LOUIS PASTEUR UNIVERSITY - STRASBOURG I

Ecole Doctorale des Sciences de la Vie et de la Santé

Discipline :   Sciences médicales

Spécialité :   Neuropsychologie

DOCTORAL DISSERTATION

Prepared by Ekaterina DENKOVA

Submitted for the degree of Doctor of Philosophy in the University Louis Pasteur of

Strasbourg

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THE NEURAL BASES OF AUTOBIOGRAPHICAL MEMORY: HOW PERSONAL RECOLLECTIONS INTERACT WITH EMOTION AND INFLUENCE SEMANTIC MEMORY

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Presented on Monday 25th September 2006

Examining Committee:

Mme Lilianne MANNING (Supervisor)

Mme Marie-Noëlle METZ-LUTZ (Louis Pasteur University Reporter)

M. Hans MARKOWITSCH (External Reporter)

M. Xavier SERON (External Reporter)

M. Christian SCHEIBER (Reader)

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TO MY PARENTS,

MY BROTHER AND MY HUSBAND

I want to give my best thanks to Agathe, Arthur, Sylvie and Jean-Jacques Ringeisen (*'ma famille d'accueil en France'*) for all the pleasant moments.

Finally, I wish to thank warmly my husband Nikolay for strong and endless love, help and support.

ABSTRACT

The main aim of the present thesis has to help improving our understanding of neural mechanisms underlying autobiographical memory (AbM), particularly how personal recollections interact with emotion and influence semantic memory

Our first study investigated the neural correlates of spontaneous re-living of emotion during recollection of personal event cued with personally known faces. Our findings suggested that the use of highly self-relevant stimuli and the collection of data with no previous refreshment of the memory trace (i) influenced the right lateralisation of the activation in the medial temporal lobe (MTL), and (ii) involved increased activity in the cortical midline structures and subcortical circuits, known to sustain the self-generated emotion, even though no emotion was explicitly acknowledged.

In our second study, the aforementioned nonverbal experiment was compared with a verbal one involving pre-scanning testing in order to clarify whether the lateralisation issue of the general network sustaining AbM retrieval. Our finding of a predominantly left-lateralized cerebral network in both experiments suggested that left-sided pattern of brain activations is associated with AbM retrieval *per se* in healthy subjects.

The third experimental work of the present thesis focused on the influence of autobiographical significance on the semantic memory cerebral network. Our results provided functional neuroimaging evidence that autobiographically significant semantic knowledge relies on a pattern of brain activations different from that underlying 'purely' semantic knowledge, with the core difference being located at the MTL.

The last study investigated the neuronanatomical representations of both autobiographical and semantic remote memory in two patients presenting with left temporal lobe epilepsy. (i) We provided functional neuroimaging evidence of the dissociation within remote memory (autobiographical *vs* semantic). (ii) Importantly, we documented dissociation within semantic memory for famous people according to the nature of material. Our last experimental work confirms the importance of combining neuropsychological and neuroimaging methods in appropriate patients in order to better understand human memory functions.

RESUME DETAILLE EN FRANÇAIS

La mémoire autobiographique rend possible l'encodage, le stockage et la récupération des expériences propres à chaque individu (Tulving, 2002). Elle occupe une place importante dans la cognition humaine puisqu'elle se situe au carrefour de l'identité personnelle, de l'affectivité et de la conscience. Plus précisément, elle interagit étroitement avec l'émotion et influence l'organisation et le stockage des connaissances sémantiques. La technique d'imagerie par résonance magnétique fonctionnelle (IRMf), permet d'explorer *in vivo* les régions cérébrales impliquées dans la mémoire autobiographique. Cependant, les travaux qui visent la compréhension des mécanismes neuronaux sous-tendant ce système de mémoire, sont encore peu nombreux. Généralement, ce travail de thèse a pour objectif l'étude à l'aide de l'IRMf des régions cérébrales mises en jeu (i) lors de la récupération spontanée de souvenirs émotionnels et (ii) lors de la récupération de concepts sémantiques qui ont une signification autobiographique. Il comporte 4 volets de recherche.

(1) Notre première expérience en IRMf a pour objectif de comprendre comment l'émotion influence le réseau cérébral sous-tendant la mémoire autobiographique. Il est généralement accepté que les souvenirs autobiographiques et l'émotion sont étroitement liés. L'évocation d'un événement personnel spécifique s'accompagne également du rappel de l'état affectif qui est sans doute l'élément du souvenir le plus complexe. Très peu d'études en neuroimagerie cérébrale ont à ce jour pris en compte le facteur *émotion.* (e.g., Markowitsch et al., 2003; Piefke et al., 2003). Elles ont utilisé uniquement un matériel verbal et n'ont pas apporté de conclusions consensuelles concernant le réseau cérébral qui sous-tend les souvenirs autobiographiques émotionnels. En effet, il a été suggéré que les mots permettent surtout de nommer l'émotion plutôt que de revivre l'état affectif. Selon certains auteurs, les visages de personnes proches comportent une charge émotionnelle et permettent d'étudier le réseau cérébral qui sous-tend les processus émotionnels complexes tel que l'amour maternel ou romantique (Bartels and Zeki, 2003).

Pour indiquer la remémoration d'événements personnels pendant l'examen IRMf, nous avons ainsi choisi de présenter des *visages de personnes proches*. Dix sujets ont participé à cette expérience. Nous avons recueilli des photographies de personnes proches du participant grâce à la collaboration de membres de sa famille. Afin d'éviter le rafraîchissement de la trace mnésique qui pourrait biaiser nos résultats, le sujet n'est pas

présent lors des entretiens examinateur - famille. Durant l'examen en IRMf, le participant évoque des souvenirs spécifiques suite à la présentation de visages de proches. Cette condition expérimentale est comparée à une condition de mémoire sémantique, notamment la reconnaissance de visages célèbres.

Nos données IRMf mettent en évidence l'activation de régions cérébrales qui sont impliquées dans la mémoire autobiographique mais également dans les émotions (le cortex préfrontal médian et orbitaire, la matière grise périaqueducale). Cependant, les données de l'échelle d'intensité émotionnelle de nos sujets indiquent une absence générale d'émotion ressentie. L'apparente contradiction IRMf / introspection peut être due au fait qu'une grande partie de notre émotion est non-consciente (implicite) et donc facilement masquée par le traitement cognitif de la tâche. Sur la base de nos résultats, nous suggérons que l'émotion peut accompagner de manière implicite le rappel de souvenirs personnels et influencer la latéralisation à droite du lobe temporal médian (LTM) qui est une structure clé de la mémoire autobiographique.

(2) La majorité des études en neuroimagerie de la mémoire autobiographique utilise des tests verbaux qui impliquent le recueil des souvenirs auprès des sujets avant l'examen en imagerie fonctionnelle. Les données de ces études ont mis en évidence un large réseau neuronal latéralisé essentiellement à gauche (e.g., Addis et al., 2004). Très peu d'études ont rapporté une prédominance à droite (e.g., Fink et al., 1996). Il a été suggéré que l'utilisation de matériel verbal et le rafraîchissement de la trace mnésique pourraient expliquer la latéralisation majoritairement à gauche des activations. Afin de clarifier ce point, nous avons comparé notre première expérience, qui utilise des visages et n'implique pas un test avant l'examen en IRMf, avec une expérience verbale où les souvenirs autobiographiques ont été recueillis quelques jours avant l'examen en IRMf (Thèse doctorale de Anne Botzung, ULP, 2005). Les deux expériences ont été construites sur le même dessin expérimental afin de permettre une comparaison directe. Les analyses statistiques révèlent une absence de différences significatives entre les deux expériences au niveau des activations cérébrales, à l'exception d'une petite région du lobe pariétal droit qui a été spécifiquement activé pour l'expérience verbale. En accord avec les études antérieures, nos résultats confirment la prédominance à gauche du réseau cérébral sous-tendant la mémoire autobiographique, ceci indépendamment du la nature de matériel (verbal / non verbal) et du rafraîchissant de la trace mnésique.

(3) En 2003, Westmacott et Moscovitch ont introduit le terme de *signification autobiographique* pour désigner le phénomène d'association d'un concept sémantique avec un souvenir personnel. Selon ces auteurs, les concepts qui ont une signification autobiographique occupent une place distincte dans la mémoire à long terme parce qu'ils comportent une composante sémantique et une composante autobiographique. Par conséquent, l'accès à ces concepts peut se faire par la voie de la mémoire sémantique et par la voie de la mémoire épisodique. Westmacott et al. (2004) ont utilisé le paradigme Remember/Know (R, se rappeler/ K, connaître) pour étudier l'influence de la signification personnelle sur la mémoire sémantique chez des patients présentant différentes pathologies : démence sémantique; maladie d'Alzheimer et lésions du LTM. Les résultats ont montré que les patients ayant des lésions du LTM présentent une atteinte de la composante autobiographique avec préservation de l'aspect sémantique. Ces données suggèrent que la signification personnelle est sous-tendue par le LTM. Afin de vérifier les résultats issus des travaux de Westmacott et collaborateurs, nous avons mené une étude en IRMf chez les sujets sains.

Douze sujets ont pris part à cette expérience. Pour atteindre notre objectif, nous avons suivi la méthodologie utilisée par Westmacott et al. (2004). Nous avons proposé une liste de personnes célèbres et nous avons demandé aux participants de faire, pour chacune d'elles, des jugements R et K. Les réponses R correspondent aux célébrités qui ont une signification autobiographique les réponses K correspondent aux célébrités pour lesquelles le sujet ne possède que des informations générales. Cet entretien nous a permis de sélectionner 30 personnes célèbres classées 'R' et 30 personnes célèbres classées 'K'. Durant l'examen d'IRMf, le sujet évoque un souvenir lorsque le visage ou le nom d'une célébrité 'R' est présenté. Par ailleurs, il a pour consigne de reconnaître le visage ou le nom des personnes célèbres 'K'.

Les données obtenues mettent en évidence 2 principaux résultats. (i) Seules les célébrités qui sont associées au vécu personnel (personnes R) impliquent l'activation du LTM. Ce résultat semble ainsi confirmer l'implication spécifique de cette région pour la composante épisodique des concepts qui ont une signification autobiographique. (ii) Le matériel de présentation des stimuli (nom/visage) n'influence pas la latéralisation des activations cérébrales.

(4) Le dernier volet de ce travail de thèse concerne l'étude, en IRMf, de patients présentant une *épilepsie du lobe temporal* (ELT). L'ELT est considéré comme le plus important

« laboratoire naturel » pour l'étude de la mémoire humaine (Snyder, 1997). Pratiquement toutes les études portent sur la mémoire antérograde, c'est à dire l'apprentissage et le rappel d'un matériel lors de la séance d'évaluation. Le nombre d'auteurs qui se sont intéressées à la mémoire du passé (mémoire autobiographique et mémoire des faits publics) chez les patients ELT est remarquablement réduit. Ces travaux ont rapporté soit des déficits de la mémoire autobiographique, soit des troubles de la mémoire des faits publics, soit les deux. L'étude des patients ELT constitue une opportunité inestimable pour comprendre l'effet de l'épilepsie sur l'interaction entre mémoire autobiographique et mémoire sémantique. Ainsi, l'objectif de notre dernière expérience est d'étudier les corrélats neuronaux qui sous-tendent la composante épisodique et la composante sémantique des concepts dans l'ELT. Le protocole d'étude utilisé est celui décrit dans la partie 3. Ce protocole est toutefois susceptible d'être modifié, du fait du déficit de mémoire autobiographique de ces patients. Deux patients ont à ce jour réalisé cette expérience en IRMf.

(i) Le premier patient, JR, avait subi une lobectomie temporale antéro-médiane gauche (mai 2002) suite à une épilepsie pharmaco-résistante de longue date. Le patient a été examiné en neuropsychologie avant et après l'opération (Manning et al., 2005; 2006). Les résultats montrent une dissociation peu courante, notamment un déficit de la mémoire des faits publics avec une préservation de la mémoire autobiographique. Les quelques faits publics rapportés par le patient semblent être liés à son autobiographie.

Pour comprendre l'effet du vécu personnel sur les concepts sémantiques chez ce patient, nous lui avons proposé le protocole décrit dans l'expérience 3. L'entretient préliminaire nous a permis de sélectionner 11 personnes célèbres associées à des souvenirs personnels (personnes R) et 28 personnes associées à des réponses K. JR n'a pas reconnu comme étant célèbre 70% des personnes de la liste. Ainsi, pendant l'examen en IRMf, nous avons présenté uniquement des noms de célébrités R et K. Les données IRMf indiquent 2 principaux résultats. (a) Les personnes célèbres R activent le même patron cérébral que celui observé chez les sujets sains. (b) Par contre, la comparaison entre les personnes célèbres K et les personnes inconnues montre une absence de différences significatives. Ce résultat suggère que les célébrités K sont traitées comme des inconnus. Nous confirmons ainsi que JR présente un déficit au niveau du réseau sémantique élaboré des faits publics.

(ii) Le deuxième patient, RF, souffre d'épilepsie de lobe temporal gauche. Le bilan neuropsychologique montre un déficit important de la mémoire autobiographique avec

préservation de la mémoire des faits publics. Ce patient arrive à associer des souvenirs très généraux et vagues à 14 personnes célèbres. Pendant l'examen en IRMf, nous avons présenté uniquement des noms de célébrités R et K. Les résultats indiquent que les personnes célèbres R activent exclusivement par le cortex préfrontal médian, lequel est fortement impliqué dans les processus référents à soi. Par contre, la comparaison entre les personnes célèbres K et les personnes inconnues montre une absence de différences significatives, ce qui est étonnant étant donné que RF possède des connaissances sémantiques détaillées concernant les célébrités. Nous avons fait l'hypothèse que notre patient n'arrive pas à accéder à ces connaissances sémantiques par les noms pendant l'examen IRMf dû à des contraintes de temps. Ainsi, pendant un second examen IRMf, nous lui avons proposé des visages de personnes célèbres. La comparaison entre les personnes célèbres K et les personnes inconnues en évidence l'activation d'un large réseau cérébral. Ce résultat confirme notre hypothèse et semble aller dans le sens de l'existence de systèmes sémantiques multiples en fonction du matériel (verbal/nonverbal).

En conclusion, ce travail de thèse a des apports multiples. (i) Nous avons montré que l'émotion peut accompagner de façon implicite le rappel de souvenirs autobiographiques et elle peut avoir un effet sur la latéralisation de l'activation du LTM (Denkova et al., *Brain Research,* 2006). (ii) Les données obtenues dans le cadre de notre seconde étude permettent de confirmer la latéralisation majoritairement à gauche du réseau neuronal global sous-tendant la mémoire autobiographique (Denkova et al., *Neuroscience Letters,* 2006). (iii) Notre troisième expérience a conforté l'hypothèse émise par Westmacott et collaborateurs sur la base des données neuropsychologiques que les concepts sémantiques avec signification autobiographique sont traités et sous-tendus par un réseau cérébral qui diffère de celui des concepts sémantiques dépourvus de lien personnel (Denkova et al., *Neuropsychologia*, sous presse). (iv) Enfin, nous avons pu montré qu' en cas de lésion, la signification autobiographique permettrait de préserver certains concepts sémantiques (Denkova et al., en préparation).

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CHAPTER 7 THE INFLUENCE OF AUTOBIOGRAPHICAL SIGNIFICANCE ON SEMANTIC KNOWLEDGE IN TEMPORAL LOBE EPILEPSY: EVIDENCE FROM FMRI IN TWO PATIENTS   114

GENERAL INTRODUCTION

Autobiographical memory is a neurocognitive system that enables humans to consciously retrieve then, re-experience specific events of their own life. Importantly, autobiographical memory 'works' with the rest of the cognitive systems; it closely interacts with emotion and influences semantic memory. The advent of functional neuroimaging techniques has provided a powerful tool for the *in vivo* examination of neural correlates of autobiographical memory. The general aim of this thesis is to advance our understanding of the neural mechanisms underlying retrieval of specific personal episodes. More specifically, using functional Magnetic Resonance Imaging (fMRI), we attempt to investigate how personal recollections interact with emotion and influence the retrieval of semantic knowledge.

This thesis comprises 7 chapters. The two first chapters deal with theoretical foundations of the present work. Chapter 1 presents the most influential models of autobiographical memory and its relationships with emotion and semantic memory. In Chapter 2, we provide a brief overview of neuroanatomy of autobiographical memory derived from lesion research and functional neuroimaging studies in healthy people. Chapter 3 outlines the principles of fMRI technique, the construction of experimental designs and data analysis. Chapters 4, 5, 6 and 7 develop of the experimental work of the thesis. The first three experiments are conducted in healthy subjects and the last experiment is a clinical application of our conclusions, in two brain-damaged patients. Chapter 4 focused on the relationship between autobiographical memory and emotion. The study presented in this chapter attempts to gain knowledge about the influence of emotion on the network of brain activation sustaining remembering past events cued with highly self-relevant nonverbal stimuli, i.e., faces of next of kin, relatives and friends. Chapter 5 is a comparative study of a nonverbal experiment, which did not involve testing before the fMRI session, with a verbal experiment requiring a pre-scanning interview. This comparison aims at clarifying the lateralisation issue of the cerebral network sustaining personal recollections. In Chapter 6 we report a study, which examines the influence of autobiographical significance on the cerebral network of semantic memory. The subject of the last experimental chapter is the interaction between autobiographical and semantic memory in two temporal lobe epileptic patients.

THEORETICAL BACKGROUND

CHAPTER 1

AUTOBIOGRAPHICAL MEMORY AND ITS RELATIONS WITH EMOTION AND SEMANTIC MEMORY

Scientific research findings in the 1970's onwards are inconsistent with a unitary view of memory and favour the multiple memory system approach, grounded on neuropsychological studies of patients with focal brain injuries (Tulving, 1972; 1985; Warrington, 1979). In 1994, Schacter and Tulving argued for distinctions among five major memory systems, each influenced by different variables, governed by different principles, and mediated by different neural substrates. This postulation was based initially on neuropsychological investigations of brain-damaged patients and cognitive studies of healthy subjects and, more recently, it has also been supported by functional neuroimaging investigations (Schacter et al., 2000 for review).

The existence of the following five major memory systems is firmly established by now: Procedural memory refers to the gradual acquisition of sensory, motor and cognitive skills that operate automatically and usually nonconsciously (e.g., learning to ride a bike, acquiring reading skills). Perceptual representation system (PRS) can be viewed as a collection of domain-specific modules that operates on perceptual information about the form and structure of words and objects. Working memory maintains and manipulates items in memory for a relatively short period of time. Semantic memory refers to conceptual knowledge about the world. Episodic memory makes possible the acquisition and retrieval of personally experienced events that occur at a particular time and place.

However, the term episodic memory is used in two different ways in the literature (Kopelman and Kapur, 2001; Wheeler et al., 1997). It is applied (i) to laboratory tasks, which require participants to encode and later retrieve lists of items (e.g., recognition memory tasks) and (ii) to a memory system that enables the re-experiencing of personal events from one's whole life, and thereby corresponding to autobiographical episodic memory. To clarify the terminology is essential because indiscriminate use of the same term for different concepts has been a source of confusion in theoretical discussions. Indeed, conscious recollection of autobiographical events does not have the same status as recognition or recall of a 'laboratory event'.

The present dissertation deals with remembering personal past episodes, and therefore I shall use the term *autobiographical memory* (AbM), which is in accord with recent literature in this field. However, I shall keep the term episodic memory for the description

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of the Tulving's theory as it has been called episodic theory (Tulving, 2002; Tulving and Markowitsch, 1998; Wheeler et al., 1997).

This chapter is divided into four sections. The first section provides an overview of Tulving's theory. In the second section, I shall focus on Conway's model of the structure of autobiographical memory in which the interconnection between memory and the self is highlighted. In the third section, the interaction between emotion and autobiographical memory is considered. Finally, I report recent findings that emphasise the influence of autobiographical significance on semantic memory.

1. Endel Tulving's model of episodic memory

The concept of episodic memory was introduced in 1972 by Tulving in order to distinguish episodic memory from semantic memory in terms of content. The former referred to personally experienced events, while the latter referred to general facts. This first formulation has been further developed and elaborated during the last 30 years (Tulving, 2002, 2005 for reviews). Episodic memory is considered now as a distinct neurocognitive (brain/mind) system that enables humans to consciously re-experience, spatially and temporally, specific events of their own life (e.g., when I failed my driving licence test). Semantic memory refers to knowledge of language, concepts, and facts that are shared by individuals within a culture and not tied to a particular temporospatial context (e.g., knowledge that Paris is the capital of France). It also encompasses personal knowledge (e.g., where we were born, where we live), that has been labelled personal semantics (Cermak and O'Connor, 1983; Kopelman et al., 1989).

1.1. Episodic/semantic memory systems and consciousness

In the current view, episodic and semantic memory are not only described in terms of the nature of the stored information but they also rely on different forms of consciousness, which is considered as the major distinguishing characteristic between the two memory systems (see Tulving, 1985; Wheeler et al., 1997; Wheeler, 2000 for detailed reviews). Episodic memory is associated with *autonoetic* (self-knowing) consciousness, which enables humans to mentally "represent self's existences in the past, present and future" (Wheeler et al., 1997, p. 331). At the core of autonoetic awareness are a sense of a personal self and the subjective experiences through time of that self. Semantic memory is characterised by *noetic* (knowing) consciousness, which allows a person to be aware of

knowledge that s/he possesses or thinks about. Tulving (1985) demonstrated that autonoetic and noetic awareness could be assessed by means of the *remember/know (R/K) paradigm*. 'Remember' refers to expressions of autonoetic consciousness (i.e., recollection of past experiences with the awareness of reliving mentally these events), whereas 'know' refers to expressions of noetic awareness (i.e., retrieval of a given knowledge without self-recollection). Differently stated, remembering or conscious recollection is a by-product of retrieval from the episodic system, while knowing is characteristic of retrieval from the semantic system. The R/K paradigm has been used mainly in laboratory memory tasks (see Gardiner, 2001; Gardiner and Richardson-Klavehn, 2000; Gardiner et al., 2002 for reviews). It requires participants in a memory recognition task to indicate whether they actually remember (R) seeing the item before or whether they simply know (K) on the basis of feeling of familiarity that it has occurred, without recollection of having seen it before. Although self-reports obtained with the R/K paradigm can separate the contribution of episodic and semantic processes in the laboratory investigations, such studies do not encompass the whole time spectrum and, therefore, do not capture autonoetic consciousness in its own right (see below Westmacott et al.'s studies, 2001, 2003, 2004 for application of R/K paradigm to memories previously acquired outside the laboratory). Because autonoetic consciousness is conceptualised as a high-order mental capacity that entails 'mental time travel' (i.e., the ability to represent self's experiences as a continuum from the past to the future), its scientific investigation cannot be accomplished in laboratory studies using recognition tasks (Levine, 2004; Wheeler, 2000; Wheeler et al., 1997).

Essentially, autonoetic consciousness, as stated by Wheeler et al. (1997), is an ultimate achievement of human brain-mind that makes episodic memory possible by allowing a person through recollection of sensory-perceptual details, thoughts, and feeling to become aware of an event as belonging to his/her own past as well as to project into the future. Based on a neuropsychological investigation of brain-damaged patients and on developmental psychology, the authors point out the idea that autonoetic capacity is subserved by the frontal lobe. In phylogeny, as in ontogeny, the frontal lobe is a late-developing region of the cortex dedicated to higher order cognitive functions (Fuster, 2001, 2002). By this view, episodic memory, defined in terms of its dependence on autonoetic awareness, is considered as the most advanced and late-appearing (both evolutionary and ontogenetically) memory system built on top of the earlier systems (Tulving, 2005).

1.2. Relation between episodic and semantic memory systems: SPI model

This relation has been formulated in the Serial Parallel Independent (SPI) model, which postulates that the relations among memory systems are process-specific: encoding is serial, storage is parallel and retrieval is independent (Tulving, 1995, 2001; Tulving and Markowitsch, 1998). It is applied to perceptual (PRS), semantic and episodic memory systems which are arranged hierarchically; for example, PRS is conceived as the lowest level, and episodic memory the highest. The hierarchical ordering reflects the assumption that some operations of higher systems are dependent and supported by the operations of lower levels, whereas lower systems can operate independently of the higher ones. Since the present dissertation deals with autobiographical episodic memory and its interaction with semantic memory, I focus mainly on the relation between these two systems.

