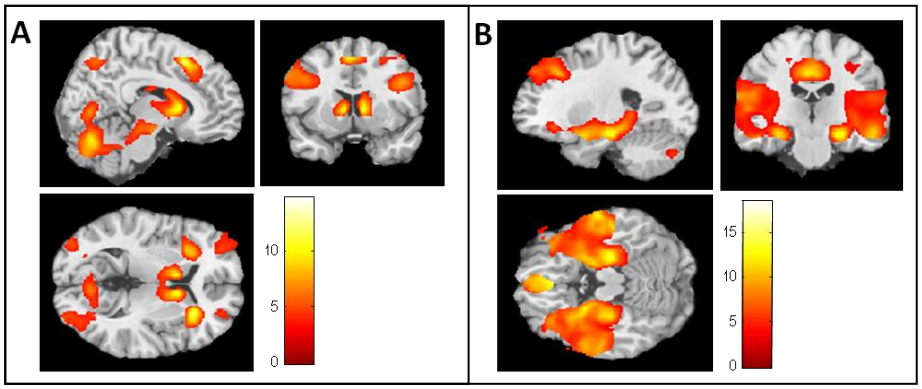


Figure 41. Statistical parametric map for the significant regions associated with (A) learning trials compared with non-learning trials and, inversely, (B) with non-learning trials compared with learning trials (P_{FWE}<0.05). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute (MNI) space.

Table 6. Activation associated with the learning trials compared with non-learning trials

A. Effect of the learning trials > non-learning trials					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**Z statistic**
3688	Right caudate nucleus	9	9	4.5	6.22
		10.5	6	15	4.93
	Left caudate nucleus	-9	9	3	6.15
5922	Right mid frontal cortex	45	52.5	25.5	5.57
		49.5	43.5	30	5.27
		46.5	36	36	5.23
1452	Left mid frontal cortex	-36	63	13.5	4.95
711	Rigth superior orbital frontal cortex	27	52.5	-1.5	4.57
1889	Right insula	31.5	25.5	0.00	7.09
	Righ inferior frontal cortex	33	27	15	4.28
1586	Left insula	-30	21	-3	6.54
45823	Left inferior parietal cortex	-30	-63	43.5	7.17
	Right superior parietal cortex	30	-61.5	51	6.25
		19.5	-63	52.5	6.24
	Right angular cortex	31.5	-51	39	6.96
	Right inferior temporal cortex	43.5	-58.5	-12	5.71
	Left inferior occipital cortex	-34.5	-88.5	-9	6.43
		-30	-90	-10.5	6.33
		-39	-73.5	-7.5	6.00
		-43.5	-69	-12	6.00
	Right mid occipital cortex	31.5	-63	40.5	5.82
	Left cerebelum	-7.5	-75	-28.5	6.23
		-28.5	-55.5	-31.5	5.71
	Right cerebelum	33	-52.5	-30	5.73
		7.5	-72	-25.5	6.02
5492	Left precentral cortex	-40.5	3	31.5	5.50
		-36	-3	49.5	5.10
		-58.5	9	36	4.81
2437	Right superior motor area	6	16.5	49.5	7.14
	Right occitpial inferior cortex	27	-90	-7.5	6.50
B. Effect of the learning trials < non-learning trials					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**Z statistic**
127882	Left hippocampus	-24	-22.5	-18	6.99
	Left mid temporal cortex	-63	-12	-15	6.96
		-57	-7.5	-13.5	6.84
		-55.5	-24	-16.5	6.59
	Left parahippocampal cortex	-24	3	-21	6.42
	Right parahippocampal cortex	30	7.5	-22.5	6.89

	Right hippocampus	31.5	-24	-16.5	6.58
		28.5	-16.5	-18	6.42
	Left olfactory/anterior cingulum cortex	-7.5	27	-6	6.89
		-7.5	22.5	-9	6.75
	Right amygdale/sup. temporal pole	25.5	3	-19.5	6.71
	Left superior medial frontal cortex	-7.5	51	3	7.79
		-6	57	33	6.68
		-7.5	63	18	6.66
	Right mid orbital frontal cortex	4.5	46.5	-4.5	7.38
		4.5	33	-12	7.31
	Left mid orbital frontal cortex	-4.5	31.5	-10.5	7.16
		-4.5	52.5	-10.5	7.15
		-4.5	37.5	-6	7.25
		-1.5	30	-15	7.17
	Left inferior orbital frontal cortex	-39	34.5	-10.5	6.93
	Right mid frontal cortex	4.5	46.5	-4.5	7.38
		4.5	33	-12	7.31
	Left anterior cingulum	1.5	37.5	-1.5	7.28
	Right anterior cingulum	4.5	34.5	0	7.24
	Left mid cingulum	-1.5	-16.5	39	6.64
	Right mid cingulum	3	-16.5	40.5	6.58
		4.5	-21	40.5	6.58
		6	-33	42	6.41
	Right posterior cingulum	-10.5	-51	28.5	7.16
		-4.5	-48	30	7.07
	Left precuneus	-6	-51	16.5	6.90
	Left mid occipital cortex	-46.5	-72	28.5	6.48
	Left calcarine cortex	-7.5	-99	13.5	6.62
461	Right cerebelum	30	-76.5	-36	5.53
		46.5	-63	-39	3.25
390	Left cerebelum	-31.5	-81	-34.5	5.28

Table 6. Significant region activation showing more (A) and less (B) activation in learning trials compared with non-learning trials (P_{FWE}<0.05). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute (MNI) space.

The movement parameters can been included in the statistical design to exclude their effects on statistics. However, in our study, most of the subjects did not move more that 2 mm (Figure 43) which minimizes the possible unwanted correlation with the effect of interest.

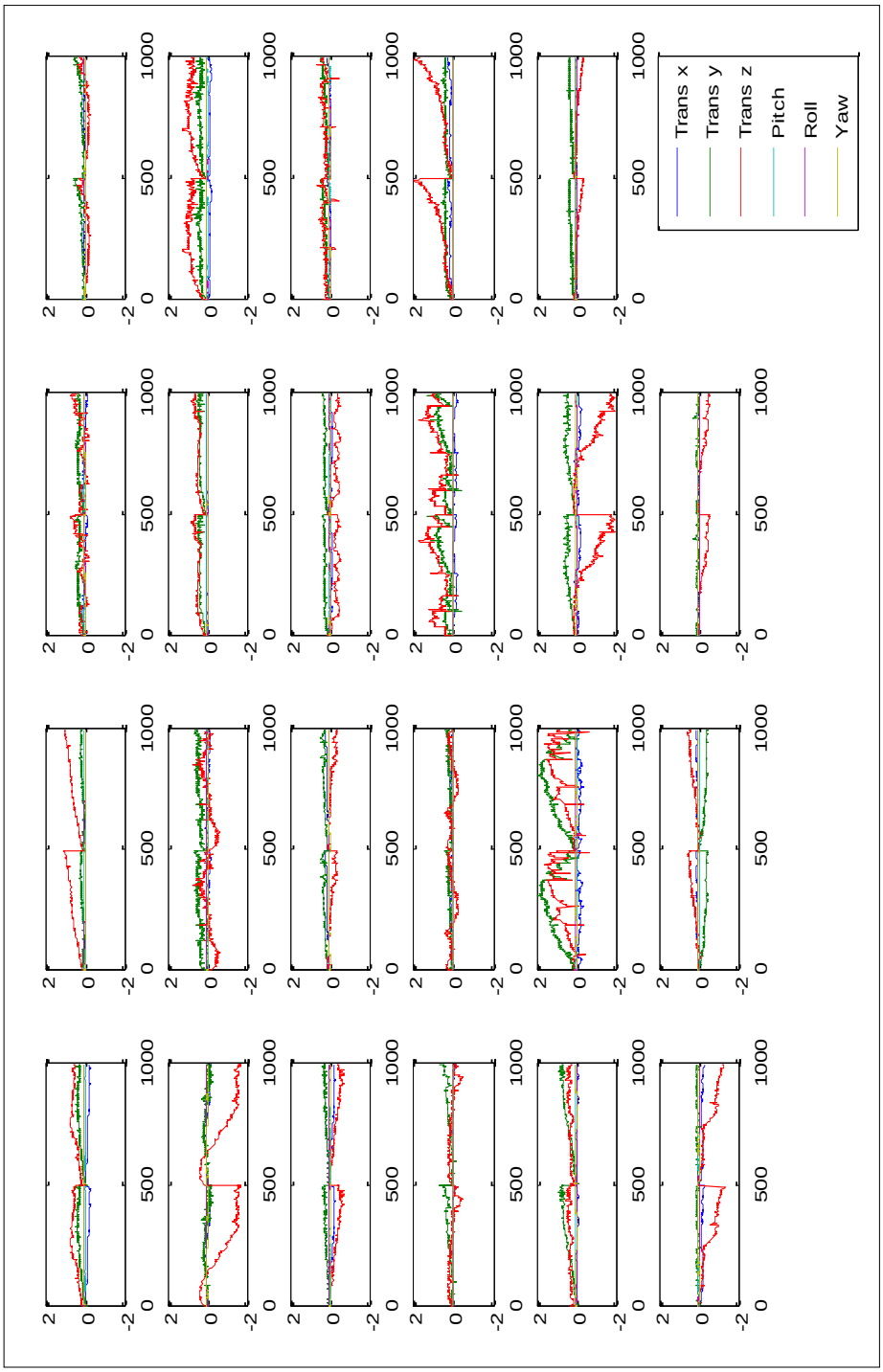


Figure 42. Illustration of 6 head movement parameters for each of the 23 subjects from top left to bottom right. Trans x, Trans y and Trans z are movements of translation in x, y and z directions. Pitch, Roll and Yaw are the three different movements of rotation. Y axis represents millimeters of movement and X axis each time of volume acquisition.

In the figure below (Figure 44), there are figures showing the different SPMs, tresholded at P_{FWE}<0.05, with and without movement parameter inclusion. Visually, we do not observe major differences between them. The left caudate (Z=4.36, xyz = [-19.5,0,16.5]) and the right caudate nuclei (Z=4.17 , xyz = [19.5,3,18]) are still significantly associated with learning trials compared to non-learning trials after whole brain multiple comparison correction and p *FWE* of 0.05. However, the left hippocampus is no more significantly associated with non-learning trials compared with learning trials.

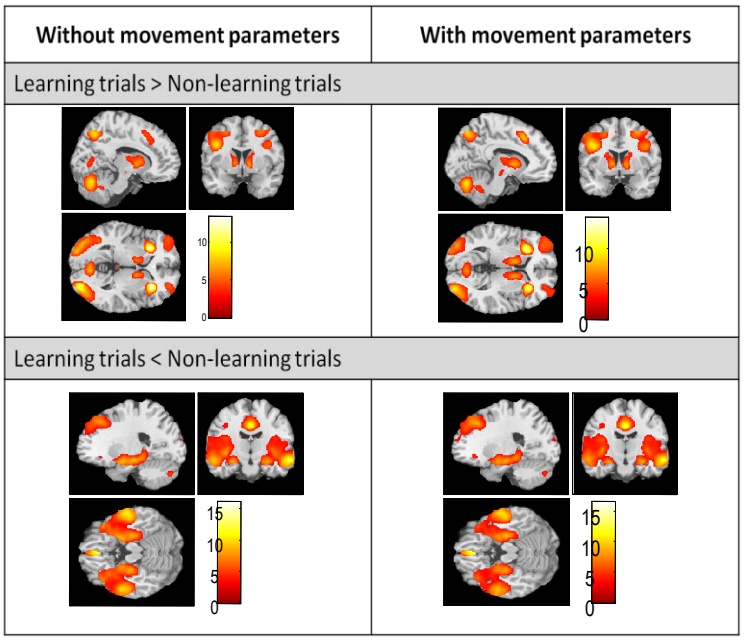


Figure 43. Statistical parametric maps of the learning trials compared to non-learning trials with or without inclusion of the six head movements parameters in the statistical design.

We also investigated whether the main regions associated with learning trials, the caudate nuclei and the hippocampus, show change of activation after 1, 2, 3 and 4 blocks of 100 trials (Figure 45). In the first and the two first blocks, the caudate nuclei and the hippocampus are not significantly activated. However, in the three first blocks, there are significant activation in the bilateral hippocampi ((Z=6.49, xyz = [28.5,-16.5,-16.5]), ((Z=6.44, xyz = [-18,-7.5,-18])

and in the bilateral caudate nuclei ((Z=5.95, xyz = [10.5,7.5,3]), (Z=4.73, xyz = [-10.5,1.5,19.5]), (Z=5.76, xyz = [-9,7.5,3]), (Z=4.84, xyz = [-9,3,19.5])) after whole brain multiple comparison correction and tresholded at p-value of 0.01 .

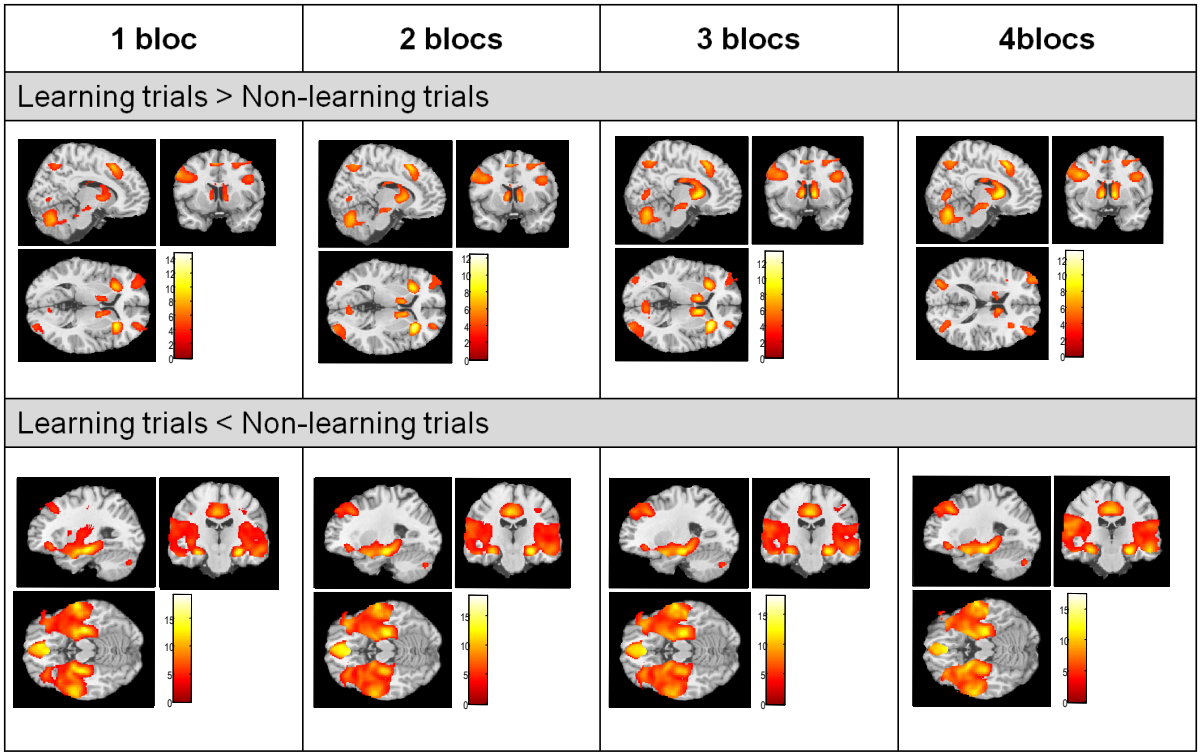


Figure 44. Statistical parametric maps of the learning trials compared with non-learning trials after 1, 2, 3 and 4 blocks of 100 trials.

Univariate analysis of brain activation associated with cues utilization weights

We report significant activation negatively associated with cues utilization weights in the left occipito-temporal (LOT) cortex (Figure 46AB), the left inferior temporal cortex, the left mid temporal cortex, the right mid frontal cortex (dorso-lateral part or Brodman's area 46) at 3mm distance with the inferior triangularis frontal cortex (Figure 46CD), the right inferior frontal cortex (Figure 46EF) more specifically in the pars triangularis, the pars opercularis (i.e. Broca's area or Brodman's areas 44 and 45 respectively), the pars orbitaris and in the mid orbital frontal cortex as well as the right insula (Table 7). We also observe that the activation

in the left OT cortex and in the right mid and inferior frontal cortices (Figure 46 B,D,F) contribute more to explain utilization weights of cues 1 and 4, strong predictive cues, than the cues 2 and 3, weak predictive cues in the contrast estimate (Figure 46 A,C,E). No significant regions were positively associated with cues utilization weights.

In the left OT cortex, the activation is in the posterior, lateral (most significant peaks at coordinates (Z=4.09, xyz= [-39,-48,-11]; Z=3.95; xyz= [-45,-54,-6]; Z=3.82, xyz= [-36,-55,-11]) and the medial parts (peaks coordinates at (Z=4.37, xyz= [-23,-57,-6]; Z=3.7, xyz=[-21.-66,-6];Z=3.51,xyz=[-15,-72,-5]).

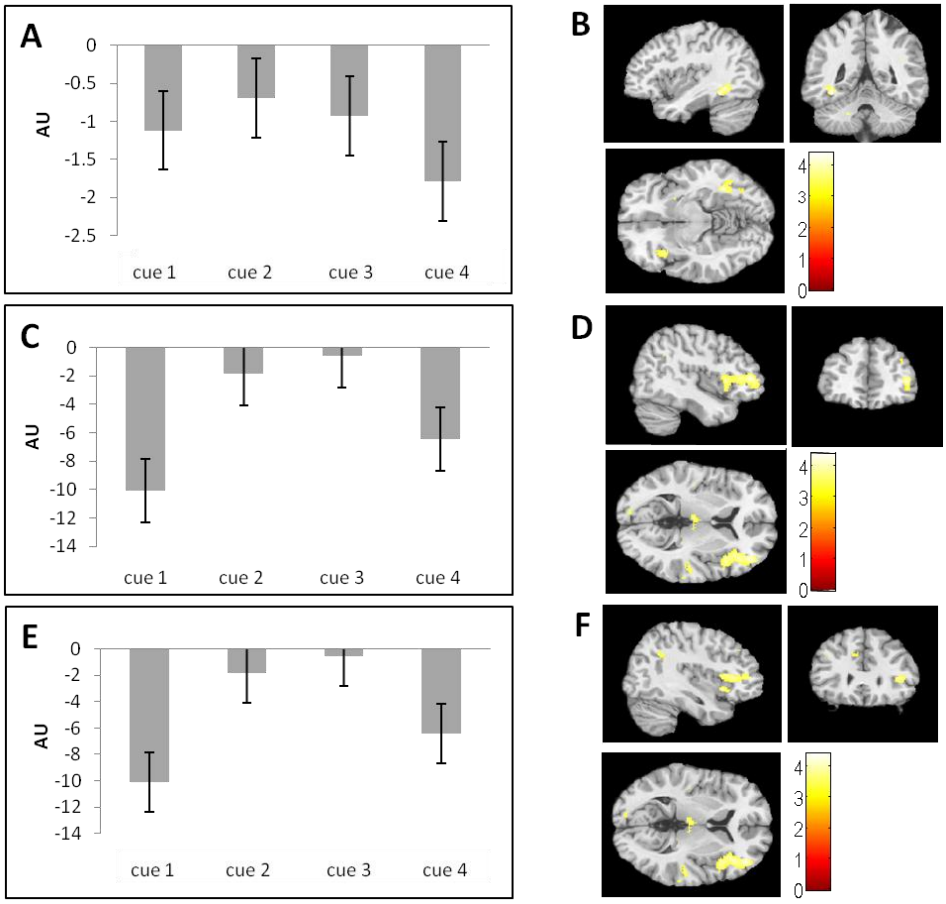


Figure 45. Contrast estimates of the cue utilization weight of the 4 cues associated with negative brain activation (A-B) in the left inferior occipito-temporal cortex (xyz=[-39,-49.5,-7.5]), (C-D) in the right mid frontal cortex (xyz=[43.5,43.5,-4.5]) and (E-F) in the right inferior frontal cortex (xyz=[39,28.5,4.5]). The 3 graphs show more contribution for weight of cues 1 and 4. Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute space (results: P_{FWE}<0.001, figures: P<0.001 uncorrected).

Table 7. Activation associated with cues utilization weights

Negative association					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**Z statistic**
531	Left inferior occipito-temporal cortex	-39	-48	-10.5	4.09
		-36	-51	-10.5	4.05
		-39	-52.5	-7.5	3.99
		-36	-55.5	-10.5	3.82
		-34.5	-43.5	-13.5	3.39
	Left inferior temporal cortex	-45	-54	-6	3.95
		-43.5	-48	-7.5	3.70
	Left mid temporal cortex	-43.5	-54	-1.5	3.92
1574	Right mid frontal cortex	43.5	43.5	4.5	3.96
	Right inferior triangularis frontal cortex	39	28.5	4.5	3.80
	Right inferior opercularis frontal cortex	43.5	13.5	6	3.75
		43.5	16.5	3	3.67
		39	19.5	7.5	3.61
		48	16.5	4.5	3.59
	Right inferior orbitaris frontal cortex	36	24	-9	3.42
	Right mid orbital frontal cortex	42	49.5	-3	3.51
	Right insula	37.5	16.5	-10.5	3.65
		43.5	15	-3	3.40

Table 7. Significant region activation showing negative association with cues utilization weights (P_{FWE}<0.05). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute (MNI) space.

In addition, we visually inspected which brain activation still remains significant after inclusion of movement parameters. We observed whether regions of interest, i.e. left IOT and right mid frontal cortex activations, were affected by movements (Figure 47). Visually, we did not observe major differences between them for the right mid frontal cortex that remains significantly associated with the negative modulation of cue utilization weight (Z=3.91, xyz= [42,43.5,6]), however, this was no more the case for the left IOT.

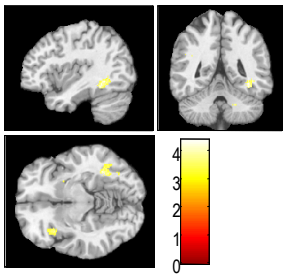
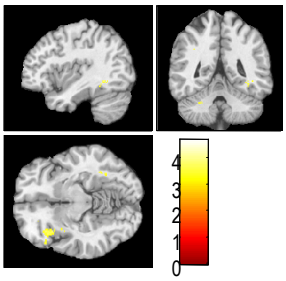
Without movement parameters	With movement parameters
Modulation of learning (negative association)	
	

Figure 46. Statistical parametric maps of the positive and negative association of behavioral learning, measured with cue utilization weights, with or without inclusion of the six head movement's parameters in the statistical design.

Effective connectivity between OT cortex and mid-frontal cortex related to learning

Bayesian Model Selection was used to compare models of effective connectivity modulated by learning between the LOT cortex and the right mid frontal cortex at group level (Figure 48A); The 3 models have bottom-up, top-down or bidirectionality influences (Figure 48B). We found that, in the first session, learning modulates the functional connectivity in bidirectional and bottom-up directions compared with top-down direction (Figure 49A), whereas, in the second session, the best model was reduced only to the bottom-up direction compared with the two other models (Figure 49B).

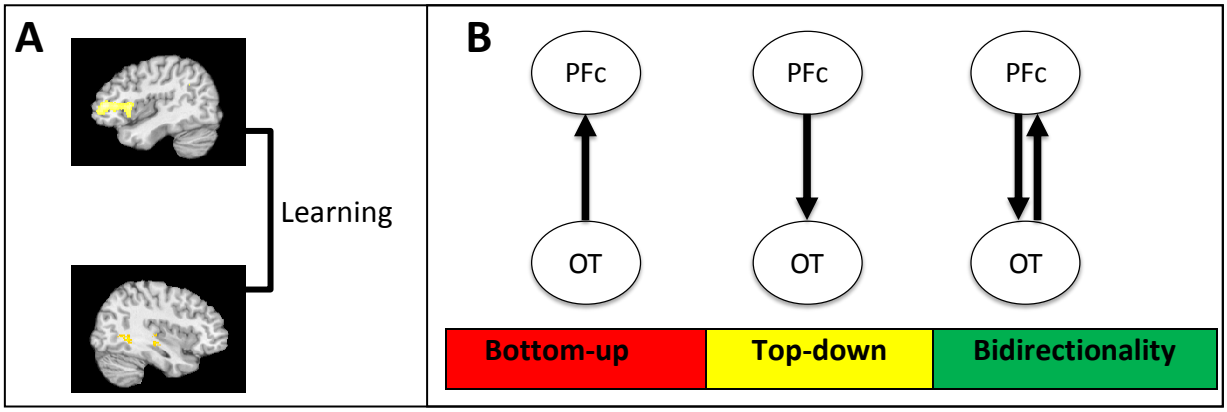


Figure 47. Illustration of (A) the two volumes of interest (VOI) in the left inferior occipito-temporal (OT) cortex and in the right mid pre-frontal cortex (PFc) and (B) the comparison of the 3 models of effective connectivity between those regions; Models have bottom-up, top-down and bidirectionality influences and are modulated by cue utilization weight.

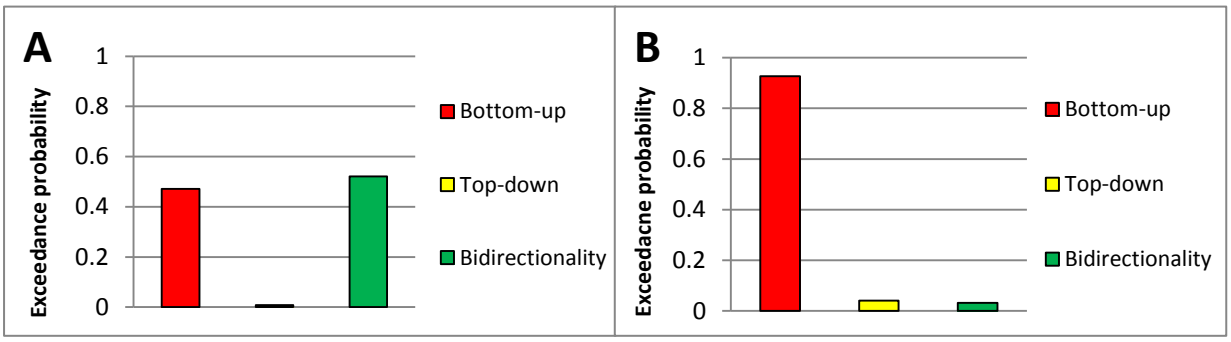


Figure 48. Comparison of three models of effective connectivity (Bottom-up, top-down and bidirectionality) between the left inferior occipito-temporal (OT) cortex and the right mid frontal cortex modulated by learning (A) in the first session of 200 trials and (B) in the second session of 200 trials. Y axis represents exceedance proabilitiy of each model to outperform the others.

3.3.4. Discussion

Behavioral learning

At the beginning of the multiple cue probabilistic learning, subjects have to associate each of the 14 cards/patterns with the correct outcome. The learning is possible with feedback information revealing the true criterion and by combining multiple cues to unify them in a single judgment. Despite the difficulty inherent to uncertainty in probabilistic learning, we observe an increase of performance/correct prediction after 200 trials and then a plateau. weights of the four cues continuously approach the correct probability of association during the task and reach nearly similar probability at the end.

Well-adapted behavior and optimal decision making require the extraction of relevant information from noisy sensory inputs, as well as weighting of evidence from multiple sources of information (Behrens et al., 2007). We also note substantial variance in learning across individuals. This is in line with previous findings (M. a Gluck et al., 2002) showing subjects can use very different learning strategies.

Memory systems related to -Medial Temporal Lobe and Basal Ganglia- in learning trials

Our results on the fact that different memory systems related to Medial Temporal Lobe (MTL) and Basal Ganglia (BG) are differently involved during learning trials is highly consistent with the literature on MCPL. The hippocampus deactivation is in accordance with many neuroimaging studies on MCPL showing that hippocampus activation is more present in the early phase before decreasing and even becomes deactivated. The inverse activation pattern is seen in the BG (M. a Gluck et al., 2005; R a Poldrack et al., 2001; R a Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Daphna Shohamy et al., 2008), again in line with our results. In the study of Poldrack et al. (1999) on MCPL, they reported activation and deactivation in similar regions to our results.