According to the SPI model, encoding of information into episodic memory is contingent upon successful processing through semantic memory (see Figure 1). Differently stated, learning of episodic information is entirely dependent on semantic memory but the acquisition of factual knowledge can occur independently of episodic memory. Concerning storage, the SPI model postulates that different aspects of information are stored separately in different systems: semantic aspects are stored in the semantic level and events are stored in episodic memory. Consequently, the retrieval of these aspects is independent between systems. Retrieval could occur from only one system or both of them. According to the subjective state of awareness associated with each memory system, as mentioned above, retrieval from episodic memory corresponds to remember while retrieval from semantic memory corresponds to know.
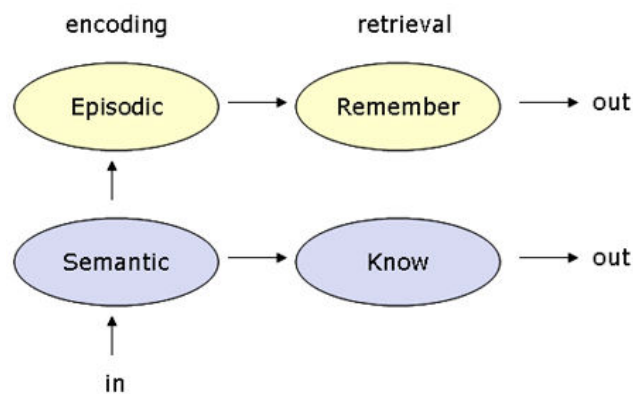
Figure 1. The relation between semantic and episodic memory according to the SPI model (adapted from Tulving and Markowitsch, 1998).

More importantly, the SPI model makes two main assumptions with respect to memory deficits in brain-damaged patients, namely anterograde amnesia (AA) and retrograde amnesia (RA). The former refers to the inability to learn new information after the onset of amnesia, while the latter refers to the inability to retrieve information acquired before the onset of amnesia. The first assumption of the SPI model is that only single dissociations are possible in AA. It means that in patients with AA, the ability to learn new facts and events can be equally impaired or only the acquisition of episodic information can be disturbed in the presence of intact semantic memory learning. The SPI model rules out the opposite pattern of deficit, namely patients showing a deficit in encoding semantic information with intact episodic memory learning. The second assumption is that both single and double dissociations are possible in RA. It means that both semantic and episodic memory retrieval could be equally impaired or that some patients may show episodic memory loss with preservation of semantic memory retrieval, while other patients may exhibit the reverse pattern of memory impairment, loss of semantic memory with relative preservation of episodic memory retrieval. The SPI model seems to provide an accurate account for several neuropsychological data observed in brain-damaged individuals (Tulving, 2001; Tulving and Markowitsch, 1998).

The key issue of this model is that episodic memory can be selectively and more easily affected by brain damage since it is considered as the highest level in the memory hierarchy, the latest and most vulnerable memory system.

1.3. The current formulation of episodic memory

Currently, Tulving's conception of episodic memory consists of three basic constructs: self, autonoetic awareness and subjectively sensed time (Tulving, 2001, 2002, 2005). *Self* refers to the identity of the individual as opposed to the others. It is a mental entity, considered to be the way that an individual reflects on his/her own existence in the past, present and future. Because this self extends beyond the present moment, it is thought to be uniquely human. In fact, the human self is viewed as a continuous entity across time. By contrast, some animals (nonhuman primates) can recognise themselves as entities different from the rest of the world, i.e., they have a self, but it is limited to the present moment. *Autonoetic consciousness* is, as stated above, the capacity to become aware of self's experiences across time. Only human beings possess this capacity that allows them "to reflect upon their own past, present or future" (Wheeler, 2000, p. 598). *Subjective time* is the time extended from self's past to the self's future in one's mind so that an individual

can go back in the past and anticipate the future in her/his mind. Differently stated, an individual can mentally re-experience an event from her/his own past and plan an event in her/his own future.

The current Tulving's formulation of episodic memory emphasises the fact that the conjunction of the self, autonoetic awareness and subjective time makes episodic memory the uniquely human and late maturing memory system that entails metal time travel and that provides the *sense of self-continuity*.

2. Martin Conway's model of autobiographical memory

The concept of the self is also a central component of Conway and Pleydell-Pearce's (2000) model of autobiographical memory, recently revised by Conway (2005). This model considers the autobiographical memory within the *Self-Memory System* (SMS); the term was coined by the authors to emphasis the reciprocal and 'intimate' connection between the autobiographical memory knowledge base and the self.

2.1. The autobiographical memory knowledge base

The autobiographical knowledge base is organised in hierarchical structures which range from the abstract and generic level to the sensory-perceptual and specific level (see Conway, 2005; Conway et al., 2004 for most recent reviews). Each level is defined in terms of content or thematic information and temporal extent (see Figure 2). *Life story schema* represents the most abstract level and they encapsulate different general themes across one's whole life (e.g., work theme, relationship theme). The next level refers to the *lifetime periods*, which contain knowledge about activities, feelings, plans and goals common to a period of time typically measured in years with distinct, although not discrete, beginnings and endings (e.g., when I was at the University, when I lived with A, when I worked at X, etc.). Because lifetime periods did not refer to chronological periods, they may overlap; for example, the period of graduate school can overlap with that of living with A. In contrast to the lifetime periods*, general events* constitute more diverse and more specific level of autobiographical knowledge. They contain information about repeated or temporally extended events that occurred over periods of weeks or months (e.g., work meetings, Sunday visits to grandparents, holiday in Italy). The most specific level refers to *episodic memories*. They correspond to the notion of event-specific knowledge (ESK) which has been developed and used in earlier versions of the model

(Conway, 1996; Conway and Pleydell-Pearce, 2000; Conway and Rubin, 1993). Episodic memories are viewed as records of sensory-perceptual- affective details of an event, and they are typically represented in the form of visual images (Brewer, 1986, 1996). Because they are experience-near and short-time representations (i.e., lasting for short periods of time, minutes and hours), they are distinguished from the conceptual long-term autobiographical knowledge including the three general levels mentioned above (life story schema, lifetime periods and general events). Episodic memory contains sensory-perceptual details of recent experiences, while conceptual autobiographical knowledge encompasses long-term representations. Therefore, the former is conceived as a separate memory system from the latter on the bases of several characteristics, such as specific content, short duration and conscious recollection (Conway, 2001, 2005).
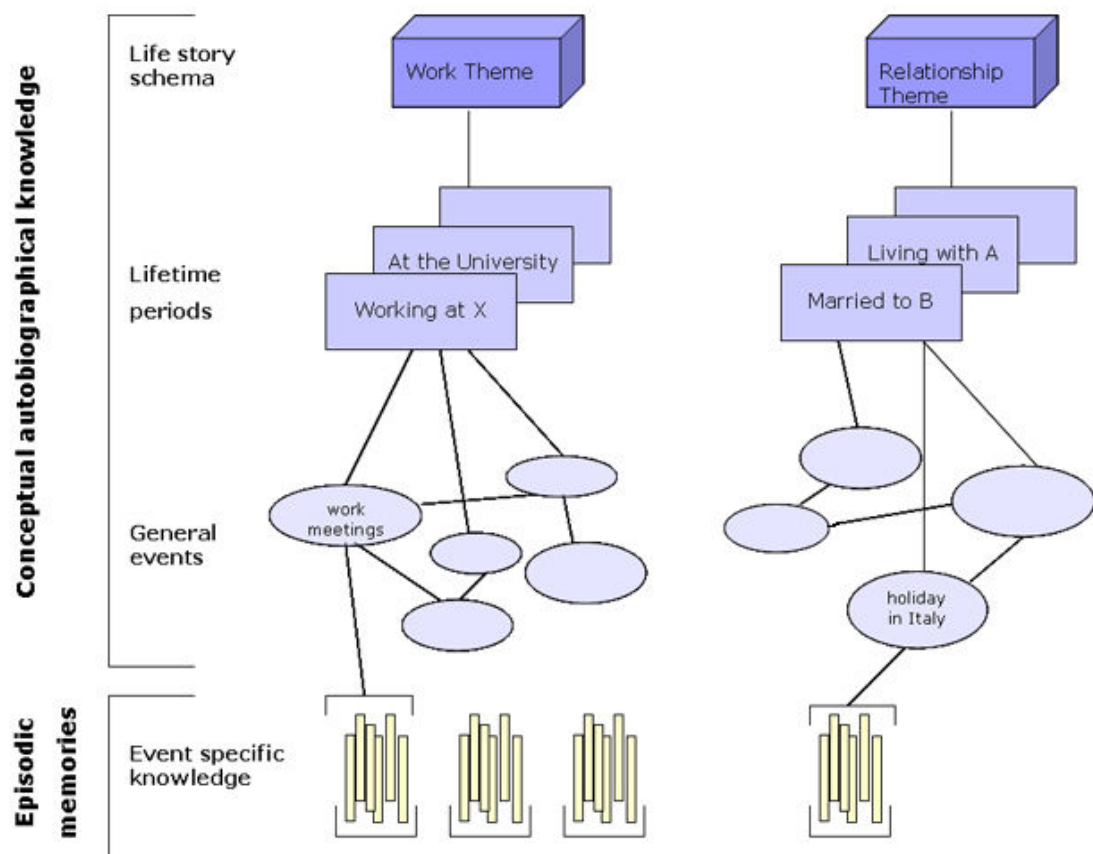
Figure 2. The autobiographical memory knowledge base within the SMS model (adapted from Conway, 2005).

From the SMS model's perspective, episodic memory is thought to appear phylogenetically and ontogenetically before the conceptual knowledge. In fact, episodic memories can be formed early in the life, but it is only when the sense of self is fully developed that they can be organised into cohesive and consistent structures, and consequently, they contribute to ground conceptual knowledge (Conway and Pleydell-Pearce, 2000; see Howe and Courage, 1997 for development of the cognitive self). Hence, conceptually organised autobiographical knowledge is viewed as a late-developing and uniquely human system, which depends on the prefrontal antero-temporal network (Conway, 2001, 2005). Concerning episodic memory, they are mediated by posterior cerebral regions (i.e., temporo-occipital areas) (see below Chapter 2 for more details concerning the neuroanatomy of AbM). This is the major issue that distinguishes Conway's model from Tulving's conception, in which episodic memory is considered as the latest appearing memory system sustained by frontal lobes (see above section 1). By contrast, according to Conway's approach, episodic memories are described as phenomenological records that could be either rapidly forgotten or linked to autobiographical knowledge.

2.2. The self

The integration of episodic memories into the long-term memory representations depends on the *working-self*. The notion of working self, derived from Marckus and Ruvolo (1989), has been developed by Conway and Pleydell-Pearce (2000) to describe the hierarchy of currently active goal structures that control the encoding and consolidation of new knowledge, and the retrieval of specific memories. The working self is conceived as a dynamic goal system which serves to categorise, evaluate and favour the knowledge relevant to the current goal state. As stated by Conway, "It is through the goal hierarchy that new knowledge enters long-term memory and it is through the working self that that pre-existing knowledge is accessed and memories are constructed" (Conway, 2005, p. 597). It is important to note that the working self and the autobiographical knowledge are reciprocally related. On the one hand, the working self 'decides' which memories will be encoded, consolidated and retrieved on the bases of their congruency with the current goals of the self. On the other hand, the autobiographical knowledge determines which goals will be held (e.g., only goals that do not contradict the autobiographical knowledge are maintained).

In addition to the working self, Conway and colleagues postulated a *conceptual self,* which corresponds to the abstract non-temporally specified knowledge about the self (Conway et al., 2004). The conceptual self encompasses knowledge structures such as personal traits, attitudes, value system, beliefs and desires that serve to define the self, the other people and the interactions between oneself and the others. Although it exists independently of the temporally specific autobiographical knowledge, it is reciprocally connected to it; each informs and constrains the other. For example, an individual retrieves more easily and preferentially memories that are in accordance with the images s/he has about her/himself. When the self changes, there are changes in the autobiographical knowledge in order to protect the self. Memories that support the self are highly available, while those that contradict the self are distorted and inhibited. It is the working self that facilitates the access to memories congruent with the self and that renders less accessible or distorted memories acting against the self (see Conway and Holmes, 2004 for details concerning accessibility of AbM).

2.3. Coherence and correspondence

The idea that memories can be either easily available or altered and distorted in order to protect the self is referred to as *coherence or self-coherence* by the authors (Conway, 2005; Conway et al., 2004). At the same time, memories are constrained by the principle of *correspondence,* which means that they must reflect reality by providing sensory-perceptive details that represent, as closely as possible, the experience. The terms of coherence and correspondence, which are derived from Bertrand Russell's philosophical reflection (Russel, 1912/re-published in 2001), have been applied to the modified version of the SMS model (Conway, 2005). They represent, in Conway's model, two simultaneous, even contradictory, demands that influence the construction of autobiographical memories. Coherence entails the notion that memories support and confirm beliefs and images of the self, while correspondence involves an accurate record of experience. The underlying assumption is that the former is the dominant force in the long-term autobiographical knowledge, whereas the latter seems to bias episodic memories. In the current version of the SMS model, both the coherence and the correspondence are taken into account by the working self during the construction of specific autobiographical memories.

2.4. Construction of autobiographical memories

In fact, the autobiographical memories are not static records of the past; rather they are considered as transitory mental constructions within SMS. By this view, construction of a specific autobiographical memory corresponds to the formation of a stable pattern of activation across the autobiographical memory knowledge base (i.e., conjunction of autobiographical knowledge with episodic memories). Specifically, SMS constructs memories either generatively or directly. *Generative retrieval* is an effortful process by which an individual wilfully constructs personal memories. Because it is mediated by a cyclic process (elaborate-search-evaluate), it is controlled by the working self and it requires important cognitive resources. The iterative cycle involves the following three stages: (i) the elaboration of a cue that permits (ii) the search of a memory and (iii) the evaluation of the accessed knowledge. Knowledge access proceeds from the abstract to the specific. In other words, it spreads from lifetime period to associated general events, which are then used to access a set of event-specific knowledge, i.e., episodic memories. The latter are linked to autobiographical knowledge through the working self control. They are represented in the form of imagery, especially visual imagery, which is considered as the hallmark of the construction of a specific autobiographical memory. The end point of the retrieval process takes place when episodic memories are recollectively experienced, i.e., when they enter consciousness. In line with Tulving and colleagues' theory (see above Tulving, 2002; Wheeler et al., 1997), autonoetic awareness is considered as the defining feature of remembering in the SMS model. Autonoetic awareness appears, therefore, as an important concept in both Tulving's and Conway's models since it distinguishes autobiographical remembering from other states, such as imaging dreaming, as well as from the retrieval of facts about the self. Autonoetic awareness allows the rememberer to have the feeling that the current mental construction is a memory of an event experienced by her/himself in the past.

Unlike generative retrieval, *direct retrieval* results in involuntary, spontaneous, unexpected recall of an autobiographical experience. It occurs outside the working self. The most famous and frequently mentioned example of direct retrieval is Marcell Proust's description of how the taste of a biscuit unintendedly brought to his mind a long-forgotten childhood memory (Proust 1925/1981 in *Conway, 2005*). Involuntary recollection can take place on average three times per day (see Berntsen and Hall, 2004; Berntsen and Rubin, 2002 for further details concerning involuntary autobiographical memories). Direct

retrieval is instantaneous, requires few cognitive resources, interrupts ongoing activity, and spreads from the specific to a more abstract level of autobiographical knowledge base. Concerning the latter point, direct retrieval entails the notion that a cue prompts first event-specific knowledge (episodic memories), which in turn activates the associated general event, and consequently, the lifetime period. A stable pattern of activation is formed only if the memory becomes linked to the goal system. In direct retrieval, the working self operates at the end of the memory construction, whereas it guides the whole constructive process in generative retrieval.

Summarising, the dynamic constructive nature of human memory is the major feature of the SMS model. Highly accessible AbM will be those that have high self-relevance. The construction of a specific autobiographical memory within the SMS is under the control of the goal system (i.e., the working self), which has the main function of protecting the *integrity of the self.*

With respect to the goal system, some authors highlight the role of emotion in achievement of goals (e.g., Bagozzi et al., 1998; Ortony et al., 1988). Accordingly, attainment of goals will be experienced as positive emotion, whereas failure to achieve desired goals will be associated with negative emotion (Oatley and Jenkins, 1996). In the following section, an attempt to clarify the relationship between autobiographical memory and emotion is provided.

3. The influence of emotion on autobiographical recollection

3.1. Definition of emotion

Emotion, like memory, cannot be seen as a unitary concept. Emotion is considered as a multidimensional construct which encompasses at least four major components, and, therefore, a general definition of emotion should take into account these characteristics (Clore and Ortony, 2000; Kolb and Taylor, 2000). Indeed, emotion could be described as a complex process involving physiological, behavioural, feeling and cognitive components in response to internal or external events. (i) The *physiological component* includes the activation of the autonomic and central nervous systems. Particularly, it is described in terms of visceral and musculoskeletal changes, and a range of neurochemical and neuroanatomical processes. Bodily changes are also called body-centred feelings by Damasio (1994). (ii) *Behavioural component* refers to different behavioural acts, for

example approach or avoidance tendencies, escape, attack, defence. (iii) The *subjective-experienced component* is the subjective feeling state usually referred to as *affect*. It is worth noting that the terms *emotion* and *affect* are often used interchangeably. However, they must be distinguished: the affects are feeling states which are only one of the constituent of emotion, while emotion designates all the components. (iv) The *cognitive component* refers to the conscious assignment of value or emotional meaning to an external or internal event (e.g., perception, thought, attitude).

Since emotion is constituted by multiple components, it may be assessed by different kind of measures, for instance physiological reactions and verbal subjective reports (Bradley and Lang, 2000 for a complete review of different measures of emotion). On the one hand, physiological response is an objective measure of emotion that involves, among others, the records of heart rate, skin conductance, electrocortical activity by means of physiological autonomic and brain imaging techniques. The skin conduction (or electrodemal activity), is an index of the sympathetic nervous system activity, namely it reflects the activity of sympathetic cholinergic neurons at the level of eccrine dermal sweat glands (Venable and Christie, 1980). It is the most widely used objective measure to access emotion (Tranel, 2000; examples of recent reports are Knight et al., 2005; Nielson et al., 2005). On the other hand, verbal reports represent an evaluative subjective measure of emotion, e.g., self-ratings. In (neuro)psychological studies, verbal assessment of emotion typically involves asking subjects to rate valence or intensity of emotion. Valence refers to attribution of a subjective positive or negative value to an event, while intensity refers to how strongly an emotion is subjectively experienced. In sum, whereas subjective reports give information on conscious evaluation of emotion, physiological reactions give information on occurrence of emotion that may not be directly available to the subject's awareness. The results obtained from the two aforementioned measures could be dissociable, evidence of physiological response in the absence of verbal report of emotion. For instance, a happy facial expression that is presented subliminally may fail to produce conscious verbal report of emotion, yet still entailing activation in autonomic and central nervous systems. Bearing in mind that emotion is considered as a multiple-component process, the failure to verbalise emotion does not mean that it is absent (Davidson, 2003; Lang, 1993). In other words, emotion can be activated without conscious recognition; this is referred to as unconscious or implicit emotion (Berridge, 2003; Öhman, 1999; Öhman et al., 2000).

Until recently, emotion has been neglected by cognitive neuroscience because it was viewed as too subjective and contradictory to the reason (Damasio, 1994; Damasio, 2000). In the recent years, however, it has been considered by cognitive neuroscientists, who posit that emotion interacts with and influences virtually all aspects of cognition, in particular attention, memory and reasoning (Dolan, 2002; Phelps, 2006). Especially, interest in the relationship between emotion and memory has rapidly increased.

3.2. Emotion and memory

From a cognitive standpoint, emotion and memory interact at various stage of information processing, from the encoding and consolidation of memory traces to their retrieval.

The research has primarily focused on emotional learning, particularly in the case of the classical fear conditioning (see Hamann, 2001; LaBar and Cabeza, 2006 for reviews of emotional memory). This form of implicit, non conscious memory describes a situation in which a neutral stimulus, through pairing in temporal contiguity with an emotional stimulus, acquires an ability to predict future occurrence of this emotional event. Converging evidence from neuropsychological studies of brain-damaged patients, fMRI investigations in normal subjects and animal experimentation demonstrates that the amygdala is a critical brain structure during emotional learning (see Bechara et al., 1995 for patients' investigations; Knight et al., 2005 for fMRI investigations; Maren, 2001 for animal research). Indeed, the amygdala has been, until recently, the primary, if not the unique, focus of much research on emotion.

Concerning explicit, conscious memory, it has been demonstrated that subjects recall the emotional items better than neutral items (see Hamann, 2001; LaBar and Cabeza, 2006 for reviews). The general improvement of memory for emotional material is called the emotional enhancement effect. Most investigations have been limited to traditional laboratory tasks. Relatively little information is available on retrieval of emotional memories after long retention interval, that is, retrieval of autobiographical events.

3.3. Emotion and autobiographical memory

Although researchers agree that emotion plays an important role in autobiographical memories (e.g., emotional events are differentially retained than neutral events), the exact relationship between emotion and autobiographical memory is far from being well-

understood. Indeed, emotion is not sufficiently developed in the current theoretical formulation of autobiographical memory.

In the earlier version of the SMS model, Conway and Pleydell-Pearce (2000) address emotion and memory only briefly. Based mainly on research on post-traumatic stress disorder, PTSD (e.g., Brewin et al., 1996; Brewin, 2001), the authors argue that two kinds of information could be combined during effortful construction of specific autobiographical memories, one containing 'factual' event-specific knowledge and the other being the affective aspect of the event. By this view, both the verbally accessible and nonverbally accessible information are thought to be stored and retrieved separately. Additionally, the authors suggest that emotional features may be represented in the form of the verbal labels (happy/unhappy), which are stored in the left hemisphere, while the emotional experiences are stored in the right hemisphere. During generative construction of memories, only verbal labels could be retrieved, while the access to feeling states might be attenuated if they disrupt the cognitive processing. Accordingly, re-living the original affect can occur only rarely.

At the empirical level, to date, relatively few studies have explored the interaction between emotion and autobiographical recollection. This paucity can explain why emotion has not explicitly and completely incorporated models of autobiographical memory.

On the one hand, studies on healthy people demonstrate that emotional experiences tend to be well-remembered. Especially, emotional memories are more vivid than neutral ones, i.e., they may be remembered better and with more sensory-perceptive details (e.g., Comblain et al., 2005; Schaefer and Philippot, 2005, Talarico et al., 2004). Retrieval of vivid autobiographical memories seems to be affected by intensity of emotion rather than its valence (Talarico et al., 2004). Additionally, the role of retrieval cues in inducing emotional states during remembering has been highlighted (Liwag and Stein, 1995; Schulkind and Woldorf, 2005). The authors suggest that because emotional words can simply label emotion rather than induce a feeling state, they might be inadequate cues for re-experiencing affect-laden memories.

On the other hand, clinical research has been primary focused on emotional memories in psychological illness, such as PTSD, in which emotion has destructive effects on autobiographical recollections (Rubin, 2005). For instance, it has been observed that vivid and distorted memories of the traumatic experience come to mind involuntarily (direct retrieval) and disrupt normal cognitive functioning (Brewin et al., 1996; Conway et al.,

2004). In generative retrieval, however, subjects with PTSD show poor recall of specific autobiographical details (e.g., Harvey et al., 1998; McNally, 1997; Raes et al., 2005). Interestingly, a hypometabolism in the medial temporal lobe (MTL) and/or a decreased hippocampal volume have been observed in subjects with PTSD (Gurvits et al., 1996; Markowitsch, 2000). Similarly, it has been demonstrated that depressed individuals have difficulty accessing specific details, i.e., they recall only general memories of emotional experiences (Williams, 1996; Williams et al., 1996). Moreover, subjects with depression retrieve fewer positive memories than control subjects (Lemogne et al., 2005). Concerning neurological patients, recently Buchanan et al. (2006) examined emotional autobiographical memories in individuals with unilateral damage to the MTL. The authors report that patients with right-sided MTL damage recall fewer negative and high-intensity emotional memories than patients with left-sided MTL while the latter show performances similar to the control subjects. These findings provide evidence that the right MTL play a crucial role in emotional autobiographical memories (see below Chapter 2 for functional neuroanatomy of AbM retrieval).