The role of **MTL** in MCPL is in line with its involvement in episodic memory for rapid, associative encoding and flexible memory (Henke, 2010). The postulated mechanism is that an initial process in MTL for acquiring appropriate new stimuli representations would facilitate the subsequent learning and make the initial representation accessible to other brain regions. This would then facilitate the recall of knowledge from previous events (M. a Gluck et al., 2005; R a Poldrack et al., 2001; Seger & Peterson, 2013; D Shohamy et al., 2008). This could reflect the role of hippocampus in consolidation and retrieval through the reinstatement in the neocortex of the activation pattern from the original encoding (Henke, 2010). In patients with MTL lesions, this mechanism would be absent, explaining their impairment early in MCPL. MTL also has a role in flexible use of knowledge and in feedback-based learning when feedback is delayed (Foerde et al., 2006, 2013; R a Poldrack et al., 2001; Russell a Poldrack & Foerde, 2008; Russell a Poldrack & Packard, 2003; Russell a Poldrack & Rodriguez, 2004; Daphna Shohamy et al., 2008). The hippocampus activation would be also

coupled with the ventral medial pre-frontal cortex, region also activated in our task, to generate integrated memories that connect past events with new experiences. This would form schemas and allow future recall of past events, inferential reasoning, generalization or transfer of the acquired knowledge to new events (Zeithamova, Dominick2, & Preston, 2012; Zeithamova, Schlichting, et al., 2012). In addition, the degree of hippocampal involvement may depend on the strategy used to learn the category (Seger & Peterson, 2013; Zeithamova, Schlichting, et al., 2012). A study on hypoxic patients suggests a possible involvement of hippocampus in adoption of complex strategies of multiple cue integration, likely through relational and configuration learning (Hopkins, 2004). In addition, we report that the **anterior part of the temporal cortex** was involved in MCPL (in hippocampus (XYZ(-24,-22.5,-18)) and MTL (XYZ(-63,-12,-15)). This anterior portion is related to goal-reward-emotional related processes. It has been shown in animals and human that the ventral/head of the hippocampus (XYZ (28,-16,-25), XYZ(-30,-18,-22)) was involved early during learning for processing global directed strategies, whereas the dorsal/body of hippocampus (XYZ(25,-30,-10), XYZ(-16,-31,-7)) was involved later for local, fine-grained or spatial strategies (Evensmoen et al., 2013; Ruediger et al., 2012). The ventral/anterior (coordinates XYZ(24,-11,-18) and XYZ(-26,-16,-20) in MNI space) and dorsal parts are also specific to different information with the first part, being more related to goal proximity or to reward expectation and arousal and the second part, being more related to cognitive and visuo-spatial functions. In our results, we also report that the ventro-medial/orbital and lateral/mid prefrontal cortices, regions that are activated in parallel to the ventral and dorsal parts of the hippocampus respectively (Viard, Doeller, Hartley, Bird, & Burgess, 2011). A recent view describes functional organization of the hippocampus into a discrete dichotomy of ventral/anterior and dorsal/posterior parts, to process stress and memory/spatial

navigation respectively. This view also highlights a gradient in the longitudinal axis of the hippocampus supported by smooth connectivity of cortical and subcortical regions with MTL subregions (Bryan a. Strange et al., 2014). In another study, they found that connectivity of right anterior hippocampus with other temporal cortex regions such as the right perirhinal cortex, involved in semantic processing, was affected by the degree of stimuli familiarity (Barense, Henson, & Graham, 2011; McLelland, Chan, Ferber, & Barense, 2014), showing that through MCPL, a process of familiarization or semanticization can occur.

In addition to the MTL, we also observed more activation of **basal ganglia (BG)** in learning trials compared with non-learning trials. The function of BG is related to incremental feedback-learning and learning of probabilistic contingencies between stimulus and outcome to adjust responses. This is in line with the role of BG in cognitive skill learning and procedural memory (Henke, 2010). This also involves integration of multiple information through learning (D Shohamy et al., 2008). Our study showed BG activation in the **anterior part of the caudate nucleus**. This part is involved in multiple functions that fit the features of the MCPL task such as probabilistic categorization with feedback, artificial grammar learning, stochastic decision, visuomotor association, shifting related to change of attention's focus, reversal learning related to learning after a change in stimulus-reward contingencies positive feedback-reward processing. This is typically related to executive functions associated with feedback and error of prediction (PE) associated with reward (Seger & Cincotta, 2005). In contrast to the BG, the hippocampus would be sensitive to delayed reward, showing differential involvement of those memory systems in MCPL (Foerde et al., 2013).

Priming memory regions -occipito-temporal cortex and frontal cortex- modulated by cue utilization weights

Our results indicate that weighting of evidence in MCPL is associated with decrease of activation in the left inferior temporal cortex, the left occipito-temporal (OT) cortex (i.e. including the fusiform gyrus), the left mid temporal cortex, the right mid frontal cortex (i.e. the dorso-lateral frontal cortex), the right inferior frontal cortex (including the Broca's area), the right mid orbital frontal cortex and the right insula. Poldrack et al., 1999 (R a Poldrack et al., 1999) report a decrease of brain activation related to learning measured with time modulation in the right inferior occipital gyrus (XYZ(36,-80,-12)), the right medial/mid frontal gyrus (XYZ(2,60,8)), the left mid frontal gyrus (XYZ(-32,54,-4)), and also learning-related increase of activation in the right mid frontal gyrus (XYZ(42,46,4)) (BA 10/46), the parietal and the left insula (36,-6,-8)). Our results show similar regional activity in the right mid frontal cortex.

We suggest that neocortical regions such as OT cortex and pre-frontal cortex deactivation represent priming memory systems. Priming means facilitation of information processing (Henke, 2010). The OT cortex is part of the extrahippocampal structures of the MTL. These structures can generate a conceptual implicit memory called priming. They are involved in combining perceptual features through repetition and facilitation of recognition memory. They also have a role in the memory of unitized items. The parahippocampal cortex is engaged after multiple episodes encountered and allows also acquisition of semantic knowledge (Henke, 2010), independently of the hippocampus. This is in line with a study showing that amnesic patients are impaired in learning the association between a label and abstract shapes, however they could still learn when they were taught to put a meaning to

these shapes. In this case, the learned association becomes a unitized familiar representation, easier to learn for them (Duff, Hengst, Tranel, & Cohen, 2005b; Henke, 2010; Yonelinas et al., 2010). The deactivated MTL was also related to syntax processing of artificial language relying more on implicit than declarative memory dependent on MTL (Petersson, Folia, & Hagoort, 2012). We suggest here that priming is a critical memory system, mainly dependent on the parahippocampal cortex and other neocortical regions, but that is independent on the hippocampus and that explains semantic knowledge acquisition through repetition and integration of information in unique representations (Henke, 2010). Converging evidence shows that high level visual processes for visual identification, recognition of objects and semantic processes occur in the left occipito-temporal (LOT) or in the so called "ventral stream" composed of visual areas and inferior temporal cortex (Ungerleider & Haxby, 1994). Whereas the early perceptual areas may categorize simple visual shapes or orientation, the LOT cortex is known to process and recognize more complex visual shape, by means of a more intricate receptive field organization, and perceptual learning. With extensive training, this plastic region can recognize meaningless objects. The LOT contains neurons that can be tuned to respond selectively to multiple aspects of an object. In addition these neurons are also selective to attended or memorized objects. This suggests a possible top down modulation of this region by various high-level perceptual, attention, expectation or working memory processes (Chelazzi, Miller, Duncan, & Desimone, 1993; Gilbert & Li, 2013; Jiang, King, Shim, & Vickery, 2006; Kherif et al., 2011; Logothetis NK, Pauls J., 1995; Odmanman, 1994; Sasaki Y., Gold J., 2010). The type of connectivity between the OT cortex and higher-level brain regions will be investigated in the chapter "Effective connectivity between fronto-temporal regions associated with cue utilization weights". In our results, we found involvement of the posterior part (-60mm in

the y axis) of the LOT with most significant peaks at coordinates (xyz=[-36,-55.5,-10.5]), the middle part (xyz=[-39,-52.5,-7.5]); xyz= [-36,-51,-10.5])), and also the anterior part, in the vicinity of -45mm in the y axis (xyz[-39,-48,-11]; Z=3.39, xyz=[-34.5,-43.5,-13.5]). Substantial evidence shows these posterior and anterior parts of the OT are involved in the integration of multiple visual stimuli and in processing specific features related to words and pictures (Kherif et al., 2011). For example, the posterior left ventral occipito-temporal (LVOT) cortex is also called the Visual Word Form area (XYZ(-41,-60,-8)) and is involved in generation of representations with ordered combination of pseudo-letters or letter with identities (L. Cohen et al., 2002). However, there is still a debate on whether that region responds to specific feature of words or pictures or both and if this is only affected by bottom up influences. It seems that the activation in this region also depends on the task demand (Starrfelt & Gerlach, 2007). Indeed, subparts of LvOT can respond to different categories, but only under specific conditions. For example, LvOT is specific to integration of shape features in a unique whole object or word and the specificity of this region (XYZ(-43,-54,-12)) to respond differently to written words than objects depends on the task demand, i.e. if the demand on shape processing decreases (Starrfelt & Gerlach, 2007). In our MCPL task, the stimuli are pseudo-words and lie between pictures and letters. The involvement of LOT cortex can be explained by the fact that features of both pictures and words can share similar automatic top-down influences and semantic network in the left ventral stream and in the inferior frontal cortex (Kherif et al., 2011; Mechelli, Gorno-Tempini, & Price, 2003; Mechelli, Josephs, Lambon Ralph, McClelland, & Price, 2007; Price & Devlin, 2011; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996; Vigneau et al., 2006).

In our results, we also found a greater deactivation in the LOT cortex for strong compared to weak predictive cues during learning. The same pattern was found in the right mid frontal

cortex. This is in accordance with a study showing that for more salient shapes detected, the OT region decreases in activation compared with less salient shapes in the aim to discriminate, segment and integrate the most relevant information to generate sparser representation and better recognition of the stimuli (Kourtzi, Betts, Sarkheil, & Welchman, 2005). This reveals more automatic priming for more associated stimuli, which is in line with a study showing a decrease of activation in the posterior part of the OT cortex (XYZ(-36,-53,-4), XYZ(-30,-46,-11)), as in our results and in the left inferior anterior frontal cortex ((XYZ(-37,25,11)) for pairs of words that are semantically related compared to unrelated and identical pairs of words (Wheatley, Weisberg, Beauchamp, & Martin, 2005). We suggest a similarity between semantically related words in the last study and the strong predictive cues in our study. The more predictive cues contain more semantic information with training compared with weak predictive cues. In another study, the reduced activity for priming of repeated objects compared to new ones in inferior frontal regions was interpreted as more efficient access to semantic features of the previously similar item encountered and/or to less attentional demand (Koutstaal et al., 2001). In addition, considering the same profiles of activation in the right mid frontal cortex, the right inferior frontal cortex and the LOT in our study, we suggest that those regions can be functionally coupled in a dynamic way during learning.

The involvement of the **prefrontal cortex**, more particularly the right inferior and right mid dorso-lateral frontal cortices, can be related to studies observing that after memory encoding dependent on the MTL, the performance could depend on episodic memory retrieval and on monitoring demands during retrieval dependent on the right pre-frontal cortex (Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998; Gluck et al., 2005; Henson, Shallice, & Dolan, 1999; R a Poldrack, Prabhakaran, et al., 1999; R a Poldrack et al., 2001;

Sakai, 2003; D Shohamy et al., 2008). The role of the inferior temporal cortex in categorization would be to process early perceptual features and distance whereas the role of prefrontal cortex is mainly to generate then the representations of boundary between categories, rules to separate them or the commonalities between features (Cromer, Roy, & Miller, 2011; Freedman, Riesenhuber, Poggio, & Miller, 2003; Muhammad, Wallis, & Miller, 2006; Seger & Miller, 2010). However, those studies do not completely explain the decrease of activation in the pre-frontal cortex. The right inferior frontal cortex was found involved in decision-making choice under risk and activation was correlated with higher risk aversion (Christopoulos GI, Tobler PN, Bossaerts P, Dolan RK, 2010; Clark, Manes, Antoun, Sahakian, & Robbins, 2003). The right insula is anatomically connected to the right inferior frontal cortex and is also sensitive to risk and uncertainty (Huettel et al., 2005). Risk is generated by the variability in reward or in value prediction. Representation ambiguity means uncertainty about exemplars that are difficult to categorize, because they are distant to one prototype or that they are at equidistance of many different prototypes. It not always clear how risk and ambiguity are dissociated. Ambiguity would lay in the association between stimuli and category and risk, in the association between categories and value. However, risk and ambiguity can recruit similar neural systems, with additional recruitment of prefrontal cortex in ambiguity (Huettel et al., 2005; Seger & Peterson, 2013). Those regions could thus both be linked to processes related to uncertainty that decreases with learning in our study. The theory of accumulation of information through repetition of trials can also explain the activation of the insula, the dorsolateral prefrontal cortex and the inferior LOT cortex (Seger & Peterson, 2013).

Effective connectivity between fronto-temporal regions associated with cue utilization weights

Using DCM analysis, we mainly found that priming memory systems in the left OT cortex and in the right mid pre-frontal cortex, showed different functional effective connectivity in early and later learning phases. We observe a bottom-up and bidirectional functional connectivity as best models in the first session of 200 trials; this was reduced to a bottom-up connectivity in the second session. This mechanism was accompanied by an increase of behavioral performance, measured by the number of correct predictions after the first session. This performance remains stable in the following session. We also reported a constant increase of discrimination between cues in each block of 100 trials. We postulate that behavioral learning is associated with repetition suppression and priming allowing continual adjustment by a cross-talk between bottom-up and top-down influences. This leads to decreased prediction error and increased discrimination of relevant features throughout learning until optimal behavior is reached. We argue that sufficient training allows discrimination of relevant features with less help from top-down processes or with facilitation from bottom-up processes. Bottom-up processes can then become sufficient to process stable and adapted representations of the relevant features in the task. This is supported by an increase and then stabilization of behavioral performance after the first session of learning.

Kumaran et al. (Kumaran et al., 2009) observed a coupling between the temporal and pre-frontal regions allowing emergence of new knowledge, while another also showed an increase of activity in both inferior OT area and prefrontal cortex in parallel to an increase of memory load (Druzgal & D'Esposito, 2003). We describe the underlying mechanism as a decrease of mismatch between bottom-up and top-down inputs leading to optimal learning

dependent on task demand. The expectations, such as reward maximization, can reach a fixed attractor, meaning that this will lead to an optimal behavior in which the value of the state will no longer change (K. Friston, 2010). This mechanism refers to the theory of **"predictive coding account"** (K. Friston & Kiebel, 2009). In the Interactive Account theory, the specific activation in ventral OT cortex is dependent on interaction between bottom-up visual stimuli and top-down expectations. A greater match between information coming from both connections leads to less prediction error and less response in OT cortex during reading (Price & Devlin, 2011). At a lower level, the OT cortex would compute the difference between perceptive information and knowledge and at a higher level, the pre-frontal cortex would compute the difference of that difference (K. Friston & Kiebel, 2009; Kherif et al., 2011a; Twomey et al., 2011). In addition, our results mainly contradict feed-forward only models for word reading (L. Cohen et al., 2002; Price & Devlin, 2011). Multiple studies are in accordance with the fact that the inferior OT cortex, and more generally the ventral stream, is not only affected by bottom up connections, but also by top-down connections driven by attention, training, knowledge, category-specific recognition memory or semantic/phonological influences. This is also in line with the fact that the OT cortex is at the interface between visual and non-visual information processing (Gauthier et al., 1999; Gilbert & Li, 2013; Golarai et al., 2007; Kherif et al., 2002, 2011; Striem-Amit, Cohen, Dehaene, & Amedi, 2012; Twomey et al., 2011) (Figure 50).

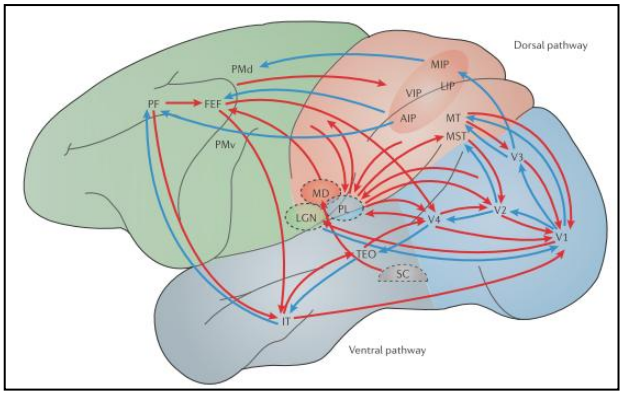


Figure 49. Illustration of feedforward and top-down pathways between ventral stream and prefrontal and parietal cortices (Source image: (Gilbert & Li, 2013)).

In addition, the connection between the lateral orbitofrontal cortex and the anterior temporal lobes allows a rapid update and modulation of memory representation in the temporal lobe based on reward/punishment history integrated in the frontal cortex. This connection is called the uncinate fasciculus and would have a role in instrumental learning with the aim to make a choice. This is also involved in episodic memory, language semantic retrieval and/or social/emotional processing allowing valuation of stimuli and representation of emotional meaning (Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009; Von Der Heide, Skipper, Klobusicky, & Olson, 2013). The functional connectivity between the OT and the frontal cortex associated with learning could also be explained by cholinergic pathways, as there are strong cholinergic projections between orbital pre-frontal cortex, hippocampus, perirhinal and entorhinal cortices (Ranganath & Rainer, 2003). In limitation, we could remark that the regions studied in our results are not in the same brain hemisphere. However, an anatomical connection exists between the left inferior OT and the right medial orbitofrontal cortex (Joshi et al., 2010). In addition, the limits of DCM are that inferences depend on knowledge about the anatomical connectivity in the human brain and ranking of models is relative (Penny, Stephan, Mechelli, & Friston, 2004).

In conclusion, our results indicate that humans have a great capacity to extract pertinent information from visually meaningless shapes in a context of uncertainty. This involves multiple brain networks related to visual, memory and language processes with bottom-up and top-down interactions. The aim of this learning is to create new and unique concepts containing a meaning. This could reflect the human ontogeny of the language's semantic acquisition underlying temporo-frontal network.

Functional connectivity between hippocampus and caudate nucleus

In our results, we found a significant **interaction** between two memory systems associated with hippocampus and caudate nucleus and the learning condition (cf. results in appendix in chapter "6.1. Functional connectivity between hippocampus and caudate nucleus"). In learning trials, we observe a negative relation between the two regions, but this is not the case in non-learning trials. Even if this result is in line with previous studies on MCPL showing a negative relation between hippocampus and BG, this is based on subject's mean statics activations over the whole learning task. However, this does not allow affirming a dynamic negative functional connectivity between them through learning trials at neuronal level. We would need to perform a psychophysiological interaction (PPI) analysis to explore how the response in one region is influenced by the interaction of another region with an experimental treatment (K J Friston et al., 1997).

In the literature, MTL and BG memory systems can be differentially activated during learning trials due to the different learning situations encountered throughout the task. MTL has an early role in encoding new stimuli representation and to form declarative memory, whereas the BG activation increases through learning trials and is related to gradual learning and non-declarative memory. The aim of competition between MTL and BG would be an adjustment of access between flexible knowledge and automatic/fast learning to adapt to different learning situations during the task (Packard et al., 1989; R a Poldrack et al., 2001; D Shohamy et al., 2008). Another study suggests that the two memory systems could act in complementary and competitive ways. For example, when development of explicit knowledge is hindered by some factor (e.g. distraction), the striatal system mediates the performance, but with the cost of decreasing flexibility in new situations (Foerde et al.,

2006). A parallel activation between those regions was also associated with cue difficulty, probability of association and with prediction error (PE) signal during feedback probabilistic learning. This indicates that they can both cooperate in different manners to facilitate learning and decision-making in case of violation of expectation. Their interaction is supported by a functional loop in which the hippocampus can detect novelty and send this signal to the ventral tegmental area (VTA) that releases dopamine into the hippocampus to facilitate long term potentiation (Dickerson, Li, & Delgado, 2011).

In a categorization task, the learning of a one dimensional rule has been associated with declarative memory and the anterior MTL, whereas the categorization and integration of more than one dimension has been associated with non-declarative memory and the posterior caudate nucleus (Nomura et al., 2007). However, caution should be given to the fact that declarative does not always represent episodic memory associated with MTL, even if it is part of it, because one can be conscious of what is learning, without putting words to it. For example, one may use implicit processes such as conditional learning or priming to associate a cue with the outcome or one may use multiple strategies associated with different neural systems in parallel (M. a Gluck et al., 2002; Henke, 2010; D. A. Lagnado et al., 2006; David A Lagnado & Newell, 2006b; Reber, Knowlton, & Squire, 1996). Interaction between memory systems could thus be better explained at the individual level.

Model of learning

Our results link categorization learning with procedural memory in BG and episodic memory in MTL and show that priming in OT is a critical mechanism underlying learning under uncertainty. In addition, conceptual categorization and optimal decision-making result from the interaction between OT and higher order regions in the frontal cortex and in the insula. Our results can also be generalised to understand language and provide evidence for an interactive model and contradict feed-forward only models for word reading (Price et al., 2011).

We propose a model of learning in which the involvement and interaction of different memory systems are modulated by feedback information and by the demand of the task through learning trials. In the schema presented below (Figure 51), the presentation of a new cue is the first input of the brain system. After visual processing, the OT cortex is involved in establishment of perceptual representation of the input. The frontal cortex, specific to working memory, can interact with the OT cortex to adjust the representation and to semanticize information with a priming process. The MTL is mainly associated with episodic memory and the basal ganglia with procedural memory. They generate a more structured, flexible and fine-grained representation of the information. All memory and cognitive systems are also affected by feedback and reward information. Through a feedback loop, information re-introduces external information in the brain system to adjust the direction of learning. Last, but not least, other factors such as reward or error of prediction or even personality and negative affects can modulate individual choices through learning (cf. next chapters “3.4. Experiment 4 – Neural substrate associated with reward and prediction error in probabilistic learning” and “3.5. Experiment 5 - Neural substrate

associated with personality and depressive/anxiety symptoms in probabilistic learning"). This model shows the importance of investigating learning and memory processes as large and interacting brain networks at the individual level.

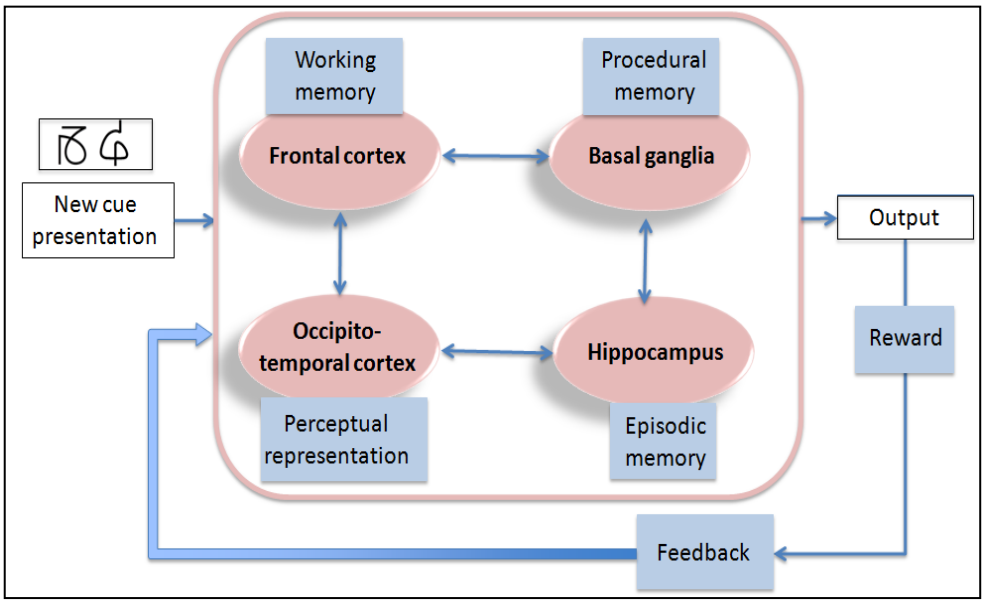


Figure 50. Model of learning in MCPL task. Multiple memory and cognitive systems interact during learning. They are also modulated by feedback information.

3.4. Experiment 4 – Neural substrate associated with reward and prediction error

3.4.1. Objectives

To investigate further the neural activation associated with MCPL, the effect of correct prediction (i.e. number of rewards collected) during learning was tested. I also used a reinforcement learning model based on prediction error (PE) (Sutton & Barto, 1998) to combine the subject's choice and the reward information. This model is based on the Rescorla-Wagner model and computes the difference between actual reward and the expected value of outcome. In contrast to more conventional models of learning, the PE acts more like a "pacemaker of learning" and is often associated with ventral striatum in neuroimaging studies (Gläscher & Büchel, 2005). During instrumental learning, PE is mainly associated with dopaminergic activity in cortico-striatal circuit and with reward-seeking behaviors to control the immediate selection of behavior to improve learning (Pessiglione et al., 2006; Schultz & Dickinson, 2000).

3.4.2. Materials and methods

Prediction Error

I computed a reinforcement learning model called the Prediction Error (PE), This measure derives from Q learning, a model-free that does not require a model of the environment. This is based on reinforcement learning model in which an agent, the learner, interacts with

its environment. The aim of the agent is to maximize his rewards. At each step, the agent has a representation of the environment's state and chooses an action based on that state. On the next trial, he receives a reward and changes of state. At each step, the agent creates his policy, meaning that he has a mapping between state and probability to select a possible action depending on his experience (Sutton & Barto, 1998). PE represents the difference between actual reward and the expected value (Gläscher & Büchel, 2005).

In MCPL, the states are the presence of absence of each of the 4 cues. The action is the choice of the symbol A or B. The monetary reward is shown only if the subject chooses the correct symbol. A correct answer means that the subject has chosen the symbol A with a probability close to the one defined for each cue (i.e. 20% for cue 1, 40% for cue 2, 60% for cue 3, 80% for cue 4).

The equation below (4) is the learning model computed at each trial t (Daw, 2009).

$$Qa_{t+1} = Qa_t + eta * PE_t \quad (4)$$

PE is the difference between the expected outcome (i.e. Qa(t)) and the actual outcome/reward (i.e. R(t)) (5). PE indices can then be inserted as parametric modulators in the fMRI matrix design for each subject.

$$PE_t = R_t - Qa_t \quad (5)$$

A softmax function (6) is used to convert Q values into action probabilities. This is called the observational model and represents a stochastic decision rule. This suggests that subject's choice is dependent on the softmax probability. This is also a generalization of the logistic function to multiple variables (Daw, 2009).

$$Pa_t = \exp(Qa_t * tmp) / (\exp(Qa_t * tmp) + \exp(Qb_t * tmp)) \quad (6)$$

In order to optimize the two parameters of Q learning curves for each subject, named the temperature (tmp) and the rate of leaning (eta), a Maximum Liekelihood (ML) function is needed. ML represents the negative logarithm of the product of probabilities to choose symbol A at each trial t (7). This value has to be minimized by means of the function "fmincon" in Matlab software *(MATLAB and Statistics Toolbox Release 2011b, The MathWorks, Inc., Natick, Massachusetts, United States)*.

$$ML = -\sum \log(P(Qa_t) \quad (7)$$

This allows optimizing the computational model of learning to maximize the "agreement" of the selected model with the observed individual data. Eta and tmp parameters are constrained in the range [0.01 to 1] and [1 to 10] respectively (Gläscher & Büchel, 2005). To avoid that the optimizer stops in a local minima, each model optimization begins with random initial values for eta and temp. In addition, the optimization was performed 50 times; the most frequent pair of optimized eta and tmp values was then selected.

For example, at trial *n*, the pattern consists of cues 1 and 3. There will be 2 Q values updated (depending on the previous learning with this pattern) for this trial: one for cue 1 and one for cue 3. Here, the Q values have to be combined in one single Q value. We propose two different non-exhaustive models for Q values integration. In the max model, the Q value of the trial *n* is the highest among the 4 Q values associated with each of the 4 cues. In the mean model, the Q value is an average of the 4 Q values associated with each of the 4 cue. This Q value represents the current expected Q value for cue 1 and cue 3 at this trial *n*. After this trial, we calculated a measure of PE and a probability to choose the symbol A by means of the softmax probability function. The initial Q value is defined as zeros and the probability to choose symbol A is 50%, because there is no expectation to choose more door A or B.

A learning rate (eta) of 1 will make the agent to take into account only the most recent information. In the literature, some fitted values exist: 0.2 to 0.7 for “explicit” learning tasks and 0.01 to 0.1 for “implicit” learning tasks. The temperature (tmp) is a parameter that controls the stochasticity of choices or the exploration rate. Low temperature, close to 0, means that all actions are equiprobable or randomly chosen. Oppositely, the temperature is high when the action with highest value is chosen. This can be linked to learning strategy, with higher temperature meaning higher exploitation and lower exploration. An agent has to balance between exploration and expoitation to find optimal actions. For example, during exploration, the agent can discover new options and during exploitation, the agent can use his knowledge to get better results (Coggan & Doina, 2004). In the equation of Q learning, there is also a discount factor, but is not shown in the equation because it is assigned to 0. A value of 0 makes the agent "opportunistic" by only considering current rewards without influence of future values in the current predictions. The policy is there deterministic. In addition, different measures of model fit are calculated in addition to the ML. One measure was computed with the sum of similar action predicted by the model and by the subject divided by the number of total trials.