In summary, emotion is considered a complex process involving multiple components, which can occur outside conscious awareness. Although emotion clearly influences autobiographical memory, its involvement seems to be complex and not well-understood (Greenberg and Rubin, 2003). Specifically, re-experiencing feelings during autobiographical recollection remains uncertain and it depends very likely on several factors, such as cues used to probe memories and current cognitive processing.

Apart from interacting with emotion, autobiographical memory interacts also with semantic memory. Recent investigations raised a most interesting hypothesis about the relationship between those memory systems.

4. The influence of autobiographical experience on semantic knowledge

Recently, Westmacott and colleagues have argued that autobiographical experience contributes to the content and the organisation of semantic memory (Westmacott and Moscovitch, 2003; Westmacott et al., 2004). In fact, the influence of autobiographical experience on semantic knowledge was first investigated in semantic dementia by Snowden and colleagues (Snowden et al., 1994, 1995, 1996). Semantic dementia (SD) refers to the progressive and multimodal loss of semantic knowledge, resulting from the

focal degeneration of the temporal neocortex, with the MTL being relatively spared (Snowden et al., 1989). Snowden and colleagues have observed that knowledge that is linked to individual experiential memories remains relatively preserved in patients with SD. For instance, patients understood place names which had personal relevance butter than other place names. A patient, KE, recognised her own objects significantly better than other examples of the same object. The authors hypothesised that concepts relating to patients' experience might be available because of their link to preserve autobiographical memory (Snowden et al., 1996, see also Graham et al., 1999; Snowden et al., 1999). This finding points toward the possibility that some knowledge considered as 'purely' semantic in nature might have also an episodic component.

4.1. The concept of autobiographical significance

The association of a semantic concept with specific personal memories has been called *autobiographical significance* by Westmacott and colleagues (Westmacott and Moscovitch, 2003; Westmacott et al., 2001; 2004). They propose that some semantic concepts may have two components: (i) a semantic component, which contains generic and abstract information, and (ii) an autobiographical component, which involves personally relevant, contextual information. The former belongs to semantic memory, while the latter belongs to autobiographical episodic memory. Consequently, autobiographically significant concepts can be accessed through both the semantic memory and the autobiographical memory route, and therefore they are easier to access. Evidence supporting the contribution of autobiographical significance to semantic knowledge has been demonstrated by Westmacott and colleagues in behavioural studies of healthy subjects and brain-damaged patients (Westmacott and Moscovitch, 2003; Westmacott et al., 2004)

4.2. Empirical evidence of the effects of autobiographical significance

In their initial study, Westmacott and Moscovitch (2003) examine the influence of autobiographical significance on semantic memory in healthy subjects. For that purpose, the authors use the *R/K paradigm* to access real-life memories. They ask the subjects to make R/K judgements about famous people (famous names). R response corresponds to famous persons associated with specific autobiographical memory, while K response corresponds to celebrities about whom the subject possesses only semantic information

without any personal significance. In other words, a subject gives an R response if s/he associates a specific personally experienced episode with the famous person, in addition to the generic, factual knowledge (e.g., I know that Princess Diana was a member of the British Royal family and I also remember I was in the hospital when I heard of her death because I had broken my leg the same day). By contrast, a K response is given if an individual knows the identity but s/he cannot recall any autobiographical event associated with the celebrity (e.g., I know that François Mitterrand was a French president who had a cancer, but I don't associate any personal event with him). Based on the subjects' responses, Westmacott and Moscovitch (2003) construct two lists of famous names: (i) a list of high-R names, i.e., famous names that had received R Reponses from at least 80% of the subjects, and (ii) a list of low-R names, i.e., famous names that had received R responses from fewer than 20% of the subjects. Consequently, those lists are used in two semantic and two episodic 'laboratory' memory tests (i.e., fame judgement, speeded reading, free recall and delayed recognition). The participants are different from those who had made R/K judgement. The authors observe that the subjects demonstrate a performance advantage in both episodic and semantic tasks for high-R famous names relative to low-R names. These results provide evidence that the autobiographical significance affects the way in which knowledge is represented in and accessed from long-term memory.

In a subsequent study, Westmacott et al. (2004) examine the influence of autobiographical significance in patients with SD, Alzheimer's disease (AD), and confirmed or suspected lesions of the MTL. Using the two lists of names in the same tests as in the previous study, the authors report that patients with SD show a preferentially preserved autobiographical component of knowledge, while it is reduced in patients with AD and MTL amnesia. In keeping with the fact that MTL structures are relatively preserved in SD, while they are damaged in the two other pathologies, these results suggest that the autobiographical component relies on MTL. It is important to note, however, that all patients demonstrated a performance advantage for personally significant knowledge when they classified the names as R or K.

Overall, Westmacott et al.'s research reveals that autobiographically significant knowledge assume a distinct status in the long-term memory because it encompasses a personally-relevant episodic component, in addition to the semantic aspect. Although, the two components exist independently, they are also interrelated, thereby creating a rich coherent

representation that is partially semantic and partially autobiographic. In normal people, the two components seem to be simultaneously and automatically accessed while in brain-damaged patients, they can be dissociated. Moreover, Westmacott et al.'s findings suggest that autobiographically significant aspects depend very likely on the MTL while semantic knowledge divorced from personal significance is mediated by the neocortical structures.

Summary

This chapter illustrates that autobiographical memory is a complex cognitive system, which relies on the self and autonoetic awareness and allows human beings to re-live their own experiences through recollection of sensory-perceptive details, thoughts, and feelings. Importantly, autobiographical memory is not isolated from the other cognitive systems. It interacts with emotion and influences semantic memory. This complexity accounts for the observation that remembering past events involves a widely distributed cerebral network.

CHAPTER 2

NEUROANATOMY OF AUTOBIOGRAPHICAL MEMORY

The present chapter deals with the neural correlates of autobiographical memory through (i) lesion research, i.e., studies of brain-damaged patients with memory impairment, and (ii) functional neuroimaging studies in healthy people.

1. Lesion studies

Until around 1980, studies of patients in whom brain damage had caused retrograde amnesia (RA) were the sole approach to identify the neural correlates of remote memory. Overall, they have indicated that AbM impairment can be caused by lesions in many different brain regions, such as the prefrontal cortex (PFC), the medial temporal lobe (MTL) and the posterior neocortical areas (Conway and Fthenaki, 2000; Fujii et al., 2000; Greenberg and Rubin, 2003; Kopelman, 2002a, 2002b; Markowitsch, 2000 for reviews).

1.1. Prefrontal cortex

From an anatomical point of view, the PFC is generally subdivided into three main regions: lateral, orbital and medial/cingulate (see Figure 3, Fuster, 2001, 2002). The lateral PFC can be further divided into anterior (APFC, Brodmann Area, BA 10), dorsolateral (DLPFC, BA 8, 9, 46) and ventrolateral (VLPFC, BA 44, 45, 47) regions. The medial PFC (MPFC) includes areas 10, 24, 25, 32, while the orbital PFC (OPFC) comprises areas 11, 13 and the more orbital part of area 47 (Ongur and Price, 2000; Ongur et al., 2003). The three prefrontal regions are reciprocally connected with one other, with the thalamus, as well as with other cortical and subcortical brain structures. More specifically, the lateral PFC is connected with the MTL and the posterior association cortices, and it is involved in high cognitive control processes (e.g., selection, monitoring, evaluation), whereas the medial and orbital regions are connected with the hypothalamus and the brainstem, in particular, the periaqueductal grey (PAG), and they are involved, among others, in emotional behaviour (Fuster, 2002; Ongur et al., 2003).
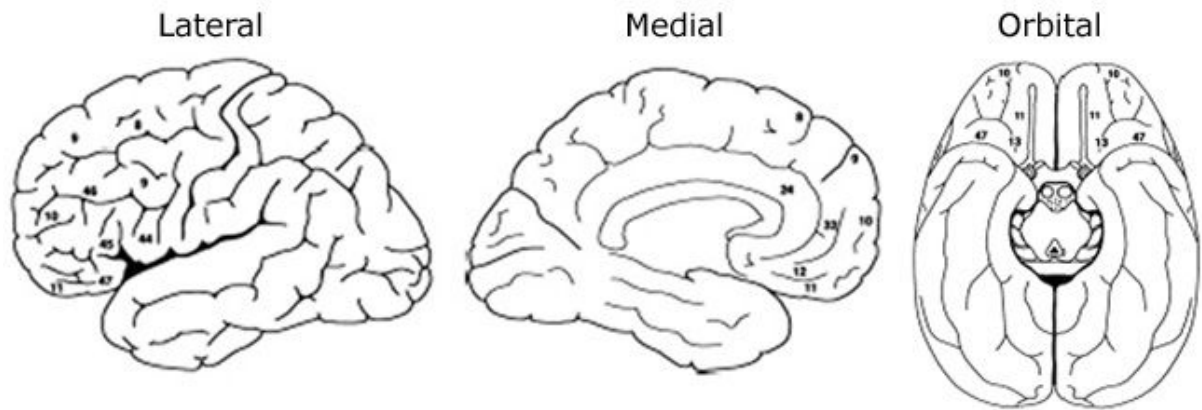
Figure 3. The lateral, medial and orbital regions of the prefrontal cortex with the cytoarchitectonic Brodmann areas (BA) (adapted from Fuster, 2002).

There is neuropsychological evidence that damage to the PFC can disrupt autobiographical memory retrieval (e.g., Conway and Fthenaki, 2000; Kopelman et al., 1999). Patients with frontal lobe lesions, particularly bilateral, are impaired in 'effortful' retrieval, i.e., in organisation of retrieval processes (Kopelman, 2002a). More importantly, based on single-case reports, Markowitsch (1995) suggested that recollection of old personal events depends on a right-sided network formed by the ventrolateral prefrontal and temporopolar cortices, which are interconnected via the ventral branch of the uncinate fasciculus. Within the frontotemporal pathway, the prefrontal region seems necessary for the effortful initiation of recall, while the anterolateral temporal region provides access to the stored representation via its connection with the posterior association cortices. In accord with Markowitsch's hypothesis, several studies have demonstrated that the damage to the right frontotemporal junction can produce deficit in retrieval of old memories (Calabrese et al., 1996; Levine et al., 1998; Kroll et al., 1997).

In short, neuropsychological data suggest that the PFC appears to act as a gating mechanism that channels the retrieval processes to temporal and posterior areas.

1.2. Medial Temporal Lobe

In anatomical terms, the MTL is not a homogeneous region, but consists of different structures that can be distinguished on the basis of histological patterns and their connectivity with other regions (Amaral and Insausti, 1990). In this dissertation, I adopt the terminology of Amaral and colleagues (Amaral, 1999; Lavanex and Amaral, 2000; Suzuki and Amaral, 2004). Accordingly, the MTL includes the hippocampal formation and the perirhinal and parahippocampal cortices (see Figure 4). The hippocampal formation is

composed of dentate gyrus, the hippocampus (*cornu ammonis* fields, CA1-CA3), the subicular complex and the entorhinal cortex. Most memory studies use the term hippocampus to refer to the hippocampal formation. The entorhinal cortex represents the anterior parahippocampal gyrus, while the parahippocampal cortex makes up the posterior parahippocampal gyrus. Importantly, the MTL structures are reciprocally connected with one another and with the neocortex. In particular, the perirhinal and parahippocampal cortices convey information of uni- and polymodal neocortical areas, via the entorhinal cortex, to the hippocampal formation (Lavanex and Amaral, 2000). With respect to the reciprocal neocortical-hippocampal connections, the MTL structures are involved in the establishment of memory traces (Lavanex and Amaral, 2000).
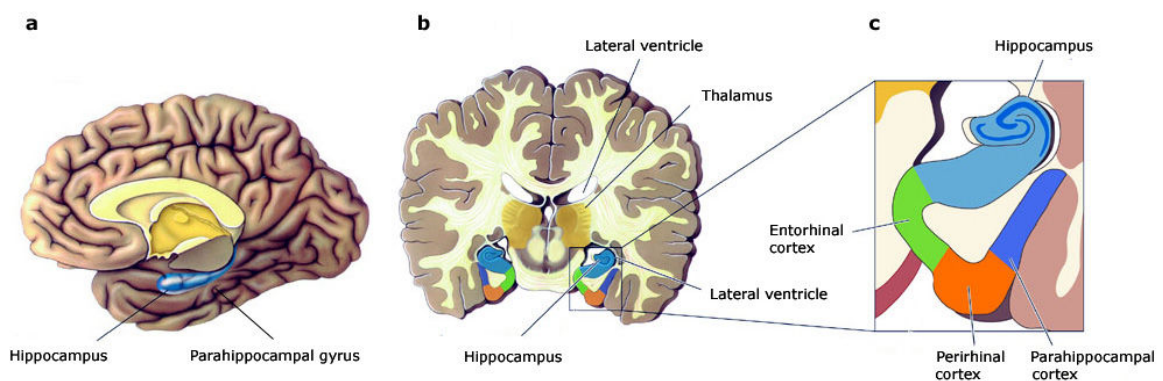
Figure 4. The medial temporal lobe in (a) medial view, (b) coronal view and (c) detailed view (taken and adapted from http://www.bioon.com/book/biology/whole/image/23/23-9.jpg).

In fact, the crucial importance of the hippocampus in episodic memory has been known for decades. However, although neuropsychological studies of brain-injured patients agree that the formation of autobiographical memories depends on the integrity of the MTL, there is a controversy concerning the MTL involvement in retrieval of very remote personal episodes. Two models have been postulated. The *standard model of consolidation* proposes that the MTL plays a time-limited role in memory until the establishment of permanent memory traces in the neocortical regions (Squire and Alvarez, 1995). As a consequence, the MTL is not needed for the retrieval of memories once the consolidation is over and, therefore, MTL lesion affects only retrieval of recent memories, while sparing recall of very remote memories, i.e., temporally graded RA. The standard model did not draw a distinction between episodic and semantic memory systems. Thus, damage to the MTL is thought to cause temporally graded RA for both episodic and semantic memory,

i.e., patients show an equal impairment in retrieval of semantic as well as episodic memories acquired recently, while all remote memories are normally recalled. The clinical data, however, are not completely consistent with this model. For instance, semantic and episodic memory can be dissociated in patients, and damage to MTL can produce RA for autobiographical episodes that covers the patient's whole life. To account for these data, Nadel and Moscovitch (1997) formulated the *Multiple Trace Theory* (MTT), which was recently updated (Moscovitch et al., 2005; see also Moscovitch et al., 2006). MTT postulates a life-long involvement of the MTL in recollection of autobiographical memories. Accordingly, the MTL is thought to be required for remembering vivid context-dependent memories regardless of their age. In fact, the memory trace consists of an ensemble of bound MTL - neocortical neurons, where the MTL appears to act as a pointer or index to the neurons of posterior association cortices where the details of one's life experiences are stored. In other words, the MTL "binds an appropriate set of neocortical traces into a representation that enables one to re-experience a particular event with many of its details" (Moscovitch et al., 2006, p. 187). Each time a personal episode is retrieved, it is subsequently re-encoded, resulting in the formation of multiple traces mediated by MTL-neocortical ensembles. As a consequence, older memories are distributed more widely in the MTL and neocortical structures than recent ones.

Evidence from recent clinical research mostly favours MTT over the standard model. For instance, several neuropsychological studies have reported amnesic patients showing a loss of personal episodes extending across the entire life (Cipolotti et al., 2001; Fujii et al., 2000; Lah et al., 2006; Steinvorth et al., 2005; Viskontas et al., 2000; Voltzenlogel et al., 2006; Westmacott et al., 2001, although there are some exceptions, for example Bayley et al.'s studies, 2003; 2005). Importantly, Gilboa et al. (2005) have found that autobiographical memory loss is associated with atrophy in bilateral, but more pronounced in the right MTL, regardless of the age of the memories. However, the involvement of the MTL in retrieval of remote memories continues to be disputed (Cipolotti and Moscovitch, 2005; Squire and Bayley, 2006).

Overall, the MTL appears to play a crucial role in binding together and indexing the multimodal representations of an event, which are stored in the posterior neocortical regions.

1.3. Posterior cortices

Lesion studies have demonstrated that damage to posterior neocortical regions can cause AbM deficit (Greenberg and Rubin, 2003 for review, see also Conway and Fthenaki, 2000). In fact, as was mentioned above, the posterior areas is thought to store the multimodal representations, namely visual images, sounds, smells, and other sensory components associated with one's life experiences. More importantly, neuropsychological findings point toward the role of visual memory, in particular visual imagery in recollection of autobiographical events. For instance, patients who exhibit visual memory deficit following injuries to occipital lobes were impaired in retrieval of vivid personal memories (O'Connor et al., 1992; Ogden, 1993; Greenberg et al., 2005a; Rubin and Greenberg, 1998). Moreover, patients with damage to the retrosplenial cortex (see Figure 5) show also a severe autobiographical RA, together with visuospatial deficits (Gainotti et al., 1998; Valenstein et al., 1987). It has been suggested that "The retrosplenial cortex may act as an interface between memory retrieval and visuospatial processes" (Gainotti et al., 1998, p. 525).
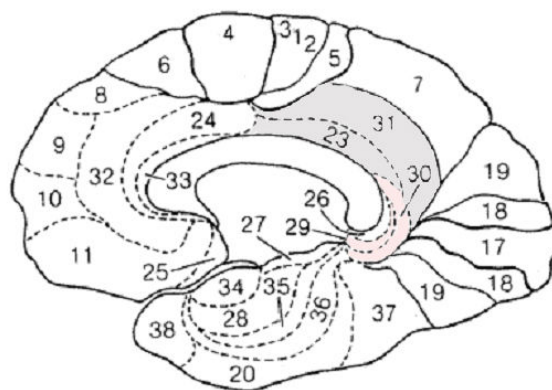
Figure 5. The posterior cingulate region comprising the posterior cingulate cortex (BA 23, 31) and the retrosplenial cortex (BA 29, 30).

Overall, evidence from lesion research has indicated that AbM depends on a widespread network involving the PFC, the MTL and the posterior association areas. Despite extensive neuropsychological investigations, a number of issues related to neural correlates of remote memory remains unclear in the literature. In particular, there is a debate as to whether the MTL plays a time-limited role in memory, or whether it is always involved in the retrieval of personal episodes. Another issue left unclear by lesion studies concerns the contribution

of the right and the left hemispheres to AbM. Although there is evidence that bilateral damage to the prefrontal region and MTL cause more extensive and severe autobiographical memory loss than unilateral damages, most studies have pointed to a particular contribution of right-sided lesions to disrupting AbM retrieval (e.g., Gilboa et al., 2005; Kopelman et al., 1999; Markowitsch, 1995; see also Buchanan et al., 2006 for emotional autobiographical memories). At least one study has demonstrated that left-sided MTL lesion causes time-limited retrograde amnesia for autobiographical memories (Eslinger, 1998).

By the end of the 1980s, the advent of functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), permitted hypotheses derived from lesion studies to be tested in normal subjects. It is important to note, however, that the combined use of lesion and neuroimaging methods has advantages over the use of either approach alone (Mayes and Montaldi, 2001; Price et al., 2003). Moreover, functional neuroimaging of appropriate patients should considerably advance our understanding of neural bases of memory (Kapur and Kopelman, 2003; Mayes and Montaldi, 2001).

Neuroimaging studies of AbM in healthy people are reviewed below, while the principle of the neuroimaging techniques, particularly fMRI, will be described in Chapter 3.

2. Neuroimaging studies of autobiographical memory

The introduction of functional neuroimaging makes it possible to confirm and extend lesion studies, particularly to attempt resolving disputes about neural bases of AbM. However, functional neuroimaging studies focusing on remembering past events are not numerous since they are time-consuming in terms of subject-specific stimulus preparation. In fact, construction of neuroimaging autobiographical experiments, by its nature, requires stimuli specific to each participant, i.e., advanced knowledge of events from his/her life. To this end, several studies collect autobiographical information from participants in a closely related way to that of testing retrograde amnesia in clinical studies, namely by means of verbal tasks. For instance, the subjects are required to describe specific episodes from their past relating to particular cue words, the 'Crovitz technique' (Crovitz and Schiffman, 1974; see Graham and Hodges, 1997 for modified version), or they are questioned about autobiographical incidents and personal semantic information from

different time periods (childhood, early adult life and recent life) through a structured interview, such as the Autobiographical Memory Interview (AMI, Kopelman et al., 1989). Consequently, most of the neuroimaging studies use verbal material to probe autobiographical memories (see Table 1).

Table 1. Functional neuroimaging studies investigating autobiographical memory retrieval.

Study	Purpose of the study	Technique	Retrieval time	PFC lateralisation	MTL lateralisation
Verbal studies with pre-scanning					
Addis et al., 2004a,b	Recollective qualities; Specific and general AbM	e-r fMRI	6s	left	bilateral >> left H and PHG
Fink et al., 1996	Emotional AbM	PET		right	right H and PHG
Greenberg et al., 2005b	AbM retrieval	e-r fMRI	24s	right	left H (ROI analysis) bilateral H and right PHG
Maddock et al., 2001	AbM retrieval	fMRI	2s	left	left PHG
Maguire and Mummery, 1999	Real-word memory retrieval	PET	8s	left	left H
Maguire et al., 2000	Connectivity	fMRI	8s	left	Connection left H-PHG
Maguire et al., 2001	Remoteness	e-r fMRI	8s	left	
Maguire and Frith, 2003a	Aging effect	e-r fMRI	8s	left	left H: young bilateral H: older
Maguire and Frith, 2003b	Remoteness	e-r fMRI	8s	left	left H: life-long involvement right H: temporal gradient
Markowitsch et al., 2000	Emotional AbM	PET	10s	right	
Markowitsch et al., 2003	Emotional AbM	PET	20s	bilateral	left: happy memories

Niki and Luo, 2002	Remoteness	fMRI	10s		left PHG
Piefke et al., 2003, 2005	Remoteness and emotion; Sex	fMRI	4,3s	bilateral >>left	bilateral H and PHG
Ryan et al., 2001	Remoteness	fMRI	20s	bilateral >>left	bilateral H
Vandekerckhove et al., 2005	Emotional AbM	fMRI	25s	bilateral >>left	Left H and PHG
Verbal studies no pre-scanning					
Conway et al., 1999	AbM retrieval	PET	5s	left	
Graham et al., 2003	AbM and SM	PET	30s	bilateral	
Levine et al., 2004	Episodic and semantic AbM	PET	30s	left	right PHG
Piolino et al., 2004	Remoteness	PET	45s	left	right H
Rekkas and Constable, 2005	Remoteness	fMRI	9s	bilateral	bilateral H and PHG
Steinvorth et al., 2006	Remoteness	e-r fMRI	Self-paced search + 6s reminiscence	bilateral >> left	Right H and PHG: search Left PHG: reminiscence
Tsukiura et al., 2002	Remoteness	PET	20s		right PHG
Nonverbal studies no pre-scanning					
Gilboa et al., 2004	Remoteness	fMRI	30s	left	bilateral >> left H and right PHG
Denkova et al., 2006	Emotional AbM	e-r fMRI	Self-paced M= 5.13	left	bilateral >> right

e-r fMRI = event-related fMRI; H = hippocampus; PHG = parahippocampal gyrus; >> = predominance

2.1. Neuroimaging investigations using verbal material

Conway and colleagues' studies

Conway and colleagues have focused on neural correlates of generative retrieval of autobiographical memories, i.e., effortful construction of specific personal memories within the SMS (see above Chapter 1 for SMS model). In a PET study, Conway et al. (1999) probed autobiographical memories by means of a variation on the Crovitz technique. Namely, participants were required to recall a specific memory in response to a given cue word within 5 s. The authors reported left-sided cerebral network involving DLPFC and temporo-occipital regions. Additionally, Conway et al. (2001; 2003) used the electroencephalogram (EEG), which provides information about temporal dynamics of neural activity, to study temporal features of AbM retrieval processes. They focused on variation on the 'slow cortical potentials' (SCPs) within the EEG. The SCPs, which are predominantly cortical in origin, have a time course lasting from seconds to minutes. As a consequence of this characteristic, this method is used to investigate complex and sustained cognitive processes, that is AbM retrieval. Conway et al. (2001, 2003) found that activation temporally extends from the left prefrontal region to posterior areas during generative retrieval of personal events. On the bases of their studies, Conway and colleagues have suggested that the early left prefrontal activation underlies control processes that accompany effortful construction of autobiographical memories, while the later posterior activation reflects the access of sensory-perceptive details. Importantly, left-lateralised network during AbM retrieval has been also documented by Maguire and colleagues (1999 to 2003), research that we expand in the next paragraph.

Maguire and colleagues' studies

In a series of experiments, Maguire and colleagues (1999 to 2003) have examined the neural bases of retrieval of real world memories, which differ along two factors: temporal context (T) and personal relevance (P). Accordingly, there are four memory types: (i) autobiographical events (AE) that are personally relevant and time-specific (T+P+); (ii) autobiographical facts (AF) that are personally relevant but without specific time context (T-P+); (iii) public events (PE) that are time specific but not personally relevant (T+P-); and (iv) general knowledge (GK) that is neither personally relevant nor time specific (T-P-). Several weeks before the scanning session, memories were elicited from participants by

means of a questionnaire. Questionnaire responses were used to construct experimental stimuli, i.e., sentences specific to each participant ("You were Mike's best man at his wedding" is an example of autobiographical event). During scanning, subjects listen to sentences and respond in up to a maximum of 8 s whether it is true or false. In an earlier study, Maguire and Mummery (1999) found that retrieval of all memory types (i.e., AE, AF, PE, general knowledge) is mediated by a predominantly left-sided cerebral network including the MPFC, anterolateral temporal gyrus, temporal pole, hippocampus, parahippocampus, posterior cingulate cortex and temporo-parietal junction. More specifically, retrieval of autobiographical events was associated with enhanced activation of the MPFC, the hippocampus and the temporal pole (Maguire and Mummery, 1999), as well as increased connectivity between parahippocampal gyrus and hippocampus and between parahippocampal gyrus and temporal pole (Maguire et al., 2000).

In an event-related fMRI study, Maguire and Frith (2003a) reported that the left and right hippocampal regions are differentially involved in retrieval of autobiographical events according to the age of participants: while only left hippocampal activation is observed in young, both right and left hippocampi are activated in older adults. The right hippocampal activation is interpreted as reflecting increased use of spatial processing as a compensatory strategy. Interestingly, Maguire and Frith (2003b) have shown that the left and right hippocampi diverge in their responses to memory remoteness in a mixed group of young and older adults: while left hippocampal activation is not affected by the age of memories, right hippocampal activation decreases according to the remoteness of autobiographical memories, showing no activation for memories older than 30 years. Although temporally graded activation of the right hippocampus seems to be, at least in part, compatible with the standard model of consolidation, the permanent involvement of the left hippocampus in AbM retrieval regardless of the age of the recollection is in accord with the MTT. In fact, several functional neuroimaging studies attempt to contribute to accounting for the long-standing debate concerning the role of the MTL in retrieval of autobiographical memories, i.e., whether the MTL is needed for recollection of long-term or very-long-term personal events or whether it is only engaged in retrieval of recent or relatively recent autobiographical episodes.

Studies focusing on remoteness of memory and MTL

The majority of functional imaging studies that examine the effects of remoteness on the neural bases of AbM involve a pre-scanning interview to elicit autobiographical

information, which is then used to create experimental stimuli for the scanning session (Addis et al., 2004a; Maguire and Frith, 2003b; Maguire et al., 2001a; Niki and Luo, 2002; Piefke and al., 2003; Ryan et al., 2001). These studies have provided somewhat mixed results. While some of these studies have observed that MTL activation did not vary with the age of the memory (Maguire et al., 2001a; Ryan et al., 2001), other investigations have shown an increased MTL activity for retrieval of recent events (Niki and Luo, 2002; Piefke et al., 2003; see above Maguire and Frith' s 2003b results). However, Niki and Luo (2002) have reported that recent memories are more detailed than remote ones. Likewise, in Piefke et al.'s study (2003), recent relative to remote recollections have been higher in richness of detail, emotion, picture-likeness and degree of re-experiencing. With respect to the phenomenological properties of memories, Addis et al. (2004a) have shown that the effects of memory age on MTL activation are reduced or eliminated when recollective qualities, such as vividness, emotion and personal significance, are taken into account. This study is important as it suggests that quality of the recollective experience, rather than age of the memory, contributes to the engagement of MTL in AbM retrieval (see also Gilboa et al.'s 2004 study, which is discussed below). However, because all the aforementioned investigations use a pre-scanning test, their findings are ambiguous with respect to whether MTL activity reflects retrieval of memories of the interview or retrieval of the original episodes.

To circumvent the problem of confounding effects of pre-testing, a small number of functional neuroimaging studies focusing on remoteness have probed autobiographical memories directly in the scanner, i.e., without previous refreshment of memory traces (Graham et al., 2003; Piolino et al., 2004; Rekkas and Constable, 2005; Steinvorth et al., 2006; Tsukiura et al., 2002, see also Gilboa et al., 2004). Generally, they have revealed that both recent and remote memories yielded increased hippocampal activation, although Tsukiura et al. (2002) found increased parahippocampal activation during retrieval of memories from recent life and childhood, but not from adolescence. Moreover, Piolino et al. (2004) and Rekkas and Constable (2005) have observed that hippocampal activation is significantly greater for remote episodes than for recent ones. These findings, although not conclusive, favour the MTT over the standard model of consolidation. Even if there is currently a growing number of neuropsychological studies of brain-damaged individuals and neuroimaging investigations in healthy people that provide support for the MTT (Moscovitch et al., 2005; 2006), some patients' reports are in accord with the standard model of consolidation (e.g., Bayley et al., 2003; 2005). On the one hand, the

inconsistency within the findings of brain-injured patients might be attributable to at least two factors: (i) the methodology used to collect and score detailed personal recollections (see Bayley et al., 2005), and (ii) the locus and the extent of the brain damage (damage restricted to the hippocampus or involving other MTL and the neocortical structures). On the other hand, the discrepancy between clinical studies and neuroimaging investigation of normal subjects might be due to the main difference between the two approaches; i.e., clinical studies identify which brain structure is *essential* for a given memory process, whereas imaging studies in neurologically intact people identify the range of brain structures that may be *necessary* for normal performance (Price et al., 2003). Further research combining neuropsychological and neuroimaging methodologies in amnesic patients should be helpful in improving our understanding of the role of MTL in remote memory.

Although neuroimaging research reveals increased activity in MTL structures (hippocampus or/and parahippocampal gyrus) during autobiographical recollections, the lateralisation of this activation varies widely across the studies mentioned above (see Table 1). While several investigations have predominantly left-sided MTL activation (e.g., Addis et al., 2004a; Maguire et al., 2001; Niki and Luo, 2002), a few studies have found right-sided MTL activation (Piolino et al., 2004; Tsukiura et al., 2002) (see Table 1 for more details). To account for the right MTL involvement, researchers put forward different interpretations: (i) delayed activation of the right hippocampus, i.e., the right hippocampus peaks later than the left hippocampus, and therefore it could be not activated in studies that allowed a relatively short time for retrieval (Gilboa et al., 2004; Moscovitch et al., 2006); (ii) retrieval of spatial details (Maguire and Frith, 2003b, see also Burgess et al., 2001), and (iii) emotional features of memories. With respect to the last point, although they did not formally manipulate emotion, Fink et al. (1996) have reported that affect-laden autobiographical memories are mediated by the right MTL structures.

Studies focusing on emotion

There are relatively few neuroimaging studies that explicitly investigate the influence of emotion on the cerebral network of AbM retrieval (e.g., Markowitsch et al., 2000, 2003; Piefke et al., 2003; Vandekerckhove et al., 2005). In all these studies, verbal cues derived from a pre-scanning interview are used to trigger highly emotional personal episodes, in particular, negative or positive memories. In general, the findings of the aforementioned

investigations point to the importance of orbitofrontal and medial frontal/anterior cingulate cortices in retrieval of emotionally laden autobiographical memories. However, there are several inconsistencies across the studies. Firstly, while a few investigations revealed enhanced activity in amygdala while participants recall emotional personal memories (Markowitsch et al., 2000, 2003), the majority found no relation between amygdala activation and emotional intensity or/and valence (Addis et al., 2004a; Maguire and Frith, 2003b; Vandekerckhove et al., 2005). Secondly, Piefke et al. (2003) and Markowitsch et al. (2003) showed that positive and negative recollections engage different cerebral regions, whereas Vandekerckhove et al. (2005) failed to find significant differences between the two memory types. Finally, while some studies observed a bilateral but predominantly left-sided cerebral network (Piefke et al., 2003; Vandekerckhove et al., 2005), others reported right-sided activations (Fink et al., 1996; Markowitsch et al., 2000). One reason for inconsistencies among studies could be that the verbal nature of stimuli acts as a confounding variable. As mentioned in the previous chapter, "Emotional words may be poor cues for autobiographical memories because they simply label an emotion rather than represent an emotion or induce an emotional response" (Schulkind and Wordorf, 2005, p. 1026; see also Liwag and Stein, 1995 for the importance of emotion-related retrieval cues). In particular, verbal labels of emotion could be retrieved, while the generation of emotion might be inhibited and attenuated (see Conway and Pleydell Pearce, 2000). Moreover, because memories have been recently refreshed and the delay between the pre-testing and neuroimaging session differs among the studies, re-living the original affect can be somewhat weakened.

Further verbal studies

Further 'verbal' neuroimaging investigations focusing on different aspects of AbM retrieval are briefly summarised below:

Graham et al. (2003) investigated the influence of time allowed for retrieval on the lateralisation of the AbM retrieval network. The authors hypothesised that the retrieval time in most studies (shorter than 30 s), is not sufficient to evoke detailed events, and therefore the lack of autobiographical specificity would explain activation in the left hemisphere. Using two retrieval times, 15 s and 30 s, Graham et al. (2003) found left-sided and bilateral activations (especially in lateral temporal regions), respectively. However, other studies using a retrieval time longer than 30 s reported a predominantly left-sided

cerebral network during re-experiencing past events (e.g., Piolino et al., 2004, who allowed 45 s for retrieval).Therefore, it is very likely that other factors would more appropriately account for the left-sided lateralisation of the AbM network.

Three recent neuroimaging studies (Addis et al., 2004a, b, who performed two different analyses on the same sample of subjects, and Levine et al., 2004) compared the neural correlates associated with the retrieval of specific and general personal memories. The former refers to temporally specific and unique personal events, while the latter refers to repeated, temporally extended events (i.e., autobiographical facts or personal semantics). The results of the aforementioned studies revealed overlapping but distinct patterns of brain activations related to the retrieval of specific and general events. However, while Addis et al. (2004a) found MTL involvement for both unique and repeated memories, Levine et al. (2004) showed an increased MTL activation for only specific memories. This could be due to methodological variables, such as the pre-scanning interview. Indeed, in the former study participants were interviewed prior to the fMRI session, whereas the latter investigation utilised a prospective method avoiding a pre-scanning testing. Moreover, while Addis et al. (2004a, b) examined retrieval of memories from the subject's whole life, Levine et al. (2004) investigated retrieval of memories from the 6-8 months before the scanning session. Interestingly, using the Partial Least Squares (PLS) statistical model to detect activation changes during the duration of the retrieval, Addis et al. (2004b) reported that the activation pattern of specific memories peaked at 6 to 8 s, while that of general memories reached a peak between 2 and 6 s after stimulus onset.

Using event-related fMRI, Greenberg et al. (2005b) investigated the pattern of brain activations while the subjects retrieved autobiographical recollections in response to cue words derived from a pre-scanning questionnaire. The authors documented functional connectivity among the left amygdala, left hippocampus and right inferior PFC. This finding highlights the role of the frontotemporal pathway in AbM retrieval.

Piefke et al. (2005) examined sex influence on the cerebral network of AbM retrieval. Although they did not observe a difference between the male and female groups on behavioural scores (reaction times, error rates, rating of autobiographical memory features), they found that males relative to females differentially engaged the left parahippocampal gyrus, while females differentially engaged the right insula and right DLPFC. The sex difference is interpreted in terms of different context related strategies

(spatial for males and temporal for females) used during recollections. However, Maguire and Frith (2003a) failed to observe sex differences.

2.2. Neuroimaging investigations using nonverbal material

A few neuroimaging studies of episodic retrieval use nonverbal material (Burgess et al., 2001; Cabeza et al., 2004; Gilboa et al., 2004). However, the two former investigations are more similar to studies of episodic retrieval, which involves recognition of items after a delay. Typically, in episodic memory retrieval tasks, also called 'laboratory' tasks, the subjects encode experimental stimuli, such as lists of words or sets of pictures, and they retrieve them after a short delay. Importantly, memories for stimuli studied in a laboratory setting are dissimilar to naturally acquired autobiographical memories because the latter are complex and multimodal memories embedded in a rich personal and emotional context and formed over time periods of months, years and decades. It is now widely accepted that autobiographical memory retrieval differs from episodic memory retrieval, and most importantly, it is mediated by a distinct cerebral network (Gilboa, 2004 for review).

Burgess et al. (2001) have investigated the cerebral network of retrieval of lifelike events (see also King et al., 2005). Participants navigate around a virtual town meeting objects and people. During the scanning session, they must recognise object and people previously seen. In Cabeza et al.'s (2004) study, undergraduate students took photos of different locations within the University Campus and they were later scanned (about 10 days later) while recognising the photos.

Gilboa et al.'s (2004) study is relevant to autobiographical memory retrieval. The authors examined autobiographical recollections using family photographs, which allowed them to eliminate some methodological variables that could have biased the results in the previous verbal studies. Indeed, the use of personal photographs represents several methodological advantages, particularly concerning the non-refreshment of the memory traces before scanning. In the study by Gilboa et al. (2004), photographs depicting events from five time periods were selected by confederates without the participant's involvement. During the fMRI session, the subjects were asked to re-live the event shown in the photograph. The major finding of this study is that the hippocampus (left more that right) is involved in retrieval of recent (the five last years) and remote memories (events that are more than 15 years old), which are matched for richness. Interestingly, although hippocampal activations were equivalent for vividly recalled recent and remote memories, they were distributed differently in these two conditions: while activations for recent events were centred in the

anterior region of the hippocampus, they were distributed along its antero-posterior axis for remote memories. This experiment provides further support for the MTT. Unfortunately, this study did not deal with emotion.

It is worth noting that using nonverbal stimuli, two PET case-reports have investigated AbM retrieval in amnesic patients (Costello et al., 1998; Markowitsch et al., 1997). Costello et al. (1998) scanned a patient with isolate RA while being presented with family photographs referring to his non-amnesic period and with those belonging to his amnesic period. Relative to the 'non-amnesic', the 'amnesic' photographs involved enhanced activity in the precuneus, which has been interpreted as sustaining visual representations of the initial elements of AbM retrieval (i.e., early stages in retrieval). Of special interest is a single-case study by Markowitsch et al. (1997) with a patient, DO, who had been repeatedly sexually abused as a child. DO can produce drawings of scenes of interactions with adults from her childhood, which were used as stimuli during scanning. Whereas from some of them she was able to vividly recall the depicted episode (conscious memory condition), for others she did not provide specific details although she knew they referred to traumatic experiences (semi-conscious memory condition). Both conditions have yielded activation in the right temporopolar cortex, which appears to play an important role in the retrieval of old emotional memories. More specifically, the left hippocampus and the right parahippocampal gyrus were activated in the semi-conscious memory condition. The authors have suggested that the former might be related to judgement on veracity of memory, while the latter could reflect processing of meaningful visual material.

In summary, neuroimaging studies on AbM retrieval have confirmed the findings that have emerged from lesion studies about the role of the MTL and PFC in AbM. Specifically, they reported increased activity within these structures during recollection of personally experienced episodes. Moreover, the majority of the above-discussed experiments have provided support for the proposal that the MTL is involved in re-experiencing detailed recent and remote personal events. However, several issues remain uncertain. For instance: (i) functional neuroimaging studies are yet inconclusive concerning the role of the right and left hemispheres in AbM retrieval. Although most neuroimaging studies have reported a predominantly left-lateralised cerebral network, a few investigations indicated right-sided pattern of brain activation. The left-sided cerebral network may to some extent reflect the fact that most studies utilised verbal stimuli to cue recollection, even if this possibility

seems unlikely to account fully for inconsistent findings across studies because using nonverbal stimuli Gilboa et al. (2004) found also a predominantly left-lateralised pattern of brain activation. (ii) Very little research has addressed the impact of emotion on the AbM retrieval cerebral network, and the few studies on the topic provide somewhat divergent results. As already discussed, the use of verbal material and the pre-scanning interview in all neuroimaging studies focusing on affect-laden recollections might confound the results. How emotion influences the AbM retrieval network remains unclear. Further work that favours a more ecological approach, eliminating the methodological constraints of previous studies, is needed to help understanding this issue.

TECHNIQUE

CHAPTER 3

FUNCTIONAL MAGNETIC RESONANCE IMAGING

The literature reviewed in the two previous chapters provides the basic theoretical background for the present doctoral thesis. The general aim of the experimental work presented in here is to examine the neural bases of autobiographical memory retrieval. More specifically, we attempt to investigate how personal recollections interact with emotion and influence the retrieval of semantic knowledge. For that purpose, we have used the fMRI technique. To make the best use of the technique, it is important to understand its principles, its strengths and its limitations. Thus, before describing the experiments performed in the context of this work, a brief overview of the fMRI is provided in the present chapter. It outlines the principles of this technique, the construction of experimental designs and data analysis.

As stated in the Introduction, the advent of functional neuroimaging techniques provides powerful tools for the *in vivo* examination of neural correlates of autobiographical memory. Early functional neuroimaging studies used the PET technique because fMRI appeared later. It is important to keep in mind that both PET and fMRI represent indirect measures of neural activity. Indeed, they depend on the fact that there is a close coupling between changes in the activity of a neuronal population and the changes in its blood supply, i.e., an increase in neuronal activity is associated with an increase in blood flow, blood volume and blood oxygen concentration (Roy and Sherrington, 1890). Whereas PET provides the capability of measuring regional cerebral blood flow, indexed by the accumulation over time of a radiotracer introduced into the bloodstream (usually $^{15}O_2$), fMRI detects changes in blood oxygenation. Because fMRI offers a number of important advantages over the PET technique, it has become the method of choice for many studies. For instance, relatively to PET, fMRI strengths include: (i) improved spatial and temporal resolution (e.g., ~3 mm compared to 6-7 mm; a few seconds compared with 40 to 60 s); (ii) absence of radiation exposure and, therefore, unrestricted number of observations per subject; (iii) relatively fast speed of data acquisition and, consequently, the possibility of using more flexible experimental designs. Although fMRI provides the most promising new imaging methods, it is important to keep in mind that it has some relative limitations, which include the confining scanner environment (restricted movement) and acoustic noise (with mechanical vibration). Moreover, there is a reduction of the signal in brain regions

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adjacent to bone and air sinuses, such as the orbitofrontal and inferior temporal cortices, because of susceptibility artefacts (Devlin et al., 2000; Ojemann et al., 1997).

Most importantly, however, advances in fMRI provide new ways to design experiments in order to improve our ability to address hypotheses about the neural correlates of autobiographical memory. Because the optimal choice of an MRI experimental paradigm is constrained by, among others, the properties of physiology being measured, physiological mechanisms of fMRI signal are briefly considered below.

1. Principles of fMRI

fMRI is based on the nuclear magnetic resonance phenomenon (Bloch et al., 1946; Purcell et al., 1946), i.e., on the imaging of protons of hydrogen nuclei that are abundant in the water and fat of the human body. MRI uses (i) a magnetic field to align protons along the direction of the field resulting in a net magnetisation and (ii) a pulse of radiofrequency (RF) waves to excite these protons. After excitation, the protons return to their initial state ('relaxation') by emission of RF energy; this is the signal detected in MRI. Two relaxation processes begin to restore the magnetisation to its initial state. Whereas T_1 relaxation is a recovery of longitudinal magnetisation back to the equilibrium, T_2 relaxation is a decay process of transverse magnetisation back to zero. There is also T_2^* relaxation, which further incorporates the effects of local magnetic field inhomogeneities into the T_2 relaxation. Most relevant to current fMRI studies is the T_2^* relaxation (T_2^*- weighted fMRI sequence).

The mechanism connecting neural activity to the measured T_2^* value is referred to as the *Blood-Oxygen-Level-Dependent (BOLD)* contrast mechanism, which is currently the most widely used fMRI method (Kwong et al., 1992; Logothetis, 2002; Logothetis and Wandell, 2004; Ogawa et al., 1992). As its name suggests, this method exploits the amount of oxygen in the blood as an indirect measure of neuronal activity. When neuronal activity increases, local blood flow and oxygen consumption increase, but the former increases more than the latter, resulting in a local increase in the amount of oxygenated blood and a net decrease in desoxyhemoglobine (dHb). The BOLD method uses the desoxyhemoglobine as an endogenous contrast agent. dHb is paramagnetic, and therefore causes local inhomogeneities in the magnetic field. This reduces the T_2^* -weighted MR signal. During neuronal activation, dHb concentrations decrease in relevant brain regions, i.e., inhomogeneities are not created, leading to an increase in T_2^* and thereby an elevation of signal intensities in MR images. In other words, the positive BOLD fMRI signal during

neuronal activation represents a decrease in the concentration of the paramagnetic dHb. The BOLD response (referred to as the 'hemodynamic response') to a single stimulus trial is delayed in relation to the neuronal activity and extends over many seconds. It has a characteristic time course, which is thought to consist of three phases (see shape of the BOLD response in Figure 6). (i) First, there is an 'initial dip' of the signal intensity below the baseline level due to intravascular desoxygenation before the overcompensatory increase of cerebral blood flow. (ii) Subsequently, the BOLD response increases, yielding a 'positive BOLD response' due to an oversupply of oxygenated blood and simultaneous decrease in the desoxyhemoglobine concentration of the capillary and venule beds of the activated brain area. This positive BOLD response peaks approximately 4-6 s post stimulus and forms the main source of the BOLD fMRI signal. (iii) Finally, the signal returns to baseline after approximately 10 s and it is sometimes followed by an 'undershoot' of the signal below the baseline level that is considered to be due to the return of normal blood flow but with a slow recovery of blood volume leading again to an effective increase in desoxyhemoglobine.
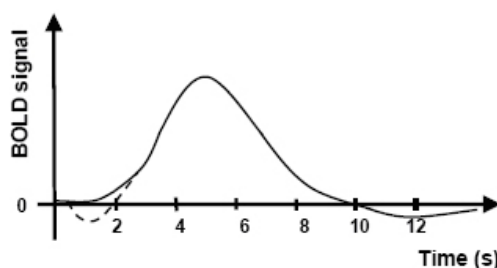
Figure 6. The BOLD signal response to a single stimulus event.

Briefly, although neural activity can occur very rapidly (in order of ms), changes in hemodynamic response occur much more slowly, i.e., the BOLD response starts 1-2 s after the onset of stimulation and evolves over a 10-12 s period (Buckner and Braver, 1999). The fact that the hemodynamic response exhibits considerable temporal blurring in relation to the underlying neuronal activity constrains the development of neuroimaging experimental designs.

2. fMRI experimental designs

Generally, the signal increase elicited by a task of interest (called experimental task or experimental condition) is not measured absolutely but relative to a control task (or control

condition) that is designed to comprise the same sensory, motor and cognitive processes as the experimental task except the process of interest. Differences in neural activity between the two conditions are then attributed to the cognitive process of interest.

2.1. Blocked designs

Hemodynamic imaging was originally limited to the use of *blocked designs*, whereby a series of trials in one condition is presented during a discrete epoch of time. The duration of each block of trials of the same condition is very long (typically 20- 60 s) with respect to the hemodynamic response. The signal reflects an average response from all trials presented in close succession within a block. This time-integrated averaging procedure permits to obtain sufficient signal-to-noise ratios to generate functional activation images. The signal acquired during one blocked condition (e.g., the experimental condition) is then compared with other blocks involving different task conditions (e.g., control condition). Because blocked designs do not allow the randomisation of the order of stimuli and are constrained to grouping trials of the same type with one another in the time, they suffer from a number of disadvantages (Aguirre and D'Esposito, 1999; D'Esposito et al., 1999): (i) The predictability of trial type may cause potential confounds, such as habituation, anticipation or other strategy effects. (ii) It is very difficult to distinguish between experimental effects that are item-related, i.e., which reflect changes in neural activity associated with processing of individual trials, and effects that reflect tonic, state-related changes in activity due to different reasons (e.g., changes in task set or arousal level). (iii) Moreover, blocked designs do not allow data associated with different experimental trials to be sorted and analysed *post hoc* on the basis of subjects' performance, such as correct and incorrect responses. Analysing together events associated with correct response and failure to respond could produce errorless results.