3.4.3. Results

Univariate analysis of brain activation associated with reward in learning trials

Several brain regions were positively associated with modulation of reward, meaning with the presence or absence of reward in learning trials. The significant regions were the bilateral OT cortices, the left lingual cortex and the left mid occipital cortex. No significant

brain regions were found for the negative association (Table 8). There was probably a slight trend for the right caudate nucleus (XYZ(7.5,4.5,-7.5)) to be positively associated with the first contrast (with a peak p-value uncorrected of p<0.001, but p-value *FWE*-corrected of 0.98, Z=3.4). In addition, no significant voxels were associated with modulation of probabilistic reward, meaning the probability of having a correct prediction, in learning trials.

Table 8. Activation associated with modulation of reward in learning trials

Positive association					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**Z statistic**
43	Left occipital inferior cortex	-36	-76.5	-12	4.84
	Left lingual cortex	-30	-88.5	-10.5	4.46
	Left mid occipital cortex	-39	-70.5	3	4
	Rigth inferior occipital cortex	36	-72	-9	4.71
	Right inferior occipito-temporal cortex	36	-57	-13.5	4.63
		34.5	-49.5	-18	4.22

Table 8. Significant region activation associated with reward modulation in learning trials (P_{FWE}<0.05). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute space.

Prediction Error

The best model was the one which combines the 4 Q values with a mean function and includes binary reward compared to the maximum function and probabilistic reward. This result is based on optimization by minimization of Maximum Likelihood (ML). The mean of ML and model fit for all subjects were 261.29 for the first model (mean, binary reward), 261.31 for the second (mean, probabilistic reward), 261.38 for the third model (max, binary reward) and finally 262.36 for the fourth model (max, probabilistic reward).

The table 9 shows the optimized parameters of rate of learning (eta) and temperature (tmp) by means of maximum likelihood (ML) minimization. We report that the optimized model explains 64% of subject's actions.

Q learning curves and prediction error related to the 4 cues are shown in figure 52 and figure 53 respectively for each of the 23 subjects (from top left to right bottom). There is clear discrimination of the 4 Q learning curves in most of the subjects except for 5 subjects (num. 3, 5, 6, 17, 20). The subject' curves that show less discrimination between the 4 cues are less stable and coherent through trials (Figure 52). They are characterized by a higher value for temperature (higher or equal to 1.55) (Table 9, in yellow).

Table 9. Optimized parameters of the prediction error

Subjects	ML	eta	tmp	model fit sub
1	263.16	0.05	0.96	0.58
2	268.27	0.07	1.22	0.64
3	266.24	0.20	1.70	0.86
4	250.53	0.06	0.71	0.84
5	275.42	0.39	10.00	0.36
6	265.31	0.30	1.55	0.75
7	233.61	0.05	0.44	0.72
8	259.67	0.10	0.92	0.49
9	252.88	0.05	0.68	0.76
10	259.65	0.02	1.25	0.38
11	260.32	0.07	0.75	0.58
12	257.72	0.06	0.90	0.78
13	264.64	0.03	7.25	0.41
14	272.18	0.06	2.21	0.52
15	265.26	0.03	0.81	0.44
16	246.86	0.06	0.58	0.65
17	273.74	0.45	3.32	0.80
18	255.79	0.05	0.90	0.65
19	263.16	0.07	1.04	0.49
20	268.01	0.25	1.55	0.87
21	264.08	0.11	1.10	0.78
22	258.02	0.05	1.23	0.61
23	265.26	0.20	1.23	0.79
Mean	261.29	0.12	1.84	0.64

Table 9. Optimized parameters of rate of learning (eta) and temperature (tmp) by means of maximum likelihood (ML) for each subject (n=23). A percentage of model fit with subject's actions (model fit subj) is also computed. The inconsistent subjects with no coherence of the Q learning curves are shown in yellow color.

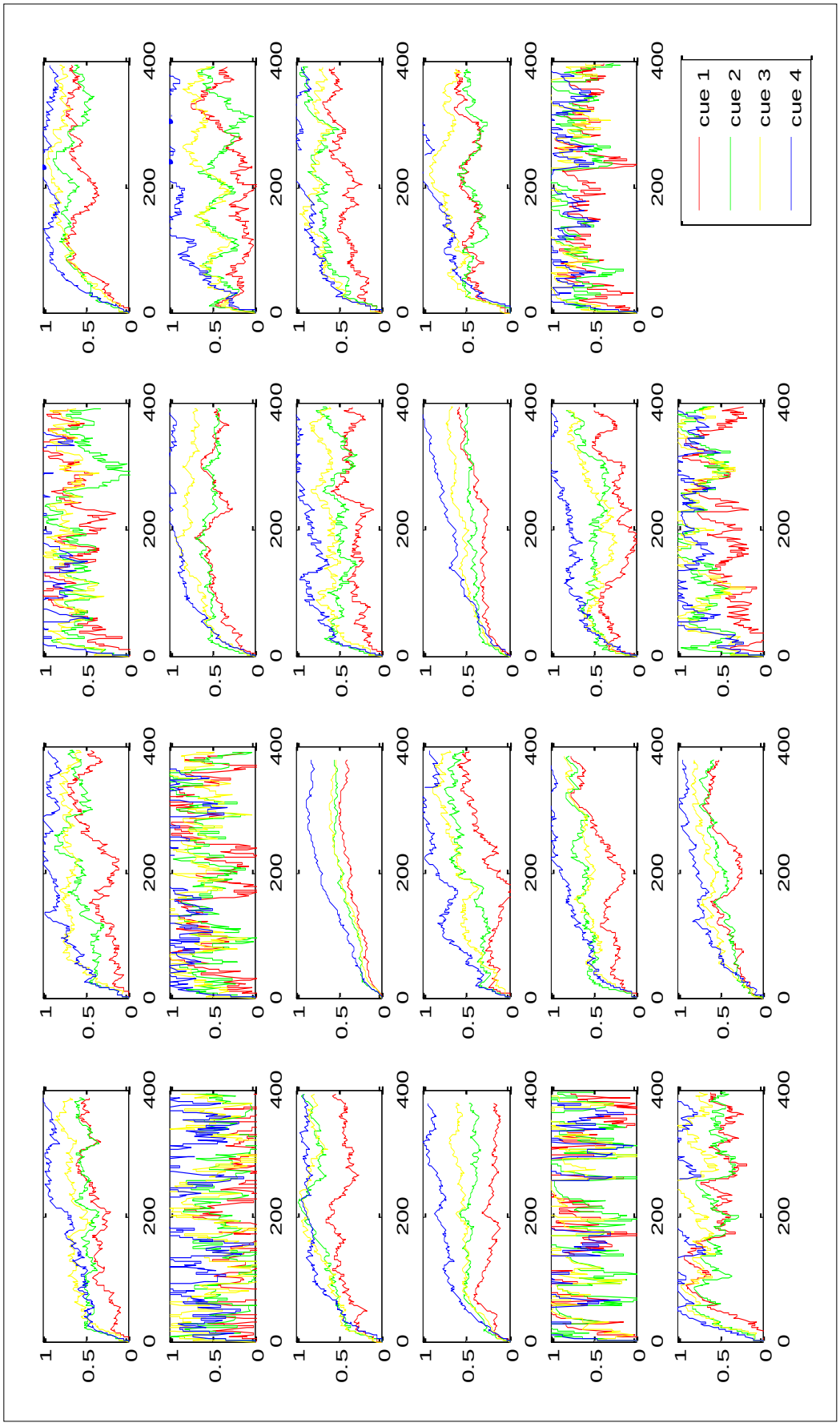


Figure 51. Q learning curves for the 4 cues and for each subject from top left to bottom right. Y axis represents Q value to choose the outcome A for each cue and X axis represents the 400 learning trials.

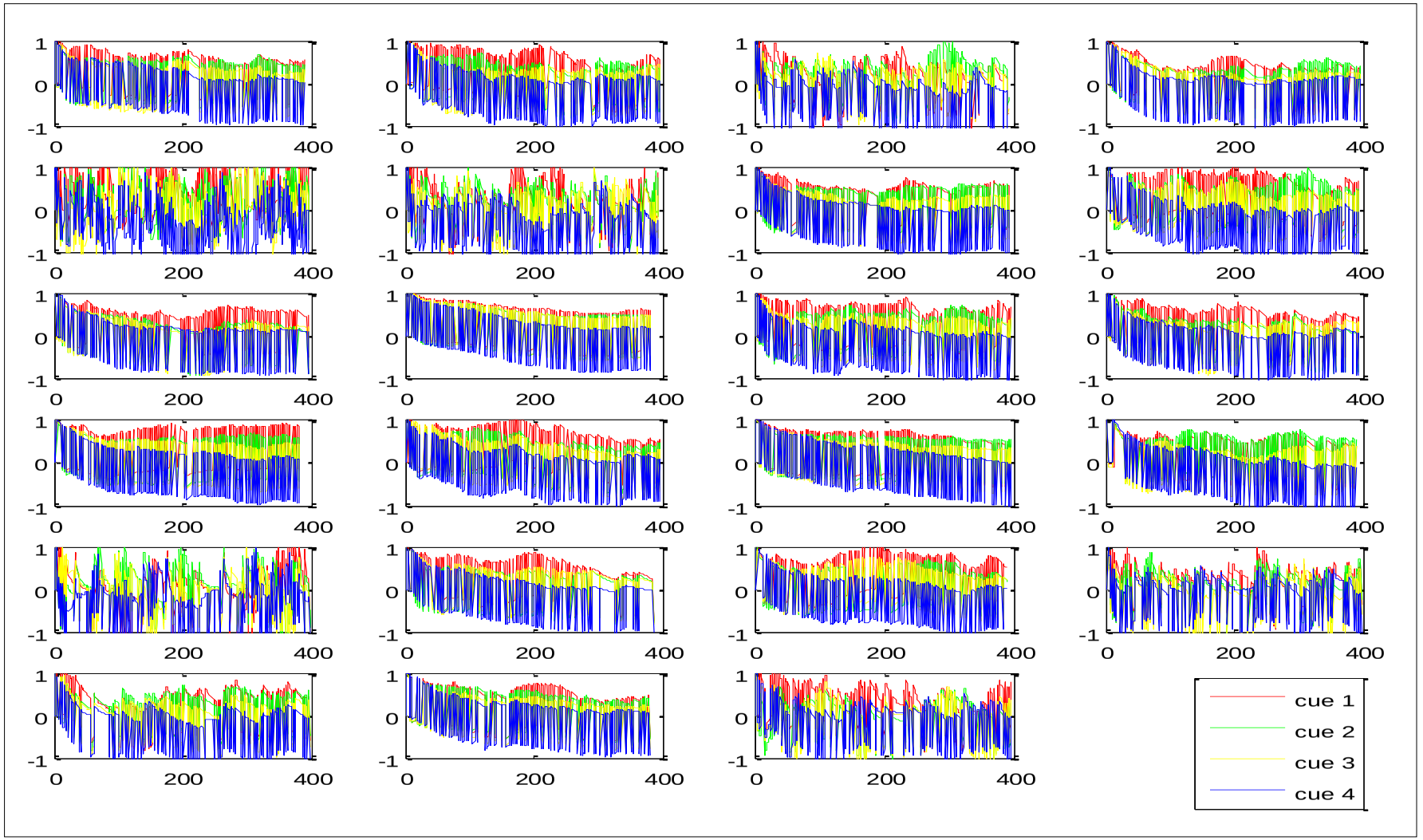


Figure 52. Prediction error measures for the 4 cues and for each subject from top left to bottom right. Y axis represents prediction error value for each cue and X axis represents the 400 learning trials.

Univariate analysis of brain activation associated with prediction error

After having found the best model of prediction error that fits the best the subject's answers, this measure was associated with brain activation. The model consists of a mean function to combine the 4 Q values related to each of the 4 cue and with a binary reward.

No significant brain region was associated with the modulation of prediction error. In the second best model of prediction error, that consists of a maximum function to combine the 4 Q values with a binary reward, there was also no significant voxels, but there was a trend for the left caudate nucleus (XYZ(-17,21,21)) to be negatively associated with prediction error (p*FWE*-corr=0.068, Z=4.75,k =248) (Figure 54).

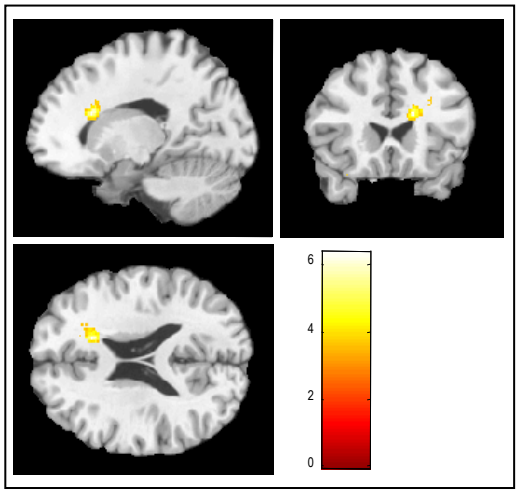


Figure 53. Statistical parametric map for the trend of the left caudate nucleus to be negatively associated with prediction error (P_{FWE}<0.05). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute space.

3.4.4. Discussion

Prediction Error

In a reinforcement learning framework, the aim of an agent is to maximize the reward coming from his environment. The agent chooses an action based on the representation of the environment's state. At each trial, the agent creates his policy, meaning a mapping between state and probability to select a possible action depending on his experience. Prediction error (PE) appears when the predicted outcome differs from expected value and would represent a teaching signal to allow learning (Sutton & Barto, 1998).

An accurate measure of PE depends on optimization of Q learning curves to fit subject's actions. Here, the best model combines the Q values of each cue with a mean function and includes binary reward compared to the maximum function and probabilistic reward. This model suggests that the subject tries to integrate all the information/cues to choose an action, and does not focus on the most rewarding cue only. This could be in line with studies reporting subjects often adopt more of a matching than maximization strategy even it is less optimal in terms of reward maximization. Matching means that subject response is based on the probability of association between the pattern and the outcome (e.g. 70%), whereas for maximization the response is based on the most probable outcome (e.g. 100% for a pattern association of 70%) (D. A. Lagnado et al., 2006; Shanks, Tunney, & Mccarthy, 2002).

Univariate analysis of brain activation associated with reward in learning trials

Effect of reward in learning trials was found in the bilateral occipito-temporal cortices. It is known that neurons in this region are affected by expertise (Gauthier et al., 1999) and by more salient/relevant stimuli (Kourtzi et al., 2005). In addition, there is not only bottom up integration of visual input in this region, but also top-down integration from more anterior part of the anterior inferior temporal cortex that can store structural knowledge (Gerlach et al., 2002). In our study, we suggest that reward can modulate learning, because reward could make the strong predictive cues more salient. This could shape neuronal response in this region by means of the knowledge accumulated.

Univariate analysis of brain activation associated with prediction error

After having calculated the best fit of a prediction error (PE) model using subject's actions for each cue, we inserted this measure as parametric modulator during learning trials. No brain regions were significantly associated with that measure. It is possible that functions other than mean Q value can better capture subject's actions and the associated neuronal coding. In addition, to explain the fact that reward modulation was significantly associated with some brain regions (cf. chapter "Univariate analysis of brain activation associated with reward in learning trials"), but not PE, we can report that PE seems a more subtle marker of reinforcement learning than reward presence/absence only. For example, a study showed that PE signal was larger in unexpected compared with expected absence of reward (Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003), whereas with reward modulation, the signal is only binary.

However, we observed a trend in which the left caudate nucleus activation was associated with the PE computed with the second best model, which selects the maximal Q value from the 4 cues. Regarding the specificity and the coherence of activation for PE coding in this region containing mainly dopaminergic neurons, we believe that the statistical effect size of our results would increase with inclusion of more subjects or with exclusion of worst performers. Indeed, it has been shown that coding of reward PE in instrumental learning is mainly associated with dopamine and with bilateral striatum and left posterior putamen for gain and loss conditions (Pessiglione et al., 2006b). The activation of the left caudate nucleus (XYZ(-17,21,21)) was in the dorsal striatum (y axis coordinates = 20-22mm), which has the role of "actor" that aims to memorize rewarding outcomes based on stimulus-response association policy, in contrast to the ventral striatum (y axis coordinates = 8-14mm) that represents a "critic" that learns to predict future rewards based on temporal difference PE correlated with phasic activity of dopaminergic neurons (O'Doherty et al., 2004).

In addition, the fact that the first, but not the second model, was associated with the left caudate nucleus could reflect the specific function of PE and dopaminergic neurons highly concentrated in striatum, to maximize reward collection. However, in our results, we found a negative correlation between the caudate nucleus activation and PE. In a study, a decrease of activity in striatum has been associated with negative PE. Negative PE means absence of expected reward (Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Tobler, O'doherty, Dolan, & Schultz, 2006). Regarding that last study, it could be pertinent to split trials in positive and negative PE and to test the associated brain activity.

3.5. Experiment 5 - Neural substrate associated with personality and depressive/anxiety symptoms in probabilistic learning

3.5.1. Objectives

A recent study has shown that stress induction can change learning strategy and the brain activation related to it during MCPL. They found that stress shifts the engagement of memory systems from the hippocampus dependent system to the striatal one. The aim would be to keep the learning performance at normal level in case the hippocampus shows vulnerability to stress (Schwabe & Wolf, 2012). In our study, factors related to personality and depression/anxiety will be associated with behavioral learning and brain activation related to it. As it is known that personality and negative affects can affect subject's choice and learning strategies (Alttoa, Seeman, Kõiv, Eller, & Harro, 2009; Benjamin et al., 1996; Vermetten et al., 2001), we expect that they will be associated with specific parameters such as exploration rate (i.e. temperature) (Coggan & Doina, 2004) extracted from the model of PE and choice aspect of learning.

3.5.2. Materials and Methods

Psychological tests

Participants from the MCPL task (n=26) underwent a personality questionnaire called Neo-FFI-R of 150 items (P. Costa & Mccrae, 2004) and the Hospital Anxiety and Depression Scale (HADS-A and HADS-D respectively) (Zigmond, AS, Snaith, 1983) in addition to Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996). The personality questionnaire contains 5-point agreement scale for each item and is based on the Five-Factor Model of personality (P. Costa & MacCrae, 1992). TPQ-Novelty Seeking score was calculated with a weighted combination of NEO-FFI-R five personality traits (Jonathan Benjamin, Lin Li, Chavis Patterson, Benjamin D. Greenberg, Dennis L. Murphy, 1996).

Mutlivariate association between personality and learning

The learning variable contains 4 dimensions (i.e. scores of the 4 cues) and the personality variable, 5 dimensions (i.e. 5 traits of personality) that are interdependent. Each variable has a meaning only if its dimensions remain combined in one whole model. Therefore, to link them, we need a multivariate method. I used two types of approach: principal component analysis (PCA) and partial least square (PLS) regression.

In the first approach, we used PCA (cf. method described in appendix, in the chapter “6.5. Multivariate Linear Method”) with oblique rotations allowing correlation between variables. The aim is to reduce dimension of learning variable for each subject. We extracted the first components that explained most of the variance in learning, after applying an oblique

rotation, and computed a linear combination of the 4 cues with the weights/loadings extracted from those components. This weighted score is then correlated with personality scores.

In the second approach, we performed a PLS regression in order to find which personality profile explains maximal covariance with a profile of learning for the 4 cues. This combines principles of principal component analysis and multiple regression analysis and searches latent variables that explain the manifest ones. Those methods are implemented in Matlab software *(MATLAB and Statistics Toolbox Release 2011b, The MathWorks, Inc., Natick, Massachusetts, United States).*

3.5.3. Results

Personality profile associated with correct prediction and learning

Personality scores of the subjects are 34.85±7 for neuroticism, 41.5±6 for extraversion, 43.58±5 for openness, 44.5±5 for agreeableness and 44.31±6 for conscientiousness. Those scores will be correlated, by means of regression analysis and correlations of Pearson, with different measures of learning: (1) correct prediction in term of binary or probabilistic reward, (2) subjective utilization weights and (3) parameters related to the optimized model of prediction error, i.e. temperature and learning rate. Note that the results are not corrected for multiple comparisons. With Bonferroni correction (corrected for 50 tests), the p-value is 0.001 and none of the results have a lower p-value to be significant.

The correct prediction, measured with correct binary reward (1 or 0), was not correlated with the five personality trait scores that are neuroticism (N), extraversion (E), openness (O),

agreeableness (A) and conscientiousness (C), nor with the score of novelty seeking (Table 10).

The correct prediction, measured with correct probabilistic reward (i.e. value of the reward weighted by the probability of association of each pattern), was also not correlated with the five personality trait scores, nor with the score of novelty seeking (Table 10).

Table 10. Correlation between personality traits and performance			
A. Association with correct prediction (binary)			
	Beta	**p-val**	**T**
Neuroticism	0.11	0.67	0.43
Extraversion	-0.17	0.52	-0.65
Openness	-0.2	0.38	-0.89
Agreeableness	0.065	0.76	0.3
Conscientiousness	-0.068	0.77	-0.3
Novelty-seeking	-0.12	-0.58	0.56
B. Association with correct prediction (proba)			
	Beta	**p-val**	**T**
Neuroticism	0.1	0.68	0.41
Extraversion	-0.15	0.58	-0.55
Openness	-0.1	0.65	-0.46
Agreeableness	0.077	0.73	0.34
Conscientiousness	-0.16	0.94	-0.068
Novelty-seeking	-0.1	0.6	-0.53

Table 10. Regression between the five personality trait and performance measured by the number of correct binary reward and by the number of probabilistic reward (i.e. reward weighted by the probability of association of each pattern of cues).

Then, the aim was to test whether there is a link between personality profile and learning. Learning is defined by subjective utilization weights of the 4 cues in the last block of 100 trials, as it represents the final learning score. To this end, I reduce the dimensions of the learning variable with a principal component analysis (PCA) and then perform a multiple linear regression with the five personality trait scores. Kaiser-Meyer-Olkin measure of Sampling Adequacy is 0.46 and the Bartlett's test of sphericity is significant ($p<0.001$, Approx. $\lambda 2 = 29.3$, df=435, n=26, df=6). Those tests are the minimum standards to accept PCA assumptions. The first, measuring the "factoriability" of the data, should be superior than 0.6 and the second, testing the sphericity of the data, should be significant. As this is significant and that there are not too few subjects in each variable leading to oversensitive analysis, I continued the analysis. PCA revealed that two main components, with eigenvalue greater than 1, explain 83.7% of the data; The first component explains 42.95% of the data. The loadings of the first component are 0.89, 0.86, -0.29, 0.28 and the loadings of the second component are -0.274, 0.272, 0.878 and 0.848, which clearly define cues 1, 2 and cues 3, 4 in the two components (Figure 55).

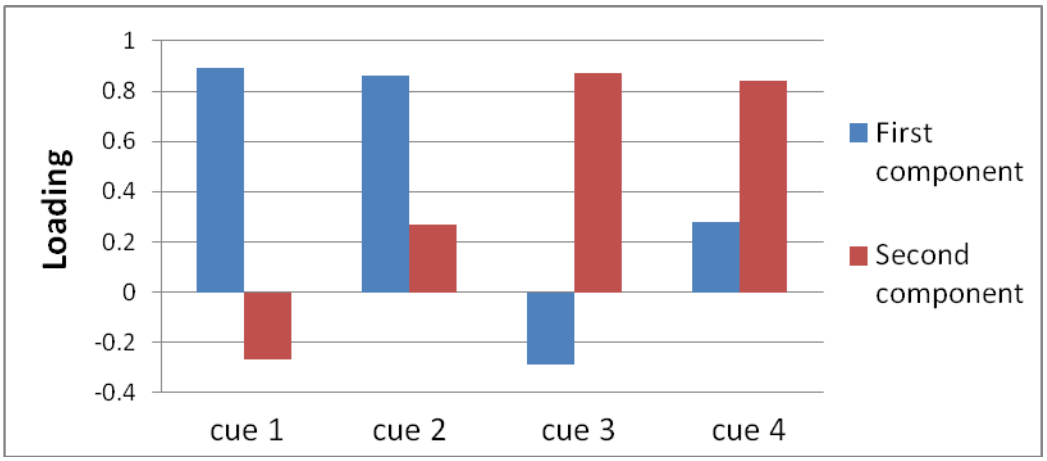


Figure 54. Figure representing the loading values of the first and the second component of the principal component analysis (PCA) on the learning of the 4 cues.

The weighted score extracted from the first component of learning were correlated with the five personality trait scores. We reported that the model explains 31.2% of the variance (R^2=0.32, R=0.56) and does not assume a significant linear relationship between variables (F(5,20)=1.87,p=0.145). However, extraversion score was significantly associated with learning, but not neuroticism, openness, agreeableness, nor conscientiousness (Table 11A). Then, the weighted scores extracted from the second component of learning were correlated with the five personality trait scores by means of a multiple linear regression. We reported that the model explains 28.2% of the variance (R^2=0.28, R=0.53) and does not assume a significant linear relationship between variables (F(5,20)=1.57,p=0.21). However, we found no correlation between this component and the five personality traits (Table 11B).

A partial least square (PLS) regression was also performed in order to find which personality profile explains maximal covariance with learning of the 4 cues. The first component explains only 10.1% of variance of the learning dataset and 35.11% of variance of the personality dataset. In addition, inclusion of the next components in the model did not increase a lot the variance explanation; therefore we only investigated the first component (Figure 56). The profiles of this component are shown in figure 57. Regression coefficients (Beta) of each score in this component are 0.51, 1.19, 1.31, 0.67.

Table 11. Regression between personality traits and components of learning			
A. Association with Component 1			
	Beta	**p-val**	**T**
Neuroticism	-0.26	0.25	-1.17
Extraversion	-0.68	0.009	-2.91
Openness	0.1	0.61	0.51
Agreeableness	-0.09	0.64	-0.46
Conscientiousness	-0.24	0.25	1.16
B. Association with Component 2			
	Beta	**p-val**	**T**
Neuroticism	0.09	0.67	0.43
Extraversion	0.2	0.41	0.84
Openness	-0.51	0.23	-2.46
Agreeableness	-0.23	0.24	-1.21
Conscientiousness	0.03	0.89	1.14

Table 11. Multiple regression between personality traits and learning components from principal component analysis (PCA). Learning measure represent the subjective cue utilization weights in the last block of 100 trials.

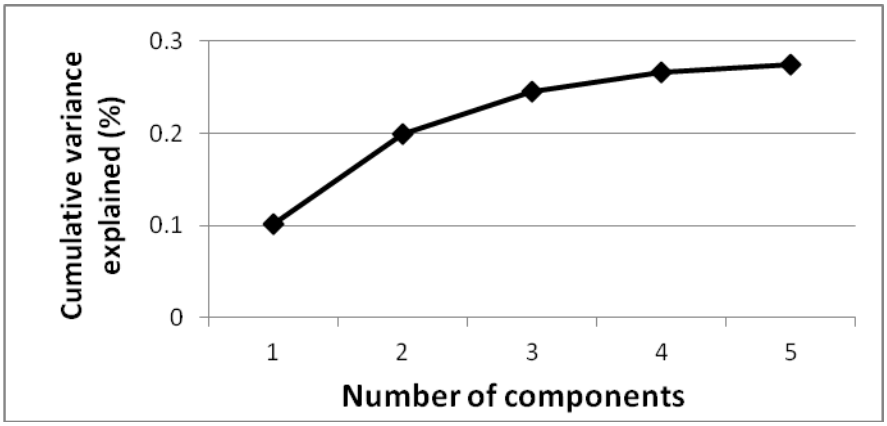


Figure 55. Figure representing the percentage of cumulative variance explained by personality with inclusion of 1 to 5 component of the partial least square (PLS) regression analysis.

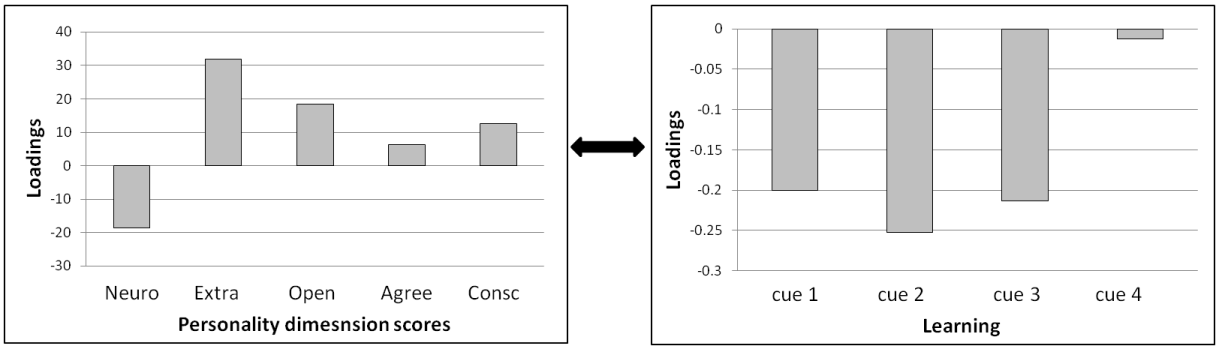


Figure 56. Figure representing the loading values of the first component of the partial least square (PLS) regression analysis with the profile of personality five scores and learning of 4 cues extracted.