The blocked designs are a necessity for experiments using the PET technique, which needs relatively long intervals to acquire functional data. However, the advent of high-speed MRI methods, capable of imaging the entire brain with a temporal resolution of a few seconds (< 3 s), makes it possible to obtain data on a trial-by-trial basis, so-called *event-related* fMRI (Buckner and Braver, 1999; D'Esposito et al., 1999; Josephs and Henson, 1999; Rosen et al., 1998 for reviews).

2.2. Event-related designs

Event-related designs differ from blocked designs in that individual trials are measured, rather than a temporally integrated signal. It consists of presenting stimuli as isolated, brief events separated in time so that the individual response to a single event can be identified. Such designs may seem counterintuitive given the temporally blurring inherent in the hemodynamic response. However, two main empirical observations have allowed for the development of event-related procedures (Donaldson and Buckner, 2001; Rosen et al., 1998 for reviews). Firstly, even a very brief period of stimulation (as little as 0.5 s) could produce detectable signal changes, despite the delayed and prolonged nature of the time-course of the hemodynamic response (e.g., Bandettini and Cox, 2000). Secondly, it has been demonstrated that the shape of the BOLD response to a given brief stimulation is predictable and relatively stable across events (Dale and Buckner, 1997).These data have suggested that fMRI is sensitive to transient phenomena. However, an important challenge has been to choose optimal spacing between trials in order to avoid any overlap in the hemodynamic response of one trial to the next. To allow the hemodynamic response from one event to be fully restored before the beginning of the next event, early event-related fMRI studies have used long (at least 15 s) and fixed inter-stimulus intervals (ISI) (Bandettini and Cox, 2000). However, other studies have demonstrated that it is possible to obtain robust activation for rapidly and randomly presented trials with short (as little as 2 s) and variable ISI (e.g., Dale and Buckner, 1997; Dale, 1999). The use of variable ISI ('jitters') improves the sensitivity in an event-related design, i.e., improves efficiency from the statistical perspective (Aguire and D'Esposito, 1999; D'Esposito et al., 1997; Dale, 1999; Miezin et al., 2000). It also allows reducing the ability of the subject to engage in anticipatory behaviours prior to the onset of each trial.

Importantly, event-related paradigms offer several advantages over blocked ones: i) Because the order of trials can be randomised, the response to any one event is not influenced by prior events, nor confounded by differences in the subject's cognitive state. (ii) Trials can be categorised *post hoc* according to the subject's performances. For instance, it is possible to exclude incorrect responses, as well as to compare correct *vs* error trials. (iii) It permits the study of unpredictable events, which occurrence can be indicated only by the subjects (e.g., spontaneous transitions in the perception of an ambiguous visual stimulus). (iv) Some events, such as 'oddball' stimuli that, by their nature, violate the prevailing context cannot be blocked. (v) Event-related fMRI experiments can be more

directly compared with other trial-based methods, such as electrophysiological evoked potentials. (vi) It provides a more flexible approach to study brain activations in brain-damaged patients. Because of these advantages, event-related experimental designs have become popular in fMRI research in the recent years.

3. fMRI data analysis

The goal of analysis is to detect, in a robust, sensitive, and valid way, those parts of the brain that show increased intensity at the points in time that stimulation was applied (e.g., Lange, 1999; Smith, 2001 for overview of fMRI analysis). Currently, the most popular approach to obtaining activation maps is Statistic Parametric Mapping (SPM) software (Wellcome Department of Imaging Neurosciences, London, UK; Friston et al., 1995), which is also used to analyse fMRI data of the experiments presented in this thesis.

Initially, the data are pre-processed to remove various kinds of artefacts in the data, and to condition the data, in order to aid the later statistics. The main pre-processing steps involve: (i) realignment that removes the effects of subject movement; (ii) spatial normalisation that transforms images into standard anatomical space and (iii) smoothing, which is a process by which data points are averaged with their neighbours in a series. Statistical analysis is then carried out to determine which voxels are activated by the stimulation. SPM uses the General Linear Model (GLM) model for the way in which BOLD response depends on the stimulus (Friston et al., 1995). GLM sets up a model (i.e., a general pattern which one expects to see in the data) and fits it to the data. The GLM is often formulated in matrix notation that includes all variables that may explain the evoked neuronal responses. Each column of the design matrix ('regressors') corresponds to effects of interest (manipulations designed within the experiment) and effects of no interest (e.g., confounds, error). Statistical inferences are made about the size of a given effect of interest in relation to the error variance or the other effects using F and T statistics, respectively.

Typically, data analysis from multiple subjects proceeds in two stages. The first level represents within-subject analysis, i.e., it takes into account within-subject variability. A model is constructed for each subject, and there are as many models as there are subjects. The results of these analyses are entered into a second level that is called random effects analysis (RFX). RFX takes into account within-subject and between-subjects variability and therefore makes it possible to make inference about the population from which the subjects are drawn. It is generally accepted that groups containing fewer than about 10

subjects are suboptimal to perform random effect analysis (Smith, 2001; Friston et al., 1999).

fMRI is undergoing rapid development so that theoretically driven questions about neural substrates of a variety of functions could be more confidently tested.

EXPERIMENTAL WORK

The thesis' experimental work comprises 4 studies described in chapters 4, 5, 6 and 7, respectively. Three of them are conducted in healthy subjects, while study 4 examines two brain-damaged patients. The aim of each of these experiments is briefly presented below.

Study 1

The aim of this study is to improve our understanding about the relationships between emotion and AbM. Using highly self-relevant stimuli, i.e., faces of relatives and friends, we attempted to investigate, most particularly, how emotion influences the neural correlates of autobiographical recollection. (Denkova E et al., *Brain Research* 2006, 1078, 143-150).

Study 2

The purpose here is to help to clarify the lateralisation issue of the cerebral network sustaining personal recollections. To this end, we compared a nonverbal experiment, which did not involve testing before the fMRI session (study 1), with a verbal experiment requiring a pre-scanning interview (Anne Botzung's PhD dissertation). (Denkova E et al., *Neuroscience Letters* 2006, 407, 32-36).

Study 3

This study was designed to examine the influence of autobiographical significance on the cerebral network of semantic memory. We particularly investigated whether semantic knowledge associated with personally experienced episodes relies on a different pattern of brain activations than 'purely' semantic knowledge. (Denkova E et al., *Neuropsychologia,* in press).

Study 4

The aim of study 4 was to investigate the effects of autobiographical significance on the semantic memory cerebral network in two patients presenting with MTL damage.

Every experiment was approved by the Alsace Ethics Committee. Functional MR imaging was performed on a Bruker 2 Tesla (Karlsruhe, Germany) scanner in the Laboratory of Neuroimaging *in vivo*, University Hospital of Strasbourg (see Figure 7). During fMRI sessions, experimental stimuli were projected onto the centre of a semitransparent screen, which was positioned behind the subject's head (see Figure 8). They were viewed by the participants through prism glasses.

Figure 7. The Bruker 2 Tesla scanner in the Laboratory of Neuroimaging in vivo where all fMRI experiments were conducted.

Figure 8. The system of stimuli projection.

<p style="text-align:center">CHAPTER 4</p>

<p style="text-align:center">IMPLICIT EMOTION DURING RECOLLECTION OF PAST EVENTS: A NONVERBAL FMRI</p>

<p style="text-align:center">STUDY</p>

1. Synopsis

Although it is generally acknowledged that AbM interacts closely with emotion (i.e., an event is more vividly remembered when it is emotional), our understanding of neural correlates of this interaction is still at an early stage. Little research has been addressed concerning the impact of emotion on the cerebral network underlying AbM retrieval (e.g., Markowitsch et al., 2003; Piefke et al., 2003). As outlined in Chapter 2, the results of these few studies were not conclusive. Importantly, all investigations used verbal stimuli to cue recollections, and they involved pre-scanning interview. These methodological issues might have confounded the results. Generation of emotion during recollection could be modulated by the verbal nature of stimuli and the refreshment of memory trace.

The present study was designed to gain knowledge regarding the influence of emotion on the network of brain activation sustaining remembering past events. Several studies investigated the neural correlates of different affective states by means of next of kin faces. Such stimuli are experienced as strongly related to one's own history. Consequently, we decided to use photographs of faces of relatives and close friends in order to probe the emotional component of AbM retrieval. The underlying assumption is that providing the subject with faces of other significant people might result in spontaneous re-living of emotion. Photographs were collected from family members without the participant's involvement, thereby avoiding the refreshment of the memory trace prior to the scanning session. During the fMRI session, participants performed an AbM task and a semantic memory control task. In the former, participants were asked to evoke a unique autobiographical episode following the presentation of personally known faces. The latter consisted of famous faces recognition. We carried out a post-fMRI debriefing session to collect participants' memories and their emotional intensity.

Surprisingly, subjects' verbal reports indicated low or no emotion during remembering. However, comparing the AbM task with the semantic task, we found increased activation in regions associated with emotion, such as the medial and orbital prefrontal cortices and the subcortical structures. The post-scanning behavioural data together with the neuroimaging data provided evidence that emotional aspects were implicitly involved

during recollections. Our findings suggest that the use of highly self-relevant stimuli and the collection of data with no previous refreshment of the memory trace influence the right lateralisation of the activation in the medial temporal lobe (MTL).

2. Introduction

Remembering by consciously re-experiencing detailed spatially and temporally specific events of one's own life characterises autobiographical memory (Tulving, 2002). Functional neuroimaging techniques used to explore the neural bases of this memory system in healthy people show an extended medial and predominantly left-sided cerebral network (see Gilboa, 2004; Maguire, 2001 for reviews) more frequently than right-lateralised (e.g., Fink et al., 1996) or bilateral (Graham et al., 2003) activations. Refreshment of the memory trace before the imaging experiment and the use of verbal stimuli to cue autobiographical recollections were the two methodological issues deemed likely to influence the left-lateralisation findings (Maguire, 2001; Piefke et al., 2003). Recently, Gilboa et al. (2004) investigated retrieval of personally experienced events by means of family photographs, a technique that presents the advantage of avoiding reactivation of the memories prior to the scanning session using fMRI devices and an ecological method of studying recollection of past events. The authors reported MTL involvement during the remembering of both recent and remote vivid episodes, and predominantly left-lateralised prefrontal activation, which seemed to characterise autobiographical memory retrieval (Gilboa, 2004).

Human faces are the most frequently used nonverbal stimuli in neuropsychology (McCarthy and Warrington, 1990). According to the degree of familiarity, facial stimuli usually belong either to the category of famous faces, known mostly through the media, or to the category of personally known faces of relatives, friends and acquaintances. The former have been used in neuroimaging studies to explore the cerebral correlates of semantic memory as identification of these faces involves retrieval of person-identity information stored in long-term memory (Bernard et al., 2004; Haist et al., 2001; Leveroni et al., 2000). Concerning faces of personal acquaintance, such as family members, friends and colleagues, Gobbini et al. (2004) demonstrated that they induced stronger cerebral activations than famous faces. The authors suggested that processing personally known faces might be *spontaneously* associated, beyond the facial recognition, with knowledge about a person's personality, episodic memories and an emotional response to that person.

Next of kin faces were typically used to investigate brain areas responsible for producing different affective states since they belong to one's own life history and they are emotionally indistinguishable to an external observer (for example Gundel et al., 2003; Leibenluft et al., 2004; Nitschke et al., 2004). Studying romantic and maternal love, i.e., complex affective states, Bartels and Zeki (2000, 2004) showed a specific network of brain areas when an individual views the face of "someone who elicits a unique and characteristic set of emotions" (Bartels and Zeki, 2000, p. 3833). To investigate the emotional aspect of autobiographical memory, we used the same stimuli to warrant the affective-laden feature of the recollections. Indeed, emotion is a crucial component of autobiographical memory and one of the most complicated (Greenberg and Rubin, 2003). Neuroimaging studies focusing on the influence of emotion on the cerebral network underlying personal recollections have used different experimental designs and obtained, not surprisingly, a variety of results. Thus, some studies compared brain networks sustaining positive and negative memories selected prior to the imaging experiment (Markowitsch et al., 2003; Piefke et al., 2003), while other reports investigated how emotion modulated cerebral activations (Addis et al., 2004a, emotional intensity; Maguire and Frith, 2003b, emotional valence and intensity). In general, the medial prefrontal cortex, considered as one of the key structures in the literature on emotion (Phan et al., 2002), has been almost invariably found to be activated in autobiographical studies, "as memories carry emotional meaning" (Gilboa, 2004, p. 1346). On the contrary, the activation of amygdala was not directly correlated with emotional intensity or the valence of autobiographical recollections (Addis et al., 2004a; Maguire and Frith, 2003b). Although the neural correlates of emotional memory have been investigated within the context of autobiographical memory, none of the neuroimaging studies, to our knowledge, have documented spontaneous remembering of emotionally laden recollections with no previous testing.

The aim of the present study was to investigate the neural correlates of emotion induced by spontaneous (i.e., close to real life) remembering of personal episodes. To address this issue, we used highly self-relevant stimuli, namely photographs of relatives' and friends' faces avoiding refreshment of the memory traces before the neuroimaging experiment. We hypothesised that autobiographical recollection cued with personally known faces might involve joint activation in structures associated with affect and memory retrieval.

3. Material and methods

3.1. Subjects

Ten healthy subjects (4 males and 6 females) participated in the fMRI study, which was approved by the local ethics committee. The subjects were right-handed and native French speakers (mean age = 40.6 years; SD = 5.7; mean years of education = 18.0; SD = 2.8). As a matter of routine, subjects were screened to rule out medical or neurological problems, current medications and/or MRI contraindications. They had normal or corrected to normal vision. The subjects gave written informed consent and were paid for their participation.

3.2. Experimental stimuli and tasks

The experimental fMRI stimuli consisted of 590 coloured photographs (50 pictures of relatives and friends x 10 participants, plus a pool of 50 famous faces and 40 unknown faces used for the 10 subjects) processed using Adobe PhotoShop (version 7.0) to have the same size (250x300 pixels) and neutral background in order to guarantee similar perceptual input. Luminance and contrast were adjusted to make the images as comparable as possible. Both the personally familiar faces and the famous faces belonged in different periods of the past (from 1950 to 2004). The 50 photographs per participant of faces of next of kin, other relations and close friends were the cues for the 'autobiographical task'. The photographs were collected with the help of the participant's family (parents, spouse and, in a few cases, children). The participant did not know which photographs were selected by the examiner and the precise task he/she would be asked to perform during the fMRI session. The collection and preparation of photographs were extremely time-consuming. The pictures were all scanned using a Hewlett Packard Scan Jet 63000C. The faces of people relevant for the subject were extracted from photographs and made up the pool of experimental cue stimuli (one face = one stimulus). No two stimuli were identical. Photographs of the subject were never presented to avoid confounding cerebral activations sustaining autobiographical memory with those underlying self-recognition. Our decision to show faces alone was to minimise the differences in visual stimulation.

In line with several functional neuroimaging studies (Greenberg et al., 2005b; Maguire and Mummery, 1999), we chose a control condition involving semantic retrieval, namely the identification of faces of celebrities. Fifty famous faces constituted the stimuli of the control task. The faces were those of politicians, actors, musicians and sports figures

whose fame is associated with a particular period from the 1950s to the present (e.g., President J.F. Kennedy, Celine Dion). They were selected through a behavioural pilot study (n = 18 normal subjects), in which we carried out a random presentation of 70 photographs of celebrities and 30 photographs of unknown faces on a computer screen using Inquisit 1.33 (Seattle, WA: Millisecond Software LLC).We retained the 50 photographs of famous faces that were associated with the fastest reaction time for correct recognition scores for the fMRI experiment.

Selection of the unknown faces was carried out as follows: half of them were collected through the behavioural study mentioned above on the basis of the reaction time for rejecting a foil. The other half consisted of the faces of other participants' relatives. Independently of the condition, all unfamiliar faces were used as foils to maintain the subject's attention during the tasks. The first 20 unknown faces were presented as distractors during the 'control condition' and the remaining 20 items as distractors in the 'autobiographical condition'.

Prior to the scanning session, subjects were given detailed instructions about the two tasks (autobiographical and control tasks). Examples of autobiographical events and a practice trial were provided in order to ensure that subjects tried to remember a specific single episode from their past rather than general or repeated events. (i) In the autobiographical task, the subjects were asked to recollect a personal episode when a face of relative or friend appeared on the screen. They were instructed to pressing the left button of a PC mouse *yes* once retrieval of an autobiographical event was over. If they viewed the face of an unknown person (distractor) or if they failed to evoke a specific autobiographical episode, the right button *no* was to be pressed. (ii) In the control task, the participants were instructed to press the left button *yes* if they successfully identified the face of a famous person and the right button *no* if the face was unknown (distractor). The subjects were asked to focus on the centre of the display throughout the fMRI session.

3.3. Experimental design

Retrieval of autobiographical memories is an effortful process characterised by variable speed in evoking memories between and within subjects. Therefore, the self-paced event-related fMRI design (Daselaar et al., 2001) was chosen as a flexible and suitable approach for autobiographical remembering during scanning. The fMRI conditions, 'autobiographical' and 'control', each comprised ten sequences with seven faces per

sequence (see Figure 9). Independently of the condition, the seven faces forming any sequence were presented in a random order and with the same 5:2 ratio of known to unknown faces. Thus, five faces of relatives and friends and two unfamiliar faces were presented within an 'autobiographical' sequence and five famous faces and two unknown faces were presented within a 'control' sequence. The two types of sequences were presented alternately and were separated by a fixation cross that lasted 15 s. Each facial stimulus was shown during 1.24 s on the screen, which was blank during the interval between stimulus offset and onset of the next face. Although presentation of facial stimuli was self-paced, a time limit of 11.24 s was maintained in the event of no response in the autobiographical condition and a time limit of 3.74 s in the control condition. These time limits were based on pilot experiments showing that all the responses fell within these interval periods (Botzung et al., 2003). Once the subject's response was given or the time limit reached, the post-trial interval started. This interval varied from 2 to 5 s in the autobiographical condition and from 1.5 to 4.5 s in the control condition according to the variable time-limit duration in the two conditions. The variable inter-stimuli intervals ('jitter') as well as the random presentation of stimuli within a sequence have the advantage of reducing potential confounds, such as habituation, anticipation, or set strategy effects (Aguirre and D'Esposito,1999; Rosen et al., 1998).

Presentation, timing of stimuli and response recording were performed using Inquisit 1.33 (see above).
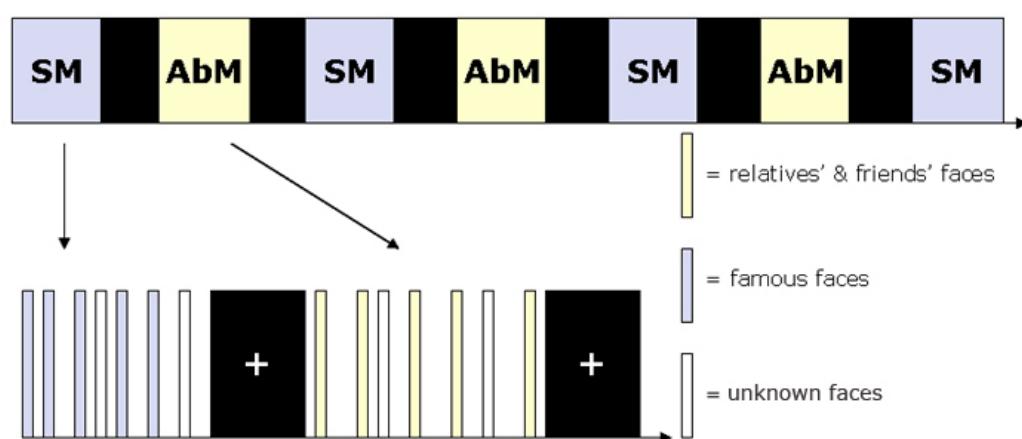
Figure 9. Schematic illustration of the experimental design of study 1. The autobiographical memory (AbM) sequences and the semantic memory (SM) control sequences are presented alternately and separated by a fixation cross. Stimuli are randomly presented within each sequence.

3.4. Post-scanning debriefing

Immediately after scanning, we carried out a debriefing session. Each participant was shown again the faces of subjects' relatives and friends he/she had just viewed during the scanning session. The subjects were asked to verbalise the events they evoked during the fMRI session and they rated each memory on a five-point scale for the intensity of emotion, ranging from 1 = no emotion to 5 = highly intense emotion. They also dated approximately their memories. The debriefing data were used (i) to take into account only the stimuli that triggered recollections of detailed spatially and temporally specific personal episodes during the fMRI session and (ii) to compare the intense emotion ratings with low or absent emotional evocation.

3.5. fMRI scanning parameters

Whole-brain imaging was performed on a 2 Tesla S200 (Bruker, Karlsruhe, Germany) whole-body MRI system. Functional images were acquired in the axial plane with echo planar imaging (EPI) pulse sequence using BOLD contrast with the following parameters: TE = 40 ms, TR = 2500 ms, matrix size = 64x64, 32 slices per volume, slice thickness = 4 mm. Functional MRI was followed by a structural MRI session, where data were obtained using a three-dimensional T2-weighted sequence (TE = 73.8 ms, TR = 14000 ms, matrix size = 128x128x48). Functional MRI images were acquired after five dummy scans, once magnetization had reached equilibrium.

3.6. fMRI data analysis

All fMRI data were processed and analysed using the SPM2 software (Wellcome Department of Imaging Neurosciences, London, UK; Friston et al., 1995) implemented in Matlab6 (The MathWorks, Inc.). Time-series were realigned to the first volume and then were spatially normalized to an EPI template based on the Montreal Neurological Institute (MNI) reference brain, which approximates Talairach and Tournoux's (1988) atlas space, and resampled to 2x2x2 mm. The normalised images were spatially smoothed with an isotropic 4-mm full width at half maximum (FWHM) Gaussian kernel. Data were high-pass filtered (cut-off period 128s) to remove low-frequency drifts. We did not apply global scaling following advice (fMRI analysis defaults for SPM2, http://www.mrc-cbu.cam.ac.uk/Imaging/Common/spm2 _analysis_defaults.shtml). Statistical analysis was based on a random effects approach (Holmes and Friston, 1998). First, for each subject, the

haemodynamic response to each stimulus event (face presentation plus motor response) was modelled using a canonical haemodynamic response function (Friston et al., 1998). We took into account only correct trials, i.e., *yes* responses to the stimuli events that triggered recollections of autobiographical episodes and the correct identification of famous faces. Linear contrasts were constructed for each subject to compare the conditions (autobiographical retrieval *vs* semantic retrieval). A random effects analysis was then performed in which the first level linear contrasts for each subject were subjected to a one-sample t test. A threshold of $p < 0.001$ uncorrected for multiple comparisons was employed. We retained only clusters (k) of at least 20 voxels in order to minimise the proportion of false positive activations. To check for small activation in the limbic regions, we used a voxel extent threshold of 3 voxels. We did not observe additionally activated brain regions, except the left hypothalamus. For the sake of brevity, we reported only activations involving clusters of at least 20 voxels.

Additionally, *yes* events of each condition were modelled by convolving onset times with a canonical haemodynamic response function and its derivatives to capture possible delayed responses (Simons et al., 2005).

Due to the temporally-extended nature inherent in the autobiographical memory retrieval process, it is difficult to find a perfect control task, which matched it in duration. In order to ensure that the autobiographical memory cerebral pattern we observed was not due to the reaction time differences between the experimental and the control condition (see behavioural results), we undertook an additional statistical analysis, in which the autobiographical and the semantic tasks were matched as closely as possible for duration (duration matched data set). The matching was achieved by removing from the analysis autobiographical memory events characterized by the longest reaction times, while keeping however a minimum number of 15 memory events per subject.

4. Results

4.1. Behavioural data

We obtained 81.4% (SD = 4.8) of recollections of specific autobiographical events for the autobiographical memory condition and 88.8% (SD = 3.58) of correct identification of famous faces. The corresponding reaction times were 5.13 s (SD = 2.50 s) and 1.35 s (SD = 0.48 s), respectively. The total duration of the autobiographical condition was 215.25 s and that of the control condition was 59.70 s. When we discarded the personal

recollections associated with the longest reaction times in order to match the two conditions for duration, the total duration of the experimental condition was reduced to 70.39 s (Table 2).

Table 2. Mean and Standard deviation of *yes* responses, reaction times and total duration for the autobiographical memory (AbM) condition (full and reduced data sets) and the semantic memory (SM) control condition.

	Yes **responses (%)**	**Reaction time (s)**	**Total duration (s)**
AbM (full)	81.4 ± 4.8	5.13 ± 2.50	215.25 ± 113.89
SM	88.8 ± 3.58	1.35 ± 0.48	59.70 ± 21.23
AbM (reduced)	_	4.09 ± 2.11	70.39 ± 25.15

The emotional scale yielded an average result corresponding to the 'slightly emotional' interval (M = 2.25, SD = 0.79). On average, we obtained 58.87% of low or non emotional memories and 17.17% of high recollection (see Table 3). Importantly, data varied widely across the subjects. At one end of the scale one subject did not report any emotion, all her recollections being rated 1. At the other end, only one participant provided ratings between 3 and 5. The post-scanning subjects' responses on the emotional scale, in particular their variability, did not allow us to compare recollections rated as high emotional (rated 4, 5) with those rated low or non emotional (rated 1, 2).

The mean age of recollections across participants was 7.67 years (range: 1week – 40 years). The percentage of memories older than 5 years (M = 14.19, SD = 2.25) was 46.89%.

Table 3. Behavioural ratings of emotional intensity of memories for each subject and the mean scores and standard deviation across subjects.

Subjects	Mean score on the scale	High emotional recollections %	Low or non emotional recollections %	Fairly %
1	1	0	100	0
2	2.81	27.9	51.1	21
3	1.86	4.8	73.8	21.4
4	1.63	7.9	78.9	13.2
5	2.45	16.7	57.1	26.2
6	1.84	18.7	78.1	3.2
7	2.67	16.3	37.2	46.5
8	3.15	28.3	15.2	56.5
9	1.6	2.3	88.4	9.3
10	3.51	48.8	8.9	42.3
mean	2.25	17.17 %	58.87 %	23.96 %
SD	0.79	14.90	30.72	19.03

4.2. fMRI data

The significant activations for the comparison autobiographical memory *vs* control condition were all found when a model based on the canonical haemodynamic response function alone was applied; no further significant activations were observed with two derivatives.

The contrast of autobiographical retrieval *vs* semantic retrieval yielded a distributed set of bilateral but predominantly left-sided brain activations (see Figure 10) that involved lateral (dorsolateral BA 8, 9, 46 and ventrolateral cortex BA 47) and medial prefrontal regions (including anterior cingulate cortex BA 24, 32), the temporo-parieto-occipital junction (BA 39, 40, 19), the precuneus (BA 7), the fusiform gyrus (BA 20), the subcortical areas (head of the caudate nucleus, putamen and thalamus), the region overlapping the periaqueductal grey (PAG) of the midbrain and the cerebellum. Bilateral but predominantly right-sided activation were observed in the posterior cingulate region (including the retrosplenial cortex BA 30, 31) (see Table 4).
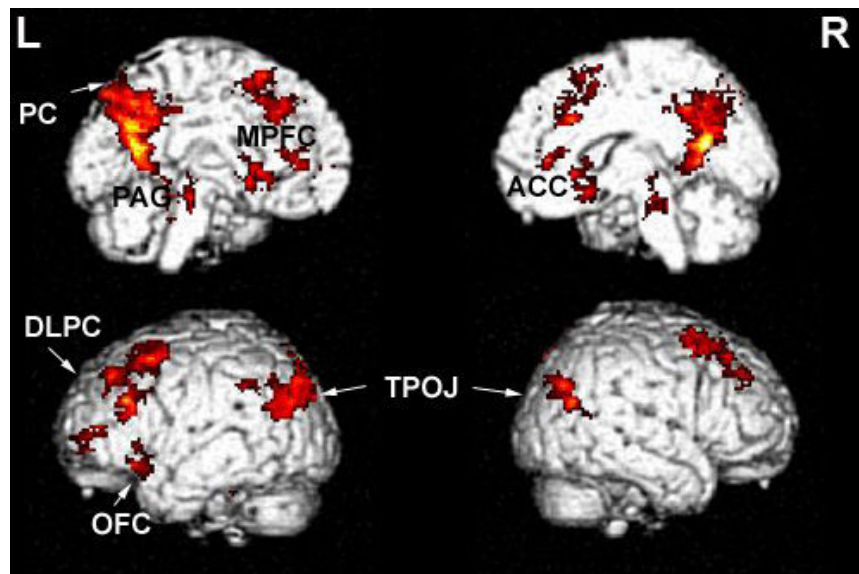
Figure 10. Significantly activated areas for the comparison autobiographical condition *vs* control condition are shown on a 3-D rendered standard MRI (one-sample *t* test; p < 0.001 uncorrected; k ≥ 20 voxels). Abbreviations: PC = posterior cingulate region; ACC = anterior cingulate cortex; PAG = periaqueductal grey; MPFC = medial prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; TPOJ = temporo-parietal-occipital junction; L = left; R = right.

Table 4. Significant activated areas for the comparison autobiographical condition *vs* control condition (p< 0.001; k ≥ 20 voxels).

Brain region (BA)	x, y, z	Z score	Cluster size
R Posterior Cingulate (BA 30, 31)	16 -54 8	5.37	2887
L Precuneus (BA 7)	-6 -74 48	4.82	
L Superior/Middle Frontal (BA 6, 8)	-30 6 56	5.01	1333
R Temporo-parietal-occipital junction (BA 19, 39)	48 -72 32	5.01	316
L Temporo-parietal-occipital junction (BA 19, 39)	-34 -88 30	4.95	746
R Superior/Middle Frontal (BA 6)	28 10 54	4.88	549
L Temporo-parietal junction (BA 39, 40)	-42 -50 38	4.55	60
L Middle Frontal (BA 9, 46)	-42 28 28	4.51	308
R Parahippocampal (BA 35, 36)	20 -32 -20	4.49	99
R Medial Frontal (BA 25)	12 18 -16	4.27	209
R Caudate (Head)	10 22 0	4.17	
L Putamen	-12 10 -6	4.27	244

L Caudate (Head)	-10 16 0	3.85	
L Cerebellum	-22 -40 -20	4.23	341
L Midbrain	-12 -24 -16	4.13	
L Fusiform (BA 20)	-30 -34 -16	3.90	
L Medial Frontal/Anterior Cingulate (BA 10, 32)	-4 44 4	4.23	192
R Anterior Cingulate (BA 24)	4 38 6	3.79	
L Superior/Middle Frontal (BA 10, 46)	-30 48 12	4.16	144
L Inferior Frontal (BA 47)	-34 14 -14	4.13	142
L Middle Frontal (BA 9)	-42 8 32	3.80	31
R Superior Frontal (BA 6)	8 10 54	3.71	66
R Cingulate (BA 32)	12 18 44	3.52	
R Medial Frontal (BA 8)	14 28 44	3.41	
R Midbrain	4 -28 -14	3.61	47
R Thalamus	6 -26 -2	3.59	

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right.

Likewise, although the MTL activation was bilateral, the local maximum for this structure was *right-lateralised* (R>L) (right: 20,-32, -20; Z-score = 4.49, k = 99; left: -22, -36, -20; Z-score = 3.74, k = 24) (see Figure 11). Since the left MTL activation was included within a large cluster comprising cerebellum, midbrain and fusiform gyrus (k = 341), it was detected by a small volume correction approach (a sphere of 5mm radius centred on -20, -32, -20).

Analyses involving both the full data set and those where the conditions were matched as closely as possible for duration yielded virtually identical results (see Figure 12).
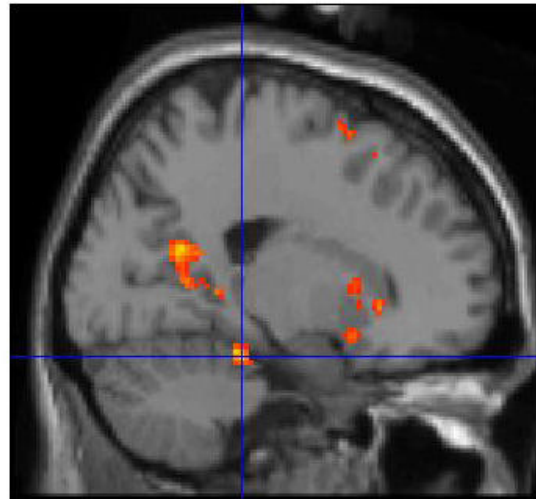
Figure 11. The right parahippocampal gyrus activation was displayed on a sagittal brain section.
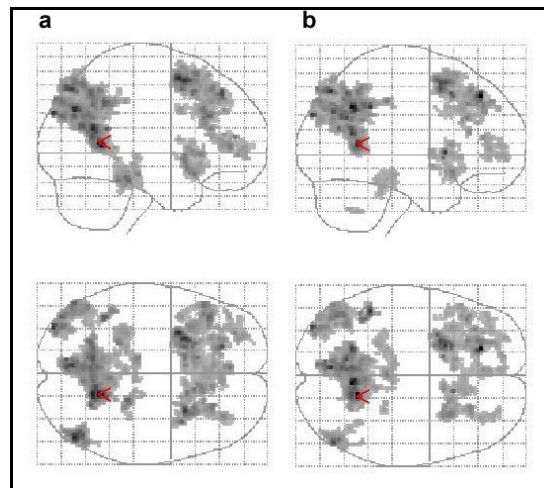
Figure 12. The Statistical Parametric Maps showing the autobiographical memory network obtained with (a) the full data set and (b) the duration matched data set (one sample *t* test, $p < 0.001$ uncorrected, $k \geq 20$ voxels).

5. Discussion

We have documented the influence of nonverbal self-relevant stimuli, presented with no refreshment of the memory trace, on emotional processing, hemispheric lateralisation and MTL involvement during retrieval of personal recollections.

Our central finding is the predominantly right-sided increased activation of the MTL during the retrieval of personal lifespan events. The left-sided activation of the MTL and the prefrontal regions has been reported in the majority of autobiographical memory neuroimaging reports (Gilboa, 2004; Maguire, 2001 for reviews), whereas few studies have

demonstrated preferentially right-sided hippocampal involvement. Fink et al. (1996) suggested that activations in the right MTL might reflect the emotional character of recalled autobiographical memories. Piolino et al. (2004) pointed out the time for retrieval (45 s) that permits recollection of detailed memories. In the same vein, Gilboa et al. (2004) suggested that the right hippocampus takes longer than the left to reach a peak response (from 6 to 8 s). Using a design where the retrieval time was fixed by the subjects themselves, we observed right parahippocampal activation during autobiographical recollections that lasted for about 5 s (see Results). It appears, therefore, that the right MTL activation might reflect some other factors besides the time allowed for retrieval. In line with our own study, the four recent works (Gilboa et al., 2004; Levine et al., 2004; Piolino et al., 2004, Tsukiura et al., 2002) that revealed right hippocampal or parahippocampal activations, all avoided refreshment of the memory trace prior to scanning. This points to the possibility that remembering past events not previously 'reactivated' might be more readily emotionally marked, hence the right-sided MTL activations.

Concerning the left-lateralised frontal activation frequently reported in previous neuroimaging studies of autobiographical memory (Gilboa, 2004) as well as in the present work, the dorsolateral prefrontal cortex (DLPFC) was interpreted as sustaining the anterior control processes that accompany effortful reconstruction of recollections, whereas the medial prefrontal cortex (MPFC) has an essential role in the processing of self-relevant information.

The self, in Tulving's theory, is one of the three central components of autobiographical memory, together with autonoetic awareness and subjectively sensed time (Tulving, 2002). Recently, Northoff and Bermpohl (2004) discussed the relationship between self-referential processing and the cortical midline structures, which included four regions, each involved in different processes: the orbital and medial prefrontal cortex seems to be implicated in the representation of self-referential stimuli, which are monitored in the supragenual anterior cingulate cortex and evaluated in the dorsomedial prefrontal cortex; the posterior cingulate (PC) region (including the restrosplenial cortex) plays a role in "the integration of these stimuli in the emotional and autobiographical context of one's own person" (p. 104) (see Northoff et al., 2006 for a recent review). The MPFC together with the PC have very frequently been reported in the autobiographical neuroimaging literature (for example, Maguire and Frith, 2003a) as well as in studies of 'theory of mind' (e.g., Den Ouden et al., 2005; Frith and Frith, 2003). This is not surprising as both remembering past events and mentalising require self-referential processing. In addition, the already

mentioned midline regions (MPFC and PC) are also implicated in processing emotional information (Northoff and Bermpohl, 2004). This is particularly the case for stimuli that are processed as emotional on the basis of their self-relatedness, as determined by the emotional memories that an individual has associated with them (Bechara et al., 2003; Phan et al., 2004), as in the current study.

Several recent neuroimaging studies have investigated the influence of emotion on the cerebral network underlying autobiographical recollections. These studies used verbal stimuli previously collected from the participants and discussed preferentially the relationship between emotion and the amygdala (e.g., Addis et al., 2004a; Markowitsch et al., 2000). Our subjects' responses on the emotion scale precluded any attempt to study emotionality by comparing brain activations sustaining intense with slightly emotional memories (see Results). Nevertheless, despite, the low emotionality rating, we observed the involvement of cerebral regions that are related to emotion processing, namely the MPFC, the anterior cingulate cortex (ACC), the orbitofrontal region and subcortical structures (Phan et al., 2002). As mentioned above, Bartels and Zeki (2004), studying attachment, reported increased activations in the lateral orbitofrontal cortex, the ACC and the PAG when mothers were presented with photographs of the face of their own child. These regions were interpreted as reflecting maternal behaviour and pleasant emotions associated with maternal love. It appears, therefore, that the PAG and ventrolateral prefrontal activations revealed in the present study may sustain the emotional aspects not consciously involved in autobiographical recollections cued with faces of next of kin.

We reported striatal activations, namely in the caudate nucleus and putamen, and, bearing in mind that the photographs included those of partner and child, we interpret this observation in accordance with Bartels and Zeki (2004). These authors suggested that particular subregions of the reward circuitry in the human striatum reveal a general network specialised in the mediation of romantic and maternal attachment.

The absence of increased amygdala activation in our study is not surprising in view of a recent meta-analysis study that states that "very few recall-driven emotion activation studies engaged the amygdala (at 7% frequency)" (Phan et al., 2002, p. 343). This conclusion is also in accordance with recent autobiographical memory studies that failed to find direct correlation between amygdala activity and ratings of emotional valence and/or intensity (Addis et al., 2004a; Maguire and Frith, 2003b).

Turning back to the important issue of the apparent contradiction between our behavioural and neuroimaging data, we ask why our participants reported low emotional intensity

where we observed increased activation in regions associated with emotion. Several reasons could account for such a discrepancy. Firstly, according to Davidson (2003), the verbal self-report on emotion should be interpreted with caution since it is not always a reliable indication of the presence or the absence of an emotional state: he asserted that "much of the affect that we generate is likely to be non-conscious" and that there are "regulatory processes in emotion that occur automatically" (p. 131). Secondly, the increased cognitive effort necessary for retrieval of memories not previously refreshed could divert the attentional resources from the emotional value of recollections (Phan et al., 2004). Thirdly, the fMRI environment, namely limited space, closeness of the head coil, strong acoustic noise, restriction of movement, could act as a psychological stressor (Raz et al., 2005) and thus render the participant unaware of the emotional re-experiencing of a personal event. Our participants did indeed report that the fMRI condition had inhibited their ability to fully re-live the original emotion during recollections.

In future studies, it would be of interest to use behavioural indices such as the electro-galvanic skin response in order to probe as objectively as possible the emotional states accompanying the retrieval of personal memories. Another goal for future research should be to distinguish a possible early emotion induced by mere face presentation from emotion evoked following recall of a life event.

In conclusion, the present study provides evidence that the autobiographical recollections cued with highly self-related stimuli presented directly during the scanning session involved the right MTL, cortical midline structures and subcortical circuits, known to sustain the self-generated emotion, even though no emotion was explicitly acknowledged.

CHAPTER 5

MATERIAL-INDEPENDENT CEREBRAL NETWORK OF RE-EXPERIENCING PERSONAL

EVENTS: EVIDENCE FROM TWO PARALLEL fMRI EXPERIMENTS

1. Synopsis

Although most neuroimaging studies reported a predominantly left-sided pattern of brain activations during autobiographical memory retrieval, few investigations revealed right-sided or bilateral activations. It has been suggested that the nature of material as well as the pre-scanning session might confound the results. To clarify the lateralisation issue of the cerebral network underlying autobiographical memory retrieval independently of the stimulus material and the refreshment of the memory trace, we compared the results of study 1 with those obtained in a verbal experiment requiring a pre-scanning interview (Botzung, 2005). Both experiments were constructed using the same experimental design to eliminate methodological variables in order to render comparisons possible. We found a predominantly left-lateralised cerebral network independently of material and regardless of whether or not memory traces were reactivated prior to the scanning session.

2. Introduction

Generally, the neuroimaging studies of autobiographical memory (AbM) retrieval have reported a predominantly left-lateralised cerebral network (see Gilboa, 2004; Maguire, 2001 for reviews). In most of the studies, autobiographical information was elicited from subjects prior to the imaging experiment and cued by means of verbal stimuli during scanning (e.g., Addis et al., 2004a; Maguire and Frith, 2003a). These two methodological issues, the time of collecting data for testing recollections and the verbal material, have been seen as naturally contributing to the predominantly left-lateralised activation pattern. Some authors addressed this point by avoiding refreshment of the memory trace prior to the fMRI experiment, reporting nonetheless, a predominantly left lateralisation of the cerebral network while remembering past events, elicited with verbal material (e.g., Piolino et al., 2004; Steinvorth et al., 2006). Additionally, using nonverbal stimuli and circumventing the pre-scanning interview, Gilboa et al. (2004) and Denkova et al. (2006) found also a predominantly left-sided pattern of brain activations for autobiographical recollections. Interestingly, however, there are, on the one hand, a few neuroimaging studies that indicated right-lateralised or bilateral activations (e.g., Fink et al., 1996;

Graham et al., 2003). Various interpretations have been put forward to account for the results: the emotional feature of autobiographical memories (Fink et al., 1996), retrieval of detailed memories when sufficient time is allowed (Graham et al., 2003), and the self perspective (Piefke et al., 2003). On the other hand, lesion studies have also suggested a particular contribution of right-sided lesions in AbM impairment (Kopelman and Kapur, 2001).

The aim of the present study was to identify the neural correlates underlying personal recollections independently of the nature of the stimuli and the time of testing. We attempt to investigate whether the left-sided cerebral network revealed by previous neuroimaging studies is related to AbM retrieval per se or to some methodological confounds. For that purpose, we compared two parallel fMRI studies: (i) a verbal experiment requiring a pre-scanning interview, and (ii) a nonverbal experiment, which did not involve testing before the fMRI session. They were constructed according to the same experimental design to eliminate at least the more obvious methodological variables (e.g., control condition, time allowed for recollection, type of the experimental protocol) influencing the pattern of activations in order to perform a direct and as adequate as possible comparison between them. Importantly, we used a self-paced design, thereby preventing the potential effect of time allowed for retrieval on the lateralisation of brain activations. If the left-sided pattern of brain activations is associated with AbM retrieval *per se*, predominantly left-lateralized cerebral network should be observed in both experiments. If it depends on methodological factors, left-sided activation should be observed only in the verbal study.

3. Material and methods

3.1. Subjects

Twenty healthy, right-handed, French native speaker subjects with no neurological impairment or psychiatric disorder, participated in the study. Ten subjects (5 females; mean age = 42.4; SD = 2.27; mean number of years of education = 17.8; SD = 3.5) took part in the *verbal* experiment, and 10 subjects (6 females; mean age = 40.6; SD = 5.7; mean number of years of education = 18.0; SD = 2.8) were recruited in the *nonverbal* study. Both groups were matched for age (t = 0.92; p = 0.37) and for the number of years of education (t = -0.14; p = 0.89). Our subjects gave written informed consent and were paid according to the guidelines of the Alsace Ethics Committee, who approved the study.

3.2. Experimental design

We used in the verbal and nonverbal studies an autobiographical memory retrieval test as the experimental condition, and a semantic memory task as the control condition. The conditions encompassed ten sequences that were presented alternately; each sequence consisted of seven stimuli including five targets and two foils. The latter were used to warrant efficient attentional processes during scanning. Targets and foils in both conditions were randomly displayed on a screen for 1.24 s. The baseline between sequences consisted of a fixation cross, which was displayed for 15 s. We used a design where the retrieval time was fixed by the subjects themselves (self-paced design). The Inquisit 1.33 (see above Chapter 4) was used to set the timing of stimulus presentation, and to record the responses.

3.3. Verbal experiment

This experiment included a pre-scanning test five days prior to the fMRI session. During this test, the subjects remembered personal events by means of the Modified Crovitz Test (Graham and Hodges, 1997; French version: Manning, 2002) and summarised each recollection in a two-word code to be used as a cue in the subsequent fMRI experiment. The stimuli of the autobiographical task comprised 50 pairs of words belonging to the subject and 20 pairs of words belonging to someone else. The control condition consisted of 50 semantically related pairs of words, plus 20 foils that were unrelated pairs. Immediately prior to scanning, the two tasks were explained to participants. (i) In the autobiographical condition, the subjects were instructed to remember an autobiographical event corresponding to the coded words and to press the *yes* switch once the recollection was built up; they were asked to press the *no* button in the two other possible situations (the recognised code failed to trigger a recollection or the pair of words was unknown). (ii) In the control condition, the participants were instructed to press the *yes* button for semantically linked words and the *no* key for unrelated items.

3.4. Nonverbal experiment

The nonverbal experiment is described in details in chapter 3. A set of 50 photographs of relatives and friends of the participants made up the material of the experimental condition. The photos were obtained thanks to the participants' families without involvement of the participants themselves. The material of the control condition consisted of 50 photographs of famous faces (politicians, actors, musicians and sports figures). Twenty unknown faces

were used as foils to control the subjects' attention in the experimental condition and the same number of unknown faces served as distractors in the control condition. Just before the fMRI session, subjects were given detailed instructions about the two tasks. (i) In the autobiographical condition, the subjects were asked to recollect a personal episode when a face of relative or friend appeared on the screen and to press the *yes* button once the autobiographical event was evoked. The *no* response followed the view of unknown face or the failure to evoke a specific autobiographical episode. (ii) In the control condition, the participants were instructed to press the *yes* button if they successfully identified the face of a famous person and the *no* button if the face was unknown.

3.5. fMRI scanning parameters

The same parameters described in the previous chapter (see Chapter 4) were used in the two experiments.

3.6. fMRI data analysis: Verbal and nonverbal experiments

All fMRI data were processed and analysed using the Statistical Parametric Mapping (SPM99) software (Wellcome Department of Imaging Neurosciences, London, UK). The pre-processing steps involved within-subject image realignment, spatial normalisation and spatial smoothing using a Gaussian kernel.

Firstly, an individual subject analysis was performed for each experiment separately. The haemodynamic response to each stimulus (pair of words or face presentation plus the motor response) was modelled by a canonical haemodynamic response function. We took into account the stimulus events corresponding to *yes* responses only. Linear contrasts were constructed for each subject by comparing the autobiographical condition to the control condition. A random effect analysis was then performed in which the first-level linear contrasts for each subject were submitted to a one-sample *t* test (Holmes and Friston, 1998). The statistical parametrical maps were thresholded at $p < 0.001$ uncorrected. The less conservative threshold of $p < 0.01$ uncorrected was used in the medial temporal lobe (MTL). This choice was decided on the basis of the observed systematic activation of this region in the first-level linear contrasts plus our stringent *a priori* hypothesis regarding the role of the MTL. The next step, in order to test for possible differences between the verbal and nonverbal studies, was to perform a two-sample *t* test ($p < 0.001$ uncorrected). Only

clusters with a spatial extent equal to or exceeding 10 (contiguous) voxels were taken into consideration for the statistical test.

4. Results

4.1. Behavioural data

The reaction times (RTs) for the experimental conditions were 6.45 s (SD = 2.82 s) and 5.13 s (SD = 2.50 s), and for the control conditions 1.46 s (SD = 0.23 s) and 1.35 s (SD = 0.48 s) in the verbal and nonverbal experiments, respectively.

There was no significant difference between the two experiments as regards RTs, whether these were related to the retrieval of autobiographical memories (t = 1.10; p = 0.28); or to the control condition (t = 0.7; p = 0.49). Owing to the self-paced design, however, the RTs measured for experimental and control tasks were significantly different. In order to ensure that the AbM cerebral pattern observed was not due to the duration difference, we undertook an additional statistical analysis in which the conditions were matched for duration. Analyses involving both the full and matched data sets yielded virtually identical results (see previous chapter, study 1).