I also tested whether parameters of learning related to prediction error could be explained by the personality scores (Table 12). I report that the measure of temperature (Tmp) was not significantly explained by the personality traits as a whole model (R^2=0.1, F(5,17)=0.4, p=0.84) and by each of those traits separately. It was the same for the measure of rate of learning (Eta) in the whole model (R^2=0.1, F(5,17)=0.44, p=0.81) and for each trait separately. Eta and Tmp were also not significantly associated with novelty seeking trait (Eta: p=0.08, r=-0.36; Tmp: p =0.1, r=-0.34).

Table 12. Regressions between personality and parameters of prediction error

A. Association with parameter of temperature			
	Beta	**p-val**	**T**
Neuroticism	-0.31	0.26	-1.1
Extraversion	-0.19	0.51	-0.66
Opennes	0.15	0.54	0.61
Agreeableness	0.042	0.85	0.18
Conscientiousness	0.1	0.67	0.42
B. Association with parameter of rate of learning			
	Beta	**p-val**	**T**
Neuroticism	-0.34	0.22	-1.27
Extraversion	-0.33	0.25	-1.16
Opennes	0.065	0.79	0.26
Agreeableness	-0.033	0.88	-0.14
Conscientiousness	-0.017	0.94	-0.07

Table 12. Multiple regression between personality traits and parameters of prediction error that are the temperature and the rate of learning.

Depression/anxiety associated with correct prediction and learning

Depressive/anxiety symptoms scores were collected from 26 participants with Beck Depression Index (BDI) and Hamilton Depressive and Anxiety scales (HAD-D and HAD-A). BDI score for those subjects was 5.84±6 (range [2-22]), HAD-D score was 3± 2.99 (range [0-11]) and HAD-A score 6.15± 3.39 (range [2-14]). Correlation of those affective scores with

performance was calculated with the Pearson's linear correlation coefficient. Note that the results are not corrected for multiple comparisons. With Bonferroni correction (corrected for 58 tests), the p-value is 0.001 and none of the results have a lower p-value to be significant.

The correct prediction, measured with correct binary reward (1 or 0), was not correlated with depressive scores measured with BDI test or with HAM-D test, nor with total depressive and anxiety scores measured with HAD test, nor with anxiety score measured with HAD-A test (Table 13).

The correct prediction, measured with correct probabilistic reward, was also not correlated with depressive scores measured with BDI test nor with HAM-D test, nor with total depressive and anxiety scores measured with HAD test, nor with anxiety score measured with HAD-A test (Table 13).

Table 13. Correlation between depressive/anxiety scores and perfomance

	Correct prediction (binary)		**Correct prediction (proba)**	
	r	**p-val**	**r**	**p-val**
Depressive score (BDI)	0.067	1	0.016	0.93
Depressive score (HAM-D)	0.33	0.09	0.33	0.09
Anxiety score (HAM-A)	0.21	0.29	-0.01	0.95
Total score (HAM-A/HAM-D)	0.29	0.14	-0.02	0.91

Table 13. Pearson's correlation (r) between depressive/anxiety score (measured with BDI and HAM tests) and performance (measured with the number of correct binary reward and by the number of probabilistic reward).

Correlation of affective scores with the two components of learning of the 4 cues (from previous PCA analysis) was calculated with Pearson's correlations. The first component of learning was correlated with depressive score measured with HAM-D test, with total depressive and anxiety scores measured with HAM test, but not with anxiety score

measured with HAD-A test, nor with BDI test. The second component of learning was not correlated with any depressive and anxiety scores (Table 14).

Table 14. Correlation between depressive/anxiety symptoms and subjective utilization weight

A. Association with Component 1		
	r	**p-val**
Depressive score (BDI)	0.22	0.28
Depressive score (HAM-D)	0.41	0.035
Anxiety score (HAM-A)	0.33	0.1
Total score (HAM-A/HAM-D)	0.45	0.02
B. Association with Component 2		
	r	**p-val**
Depressive score (BDI)	-0.17	0.41
Depressive score (HAM-D)	-0.07	0.97
Anxiety score (HAM-A)	0.18	0.36
Total score (HAM-A/HAM-D)	0.07	0.72

Table 14. Pearson's correlation (r) between depressive/anxiety score (measured with BDI and HAM tests) and learning components from principal component analysis (PCA). Learning measure represent the subjective cue utilization weights in the last block of 100 trials.

I also tested whether measures of learning related to prediction error could be explained by the depressive and anxiety scores. We report the measure of rate of learning was significantly correlated with depressive symptoms of BDI test, with anxiety symptoms of HAD-A test and with the total depressive and anxiety score of HAD, but not with depressive symptom of HAD-D test (Table 15). The measure of temperature was not correlated with anxiety symptoms of HAD-A test, with depressive symptom of HAD-D test, nor with the total depressive and anxiety score of HAD (Table 15).

Table 15. Correlation between depressive/anxiety scores and prediction error measures

	Temperature		Rate of learning	
	r	p-val	r	p-val
Depressive score (BDI)	-0.23	0.29	0.52	0.013
Depressive score (HAM-D)	-0.22	0.31	0.39	0.066
Anxiety score (HAM-A)	-0.14	0.52	0.45	0.029
Total score (HAM-A/HAM-D)	-0.19	0.37	0.47	0.023

Table 15. Pearson's correlation (r) between depressive/anxiety symptoms scores (measured with BDI and HAM tests) and parameters of prediction error (measured with temperature and rate of learning).

Personality profile and brain activation associated with learning

Multivariate MLM analysis of brain activation associated with subject's learning (i.e. measured with cue utilization weight) showed a significant contribution of personality to the first component (F=4.18, $p=4.2*10^{-6,}$ p<e-1), which explained 63.47% of the covariance. The domains of neuroticism, extraversion and conscientiousness had more weight than the other three domains (Figure 58A) and a specific distributed spatial pattern of brain differences was revealed in multiple regions.

Post-hoc univariate analyses of subject's learning with the first component of the MLM analysis revealed significant brain differences in multiple regions (Table 16) such as the right occipito-temporal cortex (Figure 58B), the right lingual cortex, left mid occipital cortex, the right caudate nucleus (Figure 58C), the left superior orbital frontal cortex (Figure 58D) and the right mid frontal cortex.

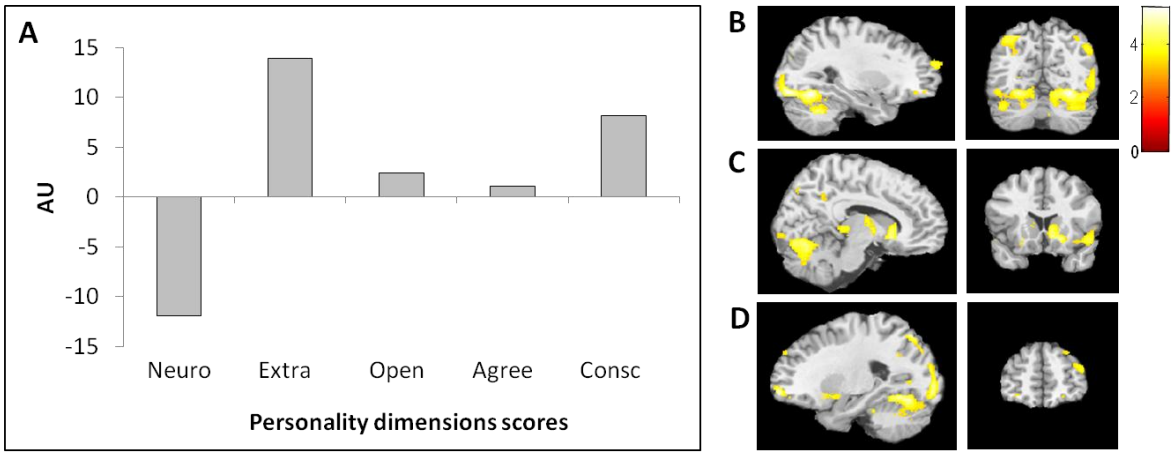


Figure 57. MLM analysis of personality profile at domain level. (A) First Eigen-component (p<0.05) of the MLM analysis for the combination of the personality domains associated with spatial brain activation distribution associated with learning within whole brain. Contrast estimate of the 5 personality domains associated with (B) the right inferior occipital cortex (xyz=[28.5, -64.5, -15]), (C) the right caudate nucleus (xyz=[10.5, 16.5, -7.5]) and (D) the left superior orbital cortex (xyz=[-27, 60, -7.5]). Abbrev: Neuro= Neuroticism, Extra= Extraversion, Open= Openness, Agree= Agreeableness, Consc= Conscientiousness. Y axis is an arbitrary unit (AU).

Table 16. Personality profile associated with subject's utilization weight activation

Positive association					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**Z statistic**
18247	Right lingual cortex	28.5	-88.5	-12	4.91
	Right occipito-temporal cortex	28.5	-64.5	-15	4.86
	Right cerebelum	18	-72	-16.5	4.73
815	Right superior temporal cortex	58.5	-25.5	6	3.94
	Right temporal cortex	64.5	-33	-10.5	3.78
		60	-42	3	3.71
861	Right angular gyrus	49.5	-63	39	3.87
	Right inferior parietal cortex	57	-54	40.5	3.67
	Right mid occipital cortex	46.5	-70.5	30	3.53
1560	Left superior parietal cortex	-25.5	-72	52.5	4.30
		-37.5	-66	48	4.02
	Left mid occipital cortex	-28.5	-79.5	37.5	3.89
2261	Right superior orbital frontal cortex	19.5	15	-10.5	4.73
	Right caudate nucleus	10.5	16.5	-7.5	4.40
		13.5	19.5	1.5	3.91
348	Left superior orbital frontal cortex	-27	60	-7.5	4.67
		-21	52.5	-13.5	3.29
	Left mid orbital frontal cortex	-31.5	48	-15	3.49
903	Left inferior orbital frontal cortex	51	22.5	-12	4.60
513	Right mid/superior frontal cortex	34.5	61.5	22.5	4.37
792	Left cuneus	1.5	-82.5	40.5	4.37
		-10.5	-84	40.5	3.37
	Left precuneus	3	-73.5	42	3.57
878	Left postcentral gyrus	-54	-12	40.5	4.11
		-45	-18	39	3.74
	Left precentral gyrus	-52.5	-3	39	3.63

Table 16. Significant region associated with personality related to subject's utilization weight activation (P_{FWE}<0.05). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute space..

Depression/anxiety associated with learning brain activation

The total score of depressive and anxiety symptoms measured with the Hamilton Rating Scale (HAM) was associated with brain activation related to subject's learning measured with cue utilization weight. Using a whole-brain family-wise error corrected threshold, we found significant brain regions negatively associated with brain activation in the bilateral lingual cortices (Figure 59A), the right precentral gyrus, the left precuneus and the parietal inferior and superior cortices (Table 17A). No significant voxel was found with the positive association. The total score of depressive symptoms measured with the Beck Depression Inventory (BDI) was also associated with brain activation related to subject's learning (i.e. measured with cue utilization weight). Using a whole-brain family-wise error corrected threshold, we found significant brain regions negatively associated with brain activation in the right parahippocampal cortex (Figure 59B), the left lingual cortex, the right insula, the left supramarginal gyrus and the left superior temporal cortex (Table 17B). No significant voxels were found with the positive association.

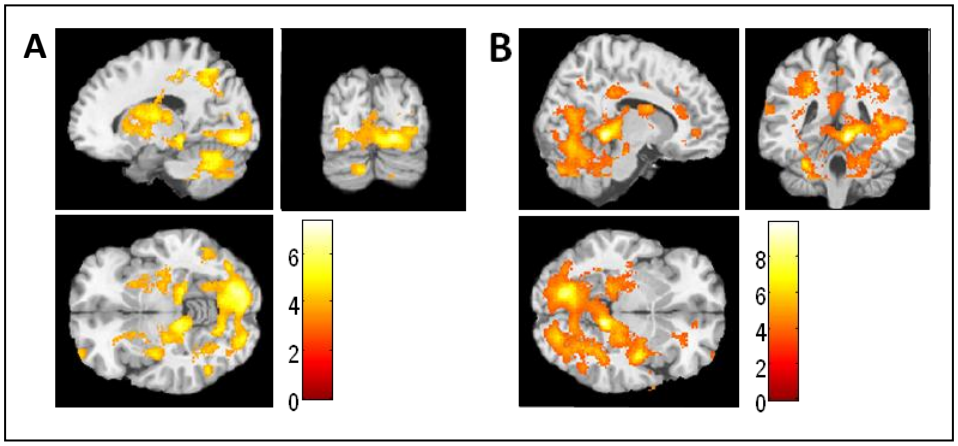


Figure 58. Statistical parametric map for (A) depressive and anxiety symptoms measured with HAM in the left lingual cortex and (B) only depressive symptoms measured with BDI in right parahippocampal cortex that modulate learning's activation (P_{FWE}<0.05). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute space. HAM: Hamilton Rating Scale, BDI: Beck Depression Inventory.

Table 17. Depressive/anxiety symptoms modulation of learning's activation

A. Depressive/anxiety score with HAM rating scale - Negative association					
Cluster (Voxels)	**Region (Label)**	**X**	**Y**	**Z**	**Z statistic**
48668	Right lingual cortex	7.5	-30	-4.5	5.12
	Right precentral gyrus	24	-4.5	52.5	4.92
	Left lingual cortex	-16.5	-82.5	-7.5	4.90
5410	Left precuneus	-10.5	-63	51	4.87
	Left inferior parietal cortex	-24	-48	37.5	4.85
	Left superior parietal cortex	-25.5	-52.5	49.5	4.73
B. Depressive score with BDI test - Negative association					
90628	Right parahippocampal cortex	10.5	-40.5	-6	5.98
	Left lingual cortex	-15	-75	-6	5.78
	Right insula	39	-9	-4.5	5.49
376	Left supramarginal gyrus	-67.5	-24	31.5	4.10
	Left superior temporal cortex	-66	-40.5	19.5	3.87
		-57	-45	18	3.61

Table 17. Significant region associated with depressive symptoms modulation of learning (i.e. subject's utilization weight) activation (P_{FWE}<0.05). Coordinates [X, Y, Z] are reported in the Montreal Neurological Institute space. HAM: Hamilton Rating Scale, BDI: Beck Depression Inventory.

3.5.4. Discussion

Personality profile associated with correct prediction and learning

To explain the high inter-individual variability in behavioral learning, we tested whether there was a link between learning and individual factors such as personality traits. I mainly report that extraversion was the only personality trait negatively associated with the weighted score extracted from the first component of learning (measured with subjective utilization weights) in PCA analysis (considering that the results interpreted here are not corrected for multiple comparisons). This component included mainly cues that are less associated with outcome A (i.e. 20% and 40% for cues 1 and 2). This trait was also the most contributive trait in PLS regression analysis.

However, we do not observe a significant link between personality and correct prediction measured by number of rewards. Therefore, we postulate that personality affects subject choice or decision-making, but not their performance in correct prediction.

This can be explained by the fact that in probabilistic learning, there is the involvement of decision-making, which is a two steps complex process. First, there is a valuation process that computes the value of options and secondly, a choice can be made by combining the previous value with other factors such as uncertainty, motivation or personality. Choice is thus not solely determined by valuation steps. In an uncertain situation such as in probabilistic learning, where probabilistic associations have to be learned, there is "reward uncertainty" or "representational uncertainty related to unclear boundaries in category". The subject can decide in a suboptimal and irrational way compared to the expected value showing the importance of including other factors to understand the role of the subject's

decision and learning (Seger & Peterson, 2013). In addition, personality can also affect subject choice by means of learning strategy selection (Vermetten et al., 2001).

Extraversion may explain inter-individual variability related to reward sensitivity and motivation for behavioral approach (Canli, 2004; Depue & Collins, 1999). The negative impact of extraversion on learning could be explained by an emotional reaction to features of the task, such as feedback information, that may interfere with executive function (Matton, 2013) and disturb selection of action for cues that are difficult to learn.

In our results, openness was also negatively correlated with learning. This is in line with a study showing a negative correlation of openness with surface learning, whereas this was positive with deep learning. It has been shown that open individuals have more intellectual curiosity and are more engaged and motivated by their learning experience, which increases their knowledge and skills. They would thus be more engaged in deep task-oriented learning, i.e. with interest in the task in itself and less with surface or effort/ego-oriented leaning in which the minimal requirement to do the task is achieved (Chamorro-Premuzic & Furnham, 2009). Our results fit that study, however, in the literature, openness was mostly associated with general and crystallized intelligence (Ackerman & Heggestad, 1997; Gignac, 2004), with the observation that openness leads to more experiences and to better adaptation (McCrae, 1994). It has been shown for example that openness and general intelligence were both correlated with decision making under changing conditions with a task of multiple cue probabilistic learning (Pine, Colquitt, & Erez A, 1999). This shows that there is a link between openness and learning. However we suggest that the type of association between them depends on the task demand and the learning measure.

In the multivariate PLS analysis, neuroticism also has a high contribution, like extraversion and openness, to learning weights. In the result, there is a positive association between

neuroticism and learning. This can be supported by a study showing that stress increases learning of cues associated with positive outcomes. The postulated mechanism is that stress could increase reward saliency and related learning though higher brain dopamine level (Lighthall et al., 2013). High score of neuroticism has also been positively related to surface learning (Chamorro-Premuzic & Furnham, 2009). In other studies, there are mixed results. It was shown that neuroticism can cause cognitive impairment (Burt et al., 1995). This can even favor cognitive style such as rumination (i.e. thinking about an idea such as causes, meanings and consequences of depressive symptoms in a sustained and repetitive way), which is associated with bias in memory and attention and with vulnerability to persistent depressive symptoms (Roberts, Gilboa, & Gotlib, 1998). In another study, emotional stability, related to neuroticism and extraversion, was not associated with deep or surface learning types, but this could be due to the type of academic setting studied (Vermetten et al., 2001). This suggests that the effect of personality is highly dependent on the task demand.

We also did not observe a significant link between novelty seeking trait score and any of the learning parameters, even with the temperature which measures the exploration rate. This is in contradiction with the fact that novelty seeking trait, linked to the dopaminergic gene, has been related to high exploratory behavior (Alttoa et al., 2009; Benjamin et al., 1996). The lack of of link could be explained by the fact that novelty-seeking is mostly dependent on the conscientiousness trait (Jonathan Benjamin, Lin Li, Chavis Patterson, Benjamin D. Greenberg, Dennis L. Murphy, 1996) which had no significant impact on learning measures in this study.

Depressive/anxiety symptoms associated with correct prediction and learning

In our results, there was significant association between anxiety symptoms and the parameters of the prediction error (PE) (considering that the results interpreted here are not corrected for multiple comparisons) . The rate of learning was positively correlated with anxiety symptoms. This result indicates that individuals with higher anxiety symptoms exploited more the environment. Few studies have investigated the effect of stress on PE. However, our result is in line with studies showing a positive impact of stress on learning cues predicting positive outcome/reward (Lighthall et al., 2013) and on the type of strategy, with a change of simple-based strategy to multiple cue-based procedural strategy (Schwabe & Wolf, 2012). Stress decreases the use of negative feedback (Petzold, Plessow, Goschke, & Kirschbaum, 2010) and facilitates aversive conditioning learning (Lissek et al., 2005); It was even demonstrated in a recent study that stress can increase aversive PE signal in ventral striatum, and thus the responsiveness to threat associations (Robinson, Overstreet, Charney, Vytal, & Grillon, 2013). In another study, they found that stress hinders the use of complex strategy, however they tested more the maintenance than the application of complex strategy (Van Hiel & Mervielde, 2007).

Regarding the variability of stess effects on cognition, we can also explain the positive effect of anxiety on cognition as a higher sensitivity to danger or mistake that make some individuals exploiting more the environment with less waste of time and energy on exploring new options. In unfavorable or unpredictable context, exploration is deterred for individuals with too high anxiety levels, because they become stuck in sampling the environment and fail to correct their misperceptions (Meacham & Jan, 2015).

In the results, there was also a significant positive correlation between the rate of learning and depressive symptoms score of BDI test, but not the HAM-D. The same result has been found in the correlation between the weighted scores extracted from the first component of learning (measured with subjective utilization weights) and depressive symptoms measured with HAM-D, but not with BDI test.

This association is in contradiction with studies showing a negative effect of depressive symptoms on rate of implicit learning (Naismith, Hickie, Ward, Scott, & Little, 2006), on complex reasoning or on sorting categories (Channon, 1996) and on task with feedback. Depressive patients would respond worse than controls in front of perceived failures (Roiser & Sahakian, 2013). However, the two tests evaluating depressive symptoms in our results are not similarly correlated with rate of learning and subjective utilization weights. The results are thus difficult to interpret. This inconsistency could arise from the fact that depressive symptoms are evaluated in a population including mostly "healthy" persons, meaning that their scores in anxiety and depression levels could be too low or not enough variable to correlate with inter-individual differences in learning..

In addition, in our study, the measures of correct prediction or learning weights were not significantly associated with depressive and anxiety symptoms. The lack of association with the correct prediction is in line with a study showing that stress does not affect performance in the MCPL task (Schwabe & Wolf, 2012). In that last study, stress affects more the type of strategy used.

Personality profile associated with learning brain activation

Using a multivariate MLM analysis, we extracted a significant personality profile associated with whole brain activation related to learning. The profile outlines a high contribution of extraversion, neuroticism and conscientiousness compared to other traits. The regions associated with the profile are the right OT cortex, the right lingual cortex, the left mid occipital cortex, the right caudate nucleus, the left superior orbital frontal cortex and the right mid frontal cortex.

Personality can thus modulate brain regions related to learning. The involvement of the orbitofrontal cortex can be explained by its role in emotional and motivational aspects of coding value of a stimulus during learning and decision-making. The ventral striatum can also interact with the orbitofrontal cortex in the motivational loop (Seger & Peterson, 2013).

Extraversion was the most contributive trait explaining brain activation related to learning. That personality trait can explain inter-individual differences in learning and can lead to greater sensitivity to positive incentive and greater motivation for approach behavior. Extraversion was also associated with the medial prefrontal cortex, the amygdala and the hippocampus. Dopaminergic structures such as nucleus accumbens, ventral pallidum and ventral tegmental area have a role in processing the intensity of the incentive and producing motivational state to approach (Depue & Collins, 1999). This is also in line with a study reporting that extraversion and presence of a specific dopaminergic receptor gene allele predicted both the magnitude of brain activation related to reward system, including bilateral medial, mid/superior orbitofrontal cortices ((XYZ(21,39,-21), XYZ(-10,42,-24)), the right amygdala, the left hippocampus and the right nucleus accumbens (M. Cohen et al., 2005). This confirms our result that the personality profile found in our results, mainly driven

by extraversion, explains activation in the mid/superior orbitofrontal cortex activation related to MCPL that involves reward-learning.

In a study on healthy adults, the five personality traits have also been differentially associated with brain region volumes. Extraversion was associated with medial orbitofrontal cortex for reward processing. Neuroticism was associated with regions involved in processing negative information and in self-evaluation and emotion regulation, including temporal cortices, the posterior hippocampus in the MTL, the right dorsomedial pre-frontal cortex and other regions such as the left globus pallidus and bilateral subthalamic nuclei. Conscientiousness was associated with posterior fusiform gyrus and lateral pre-frontal cortex; this last region is involved in control of behavior and self-regulation. The two other personality traits, openness and agreeableness, contribute less to the profile extracted from our results. However, openness includes intellectual engagement, imagination. Agreeableness was related to regions inferring the mental states of others, which includes the posterior cingulate cortex, the superior temporal cortex and the fusiform (Deyoung et al., 2010).

In addition, the most notable finding in our multivariate analysis is that the personality profile associated with learning activation is driven by traits related to impulsivity (i.e. neuroticism, extraversion and conscientiousness). Knowing that impulsiveness (i.e. loss of self-control) is a facet of neuroticism, the negative contribution of neuroticism in the right mid/superior frontal cortex activation (XYZ(24.5, 61.5, 22.5)) associated with learning can be related to a study showing that increased impulsivity relates to less activation in the right anterior medial pre-frontal cortex and the right superior medial frontal cortex (XYZ(6,54,15)) in the presence of immediate reward (Sripada, Gonzalez, Phan, & Liberzon, 2011). Those regions, encompassing the anterior rostromedial pre-frontal cortex (XYZ(3,60,15)) and the

rostrolateral prefrontal cortices (XYZ(24,51,-9)), also represent a gateway for attentional control between external and internal information respectively (Henseler, Krüger, Dechent, & Gruber, 2011). Furthermore, as observed in the multivariate analysis, extraversion and conscientiousness were positively correlated with the striatum. This correlation can be explained with impulsivity. Impulsivity is part of those two traits, more particularly to the excitement seeking facet of extraversion and to the low self-discipline facet of conscientiousness (P. Costa & MacCrae, 1992; Whiteside & Lynam, 2001). A study showed that reward-related ventral striatum activity was correlated with impulsivity score measured with the Baratt Impulsiveness Scale and with dopamine (DA)-related polymorphisms related to DA release (DRD2 -141C deletion), availability (DAT1 9-repeat) and to DA post-synaptic decrease inhibition (DRD2 -141C deletion and DRD4 7-repeat) (Forbes et al., 2009). Impulsivity has also been related to activation of the prefrontal cortex in preferential choice of immediate reward (Seger & Peterson, 2013).

Depression/anxiety associated with learning brain activation

Scores of depression and anxiety symptoms were associated with whole brain activation related to learning. Only depressive symptoms showed significant negative correlation with the right parahippocampal cortex activation, among other regions. A study reported that stress can affect memory systems during classification learning. After stress induction, they observed not only a difference in learning strategy, but also a decreasing negative correlation of right hippocampal activity with learning performance. They also observed that stress induces a positive association of striatum activity with performance. They even suggest a shift from declarative hippocampal memory system to a procedural one to control

behavior with stress. This could be due to the fact that the hippocampus is very vulnerable to stress and glucocorticoid stress hormones (Schwabe & Wolf, 2012). This finding, in addition to the evidence suggesting depression is often accompanied by anxiety (Kaufman & Charney, 2000), we suggest that stress could explain the negative association of the right parahippocampal cortex with depressive symptoms in our study.

3.3-5. Limitations and perspectives

Limitations. Knowing the high inter-individual variability in strategies used during MCPL, we can wonder whether models of learning (i.e. models of cue utilization weight and prediction error) computed in this study are best in terms of fit with subject's behavioral learning and in term of neural coding. Inclusion of more individualized parameters in learning models such as personality, affective state or strategy could improve accuracy.

Perspectives. We could also test the effect of different parameters of the model of PE (e.g. predicted value of the reward/Q-value, learning rate, temperature) and their interaction with other factors in the brain. In the model of prediction error, we could also include dynamic parameters, such as a temperature term evolving over time as it is known temperature is linked to exploration decay through learning of the environment (Andalora, 2007). In addition, after having explicitly asked participants which strategies they used during MCPL, they reported variable and imaginative answers. For example, a subject tried to assimilate cues to letters and to form meaningful words, another associated cues with sounds or animals to create a story, another tried to associate some cues with positive or negative affect or another subject focused on the horizontal and vertical lines of the cues.

To go further in the understanding of MCPL at the individual level, we could create more individualized models of learning including parameters related to the individual (e.g. personality, affect, strategy), and we could test whether they can predict learning and associated brain activation. For example, individuals with a degree of depressive symptoms, called dysphorics, but without depression diagnosis, are impaired in the recall of detailed positive memories. In addition, some specific depression symptoms could be more informative on those mechanisms at individual level. For example, the maladaptive brooding aspect of rumination in depression was correlated with more impaired memory performance than the positive aspect of reflection (Romero, Vazquez, & Sanchez, 2013). In our study, the lack of variability in depressive symptom scores could explain the non-significant association with learning performance. We are currently recruiting participants with more depressive symptoms to obtain a wider range of variability in depressive symptom scores.

Investigation of MCPL in AD patients could also be an innovative project to understand brain and memory deficits as global and interactive systems. Indeed, learning of procedures has been rarely studied in AD and it seems this type of learning could be impaired in the early phase in the presence of other cognitive impairments, such as episodic or working memory (Beaunieux et al., 2012). However, the procedures already acquired and automated long before the disease appear unaffected (Amieva et al., 2014).

4. CONCLUSIONS AND PERSPECTIVES

In this thesis, I propose a new approach to investigate population with mild with cognitive impairment (MCI) at risk for Alzheimer's disease (AD). The findings highlight that abnormalities in the medial temporal lobe (MTL), a region that is vulnerable in AD, can be explained not only by cognition, but also by inter-individual differences in population with MCI and in healthy young individuals. In AD, the inclusion of more individual factors could probably reduce diagnostic confusion, mainly based on memory assessment, and therefore improve the development of more targeted treatment.