4.2. fMRI data

Verbal experiment

The retrieval of autobiographical memories was associated with a predominantly left-lateralised cerebral network (see Figure 13a), which included activation in the middle (BA 9, 46) and superior (BA 6) frontal gyri, the inferior frontal gyrus extending to the superior temporal cortex (fronto-temporal junction, BA 47/38), the posterior cingulate region (BA 23, 29, 30, 31), the precuneus (BA 7), the temporo-parieto-occipital junction (BA 19, 39), the occipital/cuneus region (BA 19), the lateral temporal lobe (BA19 and BA 20 in the right and left hemisphere, respectively), and the parahippocampal gyrus (BA 35). Activation in the middle temporal gyrus (BA 19), the caudate nucleus and the thalamus was right-lateralised.
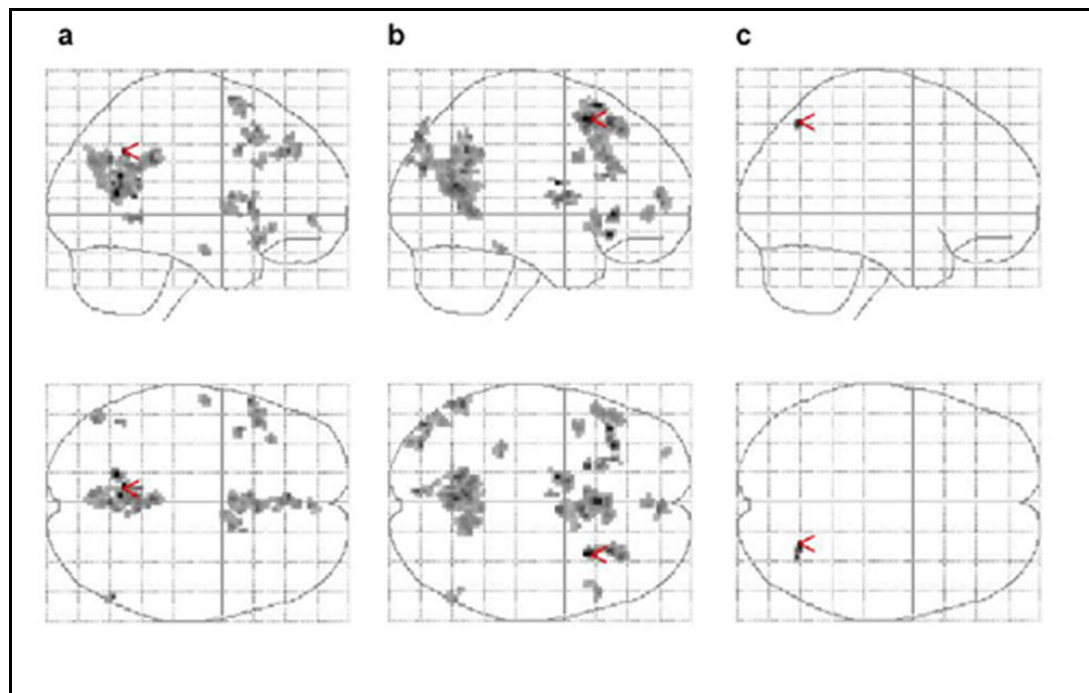
Figure 13. Areas showing significant signal increases (a) for the autobiographical *vs* control condition contrast in the verbal experiment (one-sample *t* test, p < 0.001 uncorrected, k ≥ 10 voxels); (b) for the autobiographical *vs* control condition contrast in the nonverbal experiment (one-sample *t* test, p < 0.001 uncorrected, k ≥ 10 voxels); (c) for the comparison of the verbal *vs* nonverbal experiments (two-sample *t* test, p < 0.001 uncorrected, k ≥ 10 voxels).

Nonverbal experiment

Episodes cued with photographs were associated with bilateral but predominantly left-lateralised activation in the superior (BA 6, 8), middle (BA 6, 9, 46) and inferior (BA 47) frontal gyri, the medial frontal lobe, the posterior cingulate region (BA 23, 29, 30, 31), the thalamus, the caudate nucleus (see Figure 13b). Left-lateralised activations were observed in the fusiform gyrus (BA 20), the temporo-parieto-occipital junction (BA 39, 19), the superior occipital/cuneus region (BA 19), and the precuneus (BA 7). Activation in the middle temporal gurus (BA 19) and the parahippocampal gyrus (BA 35) was right-lateralised.

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Table 5. Regions of significant activation for the autobiographical *vs* control condition contrast (p < 0.001) in the verbal experiment (on the left) and in the nonverbal experiment (on the right).

VERBAL				NONVERBAL
Z score	x, y, z	Brain Region (BA)	x, y, z	Z score
4.12	-2 6 66	L Superior Frontal (BA 6)	0 20 62	4.65
4.15	4 20 48	R Superior Frontal (BA 6, 8)	8 12 50	4.19
*	*	L Superior Frontal (BA 8)	-24 28 50	4.02
-	-	R Middle Frontal (BA 6)	30 16 54	4.90
3.69	-50 20 28	L Middle Frontal (BA 9, 46)	-50 22 36	3.87
4.13	-46 20 -16	L Inferior Frontal (BA 47)	-42 26 -12	4.63
*	*	R Inferior Frontal (BA 47)	52 20 -6	3.88
3.93	2 50 -2	R Anterior Cingulate (BA 10, 32)	2 48 0	3.76
*	*	R Anterior Cingulate (BA 24)	2 24 22	3.99
3.14	4 56 -8	R Medial Frontal (BA 10)	4 54 10	4.12
4.32	-4 38 36	L/R Medial/Superior Frontal (BA 6, 8)	*	*
4.99	-4 -58 22	L Posterior Cingulate (BA 23, 29, 30, 31)	-2 -62 16	4.47
5.02	-8 -56 36	L Precuneus (BA 7)	-4 -56 36	4.32
4.01	-48 -72 30	L temporo-parieto-occipital junction (BA 19, 39)	-44 -80 26	4.30
4.33	54 -62 18	R Middle Temporal (BA 19)	56 -62 16	3.80
3.74	-58 -10 -22	L Inferior Temporal (BA 20)	-	-
-	-	L Fusiform (BA 20)	-26 -36 -20	3.79
4.35	0 -64 32	L superior occipital/cuneus (BA 19, 7)	-8 -76 32	3.77
*	*	L Caudate body	-12 2 10	4.17
3.98	14 6 10	R Caudate body	14 8 10	3.57
3.76	6 2 2	R Caudate head	*	*
3.64	8 0 6	R Thalamus	4 -4 8	4.15
*	*	L Thalamus	-4 -8 10	3.74
3.33	-20 -26 -18	L Parahippocampal (BA 35)	-	-
-	-	R Parahippocampal (BA 35)	20 -28 -24	3.48

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z) and Z score. L = left; R = right; * = activation significant at p < 0.01.

Comparison analysis

The qualitative analysis of the results yielded by the one-sample t tests employed for each experiment separately demonstrated a predominantly left-sided pattern where almost all the activated areas were so in both studies. Overlapping regions included the lateral and medial frontal cortices, the posterior cingulate cortex, the precuneus, and the temporo-parieto-occipital junction (see Table 5). Non overlapping regions comprised the right parahippocampal gyrus (BA 35), the left fusiform gyrus (20) and the right middle frontal area (BA6), which were activated in the nonverbal experiment only (threshold at $p < 0.01$). Likewise, activation in the left inferior temporal gyrus was exclusively in the verbal study. The statistical comparison between the two data sets revealed only one significant difference: the right superior parietal lobule (BA7) (cluster size: 12 voxels), which was more intensely activated in the verbal experiment (see Figure 13c).

5. Discussion

In the present study, we have observed a predominantly left-sided cerebral network sustaining AbM retrieval independently of stimulus material and refreshment of the memory trace, which is in line with most of the previous neuroimaging studies. We suggest that the left-lateralised pattern supports AbM *per se* rather than the influence of different methodological factors, such as verbal stimuli or lack of richly detailed recollections. Concerning the latter, the use of a self-paced design allows us to suggest that subjects need 6 s on average, to fully re-experienced sensory-perceptual memories. Moreover, this finding agrees with a recent report, which investigated temporal features of AbM retrieval, and found that the related activation pattern peaked at 6 to 8 s after stimulus onset (Addis et al., 2004b).

One potential explanation of the left-sided cerebral network could be that autobiographical recollections cued either with words or faces require more verbal than nonverbal processing. However, previous verbal neuroimaging studies, using behavioural rating scales to access phenomenological properties of autobiographical memories have reported greater involvement of the nonverbal over the verbal processing during recollection (Greenberg et al., 2005; Piolino et al., 2004). These findings are in accord with the idea that retrieval and, more importantly, reliving of personal experiences rely heavily on the generation of visual images of the event (Greenberg and Rubin, 2003). It seems therefore, difficult to explain the left-lateralised brain activation observed in the present and previous

neuroimaging investigations in terms of predominantly verbal processing in autobiographical recollections.

Importantly, our findings further the inconsistencies between neuroimaging studies in the healthy individual and those carried out in clinical neuropsychological settings. Whereas the former report bilateral but predominantly left-lateralised cerebral activations during recollections, the latter indicate the contribution of the right hemisphere. The apparent contradiction might be due to the main difference between the two approaches, that is, imaging studies in neurologically intact people identify the range of brain structures that may be *necessary* for normal performance, while clinical studies identify which brain structure is *essential* for a given memory process (Mayes and Montaldi, 2001). To better clarify the lateralisation issue, selected patients with autobiographical amnesia should be examined through fMRI procedures, validated in healthy subjects.

We found some *qualitative differences* in the responsiveness of the neural network between the two experiments. These differences cannot be ascribed separately either to the stimulus material processing or to the way of eliciting recollections. However, the different brain activations preferentially involved in one and the other experiment suggest differences in mapping procedures one to one in the verbal experiment and one to many in the nonverbal experiment. While these considerations constrain conclusions regarding the differences between our two studies, they do not prevent the interpretations of the pattern of activations common to both experiments, which are central in our discussion.

The nonverbal design was associated with increased right-lateralised activation in the MTL, which could not be entirely accounted for in terms of stimulus material effect, since right-lateralised activation in the MTL was also reported in some recent studies on AbM retrieval involving verbal cues by Levine et al. (2004), Piolino et al. (2004) and Tsukiura et al. (2002). The common point between the afore-mentioned studies and our nonverbal experiment is the absence of refreshment of the memory trace. It appears that this characteristic might, to some extent, engender more emotionally marked recollections, which have been associated with right-lateralised activation in the MTL (Fink et al., 1996; see Chapter 4 for more details). The fusiform gyrus activation, in the context of autobiographical memory retrieval, has been interpreted in terms of visual imagery processing in contrast to spatial imagery, which would activate the parietal lobes, preferentially (Greenberg et al., 2005b). Taking together our present results that show left fusiform gyrus activation in the nonverbal experiment only and the literature reports showing the same structure activated bilaterally during verbal (Piefke et al., 2003) and

nonverbal (Gilboa et al., 2004) experiments, it seems plausible that the fusiform gyrus activation reflects the visual imagery nature of recollections. The nonverbal experiment also involved right-lateralised activation of the middle frontal gyrus, which has only been rarely reported in other AbM studies (see Gilboa, 2004 for review), and its interpretation remains rather uncertain for the time being.

Concerning the verbal experiment, it was specifically associated with activation in left inferior temporal gyrus, which has been also detected in a similar study, in which a brief title previously provided by participants, was used to cue memory retrieval during scanning (Addis et al., 2004a). Associating the verbal code (cue) to the recollection could account, at face value, for this activation.

Finally, the verbal design showed a *significantly* increased activation relative to the nonverbal experiment, in the right superior parietal lobule. On the one hand, this region is considered as one of the key structures involved in spatial processing, and more precisely, in the retrieval of the spatial context of an event (Burgess et al., 2001). On the other hand, following Gobbini et al. (2004), faces of relatives and friends are thought to access spontaneously elaborated representations. Taking those interpretations together, we would like to suggest that our results indicate that remembering past episodes cued with words requires more sustained reconstruction of the spatial context than recollections cued with personally familiar faces.

We are aware that we cannot pin point the effects of stimulus material and pre-scanning refreshment separately in this study. Further investigations are needed to seek to the influence of each of these factors alone. On the basis of our general finding of left-lateralised activation in AbM *per se*, further studies are needed to document the distinctive contribution of each of these two variables.

CHAPTER 6

NEURAL CORRELATES OF REMEMBERING/KNOWING FAMOUS PEOPLE: AN EVENT-
RELATED FMRI STUDY

1. Synopsis

Within the retrograde amnesia literature, identification of faces and names of famous people has been typically used as a measure of remote semantic memory (Kapur, 1999; Kopelman, 2002a; Kopelman and Kapur, 2001). However, Westmacott and colleagues (2003, 2004) have argued that the knowledge about some famous people might have an autobiographical component, in addition to the semantic information. Differently stated, some semantic concepts may comprise both a generic, semantic component and an autobiographical, episodic component. Consequently, they assume a distinct status in remote memory because they belong to the semantic as well as to the autobiographical memory systems. The neuropsychological studies of semantic dementia (SD) and Alzheimer's disease (AD) demonstrated that the semantic and autobiographical aspects of famous people knowledge are very likely to be mediated by different brain structures, with the former being mediated by neocortical structures, while the latter being highly depended on the integrity of the medial temporal lobe (Westmacott et al., 2004).

In the neuroimaging research, famous people recognition has been commonly utilised to explore cerebral correlates of semantic memory (e.g., Bernard et al., 2004; Douville et al., 2005; Elfgren et al., 2006; Leveroni et al., 2000). These studies reported extensive temporofrontal and mesial temporal activations while subjects recognised faces and names of famous people. Taking into account Westmacott et al.'s (2004) findings, the authors suggested that the possible autobiographical significance related to some celebrities would have confounded their results, namely the MTL involvement. To our knowledge, there are no neuroimaging studies that have investigated the influence of personal relevance on famous people recognition.

The aim of the present study was to investigate the pattern of brain activations sustaining the autobiographical and the semantic components of knowledge about famous persons. For that purpose, we used the Remember/Know (R/K) paradigm, which has been already described in chapter 1. During a pre-scanning interview, the subjects were presented with a list of famous personalities, and they were asked to indicate for each person if they associated an autobiographical episode with the celebrity (R response) or whether they possessed only semantic information with no personal significance (K response). Few days

later, the participants were scanned while retrieving personal episodes related to the famous people (R condition), and while recognising celebrities devoid of personal significance (K condition). Moreover, we examined if the stimulus material (verbal/nonverbal) influenced the lateralisation of the cerebral networks. To this end, we used names and faces of famous people during a 'verbal' and a 'nonverbal' fMRI session, respectively.

Our findings suggested that different patterns of brain activations corresponded to the presence or absence of personal significance linked to semantic knowledge; MTL was engaged only in the former case. Although choice of stimulus material did not influence the hemispheric lateralisation in 'classical' terms, it did play a role in engaging different cerebral regions.

2. Introduction

Some concepts considered as 'purely' semantic in nature might involve an episodic component if they are relevant to one's personal experience. The autobiographical significance, term defined by Westmacott and colleagues (2001, 2003, 2004), denoted the phenomenon of association of a semantic concept with specific personal memories. As stated by the authors, the autobiographically relevant concepts have distinct status in long-term memory because they "possess a wealth of extra information" in addition to generic, abstract knowledge (Westmacott et al., 2004, p. 26). The two aspects, semantic and autobiographical, although independent, are accessed simultaneously through a semantic and an episodic route in healthy subjects, whereas the routes can be dissociated in brain-damaged patients. The personally relevant knowledge has been initially described in semantic dementia (SD), which is characterised by a multi-modal semantic disorder with relative preservation of autobiographical memory (for example, Snowden et al., 1996, 1999). More recently, Westmacott et al. (2004) examined patients with SD, Alzheimer's disease (AD), and medial temporal lobe (MTL) amnesia in order to investigate the influence of personal significance on semantic memory and to speculate about neural mechanisms that mediate it. The authors used the 'remember/know' (R/K) paradigm when the participants make judgements about famous persons' names. R responses corresponded to celebrities associated with contextual episodic details, while K responses corresponded to those about which the subject knew factual information only. Westmacott et al. (2004) found that, in patients with SD, autobiographically significant knowledge about famous people was preferentially preserved compared to generic knowledge, whereas the opposite

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was found in patients with AD and MTL amnesia. SD is associated with temporal neocortical atrophy, which spared the MTL, and AD presents the reverse pattern of lesions. These findings suggested that personally significant information is highly dependent on the medial temporal regions, while purely semantic knowledge with no personal significance is mediated by the neocortical structures (Westmacott et al., 2004). According to the multiple trace theory (MTT) of memory, the MTL plays a permanent (life-long) role in retention and retrieval of autobiographical components (Moscovitch et al., 2005, 2006 for recent reviews). A contrasting position is that the autobiographical components of semantic memory, like the semantic components themselves, become independent of MTL over time (Squire and Alvarez, 1995). Westmacott et al. (2004) strongly recommended follow up studies combining behavioural and neuroimaging methodology to investigate the contribution of the MTL, the prefrontal cortex and the other neocortical regions to the autobiographical and semantic components.

Although there are a number of neuroimaging studies investigating cerebral correlates of famous person knowledge (Bernard et al., 2004; Gorno-Tempini et al., 1998; Gorno-Tempini and Price, 2001; Haist et al., 2001; Kapur et al., 1995; Leveroni et al., 2000) none of them have taken into account the personal relevancy of celebrities. Most of them reported MTL activation during recognition of famous faces or names (Bernard et al., 2004; Douville et al., 2005; Leveroni et al., 2000). However, based on the Westmacott and Moscovitch's (2003) study, Bernard et al. (2004) put forward the possibility that the increased activity in the MTL could be due to the autobiographical significance associated with some of the famous persons presented. A functional neuroimaging study would be necessary to distinguish the autobiographical and semantic components of famous person knowledge since lesion research (Westmacott et al., 2001; 2004) suggests that they are independent at least to certain degree.

The Westmacott and Moscovitch's (2003) version of the R/K paradigm appears to be the most adequate to distinguish between the autobiographical and semantic components of knowledge about famous people and thereby to examine the cerebral networks associated with these components.

Moreover, since information about people could be accessed either by face or name, the use of famous people as experimental stimuli represents a potentially valuable means of verifying the material-specific lateralisation hypothesis. It posits that knowledge is differentially represented in the brain according to the verbal/nonverbal nature of stimuli with the left hemisphere being particularly important for names and the right hemisphere

for faces (McCarthy and Warrington, 1988; Warrington and McCarthy, 1994). On the one hand, several neuropsychological studies have found hemispheric differences in the identification of famous names and faces, i.e., patients with left temporal lobe damage had more difficulty to access semantic information about famous people from their name than from their face, while patients with predominantly right temporal damage showed the reverse pattern (e.g., Eslinger et al., 1996; Snowden et al., 2004). However, Viskontas et al. (2002) reported that the ability to provide semantic information about celebrities from their name was impaired in left as well as in right temporal lobe epileptic patients. They argued that the semantic knowledge of celebrities depends on both left and right hemispheres. On the other hand, neuroimaging studies focusing on recognition of famous persons in normal subjects suggested that structures on the right hemisphere could underlie the necessary perceptual processes (regardless of the faces being or not famous), while left-sided regions would draw up semantic information about famous people (Gorno-Tempini et al., 1998; Simons et al., 2001). Even so, some recent neuroimaging investigations observed a bilateral pattern of brain activations while comparing famous faces and names with unknown ones (Bernard et al., 2004 for faces and Douville et al., 2005 for names). Concerning the retrieval of autobiographical information in neurologically intact subjects, we have documented left-sided lateralisation of the cerebral network regardless of the verbal/nonverbal nature of stimuli (see above Chapter 5).

On these bases, the aim of the present study was twofold: (i) to compare the pattern of brain activation associated with autobiographical significance to that sustaining the semantic knowledge devoid of personal component; (ii) to study the influence of the stimulus material (verbal/nonverbal) on both the autobiographical significance and the 'purely' semantic cerebral networks.

According to Westmacott and colleagues (2003, 2004), we hypothesised that the semantic and autobiographical components will be mediated by different, although overlapping at least to some extent, cerebral networks, with the major difference being the involvement of MTL only for personally significant concepts. Additionally, we surmised that the stimulus material would affect more likely the semantic memory network, while it would have no influence on the autobiographical memory network.

3. Material and methods

3.1. Subjects

Twelve healthy subjects (5 males and 7 females) participated in the fMRI study, which was approved by the local ethics committee. The subjects were right-handed and native French speakers [age (M = 32.75 years, SD = 5.97), number of years of education (M = 17.92, SD = 2.91)]. As a matter of routine, subjects were screened to rule out medical or neurological problems, current medication and/or MRI contraindications. They had normal or corrected to normal vision. The subjects gave written informed consent and were paid for their participation.

3.2. Pre-scanning interview

Two or 3 days before scanning, participants completed a one-hour pre-scan interview. Westmacott and Moscovitch's (2003) version of the R/K paradigm was used. The subjects were presented with a list of 116 names of celebrities that were alive and famous during the lifetime of the participants (i.e., 1970-present). They were asked to make R/K judgments about each name. R response was to be given if they could remember an autobiographical episode involving the famous person. If they knew the identity but they could not recall any specific personal event associated with the famous person, they were instructed to give a K response. Examples of autobiographical events were provided in order to ensure that subjects understood the instructions and made the R/K distinction. Additionally, participants rated on a 5-point scale each name for familiarity (0 = *barely familiar* and 4 = *extremely familiar*) and emotion (0 = *no emotional reaction* and 4 = *intense emotion*). R responses were rated also for memory vividness (0 = *very vague* and 4 = *extremely detailed*). Participants were instructed to respond as quickly as possible without engaging in detailed reconstruction and without any verbalisation. Thus, their rating of vividness and emotion of memories were based on a global apercu of the event. Based on the scale scores, we selected for each participant the 30 most richly detailed R responses [vividness (M = 2.58, SD = 0.80)] and the 30 K responses that matched as closely as possible R items for familiarity [K (M = 1.86, SD = 0.85), R (M = 2.09, SD = 0.63)] to be used in the subsequent fMRI experiment.

3.3. Experimental stimuli and tasks

The participants underwent successively a 'verbal fMRI session' where stimuli were full names and a 'nonverbal fMRI session' composed by colour facial photographs. Each scanning session included the same 3 conditions. (i) In the autobiographical memory condition (R responses), specific episodes had to be retrieved after the presentation of personally significant famous people. (ii) The semantic memory condition (K responses) consisted of the recognition of famous persons who were previously judged as not autobiographically significant. From the pool of 30 R and 30 K famous persons, 15 R and 15 K were presented in the verbal fMRI session and the same number of R and K items– in the nonverbal session. The stimuli used in the two sessions were different. R faces and names were matched primarily for details [names (M= 2.61, SD = 0.77), faces (M = 2.56, SD = 0.82)], then for familiarity [names (M = 2.04, SD = 0.63), faces (M = 2.13, SD = 0.66)] and emotion [names (M = 2.75, SD = 0.44), faces (M = 2.54, SD = 0.69)]. Likewise, K faces and names were matched for familiarity [names (M = 1.78, SD = 0.85), faces (M = 1.94, SD = 0.88)] and emotion [names (M = 1.71, SD = 0.69), faces (M = 1.66, SD = 0.49)]. Summarising, R and K famous people that we used in the fMRI experiment were all alive during the subjects' lifetime and equally familiar; they differed only in terms of autobiographical significance, which was not surprisingly closely associated with higher emotional rating (Westmacott and Moscovitch, 2003). In both R and K conditions, unknown stimuli (names and faces) were used as foils to control the subjects' attention. (iii) A baseline (B) condition to control for perceptual, decision, and motor demands, was also included, in which the participants had to make a gender judgment. This condition was composed of 60 targets (30 unknown male names and 30 male faces) and 24 foils (12 unknown female names and 12 female faces). All stimuli were processed using Adobe PhotoShop (version 7.0). Faces were placed on a neutral background that was 270x324 pixels in size. Names appeared in white letters against a black background (Arial Bold, 26 points).