Firstly, I have observed that, beyond cognitive state of impairment, the personality traits can explain the inter-individual differences in the MTL, notably with a higher contribution of neuroticism linked to proneness to stress and depression. My study has allowed identifying a pattern of anatomical abnormality in the MTL related to personality with measures of volume and mean diffusion of the tissue. That pattern is characterized by right-left asymmetry in MTL and an anterior to posterior gradient within MTL. I have interpreted that result by tissue and neurochemical properties differently sensitive to stress.

Secondly, the phenotypic diversity in AD arises also from the limited knowledge of memory and learning processes in healthy brain. For this reason, I also investigated the functional mapping of memory and learning in the structures of the MTL in healthy brain. Results of my second project have contributed to the actual debate on the contribution of MTL sub-regions in the processes of familiarity and recollection. Using a new multivariate method, the

results support firstly a dissociation of the subregions associated with different memory components. The hippocampus was mostly associated with recollection and the surrounding parahippocampal cortex, with familiarity type of memory. Secondly, the activation corresponding to the mensic trace for each type of memory is characterized by a distinct spatial distribution. The specific neuronal representation, “sparse-distributed”, associated with recollection in the hippocampus would be the best way to rapidly encode detailed memories without overwriting previously stored memories.

Thirdly, results of my third project allowed me to highlight the role of the MTL in learning and the interaction between different memory systems such as the procedural memory, the perceptual memory or priming and the working memory. We have found activations in the MTL corresponding to a process of episodic memory; the basal ganglia (BG), to a procedural memory and reward; the occipito-temporal (OT) cortex, to a perceptive memory or priming and the prefrontal cortex, to working memory. We have also observed that those regions can interact; the relation type between the MTL and the BG has been interpreted as a competition. In addition, with a dynamic causal model, I have demonstrated a “top-down” influence from cortical regions associated with high level cortical area such as the prefrontal cortex on lower level cortical regions such as the OT cortex. That influence decreases during learning. My interpretation is that this mechanism is at the origin of the semantic knowledge. I have also shown that the subject’s choice and the associated brain activation are influenced by personality traits and negative affects.

The results of this thesis have brought me to propose (1) a model explaining the possible mechanism linked to the influence of personality on the MTL in a population with MCI, (2) a

dissociation of MTL sub-regions in different memory types and a neuronal representation specific to each region. This could give cues to resolve the actual debates on recognition memory. Finally, (3) the MTL is also a system involved in learning and that can interact with the BG by a competition. I have also shown a dynamic interaction of « top –down » and « bottom-up » types between the pre-frontal cortex and the OT cortex.

In conclusion, the results could give cues to better understand some memory dysfunctions in aging and Alzheimer's disease and to improve development of treatment. In addition, given that dementia is the most costly disease in developed countries in elderly population (Bonin-Guillaume, Zekry, Giacobini, Gold, & Michel, 2005), our society needs to play a major role in deploying help, information and solutions for all the people in distress through training for caregivers, patient follow-up and the surrounding to improve our understanding of the disease. Future studies could also aim at testing whether models of memory and learning generated from healthy brain could predict memory and learning abnormalities in elderly persons and populations with MCI, AD or even with depression/anxiety disorders.

5. REFERENCES

Ackerman, P. L., & Heggestad, E. D. (1997). Intelligence, personality, and interests: Evidence for overlapping traits. *Psychological bulletin*, *121*(2), 219–245.

Aggleton, J P, & Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *The Behavioral and brain sciences*, *22*(3), 425–44; discussion 444–89. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11301518

Aggleton, John P, Vann, S. D., Denby, C., Dix, S., Mayes, A. R., Roberts, N., & Yonelinas, A. P. (2005). Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology. *Neuropsychologia*, *43*(12), 1810–23. doi:10.1016/j.neuropsychologia.2005.01.019

Alttoa, A., Seeman, P., Kõiv, K., Eller, M., & Harro, J. (2009). Rats with persistently high exploratory activity have both higher extracellular dopamine levels and higher proportion of D(2) (High) receptors in the striatum. *Synapse*, *63*(5), 443–6. doi:10.1002/syn.20620

Alvarado, M. C., & Bachevalier, J. (2005). Comparison of the effects of damage to the perirhinal and parahippocampal cortex on transverse patterning and location memory in rhesus macaques. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *25*(6), 1599–609. doi:10.1523/JNEUROSCI.4457-04.2005

Amieva, H., Belliard, S., & Salmon, E. (2014). *Les démences. Aspects cliniques, neuropsychologiques,physiopatologiques et thérapeutiques.* (DE BOECK / SOLAL, Ed.).

Andersen, K., Lolk, A., Kragh-Sørensen, P., Petersen, N. E., & Green, A. (2005). Depression and the risk of Alzheimer disease. *Epidemiology (Cambridge, Mass.)*, *16*(2), 233–8.

Apostolova, L. G., & Cummings, J. L. (2008). Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. *Dementia and geriatric cognitive disorders*, *25*(2), 115–26. doi:10.1159/000112509

Apostolova, L. G., & Thompson, P. M. (2008). Mapping progressive brain structural changes in early Alzheimer's disease and mild cognitive impairment. *Neuropsychologia*, *46*(6), 1597–612. doi:10.1016/j.neuropsychologia.2007.10.026

Archer, N., Brown, R. G., Reeves, S. J., Boothby, H., Nicholas, H., Foy, C., … Lovestone, S. (2007). Premorbid personality and behavioral and psychological symptoms in probable Alzheimer disease. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*, *15*(3), 202–13. doi:10.1097/01.JGP.0000232510.77213.10

Ashburner, J, & Friston, K. (2003). Image segmentation. In *In: Frackowiak RSJ, Friston KJ, Frith C, Dolan R, Price CJ, Zeki S, Ashburner J, Penny WD (eds) Human Brain Function. 2nd edn. Academic Press*. Retrieved from http://www.fil.ion.ucl.ac.uk/spm/doc/books/hbf2/pdfs/Ch5.pdf

Ashburner, J, & Friston, K. J. (2000). Voxel-based morphometry--the methods. *NeuroImage*, *11*(6 Pt 1), 805–21. doi:10.1006/nimg.2000.0582

Ashburner, John. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. doi:10.1016/j.neuroimage.2007.07.007

Assal, F., & Alarcón, M. (2004). Association of the serotonin transporter and receptor gene polymorphisms in neuropsychiatric symptoms in Alzheimer disease. *Arch Neurol*, *61*(8), 1249–53. Retrieved from http://archopht.jamanetwork.com/article.aspx?articleid=786358

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: a proposed system and its control processes. *In K. W. Spence and J. T. Spence (Eds.), The psychology of learning and motivation: advances in research and theory (vol. 2, pp. 89–195). New York: Academic Press.*

Baddeley, R., Abbott, L. F., Booth, M. C., Sengpiel, F., Freeman, T., Wakeman, E. a, & Rolls, E. T. (1997). Responses of neurons in primary and inferior temporal visual cortices to natural scenes. *Proceedings. Biological sciences / The Royal Society*, *264*(1389), 1775–1783. doi:10.1098/rspb.1997.0246

Bakkour, A., Morris, J. C., & Dickerson, B. C. (2009). The cortical signature of prodromal AD: regional thinning predicts mild AD dementia. *Neurology*, *72*(12), 1048–55. doi:10.1212/01.wnl.0000340981.97664.2f

Balsis, S., Carpenter, B. D., & Storandt, M. (2005). Personality change precedes clinical diagnosis of dementia of the Alzheimer type. *The journals of gerontology. Series B, Psychological sciences and social sciences*, *60*(2), P98–P101.

Barbeau, E., Didic, M., Tramoni, E., Felician, O., Joubert, S., Sontheimer, a., … Poncet, M. (2004). Evaluation of visual recognition memory in MCI patients. *Neurology*, *62*(8), 1317–1322. doi:10.1212/01.WNL.0000120548.24298.DB

Barbeau, E., Didic, M., Tramoni, E., Felician, O., Joubert, S., & Sontheimer, A. (2011). Evaluation of visual recognition memory. *Neurology*. doi:10.1212/01.WNL.0000120548.24298.DB

Barbeau, E. J., Pariente, J., Felician, O., & Puel, M. (2010). Visual recognition memory: A double anatomo-functional dissociation. *Hippocampus*, *934*(November 2011), 929–934. doi:10.1002/hipo.20848

Barense, M. D., Henson, R. N. a, & Graham, K. S. (2011). Perception and conception: temporal lobe activity during complex discriminations of familiar and novel faces and objects. *Journal of cognitive neuroscience*, *23*(10), 3052–67. doi:10.1162/jocn_a_00010

Barnes, D. E., Alexopoulos, G. S., Lopez, O. L., Williamson, J. D., & Yaffe, K. (2006). Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. *Archives of general psychiatry*, *63*(3), 273–9. doi:10.1001/archpsyc.63.3.273

Barrouillet, P., Bernardin, S., & Camos, V. (2004). Time Constraints and Resource Sharing in Adults' Working Memory Spans. *Journal of Experimental Psychology: General*, *133*(1), 83–100.

Basser, P. J., & Jones, D. K. (2002). Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. *NMR in biomedicine*, *15*(7-8), 456–67. doi:10.1002/nbm.783

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in biomedicine*, *15*, 435–455. doi:10.1002/nbm.782

Beaumont, L., Fiocco, A. J., Quesnel, G., Lupien, S., & Poirier, J. (2013). Altered declarative memory in introverted middle-aged adults carrying the BDNF val66met allele. *Behavioural brain research*, *253*, 152–6. doi:10.1016/j.bbr.2013.07.002

Beaunieux, H., Eustache, F., Busson, P., de la Sayette, V., Viader, F., & Desgranges, B. (2012). Cognitive procedural learning in early Alzheimer's disease: impaired processes and compensatory mechanisms. *Journal of neuropsychology*, *6*(1), 31–42. doi:10.1111/j.1748-6653.2011.02002.x

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. (TX: Psychological Corporation., Ed.)*San Antonio, TX: Psychological Corporation.* San Antonio.

Behrens, T. E. J., Woolrich, M. W., Walton, M. E., & Rushworth, M. F. S. (2007). Learning the value of information in an uncertain world. *Nature neuroscience*, *10*(9), 1214–21. doi:10.1038/nn1954

Belleville, S., Fouquet, C., Duchesne, S., Collins, D. L., & Hudon, C. (2014). Detecting early preclinical Alzheimer's disease via cognition, neuropsychiatry, and neuroimaging: qualitative review and recommendations for testing. *Journal of Alzheimer's disease*, *42 Suppl 4*, S375–82. doi:10.3233/JAD-141470

Benjamin, J., Li, L., Patterson, C., Greenberg, B., Murphy, D., & Hamer, D. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature genetics*, *12*(1), 81–44.

Bienvenu, O. J., Samuels, J. F., Costa, P. T., Reti, I. M., Eaton, W. W., & Nestadt, G. (2004a). Anxiety and depressive disorders and the five-factor model of personality: a higher- and lower-order personality trait investigation in a community sample. *Depression and anxiety*, *20*(2), 92–7. doi:10.1002/da.20026

Bienvenu, O. J., Samuels, J. F., Costa, P. T., Reti, I. M., Eaton, W. W., & Nestadt, G. (2004b). Anxiety and depressive disorders and the five-factor model of personality: a higher- and lower-order personality trait investigation in a community sample. *Depression and anxiety*, *20*(2), 92–7. doi:10.1002/da.20026

Bonin-Guillaume, S., Zekry, D., Giacobini, E., Gold, G., & Michel, J.-P. (2005). [The economical impact of dementia]. *Presse médicale (Paris, France : 1983)*, *34*(1), 35–41. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15685097

Bonnici, H. M., Chadwick, M. J., Kumaran, D., Hassabis, D., Weiskopf, N., & Maguire, E. a. (2012). Multi-voxel pattern analysis in human hippocampal subfields. *Frontiers in human neuroscience*, *6*(October), 290. doi:10.3389/fnhum.2012.00290

Boring, E. (1953). A History Of Introspection. *Psychological bulletin*, *50*(3).

Bowles, B., Crupi, C., Mirsattari, S. M., Pigott, S. E., Parrent, A. G., Pruessner, J. C., … Köhler, S. (2007). Impaired familiarity with preserved recollection after anterior temporal-lobe resection that spares the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(41), 16382–7. doi:10.1073/pnas.0705273104

Boyle J Gregory, Matthews Gerald, S. H. D. (2008). *The SAGE Handbook of Personality Theory and Assessment: Personality Measurement and Testing, Volume 2 (Google eBook)* (p. 744). SAGE.

Braak, H, & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, *82*, 239 – 259.

Braak, Heiko, Alafuzoff, I., Arzberger, T., Kretzschmar, H., & Del Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta neuropathologica*, *112*(4), 389–404. doi:10.1007/s00401-006-0127-z

Bremner, J. D., Narayan, M., Anderson, E. R., Staib, L. H., Ph, D., Miller, H. L., … Haven, W. (2000). Hippocampal Volume Reduction in Major Depression. *Am J Psychiatry*, *157*(1), 115–117.

Brinkmann, K., Franzen, J., Rossier, C., & Gendolla, G. H. E. (2014). I don't care about others' approval: Dysphoric individuals show reduced effort mobilization for obtaining a social reward. *Motivation and Emotion*, *38*(6), 790–801. doi:10.1007/s11031-014-9437-y

Brittlebank, A. D., Scott, J., Williams, J. M., Ferrier, I. N., Scott, J. A. N., Mark, J., & Williams, G. (1993). Autobiographical memory in depression : state or trait marker ? Memory in Depression : State or Trait Marker ? *The British Journal of Psychiatry*, 118–121. doi:10.1192/bjp.162.1.118

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nature reviews. Neuroscience*, *2*(1), 51–61. doi:10.1038/35049064

Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological bulletin*, *117*(2), 285–305. doi:10.1037/0033-2909.117.2.285

Buschke H, Sliwinski MJ, Kulansky G, L. R. (1997). Diagnosis of early dementia by the Double Memory Test: Encoding specificity improves diagnostic sensitivity and specificity. *Neurology*, *48*, 989–997.

Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science (New York, N.Y.)*, *315*(5820), 1860–2. doi:10.1126/science.1138071

Canli, T. (2004). Functional brain mapping of extraversion and neuroticism: learning from individual differences in emotion processing.de. *Journal of personality*, *72*(6), 1105–32. doi:10.1111/j.1467-6494.2004.00292.x

Carr, V. a, Rissman, J., & Wagner, A. D. (2010). Imaging the human medial temporal lobe with high-resolution fMRI. *Neuron*, *65*(3), 298–308. doi:10.1016/j.neuron.2009.12.022

Chadwick, M. J., Bonnici, H. M., & Maguire, E. a. (2012). Decoding information in the human hippocampus: a user's guide. *Neuropsychologia*, *50*(13), 3107–21. doi:10.1016/j.neuropsychologia.2012.07.007

Chadwick, M. J., Hassabis, D., Weiskopf, N., & Maguire, E. a. (2010). Decoding individual episodic memory traces in the human hippocampus. *Current biology : CB*, *20*(6), 544–7. doi:10.1016/j.cub.2010.01.053

Chamorro-premuzic, T., & Furnham, A. (2006). Intellectual Competence and the Intelligent Personality : A Third Way in Differential Psychology. *Review of General Psychology*, *10*(3), 251–267. doi:10.1037/1089-2680.10.3.251

Chamorro-Premuzic, T., & Furnham, A. (2009). Mainly Openness: The relationship between the Big Five personality traits and learning approaches. *Learning and Individual Differences*, *19*(4), 524–529. doi:10.1016/j.lindif.2009.06.004

Channon, S. (1996). Executive dysfunction in depression: The Wisconsin Card Sorting Test. *Journal of Affective Disorders*, *39*(2), 107–114. doi:10.1016/0165-0327(96)00027-4

Chelazzi, L., Miller, E. K., Duncan, J., & Desimone, R. (1993). A neural basis for visual search in inferior temporal cortex. *Nature*, *363*(6427), 345–7. doi:10.1038/363345a0

Chételat, G., Landeau, B., Eustache, F., Mézenge, F., Viader, F., de la Sayette, V., … Baron, J.-C. (2005). Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. *NeuroImage*, *27*(4), 934–46.

Christopoulos GI, Tobler PN, Bossaerts P, Dolan RK, S. W. (2010). Neural correlates of value, risk and risk aversion contributing to decision making under risk. *Journal of Neurosciences*, *29*(40), 12574–12583. doi:10.1523/JNEUROSCI.2614-09.2009.NEURAL

Chung, J. A., & Cummings, J. L. (2000). Neurobehavioral and neuropsychiatric symptoms in Alzheimer's disease: characteristics and treatment. *Neurologic clinics*, *18*(4), 829–46. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11072263

Clark, L., Manes, F., Antoun, N., Sahakian, B. J., & Robbins, T. W. (2003). The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. *Neuropsychologia*, *41*(11), 1474–1483. doi:10.1016/S0028-3932(03)00081-2

Cloninger, C. R. (1986). A unified biosocial theory of personality and its role in the development of anxiety states. *Psychiatric developments*, *4*(3), 167–226. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3809156

Coggan, M., & Doina, P. (2004). *Exploration and Exploitation in Reinforcement Learning*. *CRA-W DMP Project at McGill University*. Retrieved from http://www.cra.org/Activities/craw_archive/dmp/awards/2004/Coggan/FinalReport.pdf

Cohen, L., Lehéricy, S., Chochon, F., Lemer, C., Rivaud, S., & Dehaene, S. (2002). Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. *Brain : a journal of neurology*, *125*(Pt 5), 1054–69. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11960895

Cohen, M., Young, J., Baek, J., Kessler, C., & Ranganath, C. (2005). Individual differences in extraversion and dopamine genetics predict neural reward responses. *Cognitive Brain Research*, *25*(3), 851–861.

Cohen, R., Ph, D., Lohr, I., Paul, R., & Boland, R. (2001). Impairments of Attention and Effort Among Patients With Major Affective Disorders. *Journal Of Neuropsychiatry*, 385–395.

Costa, P., & MacCrae, R. (1992). *Revised NEO Personality Inventory (NEO PI-R) and NEO Five-Factor Inventory (NEO FFI): Professional Manual*. Odessa, FL: Psychological Assessment Resources.

Costa, P., & Mccrae, R. R. (2004). Questionnaire de Personnalité NEO-FFI-R. *Personality and Individual Differences*, *36*, 587–596.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: a framework for memory research. *J. Verb. Learn. and Verb. Behav.*, *11*, 671–84.

Cromer, J. A., Roy, J. E., & Miller, E. K. (2011). Representation of Multiple, Independent Categories in the Primate Prefrontal Cortex. *Neuron*, *66*(5), 796–807. doi:10.1016/j.neuron.2010.05.005.Representation

Crum, R. M. (1993). Population-Based Norms for the Mini-Mental State Examination by Age and Educational Level. *JAMA: The Journal of the American Medical Association*, *269*(18), 2386. doi:10.1001/jama.1993.03500180078038

Da Costa, S., van der Zwaag, W., Marques, J. P., Frackowiak, R. S. J., Clarke, S., & Saenz, M. (2011). Human primary auditory cortex follows the shape of Heschl's gyrus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *31*(40), 14067–75. doi:10.1523/JNEUROSCI.2000-11.2011

Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *Journal of neurophysiology*, *96*(4), 1902–11. doi:10.1152/jn.01029.2005

Davachi, L., Mitchell, J. P., & Wagner, A. D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(4), 2157–62. doi:10.1073/pnas.0337195100

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002a). D EPRESSION : Perspectives from Affective Neuroscience. *Imaging*.

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002b). D EPRESSION : Perspectives from Affective Neuroscience. *Imaging*.

Davies, R. R., Graham, K. S., Xuereb, J. H., Williams, G. B., & Hodges, J. R. (2004). The human perirhinal cortex and semantic memory. *The European journal of neuroscience*, *20*(9), 2441–6. doi:10.1111/j.1460-9568.2004.03710.x

Daw, N. D. (2009). Trial-by-trial data analysis using computational models, 1–26.

Defrancesco, M., Marksteiner, J., Eberhard, Deisenhammer Georg, K., Djurdjevic, T., & Michael, S. (2013). Impact of White Matter Lesions and Cognitive Deficits on Conversion from Mild Cognitive Impairment to Alzheimer's Disease - Journal of Alzheimer's Disease - Volume 34, Number 3 / 2013 - IOS Press. *Journal of Alzheimer's disease*, *34*(3), 665–672. Retrieved from http://iospress.metapress.com/content/c85818477t2p24n7/

Delgado, M. R., Miller, M. M., Inati, S., & Phelps, E. a. (2005). An fMRI study of reward-related probability learning. *NeuroImage*, *24*(3), 862–73. doi:10.1016/j.neuroimage.2004.10.002

Deng, W., Aimone, J. B., & Gage, F. H. (2010). New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nature reviews. Neuroscience*, *11*(5), 339–50. doi:10.1038/nrn2822

Depue, R. a, & Collins, P. F. (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *The Behavioral and brain sciences*, *22*(3), 491–517; discussion 518–69. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11301519

Deyoung, C. G., Hirsh, J. B., Shane, M. S., & Papademetris, X. (2010). Testing Predictions From Personality Neuroscience: Brain Structure and the Big Five. *Psychol Sci.*, *21*(6), 820–828.

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends in cognitive sciences*, *11*(9), 379–86. doi:10.1016/j.tics.2007.08.001

Dickerson, B. C., Bakkour, A., Salat, D. H., Feczko, E., Pacheco, J., Greve, D. N., … Buckner, R. L. (2009). The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cerebral cortex (New York, N.Y. : 1991)*, *19*(3), 497–510. doi:10.1093/cercor/bhn113

Dickerson, K. C., Li, J., & Delgado, M. R. (2011). Parallel contributions of distinct human memory systems during probabilistic learning. *NeuroImage*, *55*(1), 266–76. doi:10.1016/j.neuroimage.2010.10.080

Doherty, J. P. O., Dayan, P., Friston, K., Critchley, H., & Dolan, R. J. (2003). Temporal Difference Models and Reward-Related Learning in the Human Brain. *Neuron*, *28*, 329–337.

Donati, A., Studer, J., Petrillo, S., Pocnet, C., Popp, J., Rossier, J., & von Gunten, A. (2013). The Evolution of Personality in Patients with Mild Cognitive Impairment. *Dementia and geriatric cognitive disorders*, *36*(5-6), 329–339. doi:10.1159/000353895

Draganski, B., Ashburner, J., Hutton, C., Kherif, F., Frackowiak, R. S. J., Helms, G., & Weiskopf, N. (2011). Regional specificity of MRI contrast parameter changes in normal ageing revealed by voxel-based quantification (VBQ). *NeuroImage*, *55*(4), 1423–34. doi:10.1016/j.neuroimage.2011.01.052

Druzgal, T. J., & D'Esposito, M. (2003). Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. *Journal of cognitive neuroscience*, *15*(6), 771–84. doi:10.1162/089892903322370708

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., Dekosky, S. T., Barberger-Gateau, P., … Scheltens, P. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *Lancet neurology*, *9*(11), 1118–27. doi:10.1016/S1474-4422(10)70223-4

Duchek, J. M., Balota, D. A., Storandt, M., & Larsen, R. (2007). The Power of Personality in Discriminating Between Healthy Aging and Early-Stage Alzheimer ' s Disease. *Journal of Gerontology*, *62B*(6), 353–361.

Duff, M. C., Hengst, J., Tranel, D., & Cohen, N. J. (2005a). Development of shared information in communication despite hippocampal amnesia. *Nature reviews. Neuroscience*, *9*(1), 140–146. doi:10.1038/nn1601

Duff, M. C., Hengst, J., Tranel, D., & Cohen, N. J. (2005b). Development of shared information in communication despite hippocampal amnesia. *Nature reviews. Neuroscience*, *9*(1), 140–146. doi:10.1038/nn1601

Duron, E., Vidal, J.-S., Bounatiro, S., Ben Ahmed, S., Seux, M.-L., Rigaud, A.-S., … Martel, G. (2014). Relationships between Personality Traits, Medial Temporal Lobe Atrophy, and White Matter Lesion in Subjects Suffering from Mild Cognitive Impairment. *Frontiers in Aging Neuroscience*, *6*(July), 1–9. doi:10.3389/fnagi.2014.00195

Egger, K., Schocke, M., Weiss, E., Auffinger, S., Esterhammer, R., Goebel, G., … Marksteiner, J. (2008). Pattern of brain atrophy in elderly patients with depression revealed by voxel-based morphometry. *Psychiatry research*, *164*(3), 237–44. doi:10.1016/j.pscychresns.2007.12.018

Eichenbaum H. Yonelinas A.R., R. C. (2007). The Medial Temporal Lobe and Recognition Memory. *Annu Rev Neurosci.*, *30*, 123–152.

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, *25*(4), 1325–35. doi:10.1016/j.neuroimage.2004.12.034

Eustache, F., & Desgranges, B. (2008). MNESIS: towards the integration of current multisystem models of memory. *Neuropsychology review*, *18*(1), 53–69. doi:10.1007/s11065-008-9052-3

Evensmoen, H. R., Lehn, H., Xu, J., Witter, M. P., Nadel, L., & Håberg, A. K. (2013). The Anterior Hippocampus Supports a Coarse , Global Environmental Representation and the Posterior Hippocampus Supports Fine-grained , Local Environmental Representations. *Journal of Cognitive Neuroscience*, *25*(11), 1908–1925. doi:10.1162/jocn

Eysenck HJ. (1967). The biological basis of personality. *Springfield, IL: Thomas.*

Fanselow, M. S., & Hong-Wei, D. (2010). Are The Dorsal and Ventral Hippocampus functionally distinct structures? *Neuron*, *65*(1), 1–25. doi:10.1016/j.neuron.2009.11.031.Are

Fellgiebel, A., Wille, P., Müller, M. J., Winterer, G., Scheurich, A., Vucurevic, G., … Stoeter, P. (2004). Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. *Dementia and geriatric cognitive disorders*, *18*(1), 101–8. doi:10.1159/000077817

Fellgiebel, A., & Yakushev, I. (2011). Diffusion tensor imaging of the hippocampus in MCI and early Alzheimer's disease. *Journal of Alzheimer's disease : JAD*, *26 Suppl 3*, 257–62. doi:10.3233/JAD-2011-0001

Fischl, B., Sereno, M. I., Tootell, R. B., & Dale, A. M. (1999). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum. Brain Mapp.*, *8*(4), 272–284.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S., & Dolan, R. J. (1998). The functional roles of prefrontal cortex in episodic memory. II. Retrieval. *Brain : a journal of neurology*, *121 (Pt 7*, 1249–56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9679777

Fodor, J. A. (1983). THE MODULARITY OF MIND, *Cambridge,*.

Foerde, K., Knowlton, B. J., & Poldrack, R. a. (2006). Modulation of competing memory systems by distraction. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(31), 11778–83. doi:10.1073/pnas.0602659103

Foerde, K., Race, E., Verfaellie, M., & Shohamy, D. (2013). A role for the medial temporal lobe in feedback-driven learning: evidence from amnesia. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *33*(13), 5698–704. doi:10.1523/JNEUROSCI.5217-12.2013

Folstein, M. F. (1983). The Mini-Mental State Examination. *Archives of General Psychiatry*, *40*(7), 812. doi:10.1001/archpsyc.1983.01790060110016

Forbes, E. E., Brown, S. M., Kimak, M., Ferrell, R. E., Manuck, S. B., & Hariri, a R. (2009). Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Molecular psychiatry*, *14*(1), 60–70. doi:10.1038/sj.mp.4002086

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature reviews. Neuroscience*, *6*(2), 119–30. doi:10.1038/nrn1607

Freedman, D. J., Riesenhuber, M., Poggio, T., & Miller, E. K. (2003). A comparison of primate prefrontal and inferior temporal cortices during visual categorization. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *23*(12), 5235–46. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12832548

Frisoni, G. B., Fox, N. C., Jack, C. R., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature reviews. Neurology*, *6*(2), 67–77. doi:10.1038/nrneurol.2009.215

Friston, K J, Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage*, *229*(6), 218–229.

Friston, K J, Harrison, L., & Penny, W. (2003). Dynamic causal modelling. *NeuroImage*, *0*. doi:10.1016/S1053-8119(03)00202-7

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nature reviews. Neuroscience*, *11*(2), 127–38. doi:10.1038/nrn2787

Friston, K., Chu, C., Mourão-Miranda, J., Hulme, O., Rees, G., Penny, W., & Ashburner, J. (2008). Bayesian decoding of brain images. *NeuroImage*, *39*(1), 181–205. doi:10.1016/j.neuroimage.2007.08.013

Friston, K., & Kiebel, S. (2009). Predictive coding under the free-energy principle. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *364*(1521), 1211–21. doi:10.1098/rstb.2008.0300

Friston, Karl J, & Stephan, K. E. (2007). Free-energy and the brain. *Synthese*, *159*(3), 417–458. doi:10.1007/s11229-007-9237-y

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-P., Frith, C.D., Frackowiack, R. S. J. (1995). Statistical Parametric Maps in Functional Imaging: A General Linear Approach. *Human brain mapping*, *2*, 189–210.

Frodl, T., Meisenzahl, E. M., Zetzsche, T., Born, C., Groll, C., Jäger, M., … Möller, H. (2002). Hippocampal Changes in Patients With a First Episode of Major Depression. *Am J Psychiatry*, *159*(July), 1112–1118.

Gagnepain, P., Henson, R., Chételat, G., Desgranges, B., Lebreton, K., & Eustache, F. (2011). Is neocortical-hippocampal connectivity a better predictor of subsequent recollection than local increases in

hippocampal activity? New insights on the role of priming. *Journal of cognitive neuroscience*, *23*(2000), 391–403. doi:10.1162/jocn.2010.21454

Ganguli, M., Ratcliff, G., Huff, F., Belle, S., Kancel, M., Fischer, L., … Kuller, L. H. (1991). Effects of Age, Gender, and Education on Cognitive Tests in a Rural Elderly Community Sample: Norms from the Monongahela Valley Independent Elders Survey. *Neuroepidemiology*, *10*(1), 42–52. doi:10.1159/10.1159/000110246

Gardiner, J.M. (1988). Functional aspects of recollective experience. *Memory & Cognition*, *16*(4), 309–313.

Gardiner, John M, Brandt, K. R., Vargha-Khadem, F., Baddeley, A., & Mishkin, M. (2006). Effects of level of processing but not of task enactment on recognition memory in a case of developmental amnesia. *Cognitive neuropsychology*, *23*(6), 930–48. doi:10.1080/02643290600588442

Garnefski, N., & Kraaij, V. (2006). Relationships between cognitive emotion regulation strategies and depressive symptoms : A comparative study of five specific samples. *Personality and Individual Differences*, *40*, 1659–1669. doi:10.1016/j.paid.2005.12.009

Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J. C. (1999). Activation of the middle fusiform " face area " increases with expertise in recognizing novel objects. *Nature neuroscience*, *2*(6).

Geda. (2006). Depression, Apolipoprotein E Genotype, and the Incidence of Mild Cognitive Impairment. *Primary Care*, *63*.

Gerlach, C., Aaside, C. ., Humphreys, G. ., Gade, A., Paulson, O. ., & Law, I. (2002). Brain activity related to integrative processes in visual object recognition: bottom-up integration and the modulatory influence of stored knowledge. *Neuropsychologia*, *40*(8), 1254–1267. Retrieved from http://www.sciencedirect.com/science/article/pii/S0028393201002226

Gianaros, P. J., Jennings, J. R., Sheu, L. K., Greer, P. J., Kuller, L. H., & Matthews, K. a. (2007). Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. *NeuroImage*, *35*(2), 795–803. doi:10.1016/j.neuroimage.2006.10.045

Gignac, G. (2004). Openness, intelligence, and self-report intelligence. *Intelligence*, *32*(2), 133–143. doi:10.1016/j.intell.2003.10.005

Gilbert, C. D., & Li, W. (2013). Top-down influences on visual processing. *Nature reviews. Neuroscience*, *14*(5), 350–63. doi:10.1038/nrn3476

Gillespie, N. a, Cloninger, C. R., Heath, A. C., & Martin, N. G. (2003). The genetic and environmental relationship between Cloninger's dimensions of temperament and character. *Personality and Individual Differences*, *35*(8), 1931–1946. doi:10.1016/S0191-8869(03)00042-4

Gläscher, J., & Büchel, C. (2005). Formal learning theory dissociates brain regions with different temporal integration. *Neuron*, *47*(2), 295–306. doi:10.1016/j.neuron.2005.06.008

Gluck, M. a, Myers, C., & Meeter, M. (2005). Cortico-hippocampal interaction and adaptive stimulus representation: a neurocomputational theory of associative learning and memory. *Neural networks : the official journal of the International Neural Network Society*, *18*(9), 1265–79. doi:10.1016/j.neunet.2005.08.003

Gluck, M. a, Shohamy, D., & Myers, C. (2002). How do people solve the "weather prediction" task?: individual variability in strategies for probabilistic category learning. *Learning & memory (Cold Spring Harbor, N.Y.)*, *9*(6), 408–18. doi:10.1101/lm.45202

Gluck, M. A., & Myers, C. E. (2008). *Learning and Memory: From Brain to Behavior* (Worth Publ.). New York.

Golarai, G., Ghahremani, D. G., Whitfield-Gabrieli, S., Reiss, A., Eberhardt, J. L., Gabrieli, J. D. E., & Grill-Spector, K. (2007). Differential development of high-level visual cortex correlates with category-specific recognition memory. *Nature neuroscience*, *10*(4), 512–22. doi:10.1038/nn1865

Goldberg, L. R. (1990). An alternative "description of personality": the big-five factor structure. *Journal of personality and social psychology*, *59*(6), 1216–29.

Goldberg, L. R., & Rosolack, T. K. (1994). The Big Fiv Factor Structure as an integrative framework: an empirical comparison with Eysenck's P-E-N Model.

Graham, K. S., Simons, J. S., Pratt, K. H., Patterson, K., & Hodges, J. R. (2000). Insights from semantic dementia on the relationship between episodic and semantic memory. *Neuropsychologia.*, *38*(313-24), 313–324.

Gray, J. A. (1970). The psychophysiological basis of introversion-extraversion. *Behaviour Research and Therapy*, *8*(3), 249–266. Retrieved from http://www.sciencedirect.com/science/article/pii/0005796770900690

Grön, G., Bittner, D., Schmitz, B., Gro, G., Wunderlich, A. P., Tomczak, R., & Riepe, M. W. (2001). Hippocampal Activations during Repetitive Learning and Recall of Geometric Patterns Hippocampal Activations during Repetitive Learning and Recall of Geometric Patterns. *Learn. Mem.*, *8*, 336–345. doi:10.1101/lm.42901

Gross, C., & Hen, R. (2004). The developmental origins of anxiety. *Nature reviews. Neuroscience*, *5*(7), 545–52. doi:10.1038/nrn1429

Habeck, C., & Stern, Y. (2010). Multivariate data analysis for neuroimaging data: overview and application to Alzheimer's disease. *Cell Biochem Biophys*, *58*(2), 53–67. doi:10.1007/s12013-010-9093-0.Multivariate

Hämäläinen, A., Tervo, S., Grau-Olivares, M., Niskanen, E., Pennanen, C., Huuskonen, J., … Soininen, H. (2007). Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. *NeuroImage*, *37*(4), 1122–31. doi:10.1016/j.neuroimage.2007.06.016

Hammar, A., Strand, M., Ardal, G., Schmid, M., Lund, A., & Elliott, R. (2011). Testing the cognitive effort hypothesis of cognitive impairment in major depression. *Nordic journal of psychiatry*, *65*(1), 74–80. doi:10.3109/08039488.2010.494311

Hampson, S., & Goldberg, L. R. (2006). A First Large-Cohort Study of Personality-Trait Stability Over the 40 Years Between Elementary School and Midlife. In *J Pers Soc Psychol.* (Vol. 91, pp. 763–779).

Hasselmo, M. E. (2005). The role of hippocampal regions CA3 and CA1 in matching entorhinal input with retrieval of associations between objects and context: theoretical comment on Lee et al. (2005). *Behavioral neuroscience*, *119*(1), 342–5. doi:10.1037/0735-7044.119.1.342

Hebert, L. E., Scherr, P. A., Bienias, J. L., Bennett, D. A., & Evans, D. A. (2003). Alzheimer Disease in the US Population. *JAMA Neurology*, *60*.

Henke, K. (2010). A model for memory systems based on processing modes rather than consciousness. *Nature reviews. Neuroscience*, *11*(7), 523–32. doi:10.1038/nrn2850

Henseler, I., Krüger, S., Dechent, P., & Gruber, O. (2011). A gateway system in rostral PFC? Evidence from biasing attention to perceptual information and internal representations. *NeuroImage*, *56*(3), 1666–76. doi:10.1016/j.neuroimage.2011.02.056

Henson, R N, Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *19*(10), 3962–72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10234026

Henson, R N, Shallice, T., & Dolan, R. J. (1999). Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. *Brain*, *122*, 1367–81.

Henson, R N, Shallice, T., Gorno-Tempini, M. L., & Dolan, R. J. (2002). Face Repetition Effects in Implicit and Explicit Memory Tests as Measured by fMRI. *Cerebral Cortex*, *12*, 178–186.

Henson, R. (2005a). What can functional neuroimaging tell the experimental psychologist? *The Quarterly journal of experimental psychology. A, Human experimental psychology*, *58*(2), 193–233. doi:10.1080/02724980443000502

Henson, R. (2005b). A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. *The Quarterly journal of experimental psychology. B, Comparative and physiological psychology*, *58*(3-4), 340–60. doi:10.1080/02724990444000113

Henson, Richard N, & Gagnepain, P. (2010). Predictive, interactive multiple memory systems. *Hippocampus*, *20*(11), 1315–26. doi:10.1002/hipo.20857

Holdstock, J. S., Hocking, J., Notley, P., Devlin, J. T., & Price, C. J. (2009). Integrating visual and tactile information in the perirhinal cortex. *Cerebral cortex (New York, N.Y. : 1991)*, *19*(12), 2993–3000. doi:10.1093/cercor/bhp073

Holroyd, C. B., Nieuwenhuis, S., Yeung, N., & Cohen, J. D. (2003). Errors in reward prediction are reflected in the event-related brain potential. *Neuroreport*, *14*(18), 2481–4. doi:10.1097/01.wnr.0000099601.41403.a5

Hopkins, R. (2004). Impaired probabilistic category learning in hypoxic subjects with hippocampal damage. *Neuropsychologia*, *42*(4), 524–535. doi:10.1016/j.neuropsychologia.2003.09.005

Huettel, S. A., Song, A. W., & Mccarthy, G. (2005). Decisions under Uncertainty : Probabilistic Context Influences Activation of Prefrontal and Parietal Cortices, *25*(13), 3304–3311. doi:10.1523/JNEUROSCI.5070-04.2005

Hulme, O. J., Skov, M., Chadwick, M., Siebner, H. R., & Ramsøy, T. Z. (2014). Sparse Encoding of Automatic Visual Association in Hippocampal Networks. *NeuroImage*. doi:10.1016/j.neuroimage.2014.07.020

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., … Montine, T. J. (2012a). National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, *8*(1), 1–13. doi:10.1016/j.jalz.2011.10.007

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., … Montine, T. J. (2012b). National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, *8*(1), 1–13. doi:10.1016/j.jalz.2011.10.007

Insausti, R., Juottonen, K., Soininen, H., Insausti, A. M., Partanen, K., Vainio, P., … Pitka, A. (1998). MR Volumetric Analysis of the Human Entorhinal , Perirhinal , and Temporopolar Cortices. *Am J Neuroradiol*, *19*, 659–671.

Jack, C. R., Bernstein, M. a., Fox, N. C., Thompson, P., Alexander, G., Harvey, D., … Weiner, M. W. (2008). The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *Journal of Magnetic Resonance Imaging*, *27*(4), 685–691. doi:10.1002/jmri.21049

Jack, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., … Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *The Lancet Neurology*, *12*(2), 207–216. doi:10.1016/S1474-4422(12)70291-0

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*(2), 782–90. doi:10.1016/j.neuroimage.2011.09.015

Jiang, Y., King, L., Shim, W. M., & Vickery, T. J. (2006). Visual implicit learning overcomes limits in human attention. *Paper presented at the Proceedings in 25th Army Science Conference*.

Johansson, L., Guo, X., Hällström, T., Norton, M. C., Waern, M., Ostling, S., … Skoog, I. (2013). Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: a 38-year longitudinal population study. *BMJ open*, *3*(9), e003142. doi:10.1136/bmjopen-2013-003142

Johnson, K. a, Fox, N. C., Sperling, R. a, & Klunk, W. E. (2012). Brain imaging in Alzheimer disease. *Cold Spring Harbor perspectives in medicine*, *2*(4), a006213. doi:10.1101/cshperspect.a006213

Jonathan Benjamin, Lin Li, Chavis Patterson, Benjamin D. Greenberg, Dennis L. Murphy, D. H. H. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature genetics*, *12*.

Jones, B., Fitzpatrick, A. L., Breitner, J., & Dekosky, S. (2012). Prevalence of Neuropsychiatric Symptoms Results From the Cardiovascular Health Study. *American Medical Association*, *288*(12), 1475–1483.

Jönsson, E. G., Burgert, E., Crocq, M.-A., Gustavsson, J. P., Forslund, K., Mattila-Evenden, M., … Bergman, H. (2003). Association study between dopamine D3 receptor gene variant and personality traits. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*, *117B*(1), 61–5. doi:10.1002/ajmg.b.10009

Joshi, A. A., Joshi, S. H., Dinov, I., Shattuck, D. W., Leahy, R. M., & Toga, A. W. (2010). Anatomical structural network analysis of human brain using partial correlations of gray matter volumes. In *2010 IEEE International Symposium on Biomedical Imaging: From Nano to Macro* (pp. 844–847). IEEE. doi:10.1109/ISBI.2010.5490118

Kafkas, A., & Montaldi, D. (2011). Recognition memory strength is predicted by pupillary responses at encoding while fixation patterns distinguish recollection from familiarity. *Quarterly journal of experimental psychology (2006)*, *64*(10), 1971–89. doi:10.1080/17470218.2011.588335

Kafkas, A., & Montaldi, D. (2012). Familiarity and recollection produce distinct eye movement, pupil and medial temporal lobe responses when memory strength is matched. *Neuropsychologia*, *50*(13), 3080–93. doi:10.1016/j.neuropsychologia.2012.08.001

Kahn, I., Andrews-hanna, J. R., Vincent, J. L., Snyder, A. Z., & Buckner, R. L. (2008). Distinct Cortical Anatomy Linked to Subregions of the Medial Temporal Lobe Revealed by Intrinsic Functional Connectivity, *100*(1), 129–139. doi:10.1152/jn.00077.2008.

Kalenzaga, S., & Clarys, D. (2013). Self-referential processing in Alzheimer's disease: two different ways of processing self-knowledge? *Journal of clinical and experimental neuropsychology*, *35*(April 2015), 455–71. doi:10.1080/13803395.2013.789485

Kantarci, K., Petersen, R. C., Boeve, B. F., David, S., Weigand, S. D., Brien, P. C. O., … Jr, C. R. J. (2005). DWI predicts future progression to Alzheimer's disease in amnestic mild cognitive impairement. *Neurology*, *64*(5), 902–904. doi:10.1212/01.WNL.0000153076.46126.E9.DWI

Kaufman, J., & Charney, D. (2000). Comorbidity of mood and anxiety disorders. *Depression and anxiety*, *12 Suppl 1*, 69–76. doi:10.1002/1520-6394(2000)12:1+<69::AID-DA9>3.0.CO;2-K

Kawasaki, Y., Suzuki, M., Kherif, F., Takahashi, T., Zhou, S.-Y., Nakamura, K., … Kurachi, M. (2007). Multivariate voxel-based morphometry successfully differentiates schizophrenia patients from healthy controls. *NeuroImage*, *34*(1), 235–42. doi:10.1016/j.neuroimage.2006.08.018

Keane, M. M., Gabrieli, J. D., Fennema, a. C., & Growdon, J. H. (1991). Evidence for a dissociation between perceptual and conceptual priming in Alzheimer's disease. *Behavioral Neuroscience*, *105*(2), 326–342. doi:10.1037/0735-7044.105.2.326

Kelley, H., & Friedman, D. (2002). Learning To Forecast Price. *Economic Inquiry*, *40*(4), 556–573. doi:10.1093/ei/40.4.556

Kendler, K. S. (1993). A Longitudinal Twin Study of Personality and Major Depression in Women. *Archives of General Psychiatry*, *50*(11), 853. doi:10.1001/archpsyc.1993.01820230023002

Kherif, F., Josse, G., & Price, C. J. (2011). Automatic top-down processing explains common left occipito-temporal responses to visual words and objects. *Cerebral cortex*, *21*(1), 103–14. doi:10.1093/cercor/bhq063

Kherif, F., Poline, J., Flandin, G., Benali, H., Simon, O., Dehaene, S., & Worsley, K. J. (2002). Multivariate Model Specification for fMRI Data. *NeuroImage*, *16*, 1068 –1083. doi:10.1006/nimg.2002.1094

Kirchhoff, B. A., Wagner, A. D., Maril, A., & Stern, C. E. (2000). Prefrontal – Temporal Circuitry for Episodic Encoding and Subsequent Memory. *The Journal of neuroscience*, *20*(16), 6173–6180.

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of experimental psychology*, *55*(4), 352–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/13539317

Klaas Enno, S., Kasper, L., Harrison, L. M., Daunizeau, J., den Ouden, H. E. M., Breakspear, M., & Friston, K. J. (2008). Nonlinear dynamic causal models for fMRI. *NeuroImage*, *42*(2), 649–62. doi:10.1016/j.neuroimage.2008.04.262

Knowlton, B. J., Squire, L. R., & Gluck, M. A. (1994). Probabilistic Classification Learning in Amnesia. *Learning & memory*, *1*, 106–120. doi:10.1101/lm.1.2.106

Köhler, S., Crane, J., & Milner, B. (2002). Differential Contributions of the parahippocampal place area the anterior hippocampus to human memory for scenes. *Hippocampus*, *12*(6), 718–723. doi:10.1002/hipo.10077

Kourtzi, Z., Betts, L. R., Sarkheil, P., & Welchman, A. E. (2005). Distributed neural plasticity for shape learning in the human visual cortex. *PLoS biology*, *3*(7), e204. doi:10.1371/journal.pbio.0030204

Koutstaal, W., Wagner, a D., Rotte, M., Maril, a, Buckner, R. L., & Schacter, D. L. (2001). Perceptual specificity in visual object priming: functional magnetic resonance imaging evidence for a laterality difference in fusiform cortex. *Neuropsychologia*, *39*(2), 184–99. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11163375

Krueger, R. F., Hicks, B. M., Patrick, C. J., Carlson, S. R., Iacono, W. G., & McGue, M. (2002). Personality, Alzheimer's disease and behavioural and cognitive symptoms of dementia: the PACO prospective cohort study protocol. *Journal of Abnormal Psychology*, *111*(3).

Kumaran, D., Summerfield, J. J., Hassabis, D., & Maguire, E. a. (2009). Tracking the emergence of conceptual knowledge during human decision making. *Neuron*, *63*(6), 889–901. doi:10.1016/j.neuron.2009.07.030

Kumari, V., Ffytche, D. H., Williams, S. C. R., & Gray, J. a. (2004). Personality predicts brain responses to cognitive demands. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *24*(47), 10636–41. doi:10.1523/JNEUROSCI.3206-04.2004

Kuzma, E., Sattler, C., Toro, P., Schönknecht, P., & Schröder, J. (2011a). Premorbid personality traits and their course in mild cognitive impairment: results from a prospective population-based study in Germany. *Dementia and geriatric cognitive disorders*, *32*(3), 171–7. doi:10.1159/000332082

Kuzma, E., Sattler, C., Toro, P., Schönknecht, P., & Schröder, J. (2011b). Premorbid personality traits and their course in mild cognitive impairment: results from a prospective population-based study in Germany. *Dementia and geriatric cognitive disorders*, *32*(3), 171–7. doi:10.1159/000332082

Lagnado, D. A., Newell, B. R., Kahan, S., & Shanks, D. R. (2006). Insight and strategy in multiple cue learning. *Journal of Experimental Psychology: General*, *135*, 162–183.

Lagnado, David A, & Newell, B. R. (2006a). Insight and strategy in multicue learning, (0).

Lagnado, David A, & Newell, B. R. (2006b). Insight and strategy in multicue learning, (0).

Lahey, B. B. (2009). Public Health Significance of Neuroticism. *Am Psychol.*, *64*(4), 241–256. doi:10.1037/a0015309.Public

Lebedeva, A., Westman, E., Lebedev, A. V, Li, X., Winblad, B., Simmons, A., … Aarsland, D. (2014). Structural brain changes associated with depressive symptoms in the elderly with Alzheimer's disease. *Journal of neurology, neurosurgery, and psychiatry*, *85*, 930–5. doi:10.1136/jnnp-2013-307110

Lee, G. J., Lu, P. H., Hua, X., Lee, S., Wu, S., Nguyen, K., … Thompson, P. M. (2011). Depressive Symptoms in Mild Cognitive Impairment Predict Greater Atrophy in Alzheimer ' s Disease- Related Regions. *Biological Psychiatry*. doi:10.1016/j.biopsych.2011.12.024

Lesch, K., Bengel, D., A, H., Sabol, S., Greenberg, B., Petri, S., … Murphy, D. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, *274*.

Lesch, K.-P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., … Murphy, D. L. (1996). Association of Anxiety-Related Traits with a Polymorphism in the Serotonin Transporter Gene Regulatory Region. *Science*, *274*(5292), 1527–1531. doi:10.1126/science.274.5292.1527

Lighthall, N. R., Gorlick, M. a, Schoeke, A., Frank, M. J., & Mather, M. (2013). Stress modulates reinforcement learning in younger and older adults. *Psychology and aging*, *28*(1), 35–46. doi:10.1037/a0029823

Lisman, J. E., & Grace, A. a. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*, *46*(5), 703–13. doi:10.1016/j.neuron.2005.05.002

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. a., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: A meta-analysis. *Behaviour Research and Therapy*, *43*(11), 1391–1424. doi:10.1016/j.brat.2004.10.007

Loehlin, J. C., McCrae, R. R., Costa, P. T., & John, O. P. (1998). Heritabilities of Common and Measure-Specific Components of the Big Five Personality Factors. *Journal of Research in Personality*, *32*(4), 431–453. doi:10.1006/jrpe.1998.2225

Logothetis NK, Pauls J., P. T. (1995). Shape representation in the inferior temporal cortex of monkeys. *Curr Biol*, *5*(5), 552–563.

Lucassen, P. J., Pruessner, J., Sousa, N., Almeida, O. F. X., Van Dam, A. M., Rajkowska, G., … Czéh, B. (2013). Neuropathology of stress. *Acta neuropathologica*, *127*(1), 109–35. doi:10.1007/s00401-013-1223-5

Mabbott, D. J., Rovet, J., Noseworthy, M. D., Smith, M. Lou, & Rockel, C. (2009). The relations between white matter and declarative memory in older children and adolescents. *Brain research*, *1294*, 80–90. doi:10.1016/j.brainres.2009.07.046

Madsen, K. S., Jernigan, T. L., Iversen, P., Frokjaer, V. G., Knudsen, G. M., Siebner, H. R., & Baaré, W. F. C. (2012). Hypothalamic-pituitary-adrenal axis tonus is associated with hippocampal microstructural asymmetry. *NeuroImage*, *63*(1), 95–103. doi:10.1016/j.neuroimage.2012.06.071

Marques, J. P., Kober, T., Krueger, G., van der Zwaag, W., Van de Moortele, P.-F., & Gruetter, R. (2010). MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. *NeuroImage*, *49*(2), 1271–81. doi:10.1016/j.neuroimage.2009.10.002

Matthias, J. M., Greverus, D., Weibrich, C., Roberto, P., Scheurich, A., Stoeter, P., & Fellgiebel, A. (2007). Diagnostic utility of hippocampal size and mean diffusivity in amnestic MCI. *Neurobiology of aging*, *28*(3), 398–403. doi:10.1016/j.neurobiolaging.2006.01.009

Matton, N. (2013). External validity of individual differences in multiple cue probability learning : The case of pilot training. *Judgment and Decision Making*, *8*(5), 589–602.

Mayes, A., Montaldi, D., & Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends in cognitive sciences*, *11*(3), 126–35. doi:10.1016/j.tics.2006.12.003

Mayeux, R., & Stern, Y. (2012). Epidemiology of Alzheimer disease. *Cold Spring Harbor perspectives in medicine*, *2*(8). doi:10.1101/cshperspect.a006239

Mazziotta, J., Toga, a, Evans, a, Fox, P., Lancaster, J., Zilles, K., … Mazoyer, B. (2001). A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *356*(1412), 1293–322. doi:10.1098/rstb.2001.0915

McClelland, J., McNaughton, B., Bruce, L., & O'Reilly, R. C. (1994). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, *102*(3), 419–457.

McCrae, R. R. (1994). Openness to Experience: Expanding the boundaries of Factor V. *European Journal of Personality*, *8*(4), 251–272. doi:10.1002/per.2410080404

McEwen, B S. (2000). The neurobiology of stress: from serendipity to clinical relevance. *Brain research*, *886*(1-2), 172–189.

McEwen, Bruce S. (2005a). Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism: clinical and experimental*, *54*(5 Suppl 1), 20–3. doi:10.1016/j.metabol.2005.01.008

McEwen, Bruce S. (2005b). Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism: clinical and experimental*, *54*(5 Suppl 1), 20–3. doi:10.1016/j.metabol.2005.01.008

McLelland, V. C., Chan, D., Ferber, S., & Barense, M. D. (2014). Stimulus familiarity modulates functional connectivity of the perirhinal cortex and anterior hippocampus during visual discrimination of faces and objects. *Frontiers in human neuroscience*, *8*(March), 117. doi:10.3389/fnhum.2014.00117

McTighe, S. M., Cowell, R. a, Winters, B. D., Bussey, T. J., & Saksida, L. M. (2010). Paradoxical false memory for objects after brain damage. *Science*, *330*(6009), 1408–10. doi:10.1126/science.1194780

Meacham, F., & Jan, P. E. (2015). Adaptive behavior can produce maladaptive anxiety due to individual differences in experience. *Quantitative Biology*.

Mechelli, A., Gorno-Tempini, M. L., & Price, C. J. (2003). Neuroimaging studies of word and pseudoword reading: consistencies, inconsistencies, and limitations. *Journal of cognitive neuroscience*, *15*(2), 260–71. doi:10.1162/089892903321208196

Mechelli, A., Josephs, O., Lambon Ralph, M. a, McClelland, J. L., & Price, C. J. (2007). Dissociating stimulus-driven semantic and phonological effect during reading and naming. *Human brain mapping*, *28*(3), 205–17. doi:10.1002/hbm.20272

Meeter, M, Radics, G., Myers, C. E., Gluck, M. a, & Hopkins, R. O. (2008). Probabilistic categorization: how do normal participants and amnesic patients do it? *Neuroscience and biobehavioral reviews*, *32*(2), 237–48. doi:10.1016/j.neubiorev.2007.11.001

Meeter, Martijn, Myers, C. E., Shohamy, D., Hopkins, R. O., & Gluck, M. a. (2006). Strategies in probabilistic categorization: results from a new way of analyzing performance. *Learning & memory (Cold Spring Harbor, N.Y.)*, *13*(2), 230–9. doi:10.1101/lm.43006

Meltzer CC, Smith G, DeKosky ST, Pollock BG, Mathis CA, Moore RY, Kupfer DJ, R. C. 3rd. (1998). Serotonin in Aging , Late-Life Depression , and Alzheimer ' s Disease : The Emerging Role of Functional Imaging. *Neuropsychopharmacology*, *18*(6), 407–30.

Mendez Rubio, M., Antonietti, J. P., Donati, a, Rossier, J., & Gunten, a. (2013). Personality traits and behavioural and psychological symptoms in patients with mild cognitive impairment. *Dementia and geriatric cognitive disorders*, *35*(1-2), 87–97. doi:10.1159/000346129

Merema, M. R., Speelman, C. P., Foster, J. K., & Kaczmarek, E. A. (2012). Neuroticism (Not Depressive Symptoms) Predicts Memory Complaints in Some Community-Dwelling Older Adults. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. doi:10.1097/JGP.0b013e31826d6973

Montag, C., Reuter, M., Jurkiewicz, M., Markett, S., & Panksepp, J. (2013). Imaging the structure of the human anxious brain: a review of findings from neuroscientific personality psychology. *Reviews in the neurosciences*, *24*(2), 167–90. doi:10.1515/revneuro-2012-0085

Montaldi, D., & Mayes, A. R. (2010). The role of recollection and familiarity in the functional differentiation of the medial temporal lobes. *Hippocampus*, *20*(11), 1291–314. doi:10.1002/hipo.20853

Morcom, A. M., & Friston, K. J. (2012). Decoding episodic memory in ageing: a Bayesian analysis of activity patterns predicting memory. *NeuroImage*, *59*(2), 1772–82. doi:10.1016/j.neuroimage.2011.08.071

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology*, *43*(11), 2412–2414.

Moustafa, A. a, & Gluck, M. a. (2011). A neurocomputational model of dopamine and prefrontal-striatal interactions during multicue category learning by Parkinson patients. *Journal of cognitive neuroscience*, *23*(1), 151–67. doi:10.1162/jocn.2010.21420

Msetfi, R. M., Murphy, R. a, & Kornbrot, D. E. (2012). Dysphoric Mood States are Related to Sensitivity to Temporal Changes in Contingency. *Frontiers in psychology*, *3*(September), 368. doi:10.3389/fpsyg.2012.00368

Muhammad, R., Wallis, J. D., & Miller, E. K. (2006). A comparison of abstract rules in the prefrontal cortex, premotor cortex, inferior temporal cortex, and striatum. *Journal of cognitive neuroscience*, *18*(6), 974–89. doi:10.1162/jocn.2006.18.6.974

Müller, M. B., Zimmermann, S., Sillaber, I., Hagemeyer, T. P., Deussing, J. M., Timpl, P., … Wurst, W. (2003). Limbic corticotropin-releasing hormone receptor 1 mediates anxiety-related behavior and hormonal adaptation to stress. *Nature neuroscience*, *6*(10), 1100–7. doi:10.1038/nn1123

Murray, M. E., Graff-Radford, N. R., Ross, O. a., Petersen, R. C., Duara, R., & Dickson, D. W. (2011). Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study. *The Lancet Neurology*, *10*(9), 785–796. doi:10.1016/S1474-4422(11)70156-9

Nadel, L., & Hardt, O. (2011). Update on memory systems and processes. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *36*(1), 251–73. doi:10.1038/npp.2010.169

Naghavi, H. R., Lind, J., Nilsson, L.-G., Adolfsson, R., & Nyberg, L. (2009). Personality traits predict response to novel and familiar stimuli in the hippocampal region. *Psychiatry research*, *173*(2), 94–9. doi:10.1016/j.pscychresns.2008.09.011

Naismith, S., Hickie, I., Ward, P., Scott, E., & Little, C. (2006). Impaired implicit sequence learning in depression: a probe for frontostriatal dysfunction? *Psychological Medicine*, *36*(3).

Nomura, E. M., Maddox, W. T., Filoteo, J. V, Ing, a D., Gitelman, D. R., Parrish, T. B., … Reber, P. J. (2007). Neural correlates of rule-based and information-integration visual category learning. *Cerebral cortex (New York, N.Y. : 1991)*, *17*(1), 37–43. doi:10.1093/cercor/bhj122

Norman, D. A., & Shallice, T. (1986). Attention to action: Willed and automatic control of behaviour. *In Davidson, R. J., Schwartz, G. E., and Shapiro, D., editors, Consciousness and Self-Regulation: Advances in Research and Theory. Plenum Press.*

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science (New York, N.Y.)*, *304*(5669), 452–4. doi:10.1126/science.1094285

O'Hara, R., Schröder, C. M., Mahadevan, R., Schatzberg, a F., Lindley, S., Fox, S., … Hallmayer, J. F. (2007). Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol. *Molecular psychiatry*, *12*(6), 544–55. doi:10.1038/sj.mp.4001978

O'Reilly, R. C., & Rudy, J. W. (2001). Conjunctive Representations in Learning and Memory: Principles of Cortical and Hippocampal Function. *Psychological Revuew*, *108*(2), 311–345.

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D. E., & Gross, J. J. (2004). For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage*, *23*(2), 483–499. doi:10.1016/j.neuroimage.2004.06.030

Ochsner, K. N., Ray, R. R., Hughes, B., McRae, K., Cooper, J. C., Weber, J., … Gross, J. J. (2010). Bottom-Up and Top-Down Processes in Emotion Generation: Common and Distinct Neural Mechanisms. *Psychol Sci.*, *20*(11), 1322–1331. doi:10.1111/j.1467-9280.2009.02459.x.Bottom-Up

Odmanman, H. (1994). How Inferior Temporal Cortex Became a Visual Area. *Cerebral cortex*, *4*(5), 455–469.

Olman, C. a, Davachi, L., & Inati, S. (2009). Distortion and signal loss in medial temporal lobe. *PloS one*, *4*(12), e8160. doi:10.1371/journal.pone.0008160

Olshausen, B. a, & Field, D. J. (2004). Sparse coding of sensory inputs. *Current opinion in neurobiology*, *14*(4), 481–7. doi:10.1016/j.conb.2004.07.007

Packard, M. G., White, M., & Ha, Q. (1989). Differential Effects of Fornix and Caudate Radial Maze Tasks : Evidence for Multiple Nucleus Lesions on Two Memory Systems. *The Journal of neuroscience*, *9*(5), 1465–1472.

Penny, W. D., Stephan, K. E., Mechelli, A., & Friston, K. J. (2004). Comparing dynamic causal models. *NeuroImage*, *22*(3), 1157–72. doi:10.1016/j.neuroimage.2004.03.026

Perrin, R. J., Fagan, A. M., & Holtzman, D. M. (2009a). Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature*, *461*(7266), 916–22. doi:10.1038/nature08538

Perrin, R. J., Fagan, A. M., & Holtzman, D. M. (2009b). Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature*, *461*(7266), 916–22. doi:10.1038/nature08538

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*, *442*(7106), 1042–5. doi:10.1038/nature05051

Petersen, R. C. (2004a). Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine*, *256*(3), 183–94. doi:10.1111/j.1365-2796.2004.01388.x

Petersen, R. C. (2004b). Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine*, *256*(3), 183–94. doi:10.1111/j.1365-2796.2004.01388.x

Petersson, K.-M., Folia, V., & Hagoort, P. (2012). What artificial grammar learning reveals about the neurobiology of syntax. *Brain and language*, *120*(2), 83–95. doi:10.1016/j.bandl.2010.08.003

Petzold, A., Plessow, F., Goschke, T., & Kirschbaum, C. (2010). Stress reduces use of negative feedback in a feedback-based learning task. *Behavioral neuroscience*, *124*(2), 248–255. doi:10.1037/a0018930

Pine, J., Colquitt, J., & Erez A. (1999). Adpatability to changing contexts: effects of general cognitive ability, conscientiousness, and opennes to experience. *Personnel Psychology*, *53*(3), 563–593.

Poldrack, R a, Clark, J., Paré-Blagoev, E. J., Shohamy, D., Creso Moyano, J., Myers, C., & Gluck, M. a. (2001). Interactive memory systems in the human brain. *Nature*, *414*(6863), 546–50. doi:10.1038/35107080

Poldrack, R a, Prabhakaran, V., Seger, C. a, & Gabrieli, J. D. (1999). Striatal activation during acquisition of a cognitive skill. *Neuropsychology*, *13*(4), 564–74. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10527065

Poldrack, Russell a, & Foerde, K. (2008). Category learning and the memory systems debate. *Neuroscience and biobehavioral reviews*, *32*(2), 197–205. doi:10.1016/j.neubiorev.2007.07.007

Poldrack, Russell a, & Packard, M. G. (2003). Competition among multiple memory systems: converging evidence from animal and human brain studies. *Neuropsychologia*, *41*(3), 245–51. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12457750

Poldrack, Russell a, & Rodriguez, P. (2004). How do memory systems interact? Evidence from human classification learning. *Neurobiology of learning and memory*, *82*(3), 324–32. doi:10.1016/j.nlm.2004.05.003

Preston, A. R., & Eichenbaum, H. (2013). Interplay of Hippocampus and Prefrontal Cortex in Memory. *Curent Biology*, *23*(17), R764–R773. doi:10.1016/j.cub.2013.05.041

Price, C. J., & Devlin, J. T. (2011). The interactive account of ventral occipitotemporal contributions to reading. *Trends in cognitive sciences*, *15*(6), 246–53. doi:10.1016/j.tics.2011.04.001

Quiroga, R. Q., Kreiman, G., Koch, C., & Fried, I. (2008). Sparse but not "grandmother-cell" coding in the medial temporal lobe. *Trends in cognitive sciences*, *12*(3), 87–91. doi:10.1016/j.tics.2007.12.003

Quiroga, R. Q., Reddy, L., Kreiman, G., Koch, C., & Fried, I. (2005). Invariant visual representation by single neurons in the human brain. *Nature*, *435*(June), 1102–1107. doi:10.1038/nature03687

Rajmohan, V., & Mohandas, E. (2007). The limbic system. *Indian journal of psychiatry*, *49*(2), 132–9. doi:10.4103/0019-5545.33264

Ranganath, C., & Rainer, G. (2003). Neural mechanisms for detecting and remembering novel events. *Nature reviews. Neuroscience*, *4*(3), 193–202. doi:10.1038/nrn1052

Rapp, M. a, Schnaider-Beeri, M., Grossman, H. T., Sano, M., Perl, D. P., Purohit, D. P., … Haroutunian, V. (2006). Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Archives of general psychiatry*, *63*(2), 161–7. doi:10.1001/archpsyc.63.2.161

Reber, P. J., Knowlton, B. J., & Squire, L. R. (1996). Dissociable Properties of Memory Systems : Differences in the Flexibility of Declarative and Nondeclarative Knowledge. *Behavioral Neuroscience*, *110*(5), 861–871.

Reilly, R. C. O., & Busby, R. S. (2002). Generalizable Relational Binding from Coarse-coded Distributed Representations. In *Advances in Neural Information Pr o-cessing Systems (NIPS)*.

Richards, J. M., & Gross, J. J. (2006). Personality and emotional memory: How regulating emotion impairs memory for emotional events. *Journal of Research in Personality*, *40*(5), 631–651. doi:10.1016/j.jrp.2005.07.002

Rissman, J., Greely, H. T., & Wagner, A. D. (2010). Detecting individual memories through the neural decoding of memory states and past experience. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(21), 9849–54. doi:10.1073/pnas.1001028107

Rissman, J., & Wagner, A. D. (2012). Distributed representations in memory: insights from functional brain imaging. *Annual review of psychology*, *63*, 101–28. doi:10.1146/annurev-psych-120710-100344

Robert L. Kahn, PhD; Steven H. Zarit, PhD; Nancy M. Hilbert, MA; George Niederehe, M. (1975). Memory complaint and Impairement in the Aged. *Arch Gen Psychiatry*, *32*.

Roberts, B. W., & DelVecchio, W. F. (2000). The rank-order consistency of personality traits from childhood to old age: A quantitative review of longitudinal studies. *Psychological Bulletin*, *126*(1), 3–25. doi:10.1037/0033-2909.126.1.3

Roberts, E., Gilboa, E., & Gotlib, I. H. (1998). Rum in ative Respon se Style an d Vuln erability to Episodes of Dysphoria : Gender , Neuroticism , an d Episode Duration. *Therapy*, *22*(4), 401–423.

Robins Wahlin, T.-B., & Byrne, G. J. (2011). Personality changes in Alzheimer's disease: a systematic review. *International journal of geriatric psychiatry*, *26*(10), 1019–29. doi:10.1002/gps.2655

Robinson, O. J., Overstreet, C., Charney, D. R., Vytal, K., & Grillon, C. (2013). Stress increases aversive prediction error signal in the ventral striatum. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(10), 4129–33. doi:10.1073/pnas.1213923110

Roepke, S., McAdams, L. a, Lindamer, L. a, Patterson, T. L., & Jeste, D. V. (2001). Personality profiles among normal aged individuals as measured by the NEO-PI-R. *Aging & mental health*, *5*(2), 159–64. doi:10.1080/13607860120038339

Roiser, J. P., & Sahakian, B. J. (2013). Hot and cold cognition in depression. *CNS spectrums*, *18*(3), 139–49. doi:10.1017/S1092852913000072

Rolls, E. T., & Treves, A. (1990). The relative advantages of sparse versus distributed encoding for associative neuronal networks in the brain. *Network*, *1*, 407–421.

Romero, N., Vazquez, C., & Sanchez, A. (2013). Rumination and specificity of autobiographical memory in dysphoria. *Memory*, *22*(6), 646–54. doi:10.1080/09658211.2013.811254

Rothman, S. M., & Mattson, M. P. (2010). Adverse Stress, Hippocampal Networks, and Alzheimer's Diseas. *Neuromolecular Med.*, *12*(1), 56–70. doi:10.1007/s12017-009-8107-9.Adverse

Rouch, I., Dorey, J.-M., Boublay, N., Henaff, M.-A., Dibie-Racoupeau, F., Makaroff, Z., … Krolak-Salmon, P. (2014). Personality, Alzheimer's disease and behavioural and cognitive symptoms of dementia: the PACO prospective cohort study protocol. *BMC geriatrics*, *14*(110). doi:10.1186/1471-2318-14-110

Rozzini, L., Vicini Chilovi, B., Conti, M., Delrio, I., Borroni, B., Trabucchi, M., & Padovani, a. (2008). Neuropsychiatric symptoms in amnestic and nonamnestic mild cognitive impairment. *Dementia and geriatric cognitive disorders*, *25*(1), 32–6. doi:10.1159/000111133

Ruediger, S., Spirig, D., Donato, F., & Caroni, P. (2012). Goal-oriented searching mediated by ventral hippocampus early in trial-and-error learning. *Nature neuroscience*, (September), 1–11. doi:10.1038/nn.3224

Rugg, M. D., Vilberg, K. L., Mattson, J. T., Yu, S. S., Johnson, J. D., & Suzuki, M. (2012). Item memory, context memory and the hippocampus: FMRI evidence. *Neuropsychologia*, *50*, 3070–3079. doi:10.1016/j.neuropsychologia.2012.06.004

Rushby, J. a, Vercammen, A., Loo, C., Short, B., Weickert, C. S., & Weickert, T. W. (2011). Frontal and parietal contributions to probabilistic association learning. *Cerebral cortex (New York, N.Y. : 1991)*, *21*(8), 1879–88. doi:10.1093/cercor/bhq255

Sage, J. R., Anagnostaras, S. G., Mitchell, S., Bronstein, J. M., De Salles, A., Masterman, D., & Knowlton, B. J. (2003). Analysis of probabilistic classification learning in patients with Parkinson's disease before and after pallidotomy surgery. *Learning & memory (Cold Spring Harbor, N.Y.)*, *10*(3), 226–36. doi:10.1101/lm.45903

Sagi, Y., Tavor, I., Hofstetter, S., Tzur-Moryosef, S., Blumenfeld-Katzir, T., & Assaf, Y. (2012). Learning in the Fast Lane: New Insights into Neuroplasticity. *Neuron*, *73*(6), 1195–1203. doi:10.1016/j.neuron.2012.01.025

Sahay, A., & Hen, R. (2007). Adult hippocampal neurogenesis in depression. *Nature neuroscience*, *10*(9), 1110–5. doi:10.1038/nn1969

Sakai, K. (2003). Reactivation of memory: role of medial temporal lobe and prefrontal cortex. *Reviews in the neurosciences*, *14*(3), 241–52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14513867

Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of general psychiatry*, *57*(10), 925–35. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11015810

Sasaki Y., Gold J., W. T. (2010). Perceptual Learning: Cortical Changes When Cats Learn a New Trick. *Curr Biol*, *20*(13), 1–5. doi:10.1016/j.cub.2010.05.004.Perceptual

Scale, D., National, S., & Discharge, H. (2011). Temporal Relationship Between Depression and Dementia. *Arch Gen Psychiatry*, *68*(9), 970–977.

Scheltens, P., Fox, N., Barkhof, F., & Carli, C. (2002). Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. *Lancet neurology*, *1*(1), 13–21.

Schultz, W., & Dickinson, A. (2000). Neuronal coding of prediction errors. *Annual review of neuroscience*, *23*, 473–500. doi:10.1146/annurev.neuro.23.1.473

Schwabe, L., & Wolf, O. T. (2012). Stress modulates the engagement of multiple memory systems in classification learning. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *32*(32), 11042–9. doi:10.1523/JNEUROSCI.1484-12.2012

Scola, E., Bozzali, M., Agosta, F., Magnani, G., Franceschi, M., Sormani, M. P., … Falini, A. (2010). A diffusion tensor MRI study of patients with MCI and AD with a 2-year clinical follow-up. *Journal of neurology, neurosurgery, and psychiatry*, *81*(7), 798–805. doi:10.1136/jnnp.2009.189639

Seger, C. a, & Cincotta, C. M. (2005). The roles of the caudate nucleus in human classification learning. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *25*(11), 2941–51. doi:10.1523/JNEUROSCI.3401-04.2005

Seger, C. a, & Miller, E. K. (2010). Category learning in the brain. *Annual review of neuroscience*, *33*, 203–19. doi:10.1146/annurev.neuro.051508.135546

Seger, C. a, & Peterson, E. J. (2013). Categorization=decision making+generalization. *Neuroscience and biobehavioral reviews*, 1–14. doi:10.1016/j.neubiorev.2013.03.015

Sen, S., Burmeister, M., & Ghosh, D. (2004). Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*, *127B*(1), 85–9. doi:10.1002/ajmg.b.20158

Shanks, D. R., Tunney, R. J., & Mccarthy, J. D. (2002). A Re-examination of Probability Matching and Rational Choice. *J. Behav. Dec. Making*, *250*(March), 233–250.

Sharot, T., Delgado, M. R., & Phelps, E. A. (2004). How emotion enhances the feeling of remembering. *Nature neuroscience*, *7*(12), 1376–80. doi:10.1038/nn1353

Sharot, T., Verfaellie, M., & Yonelinas, A. P. (2007). How emotion strengthens the recollective experience: a time-dependent hippocampal process. *PloS one*, *2*(10). doi:10.1371/journal.pone.0001068

Sheinberg, D. L., & Logothetis, N. K. (1997). The role of temporal cortical areas in perceptual organization. *Proc. Natl. Acad. Sci. USA*, *94*, 3408–3413.

Shohamy, D, Myers, C. E., Kalanithi, J., & Gluck, M. a. (2008). Basal ganglia and dopamine contributions to probabilistic category learning. *Neuroscience and biobehavioral reviews*, *32*(2), 219–36. doi:10.1016/j.neubiorev.2007.07.008

Shohamy, Daphna, Myers, C. E., Hopkins, R. O., Sage, J., & Gluck, M. A. (2008). Distinct Hippocampal and Basal Ganglia Contributions to Probabilistic Learning and Reversal. *Journal of Cognitive Neuroscience*, 1820–1832.

Skinner, E. I., & Fernandes, M. a. (2007). Neural correlates of recollection and familiarity: a review of neuroimaging and patient data. *Neuropsychologia*, *45*(10), 2163–79. doi:10.1016/j.neuropsychologia.2007.03.007

Slotnick, S. D. (2013). The nature of recollection in behavior and the brain. *NeuroReport*, *24*(12), 663–670. doi:10.1097/WNR.0b013e328362e47e

Song, Z., Jeneson, A., & Squire, L. R. (2011). Medial temporal lobe function and recognition memory: a novel approach to separating the contribution of recollection and familiarity. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *31*(44), 16026–32. doi:10.1523/JNEUROSCI.3012-11.2011

Sotiropoulos, I., Cerqueira, J. J., Catania, C., Takashima, a, Sousa, N., & Almeida, O. F. X. (2008). Stress and glucocorticoid footprints in the brain-the path from depression to Alzheimer's disease. *Neuroscience and biobehavioral reviews*, *32*(6), 1161–73. doi:10.1016/j.neubiorev.2008.05.007

Spasojevic, N., Jovanovic, P., & Dronjak, S. (2013). Molecular basis of chronic stress-induced hippocampal lateral asymmetry in rats and impact on learning and memory. *Acta physiologica Hungarica*, *100*(4), 388–94. doi:10.1556/APhysiol.100.2013.4.3

Speekenbrink, M., Channon, S., & Shanks, D. R. (2008). Learning strategies in amnesia. *Neuroscience and biobehavioral reviews*, *32*(2), 292–310. doi:10.1016/j.neubiorev.2007.07.005

Squire, L R, & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science (New York, N.Y.)*, *253*(5026), 1380–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1896849

Squire, Larry R, Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual review of neuroscience*, *27*, 279–306. doi:10.1146/annurev.neuro.27.070203.144130

Sripada, C. S., Gonzalez, R., Phan, K. L., & Liberzon, I. (2011). The neural correlates of intertemporal decision-making: contributions of subjective value, stimulus type, and trait impulsivity. *Human brain mapping*, *32*(10), 1637–48. doi:10.1002/hbm.21136

Staresina, B. P., Duncan, K. D., & Davachi, L. (2011). Perirhinal and parahippocampal cortices differentially contribute to later recollection of object- and scene-related event details. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *31*(24), 8739–47. doi:10.1523/JNEUROSCI.4978-10.2011

Starrfelt, R., & Gerlach, C. (2007). The visual what for area: words and pictures in the left fusiform gyrus. *NeuroImage*, *35*(1), 334–42. doi:10.1016/j.neuroimage.2006.12.003

Stephan, K. E., Kasper, L., Harrison, L. M., Daunizeau, J., Hanneke, E. M., Ouden, D., … Friston, K. J. (2009). Nonlinear Dynamic Causal Models for fMRI. *NeuroImage*, *42*(2), 649–662. doi:10.1016/j.neuroimage.2008.04.262.Nonlinear

Stephan, K. E., Penny, W. D., Moran, R. J., Ouden, H. E. M. Den, Daunizeau, J., & Friston, K. J. (2010). Ten simple rules for dynamic causal modeling. *NeuroImage*, *49*(4), 3099–3109. doi:10.1016/j.neuroimage.2009.11.015

Stern, Y., Gurland, B., Tatemichi, T. K., Wilder, D., & Mayeux, R. (2013). Influence of Education and Occupation on the Incidence of Alzheimer ' s Disease.

Strange, B a, Fletcher, P. C., Henson, R. N., Friston, K. J., & Dolan, R. J. (1999). Segregating the functions of human hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(7), 4034–9. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=22415&tool=pmcentrez&rendertype=abstract

Strange, Bryan a., Witter, M. P., Lein, E. S., & Moser, E. I. (2014). Functional organization of the hippocampal longitudinal axis. *Nature Reviews Neuroscience*, *15*(10), 655–669. doi:10.1038/nrn3785

Strauss M, Pasupathi M, C. A. (1993). Concordance between observers indescriptions of personality change in Alzheimer's disease. *Psychol Aging*, *8*(4), 475–480.

Striem-Amit, E., Cohen, L., Dehaene, S., & Amedi, A. (2012). Reading with sounds: sensory substitution selectively activates the visual word form area in the blind. *Neuron*, *76*(3), 640–52. doi:10.1016/j.neuron.2012.08.026

Studer-Luethi, B., Jaeggi, S. M., Buschkuehl, M., & Perrig, W. J. (2012). Influence of neuroticism and conscientiousness on working memory training outcome. *Personality and Individual Differences*, *53*(1), 44–49. Retrieved from http://www.sciencedirect.com/science/article/pii/S0191886912000815

Sutton, Ri. S., & Barto, A. G. (1998). *Reinforcement Learning: An Introduction* (MIT Press.). Retrieved from http://webdocs.cs.ualberta.ca/~sutton/book/the-book.html

Szeszko, P. R., Betensky, J. D., Mentschel, C., Gunduz-Bruce, H., Lencz, T., Ashtari, M., … Bilder, R. M. (2006). Increased stress and smaller anterior hippocampal volume. *Neuroreport*, *17*(17), 1825–8. doi:10.1097/01.wnr.0000246322.58814.b8

Taki, Y., Thyreau, B., Kinomura, S., Sato, K., Goto, R., Wu, K., … Fukuda, H. (2013). A longitudinal study of the relationship between personality traits and the annual rate of volume changes in regional gray matter in healthy adults. *Human brain mapping*, *34*(12), 3347–53. doi:10.1002/hbm.22145

Tamminga, C. a. (2013). Psychosis is emerging as a learning and memory disorder. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *38*(1), 247. doi:10.1038/npp.2012.187

Terracciano, A., Iacono, D., O'Brien, R. J., Troncoso, J. C., An, Y., Sutin, A. R., … Resnick, S. M. (2013). Personality and resilience to Alzheimer's disease neuropathology: a prospective autopsy study. *Neurobiology of aging*, *34*(4), 1045–50. doi:10.1016/j.neurobiolaging.2012.08.008

Thal, D. R., Arendt, T., Waldmann, G., Holzer, M., Zedlick, D., Rüb, U., & Schober, R. (1998). Progression of neurofibrillary changes and PHF-τ in end-stage Alzheimer's disease is different from plaque and cortical microglial pathology. *Neurobiology of Aging*, *19*(6), 517–525. doi:10.1016/S0197-4580(98)00090-6

Theysohn, N., Qin, S., Maderwald, S., Poser, B. a, Theysohn, J. M., Ladd, M. E., … Tendolkar, I. (2013). Memory-related hippocampal activity can be measured robustly using FMRI at 7 tesla. *Journal of neuroimaging : official journal of the American Society of Neuroimaging*, *23*(4), 445–51. doi:10.1111/jon.12036

Tobler, P. N., O'doherty, J. P., Dolan, R. J., & Schultz, W. (2006). Human neural learning depends on reward prediction errors in the blocking paradigm. *Journal of neurophysiology*, *95*(1), 301–10. doi:10.1152/jn.00762.2005

Toledo, J. B., Weiner, M. W., Wolk, D. a, Da, X., Chen, K., Arnold, S. E., … Trojanowski, J. Q. (2014). Neuronal injury biomarkers and prognosis in ADNI subjects with normal cognition. *Acta neuropathologica communications*, *2*(1), 26. doi:10.1186/2051-5960-2-26

Tondelli, M., Wilcock, G. K., Nichelli, P., De Jager, C. a, Jenkinson, M., & Zamboni, G. (2011). Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. *Neurobiology of aging*, *33*(4), 825.e25–825.e36. doi:10.1016/j.neurobiolaging.2011.05.018

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. (1999). Memory, Consciousness, and the Brain: The Tallinn Conference. *Psychology Press*, 66–68.

Twomey, T., Kawabata Duncan, K. J., Price, C. J., & Devlin, J. T. (2011). Top-down modulation of ventral occipito-temporal responses during visual word recognition. *NeuroImage*, *55*(3), 1242–51. doi:10.1016/j.neuroimage.2011.01.001

Tyler, L. K., Chiu, S., Zhuang, J., Randall, B., & Devereux, B. J. (2014). Feature statistics and object processing in the ventral stream. *J Cogn Neurosci* ., *25*(10), 1723–1735. doi:10.1162/jocn

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage*. Retrieved from http://www.sciencedirect.com/science/article/pii/S1053811901909784

Ungerleider, L. G., & Haxby, J. V. (1994). "What" and "where" in the human brain. *Current biology : CB*, *4*, 157–165.

Uttl, B., White, C. a, Wong Gonzalez, D., McDouall, J., & Leonard, C. a. (2013). Prospective memory, personality, and individual differences. *Frontiers in psychology*, *4*(March), 130. doi:10.3389/fpsyg.2013.00130

Van der Zwaag, W., Francis, S., Head, K., Peters, A., Gowland, P., Morris, P., & Bowtell, R. (2009). fMRI at 1.5, 3 and 7 T: characterising BOLD signal changes. *NeuroImage*, *47*(4), 1425–34. doi:10.1016/j.neuroimage.2009.05.015

Van Gestel, S., & Van Broeckhoven, C. (2003). Genetics of personality: are we making progress? *Molecular psychiatry*, *8*(10), 840–52. doi:10.1038/sj.mp.4001367

Van Hiel, A., & Mervielde, I. (2007). The Search for Complex Problem-Solving Strategies in the Presence of Stressors. *Human Factors: The Journal of the Human Factors and Ergonomics Society*, *49*(6), 1072–1082. doi:10.1518/001872007X249938

Van Norden, A. G. W., de Laat, K. F., Fick, I., van Uden, I. W. M., van Oudheusden, L. J. B., Gons, R. a R., … de Leeuw, F.-E. (2012). Diffusion tensor imaging of the hippocampus and verbal memory performance: the RUN DMC study. *Human brain mapping*, *33*(3), 542–51. doi:10.1002/hbm.21231

Vandenberghe, R., Price, C., Wise, R., Josephs, O., & Frackowiak, R. S. (1996). Functional anatomy of a common semantic system for words and pictures. *Nature*, *383*(6597), 254–6. doi:10.1038/383254a0

Vermetten, Y. J., Lodewijks, H. G., & Vermunt, J. D. (2001). The Role of Personality Traits and Goal Orientations in Strategy Use. *Contemporary educational psychology*, *26*(2), 149–170. doi:10.1006/ceps.1999.1042

Viard, A., Doeller, C. F., Hartley, T., Bird, C. M., & Burgess, N. (2011). Anterior hippocampus and goal-directed spatial decision making. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *31*(12), 4613–21. doi:10.1523/JNEUROSCI.4640-10.2011

Vicini Chilovi, B., Conti, M., Zanetti, M., Mazzù, I., Rozzini, L., & Padovani, A. (2009). Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dementia and geriatric cognitive disorders*, *27*(4), 390–8. doi:10.1159/000210045

Videbech, P., Ravnkilde, B., & Ph, D. (2004). Reviews and Overviews Hippocampal Volume and Depression : A Meta-Analysis of MRI Studies. *Am Psychiatric Assoc*, *161*, 1957–1966.

Vigneau, M., Beaucousin, V., Hervé, P. Y., Duffau, H., Crivello, F., Houdé, O., … Tzourio-Mazoyer, N. (2006). Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *NeuroImage*, *30*(4), 1414–32. doi:10.1016/j.neuroimage.2005.11.002

Villemagne, V. L., & Okamura, N. (2014). In vivo tau imaging: Obstacles and progress. *Alzheimer's and Dementia*, *10*, 254–264. doi:10.1016/j.jalz.2014.04.013

Vink, M., Pas, P., Bijleveld, E., Custers, R., & Gladwin, T. E. (2013). Ventral striatum is related to within-subject learning performance. *Neuroscience*, *250*, 408–16. doi:10.1016/j.neuroscience.2013.07.034

Von Der Heide, R. J., Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. *Brain : a journal of neurology*, *136*(Pt 6), 1692–707. doi:10.1093/brain/awt094

Von Gunten, A., Pocnet, C., & Rossier, J. (2009). The impact of personality characteristics on the clinical expression in neurodegenerative disorders--a review. *Brain research bulletin*, *80*(4-5), 179–91. doi:10.1016/j.brainresbull.2009.07.004

Warren, J. D., Fletcher, P. D., & Golden, H. L. (2012). The paradox of syndromic diversity in Alzheimer disease. *Nature reviews. Neurology*, *8*(8), 451–64. doi:10.1038/nrneurol.2012.135

Watkins, E. R., Baeyens, C. B., & Read, R. (2009). Concreteness training reduces dysphoria: proof-of-principle for repeated cognitive bias modification in depression. *Journal of abnormal psychology*, *118*(1), 55–64. doi:10.1037/a0013642

Waydo, S., Kraskov, A., Quian Quiroga, R., Fried, I., & Koch, C. (2006). Sparse representation in the human medial temporal lobe. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *26*(40), 10232–4. doi:10.1523/JNEUROSCI.2101-06.2006

Weingartner HG. (1981). Cognitive Processes in Depression. *Arch Gen Psychiatry*.

Wheatley, T., Weisberg, J., Beauchamp, M. S., & Martin, A. (2005). Automatic priming of semantically related words reduces activity in the fusiform gyrus. *Journal of cognitive neuroscience*, *17*(12), 1871–85. doi:10.1162/089892905775008689

Whiteside, S. P., & Lynam, D. R. (2001). The Five Factor Model and impulsivity : using a structural model of personality to understand impulsivity. *Personality and Individual Differences*, *30*.

Whitmer, A. J., Frank, M. J., & Gotlib, I. H. (2012). Sensitivity to reward and punishment in major depressive disorder : Effects of rumination and of single versus multiple experiences, *26*(8), 1475–1485.

Willard, S. L., Friedman, D. P., Henkel, C. K., & Shively, C. A. (2009). Anterior hippocampal volume is reduced in behaviorally depressed female cynomolgus macaques. *Psychoneuroendocrinology*, *34*(10), 1469–1475. Retrieved from http://www.sciencedirect.com/science/article/pii/S0306453009001528

Wilson, R S, Fleischman, D. A., Myers, R. A., Bennett, D. A., Bienias, J. L., Gilley, D. W., & Evans, D. A. (2004). Premorbid proneness to distress and episodic memory impairment in Alzheimer's disease. *Psychiatry: Interpersonal and Biological Processes*, 191–196.

Wilson, R S, Schneider, J. A., & Boyle, P. A. (2007). Chronic distress and incidence of mild cognitive impairment. *Neurology*, *28*(24), 2085–2093. doi:10.1212/01.wnl.0000264930.97061.82

Wilson, Robert S, Arnold, S. E., Schneider, J. a, Kelly, J. F., Tang, Y., & Bennett, D. a. (2006). Chronic psychological distress and risk of Alzheimer's disease in old age. *Neuroepidemiology*, *27*(3), 143–53. doi:10.1159/000095761

Wilson, Robert S, Begeny, C. T., Boyle, P. a, Schneider, J. a, & Bennett, D. a. (2011). Vulnerability to stress, anxiety, and development of dementia in old age. *The American journal of geriatric psychiatry : official*

journal of the American Association for Geriatric Psychiatry, *19*(4), 327–34. doi:10.1097/JGP.0b013e31820119da

Wilson, Robert S, Schneider, J. a, Arnold, S. E., Bienias, J. L., & Bennett, D. a. (2007). Conscientiousness and the incidence of Alzheimer disease and mild cognitive impairment. *Archives of general psychiatry*, *64*(10), 1204–12. doi:10.1001/archpsyc.64.10.1204

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., … Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of internal medicine*, *256*(3), 240–6. doi:10.1111/j.1365-2796.2004.01380.x

Wixted, J. T., Squire, L. R., Jang, Y., Papesh, M. H., Goldinger, S. D., Kuhn, J. R., … Steinmetz, P. N. (2014). Sparse and distributed coding of episodic memory in neurons of the human hippocampus. *Proceedings of the National Academy of Sciences*, *111*(26), 9621–9626. doi:10.1073/pnas.1408365111

Wolk, D. A., L., D. K., Dickerson, B. C., Aizenstein, H. J., & Dekosky, S. T. (2011). A Medial Temporal Lobe Division of Labor: Insights from Memory in Aging and Early Alzheimer Disease. *Hipp*, *21*(5), 461–466. doi:10.1002/hipo.20779.A

Worsley, K. J., Poline, J. B., Friston, K. J., & Evans, a C. (1997). Characterizing the response of PET and fMRI data using multivariate linear models. *NeuroImage*, *6*(4), 305–19. doi:10.1006/nimg.1997.0294

Yassa, M. a, & Stark, C. E. L. (2009). A quantitative evaluation of cross-participant registration techniques for MRI studies of the medial temporal lobe. *NeuroImage*, *44*(2), 319–27. doi:10.1016/j.neuroimage.2008.09.016

Yonelinas, A. P. (2002). The Nature of Recollection and Familiarity: A Review of 30 Years of Research. *Journal of Memory and Language*, *46*(3), 441–517. doi:10.1006/jmla.2002.2864

Yonelinas, A. P., Aly, M., Wang, W.-C., & Koen, J. D. (2010). Recollection and familiarity: examining controversial assumptions and new directions. *Hippocampus*, *20*(11), 1178–94. doi:10.1002/hipo.20864

Yonelinas, A. P., Otten, L. J., Shaw, K. N., & Rugg, M. D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *25*(11), 3002–8. doi:10.1523/JNEUROSCI.5295-04.2005

Young, A. L., Oxtoby, N. P., Daga, P., Cash, D. M., Fox, N. C., Ourselin, S., … Alexander, D. C. (2014). A data-driven model of biomarker changes in sporadic Alzheimer's disease. *Brain*. doi:10.1093/brain/awu176

Zeithamova, D., Dominick2, A. L., & Preston, A. R. (2012). Hippocampal and Ventral Medial Prefrontal Activation during Retrieval-Mediated Learning Supports Novel Inference. *Neuron*, *75*(1), 168–179. doi:10.1016/j.neuron.2012.05.010.Hippocampal

Zeithamova, D., Schlichting, M. L., & Preston, A. R. (2012). The hippocampus and inferential reasoning: building memories to navigate future decisions. *Frontiers in human neuroscience*, *6*(March), 70. doi:10.3389/fnhum.2012.00070

Zhang, M. Y., Katzman, R., Salmon, D., Jin, H., Cai, G. J., Wang, Z. Y., … Levy, P. (1990). The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. *Annals of neurology*, *27*(4), 428–37. doi:10.1002/ana.410270412

Zigmond, AS, Snaith, R. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*, *67*(6), 361–370.

Zuurbier, L. A., Nikolova, Y. S., Åhs, F., & Hariri, A. R. (2013). Uncinate fasciculus fractional anisotropy correlates with typical use of reappraisal in women but not men. *American Psychological Association*, *13*(3).

6. APPENDIX

6.1. Functional connectivity between hippocampus and caudate nucleus

As previously described, the left hippocampus (XYZ(-24,-22.5,-18)) and the right caudate nucleus (XYZ(9,9,4.5)) activations were associated with learning trials compared with non-learning trials, in a negative and positive way respectively (cf. in chapter "3.3.3. Results" in "Univariate analysis of brain activation associated with learning trials"). We measured the functional connectivity between them by extracting the intensity of activation at the significant maximal peak in those regions during learning and non-learning trials and testing the interaction effect with ANOVA 2 (learning and non-learning condition) X 2 (left hippocampus and right caudate nucleus) with repeated measures. We reported an effect of the region ($p<0.001$, $F=44.95$, $df=1$), no effect of the learning condition ($p=0.046$, $F=4.47$, $df=1$) and a significant interaction effect between region and learning condition ($p<0.001$, $F=35.16$, $df=1$). In learning condition, we observed a higher negative correlation between regions than in non-learning condition (Figure 60).

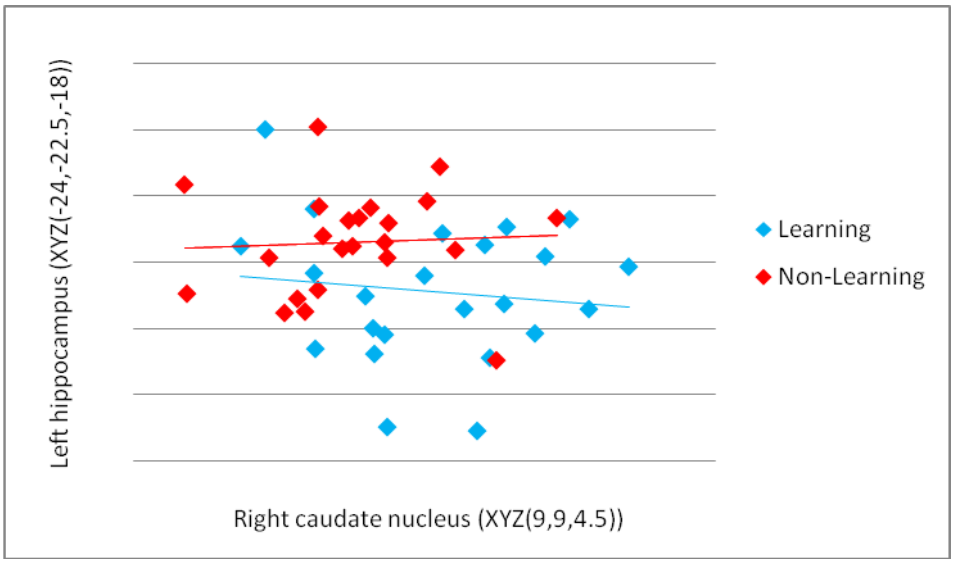


Figure 59. Graph showing significant interaction effect between mean activation of regions, i.e. the right caudate nucleus and left hippocampus, and learning conditions. The range of X axis lays between -40 to +5 and the Y axis, between -20 to +10.

6.2. Anatomical brain region associated with learning

The brain functional activity related to learning (i.e. subject's utilization weight), mainly located in the left occipito-temporal cortex (XYZ(-39,-48,-10.5)) and in the right mid frontal cortex (XYZ(43.5,43.5,4.5)), was not significantly associated with any voxels of the anatomical image (measuring volume of gray matter) from all participants. The same analysis was performed with the functional activity of the learning trial compared to non-learning trials located in the left hippocampus (XYZ(-24,-22.5,-18)) and in the right caudate nucleus (XYZ(9,9,4.5)). We report also no significant voxels associated with anatomical image of all participants.

6.3. Neuroimaging

In the thesis, I investigated MR measures of Gray Matter Volume (GMV) with T1-weighted (T1w) structural images, Gray Matter Mean Diffusivity (GMMD) and Gray Matter Fractional Anisotropy (FA) with Diffusion Weighted Images (DWI). Diffusion represents the movement of molecules driven by random motions, called Brownian motion. The root mean square displacement of the molecules over a given time can define a diffusion measure. Different factors can affect the diffusion of molecules in the tissue such as barriers and compartments related to the intra-, extra-cellular space, neurons, glials or axons. This is also sensitive to cerebral edema. The apparent Diffusion Coefficient (ADC) can be measured with MRI and is related to the interaction of the water diffusing in cellular structure over a given time. The diffusion of liquid is constrained by the orientation of the tissue type; when the diffusion measure is the same in all directions, this is called the isotropic diffusion, but when this is highly oriented, this is called anisotropic diffusion (Figure 61). DWI are sensitive to diffusion in each direction and at each point in the brain and consist of the application of different magnetic gradients that produce a MR signal change related to the amplitude and direction of diffusion. The detected signal intensity attenuation is a function of values (i.e. b-values) that are diffusion-sensitizing gradients in different directions. In Diffusion Tensor Imaging (DTI), a symmetric b-matrix, called the Diffusion Tensor, is calculated for three orthogonal directions, x, y and z from the attenuating effect of all 30 gradient directions using linear regression. By averaging the computed diffusion coefficients, the result is called the Mean Diffusivity (MD) coefficient or the Trace. Fractional anisotropy (FA) is a measure of the amount of anisotropy at each point (Basser & Jones, 2002; Beaulieu, 2002).

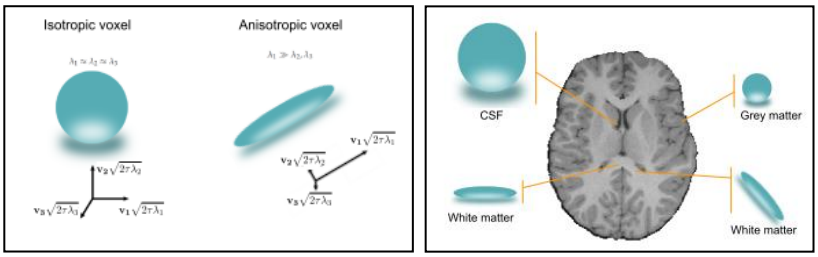


Figure 60. Models of isotropic and anisotropic voxels and how they are constrained by tissue type. CSF: Cerebrospinal Fluid (Source: FSL the FMRIB Software Library (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012).

VBM and VBQ: pre-processing. I applied a standard data pre-processing pipeline using statistical parametric mapping package (J Ashburner & Friston, 2000; Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-P., Frith, C.D., Frackowiack, 1995)(SPM8-Matlab toolbox, www.fil.ion.ucl.ac.uk/spm) to the T1w images with a bias field correction and unified segmentation into white and gray matter tissue classes. Additionally, I applied a standard pre-processing pipeline using Freesurfer software (Fischl, Sereno, Tootell, & Dale, 1999) (FSL, http://www.fmrib.ox.ac.uk/fsl/) with correction for eddy or electic currents, that are created by conductors (i.e. gradient coils) with a changing magnetic field in the conductor, and head movement distortion. This was followed by extraction of mean diffusion (MD) images. MD and T1W images were spatially realigned and normalized to MNI space with the DARTEL procedure contained in the Voxel-Based Quantification (VBQ) toolbox (Draganski et al., 2011). The final outputs were restricted to the gray matter segment to obtain voxel-wise estimations of Gray Matter Volume (GMV) and Gray Matter Mean Diffusivity (GMMD). Finally, I smoothed the images with an isotropic Gaussian kernel of 8mm full-width at half maximum. Anatomical labeling was based on the AAL atlas (Tzourio-Mazoyer et al., 2002).

In detail, Voxel-based Morphometry (VBM) provides a mass-univariate statistical analysis of between groups difference throughout all the brain's voxels. This approach avoids the

possible overlook of some brain specific regions using region of interest (ROI) technique, which consistsof drawing the region of interest and directly calculating the volume. A feature specific of VBM is the possibility to remove confounding effects on between group differences such as global differences in brain shape by a spatial normalization and the inclusion of variables of Total Intracranial Volume (TIV) and age in the final statistical analysis (J Ashburner & Friston, 2000).

Main steps of VBM are described in figure 62. Firstly, the segmentation is performed between these different brain tissues: gray matter (GM), white matter (WM) and four other tissue classes: Cerebrospinal fluid (CSF); bone; soft tissue; air/background. The classification of each voxel in each tissue class begins with the nonlinear deformation registration of the images with tissue probability maps (Figure 63). A priori brain tissue probability maps (i.e. priors) allow classifying probability of a voxel to be part of each specific tissue type using a mixture of Gaussian intensity distribution. The knowledge of the priors is combined with the probability of each voxel's intensity in order to provide posterior probabilities at each voxel using the Bayesian rule. The priors were created using 452 T1-weighted scans coming from the "International Consortium for Brain Mapping" (Mazziotta et al., 2001) and were aligned in atlas space, corrected for inhomogeneities, segmented into tissue classes and registered in MNI space.

The segmentation step includes a bias field correction, which consists of a correction of artifacts related to the physics of MR scanning and to inhomogeneities due to different tissue properties. It is possible to correct with prior knowledge about the intensity variation of those artifacts (e.g. smooth, high frequency distribution). All steps including classification, bias correction and registration are alternated in a single generative model to provide better segmentation than in a serial and separated way. The "imported" images of GM and WM (in

the Dartel format) are realigned by iterative non linear deformations in order to create a common population-average template. The final template will be more “crispy” at the end of the iterations. The aim is to match each individual’s image to a template by minimizing an objective function in order to create a generative model of the brain. A deformation field is created and allows the matching of each individual’s brain space to a common template, which can also be used to transform the images back to the individual space (Dartel procedure (John Ashburner, 2007)). In the normalization step, deformation fields are applied on each individual image in native space to place them in a standard common stereotactic MNI space defined by the ICBM, NIH P-20 project. Then, brain automated labeling can be done in this space (Tzourio-Mazoyer et al., 2002).

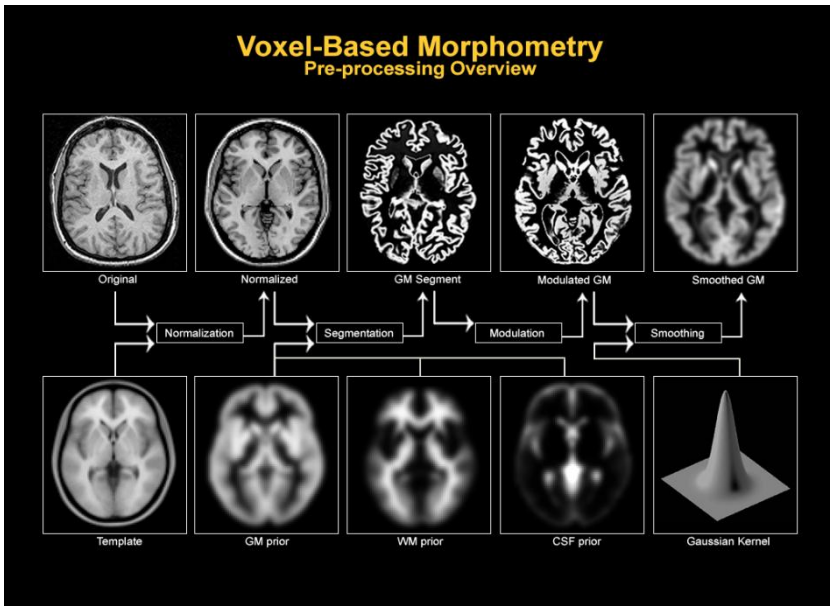


Figure 61. Schema of the main steps of VBM pre-processing (source: http://www.fil.ion.ucl.ac.uk/spm/course/).

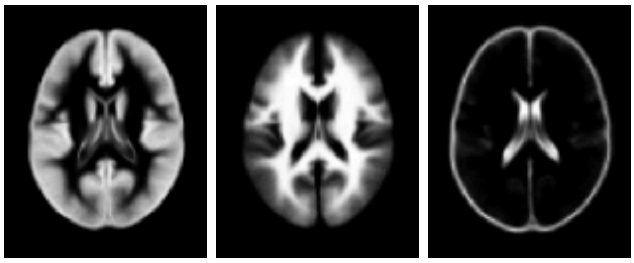


Figure 62. Tissue Probabilistic Atlases provided by the International Consortium for Brain Mapping. From left to right, they represent probabilistic maps of gray matter, white matter and cerebrospinal fluid. Source: SPM8-Matlab toolbox, www.fil.ion.ucl.ac.uk/spm).

Functional MRI: pre-processing. Functional MRI data were analysed using the Statistical Parametric Mapping (SPM8-Matlab toolbox, www.fil.ion.ucl.ac.uk/spm). All the scans were realigned to the first scan of the first session in each individual. This step accounts for head movement in the scanner using six parameters of rigid body transformations (three rotations and three translations) and for the differences in the images between sessions by means of the least squares approach. These parameters can also be included in the statistical design as confounding or nuisance factors. The mean of the functional EPI scans, called the target stationary image, is then co-registered with the anatomical one, which is of higher resolution and that change to match the target image. The matching between the two images is optimized with a cost function that maximizes mutual information. After this step, the anatomical image is bias corrected, segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) tissues and then normalized to MNI standard space. This creates a deformation field allowing all the scans (anatomical and EPI) to be put into the same MNI standard space. The final step is to smooth all the images at a specific size with the Gaussian Kernel, usually about three times more the voxel's size. All these steps are summarized in figure 64.

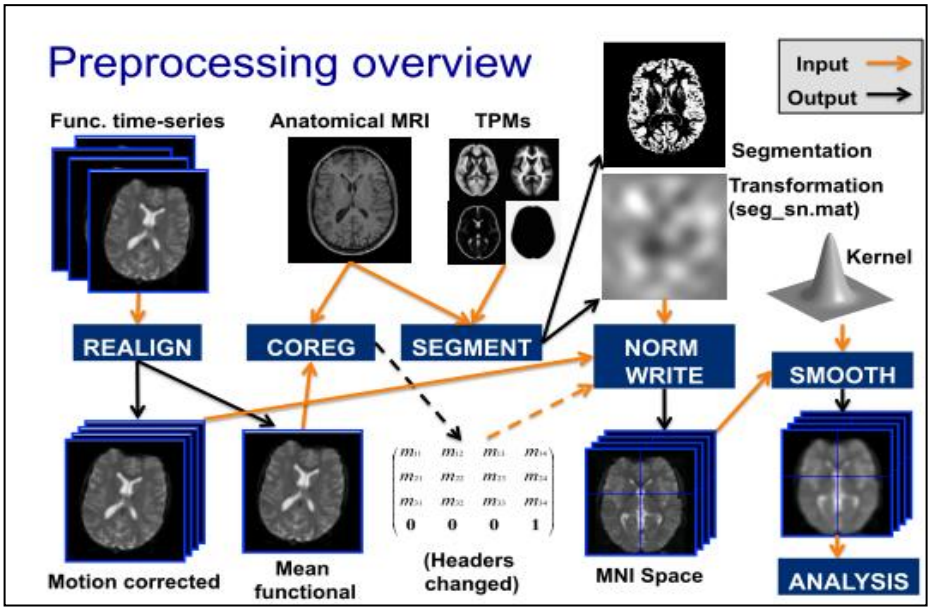


Figure 63. Schema of the main steps of fMRI pre-processing (source: http://www.fil.ion.ucl.ac.uk/spm/course/).

6.4. Statistics

In neuroimaging, the most common approach is the mass univariate statistic, meaning that a statistic is calculated at each voxel of the brain using the General Linear Model (GLM). In each voxel, the model fit of an experimental manipulation is calculated with a size effect estimation (or parameter estimates). Statistical Parametric Maps (SPMs) are then computed and inference is then possible for each hypothesis (or contrast).

The aim of the univariate analysis is to test which brain region is associated with a function, whereas multivariate analysis can test spatial or temporal patterns of multiple brain regions or the interaction between brain regions for this function. The Multivariate approach uses correlation and covariance measures between voxels and can, for example, test functional connectivity. It can also deal with high dimensional data and can directly compare the

contribution of different brain regions. It can predict outcome from independent data, facilitating reproducibility in a new dataset. They are also particularly suited for brain decoding as they can reduce the complexity of data in sparse representations that contain the most information. The multivariate approach also leads to greater statistical power than the univariate one, because the univariate statistic is more conservative in the correction for multiple comparisons at each voxel. However, multivariate statistic can require high computational demands and can be difficult to interpret (Habeck & Stern, 2010).

In this thesis, the multivariate approach was used to answer several different questions.
The multivariate relationship between personality profile and the MTL in a population with MCI is investigated using Multivariate Linear Model (MLM). This is based on singular value decomposition (SVD) to summarize the maximum of covariance between the anatomical data and personality scores (Kherif et al., 2002). The contribution and the multivariate spatial distribution of the MTL in recognition memory was investigated using multivariate Bayesian Statistics (MVB) and the Bayesian Model Selection (BMS) methods (Karl J Friston & Stephan, 2007; K. Friston et al., 2008). Finally, the effective causal connectivity between temporal and frontal brain regions was tested during multiple cue probabilistic learning. For this purpose, Dynamical Causal Modeling (DCM) was used (K J Friston et al., 2003).

6.5. Multivariate Linear Method

Principal Component Analysis (PCA) is a multivariate procedure that extracts uncorrelated components that explain most of the variance in observations. Those observations can be correlated or not. The aim is to reduce the number of variables that explain most of the variance of the data. This is based on the decomposition of co-variance matrix M between variables. The main step involves the orthogonal transformation of the coordinate system of the data into a new system that maximizes the variance explained in the data. Here is the equation of matrix M decomposition (8).

$$M = V L V' \quad (8)$$

M represents the matrix of covariance. V is a matrix whose columns are Eigenvectors of M and V' is the transposed V matrix. L is a diagonal matrix with Eigenvalues of M. The Eigenvectors are the components that combine variables and explain initial data variance. The Eigenvalues correspond to total variance of each variable explained by the component. Each component is independent. The final outputs are saturation coefficients (also called weights or loadings) allowing the combination of scores to a unique score with a multiple regression. A PCA with oblique rotations allows correlation between variables.

MLM is a multivariate extension of PLS and the linear model (9) between the observed brain data Y and a set of the predictors X (design matrix) where model β represents the model parameters.

$$Y = X\beta + \varepsilon \quad \text{with } \varepsilon \sim N(0,\delta^2) \quad (9)$$

The difference advantage of MLM and other multivariate methods PLS and PCA are described in figure 65 (Kherif et al., 2002). In comparison to PLS, the MLM corrects for problems related to scaling differences in the model regressors and the temporal correlation between scans for fMRI data. The difference between PCA and MLM is that MLM can incorporate a priori information with a linear model and is not only data-driven, which can make the results easier to interpret.

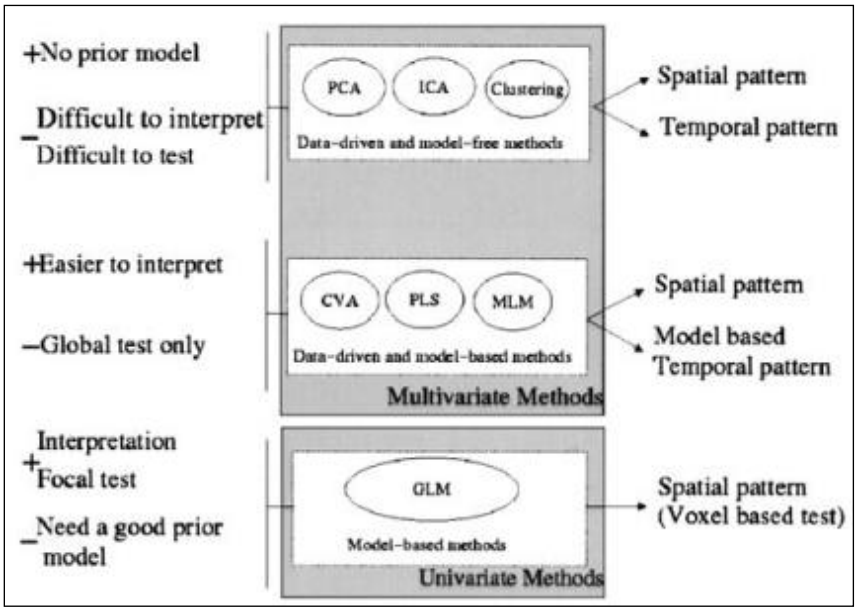


Figure 64. Overview of the advantages and drawbacks of statistical methods mainly used for fMRI analysis (Kherif et al., 2002).

MLM uses both **X** the design matrix of dimensions **n x p** containing effects of interest (with **n** the number of subjects scans and **p** the number of predictors) and the data matrix **Y** of dimension **k** x **n** (with **k** the number of voxels).

MLM decomposes the covariance Z matrix between X and Y (10) into eigencomponents **U** for predictors (X) and **V** for voxels (Y) (11). The correlation matrix X'Y is normalized with

$(X' \Sigma X)^{1/2}$ to overcome scaling differences in the model regressors and the potential temporal correlation of the data. Σ is the temporal covariance matrix of the data (10).

$$Z = (X' \Sigma X)^{1/2} X'Y \quad (10)$$

$$Z = U' \Lambda V = X Y' \quad (11)$$

$U = [U_1, U_2, ..., U_p]$ refers to the eigencomponents/eigenvectors explaining, in order of contribution, the covariance of the predictors, and Λ represents a diagonal matrix of the eigenvalues $[\lambda_1, \lambda_2, ..., \lambda_p]$.