Prior to the scanning session, subjects were given detailed instructions about the three types of tasks. Regardless of the session, they were asked to press the *yes* key (mouse button) once the original recollection associated with the famous person was evoked (R condition), when the celebrity was identified (K condition), when male name or face was presented (B condition). If they viewed the face or name of an unknown person (foil) in the R and K conditions and the face or name of female unknown person in the B condition, the

no button was to be pressed. The order of the verbal and nonverbal sessions was counterbalanced across subjects.

3.4. Experimental design

We used a self-paced event-related design. R and K conditions encompassed 6 sequences each (3 name and 3 face sequences) and B condition was composed of 12 sequences (see Figure 14). Each sequence consisted of 7 stimuli: 5 targets and 2 foils. The sequences were alternated (K/B/R/B/K/B/R etc.) and were separated by a short instruction on the screen that lasted for 15 s (*recollection: yes key* for R condition; *famous: yes key* for K condition; *a man: yes key* for B condition). Targets and foils in the three conditions were randomly displayed on the screen for 2 s. A blank screen appeared during the interval between stimulus offset and onset. Once the subject's response was given, the post-trial interval started. This interval varied from 2.0 to 5.0 s in R condition and from 1.5 to 4.5 s in K and B conditions. The mean intervals were chosen to be as proportional as possible to the longest reaction times of experimental and control conditions. Inquisit 1.33 software (see above) was used to set the timing of stimulus presentation and to record the responses.
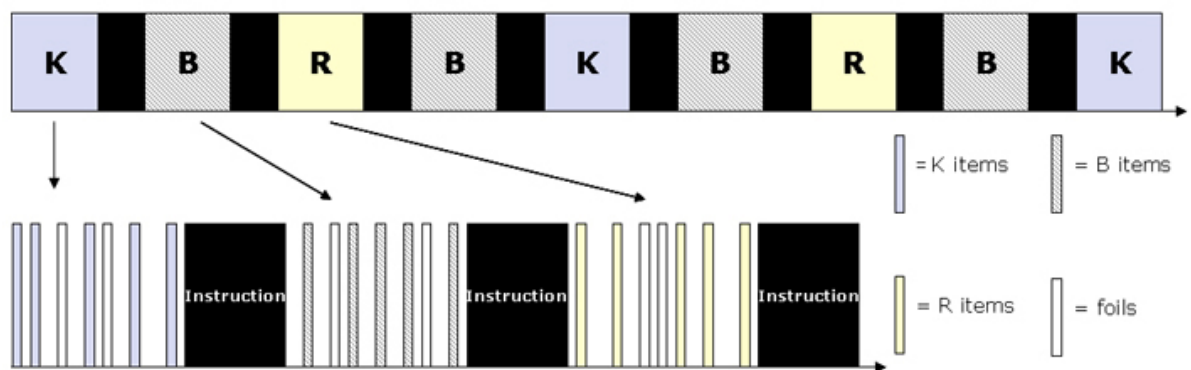
Figure 14. Schematic illustration of the experimental design of study 3. The experimental fMRI design encompassed a verbal session and a nonverbal session which were presented in a counterbalanced order across subjects. Each session was composed by 3 R, 3 K and 6 B sequences presented alternately and separated by short instruction.

3.5. Post- scanning debriefing

Immediately after scanning, we carried out a debriefing session to access successful autobiographical recollections cued with R items and correct recognition of K names and faces during the scanning session. Participants retrospectively rated on the same 5-point

scale each R response for vividness and emotion and they dated approximately their memories. Our participants declared that during scanning, the original event (not the pre-scanning interview) linked to the R stimulus was retrieved and that no K item was associated with personal episode and emotion. This was in accord with several other memory neuroimaging studies (Greenberg et al., 2005b; Maguire and Frith, 2003a).

3.6. fMRI scanning parameters

We used the same scanning parameters as in our previous experiments (see Chapter 4).

3.7. fMRI data analysis

All fMRI data were processed and analysed using the SPM2 software (Wellcome Department of Imaging Neurosciences, London, UK; Friston et al., 1995) implemented in Matlab6 (The MathWorks, Inc.). Time-series were realigned to the first volume and then were spatially normalized to an EPI template based on the Montreal Neurological Institute (MNI) reference brain, which approximates Talairach and Tournoux's (1988) atlas space. The normalised images were spatially smoothed with an isotropic 8-mm full width at half maximum (FWHM) Gaussian kernel. Data were high-pass filtered (cut-off period 128 s) to remove low-frequency drifts. We did not apply global scaling following advice (FMRI analysis defaults for SPM2, http://www.mrc-cbu.cam.ac.uk/Imaging/Common/spm2 _analysis_defaults.shtml). Statistical analysis was based on a random effects approach (Holmes and Friston, 1998). First, for each subject, the haemodynamic response to each stimulus event (stimulus presentation plus motor response) was modelled using a canonical haemodynamic response function (Friston et al., 1998). We took into account the stimulus events corresponding to *yes* responses only (i.e., recollections of autobiographical episodes, correct famous person recognition and male judgement). The following first-level linear contrasts were calculated: (1) R *vs* K name task, (2) R *vs* K face task, and *vice versa*; (3) K *vs* B name task, (4) K *vs* B face task, (5) R *vs* B name task, (6) R *vs* B face task. These contrast-images were then entered into group analyses. To examine brain activation related to R and K tasks regardless of the material, we performed one-sample *t* tests including contrasts 1 and 2, and contrasts 3 and 4, respectively. The common cerebral network of both the autobiographical and semantic aspects was revealed by employing a one-sample *t* test comprising contrasts 5 and 6. For all these analyses, we adopted a

threshold of p < 0.05 FWE-corrected and a minimum cluster size of 10 contiguously activated voxels in order to minimise the proportion of false positive activations.

To study the influence of verbal/ nonverbal material on the R cerebral network, we compared contrast 1 to contrast 2 and *vice versa* in a two-sample *t* test (p < 0.001 uncorrected). Likewise, the effect of stimulus material on the K activation pattern was analysed using two-sample *t* test (contrast 3 *vs* contrast 4 and *vice versa*) (p < 0.001 uncorrected). We chose a less conservative threshold for the two-sample *t* test than for the one-sample *t* test to adapt the analysis to the size of contrast images under study; moreover, we did not fix an extent threshold for the MTL as it is a small structure, for which we had a stringent *a priori* hypothesis.

4. Results

4.1. Behavioural data

The reaction times (RTs) were 7.25 s (SD = 3.27 s) for R condition, 1.18 s (SD = 0.23 s) for K condition, and 1.07 s (SD = 0.20 s) for the B condition. Owing to the self-paced design, the RTs measured for the experimental condition were significantly different from those of the K and B conditions. However, RT differences were not found to influence the pattern of cerebral activations in fMRI studies using a similar design (Botzung, 2005; Denkova et al., 2006). The mean percentage of *yes* responses across all subjects was found to be 80% for the R condition, 94.72% for the K condition and 98.89% for the baseline (see Table 6).

Table 6. Behavioural performance on the fMRI tasks. Mean ± standard deviation are shown.

fMRI tasks	Faces	Names	All
R task			
- *yes* responses (%)	78.89 ± 15.26	81.11 ± 10.11	80 ± 13.04
- reaction time (s)	6.90 ± 3.12	7.61 ± 3.51	7.25 ± 3.27
- vividness rating	2.39 ± 0.34	2.66 ± 0.57	2.52 ± 0.43
- emotion rating	1.46 ± 0.68	1.59 ± 0.71	1.52 ± 0.67
K task			
- *yes* responses (%)	91.11 ± 10.76	98.33 ± 4.14	94.72 ± 8.79
- reaction time (s)	1.15 ± 0.28	1.21 ± 0.30	1.18 ± 0.24
B tasks			
- *yes* responses (%)	98.61 ± 2.64	99.17 ± 1.17	99.89 ± 2.12
- reaction time (s)	0.85 ± 0.16	1.29 ± 0.37	1.07 ± 0.20

The mean age of recollections across participants was 6.385 years (range: 1month – 24 years). The most recent memories stemmed from the preceding year (M= 6.13 months, SD = 0.51), while the remote memories ranged from 5 to 24 years old (M = 11.34 years; SD = 1.95). The corresponding percentages were 30.71% and 47.75%, respectively.

We reported behavioural data related to the conditions of interest, namely the R and K tasks. Post-scanning ratings for vividness (R only) did not differ from ratings obtained during pre-scanning interview [pre (M = 2.58, SD = 0.80), post (M = 2.52, SD = 0.43), t = 0.27, p = 0.79]. However, post-scanning ratings for emotion were significantly different from those accessed before fMRI session [pre (M = 2.65, SD = 0.54), post (M = 1.52, SD = 0.67), t = 5.41, p < 0.01). Pairwise comparisons of post-scanning rating scores (Newman Keuls Tests) showed that R names were associated with significantly more details than R faces [names (M = 2.66, SD = 0.57), faces (M = 2.39, SD = 0.34), p = 0.02] as well as longer RTs [names (M = 7.61 s, SD = 3.51 s), faces (M = 6.90 s, SD = 3.12 s), p = 0.02]. Nevertheless, there was no significant correlation between the amount of details and the RTs [names (r = 0.23, p = 0.47), faces (r = 0.02, p = 0.94)]. Concerning post-scanning rating for emotion, there was not significant difference between R faces and names [names (M = 1.59, SD = 0.71), faces (M = 1.46, SD = 0.68), p = 0.21)]. K faces and names did not

differ significantly in terms of RTs [names (M = 1.21 s, SD = 0.30 s), faces (M = 1.15 s, SD = 0.28 s), p = 0.86).

4.2. fMRI data

Autobiographical /semantic components cerebral networks

The 'R *vs* K' contrast yielded increased left-lateralised activations in the dorsolateral and venrolateral prefrontal areas (BA 6, 8, 10, 45, 47), the anterior (BA 32) and the posterior cingulate cortices (BA 30, 31), the precuneus (BA 19, 7), the temporo-parieto-occipital junction (BA 19, 39), the fusiform (BA 20) and lingual (BA 18) gyri and the parahippocampal gyrus (BA 36) (Table 7, Figure 15a and Figure 16).

Table 7. Regions of significant activation for the R *vs* K contrast, regardless of stimulus material (p < 0.05 corrected, k ≥ 10 voxels).

Brain region (BA)	x, y, z	Z score	Cluster size
L Temporo-parietal-occipital junction (BA 19, 39)	-38 -84 28	6.48	611
L Precuneus (BA 19)	-32 -82 38	5.54	
L Cuneus/ precuneus (BA 30, 31)	-10 -58 8	6.33	581
L Lingual (BA 18)	-6 -52 0	6.13	
L Anterior Cingulate (BA 32)	-6 32 28	6.04	96
L Superior/ Middle Frontal (BA 6)	-26 12 58	5.48	117
L Precuneus (BA 7)	-6 -64 44	5.34	53
L Fusiform (BA 20)	-30 -34 -20	5.31	117
L Parahippocampal (BA 36)	-20 -38 -18	5.01	
L Middle Frontal (BA 8)	-22 22 44	5.25	31
L Superior Frontal (BA 10)	-40 50 16	5.23	18
L Inferior Frontal (BA 47)	-48 16 -2	5.17	21
L Posterior Cingulate/ Precuneus (BA 31, 7)	-6 -40 36	5.11	91
L Parahippocampal (BA 36)	-26 -18 -28	5.02	17
L Inferior Frontal (BA 45)	-46 28 2	5.01	16

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right.
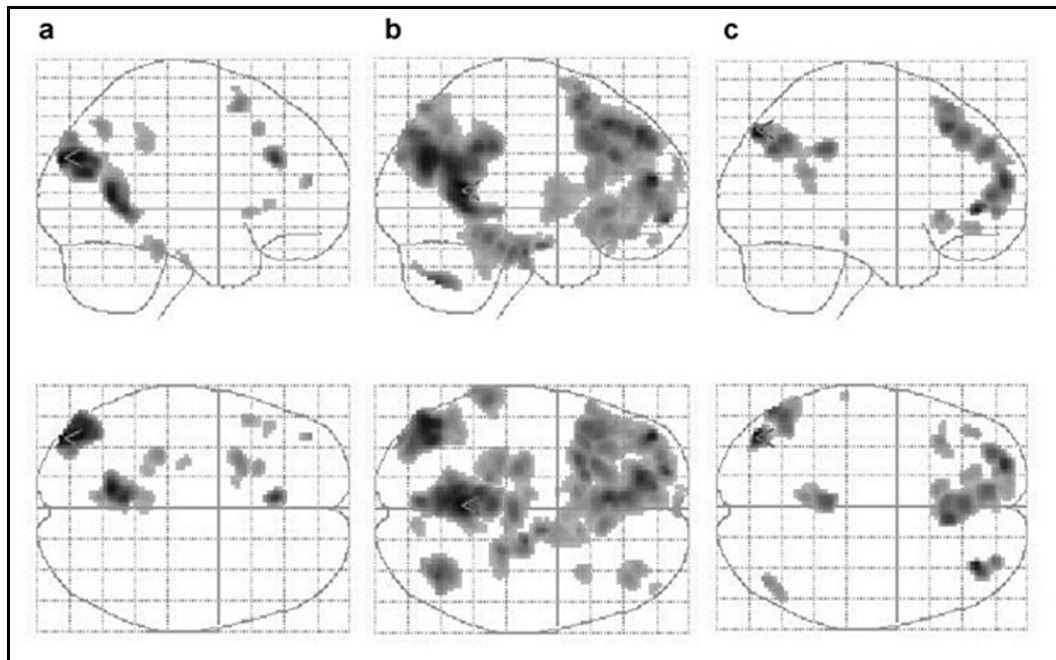
Figure 15. Statistical Parametric Maps showing significant signal increases for the following comparisons: (a) R *vs* K; (b) R *vs* baseline; (c) K *vs* baseline. The images were thresholded at p < 0.05 corrected, k ≥ 10 voxels.
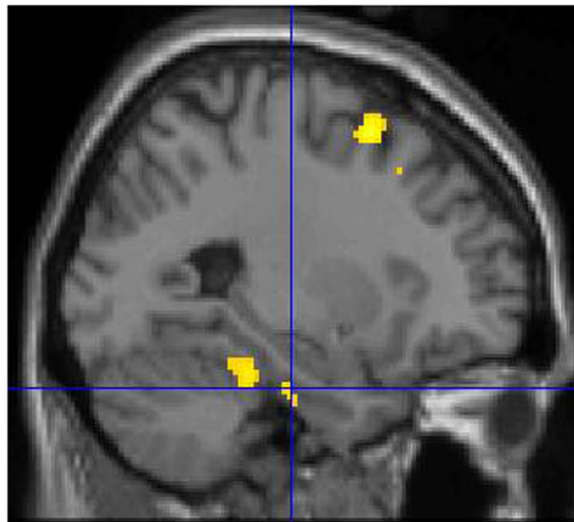
Figure 16. The left parahippocampal gyrus activation revealed by the contrast R *vs* K was displayed on a sagittal brain section.

Compared to the baseline, the R condition involved a more extended cerebral network, which also included the medial prefrontal cortex (MPFC). Since this comparison yielded a very extended pattern of brain activations and that the MTL activation was included within a large cluster, it was detected by a small volume correction approach (a sphere of 10 mm

radius centred on 26, -18, -28 and -26, -18, -28, coordinates found in the R *vs* K contrast for the left MTL) (Table 8 and Figure 15b).

Table 8. Regions of significant activation for the R *vs* B contrast, regardless of stimulus material (p < 0.05 corrected, k ≥ 10 voxels).

Brain region (BA)	x, y, z	Z score	Cluster size
L Posterior Cingulate (BA 29, 31)	-2 -52 10	7.20	4708
L Lingual (BA 18)	-6 -52 2	6.96	
L Temporo-parietal-occipital junction (BA 19, 39)	-46 -72 28	7.02	1640
L Precuneus (BA 19)	-36 -78 40	6.39	
L Superior Frontal (BA 8, 10)	-40 52 16	6.93	6688
L Medial Frontal (BA 8)	-6 28 46	6.70	
L Inferior Temporal (BA 20)	-60 -38 -16	6.17	248
R Superior Frontal (BA 9)	38 38 30	5.70	158
R Pallidus	14 -2 -2	5.60	367
R Thalamus	16 -2 12	5.35	
R Medial Frontal (BA 10)	2 66 20	5.41	63
L Superior Frontal (BA 10)	-10 70 12	4.87	
R Insula (BA 13)	34 14 -6	5.37	62
L Orbital (BA 11)	-8 52 -18	5.25	26
L Caudate Body	-12 8 10	5.16	55
R Superior Frontal (BA 10)	44 54 14	5.11	12
L Parahippocampal (BA 35, 36)*	-26 -32 -22	5.82	284
R Parahippocampal (BA 35)*	24 -30 -22	6.10	183

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right; * = regions detected with a small volume correction.

The 'K *vs* baseline' comparison revealed bilateral but predominantly left-sided activity in the medial (BA 6, 8, 9) and lateral (BA 8, 10, 11, 47) prefrontal regions, the precuneus (BA 19) and left-lateralised activations in the temporo-parietal junction (BA 39), the

inferior temporal gyrus (BA 20) and the posterior cingulate region (BA 29, 30, 31) (Table 9 and Figure 15c). There were no brain areas that demonstrated significantly greater activity during semantic than autobiographical condition (K *vs* R).

Table 9. Regions of significant activation for the K *vs* B contrast, regardless of stimulus material (p < 0.05 corrected, k ≥ 10 voxels).

Brain region (BA)	x, y, z	Z score	Cluster size
L Precuneus (BA 19)	-38 -78 44	6.30	416
L Temporo-parietal junction (BA 39)	-52 -68 34	5.76	
R Superior/ Middle Frontal (BA 10)	32 44 0	6.06	103
L Superior Frontal (BA 10)	-24 60 14	5.96	1470
R/ L Medial Frontal (BA 6, 8, 9)	6 28 46	5.88	
L Posterior Cingulate (BA 29, 30, 31)	-2 -40 34	5.69	243
L Inferior Frontal (BA 47)	-36 24 -4	5.35	76
R Precuneus (BA 19)	42 -72 44	5.28	57
L Middle Frontal (BA 11)	-40 44 -10	5.15	31
L Inferior Temporal (BA 20)	-62 -28 -16	4.96	10

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right.

Verbal/nonverbal material influence

Faces of autobiographically significant famous persons preferentially activated the right superior frontal gyrus (BA 6) [(R faces *vs* K faces) *vs* (R names *vs* K names)] (Table 10a), whereas names activated the left parahippocampal gyrus (BA 35, 8 voxels) (Table 10b). Enhanced activity in the left fusiform gyrus (FG; BA 37) was observed for K famous faces (Table 10c). The left insula (BA 13) was more activated for K names than K faces [[(K names *vs* male names) *vs* (K faces *vs* male faces)] (Table 10d).

Table 10. Interaction autobiographical/semantic conditions and faces/names material (Two-sample *t* tests, p < 0.001 uncorrected).

Brain region (BA)	x, y, z	Z score	Cluster size
a. (R faces *vs* K faces) *vs* (R names *vs* K names)			
R Superior Frontal (BA 6)	20 -14 66	3.51	13
b. (R names *vs* K names) *vs* (R faces *vs* K faces)			
L Parahippocampal (BA 35)	-20 -30 -24	3.25	8
c. (K faces *vs* unknown faces) *vs* (K names *vs* unknown names)			
L Fusiform (BA 37)	-46 -60 -16	3.52	137
d. (K names *vs* unknown names) *vs* (K faces *vs* unknown faces)			
L Insula (BA 13)	-32 -34 16	3.62	18

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right.

5. Discussion

We have obtained different patterns of brain activation sustaining the autobiographical and semantic components of famous person knowledge accessed through verbal and nonverbal material.

Autobiographical /semantic components cerebral networks

The central finding of our study is that MTL activation was associated with the retrieval of autobiographical information but not with the retrieval of semantic knowledge. Our results seem to confirm the Westmacott and colleagues' hypothesis (2003, 2004), which considers that personal significance relies crucially on the hippocampal region, whereas the semantic component depends exclusively on the neocortex. Although the present work was not specifically designed to investigate remoteness, we did observe increased MTL activation associated with the retrieval of personal episodes distributed over the individual's lifespan. This finding is in accord with lesion and neuroimaging literature. Indeed, single-case reports as well as groups studies have documented MTL damaged patients showing an extensive and ungraded autobiographical memory loss with sparing of the semantic knowledge (example of single-case reports: Cipolotti et al., 2001; Fujii et al., 2000; Steinvorth et al., 2005; Westmacott et al, 2001; example of groups reports: Lah et al.,

2006; Viskontas et al., 2000; Voltzenlogel et al., 2006). In the same vein, the majority of the autobiographical memory neuroimaging studies in healthy people, revealed the MTL activation even for very remote autobiographical memories (Conway et al., 1999; Gilboa et al., 2004; Piolino et al., 2004; Rekkas and Constable, 2005; Steinvorth et al., 2006). Moreover, our finding leads to the idea that the MTL activation observed by several neuroimaging studies using celebrity recognition tasks (Bernard et al., 2004; Douville et al., 2005; Haist et al., 2001; Leveroni et al., 2000) may be related to the personal episodes associated with some famous people rather than recognition *per se*. How could this be justified knowing that subjects were instructed to make fame judgements? As Westmacott and Moscovitch (2003) suggested the autobiographical aspect could be retrieved spontaneously without explicit demand to report it. Therefore, the personal significance could act as a confounding variable in the aforementioned studies and account for MTL activation. Furthermore, these investigations (Bernard et al., 2004; Douville et al., 2005; Haist et al., 2001; Leveroni et al., 2000) allowed relatively long time for recognition (about 4s), during which subjects may have continued, beyond the simple identification, to process a given famous person by retrieving autobiographical incidents. Gobbini et al.'s (2004) findings seem to support this suggestion: in their study, the authors did not observe greater MTL activation for famous faces than unfamiliar ones with stimuli presented briefly (1s). Overall, the present study provided functional neuroimaging evidence that the MTL is a crucial area for retrieving personally significant details associated with some semantic concepts. We surmise that increased MTL activation may be the hallmark of personal recollection making the distinction between autobiographical and semantic 'cerebral routes' to famous person knowledge.

Our results also revealed that personally relevant semantic knowledge involved a more extensive network including anterior and posterior brain regions than concepts not associated with any specific recollection. The pattern of activation observed in the left prefrontal cortex during the autobiographical condition is consistent with its well-established role in the strategic and control processes that accompany effortful reconstruction of recollections (for example, Conway, 2005; Moscovitch et al., 2005). The activated region in the temporo-parietal junction (TPJ) was much larger in the R condition than in the K one (see Figure 15). On the one hand, TPJ activation, reported by some neuroimaging studies on famous face recognition, was interpreted as playing a role in biographical knowledge (for example, Gorno-Tempini et al., 1998). On the other hand, autobiographical memory investigations also revealed increased activity in this region in

association with personal events and facts (for example, Levine et al., 2004; Maguire and Frith, 2003a; Maguire and Mummery, 1999). These findings suggest that the TPJ is involved in retrieval of biographical as well as autobiographical information. Bearing in mind both the neuroimaging literature data and our results, we view the degree and the extent of TPJ activation as reflecting the richness of the stored information: the richer the concept, the greater the activation. The lack of activation in the K *vs* R comparison also supports our suggestion.

We also observed that the TPJ activation extended into the occipital areas in the R condition only. The enhanced activity in the lingual gyrus specific to autobiographically significant famous persons could reflect the retrieval of sensory-perceptual episodic details linked to them since it was demonstrated that re-experiencing vivid specific memories engage this brain structure (Conway et al., 1999; Gilboa et al., 2004).

Although most of the neuroimaging studies dealing with remembering past memories reported increased activity in MPFC (Gilboa, 2004 for review), we did not observe its activation when we compared R to K condition. However, this region was activated in the contrast R *vs* baseline (see Table 8). The MPFC activation in autobiographical memory research has been attributed to the self-referential processing (Levine et al., 2004; Maguire and Frith, 2003a); the self, in Tulving's terms (2005), being one of the three central components of autobiographical memory, together with autonoetic awareness and subjectively sensed time. Moreover, the MPFC has been also found to be involved in 'theory of mind' (Den Ouden et al., 2005), in feeling-of-knowing judgement (Schnyer et al., 2005) and in 'felt of rightness' (Moscovitch and Winocur, 2002). The absence of MPFC activation in the contrast R *vs* K suggests that K celebrities engage MPFC (see Table 9) probably for the intuitive assessment of the 'felt of rightness', which refers to the ability to rapidly appreciate the appropriateness of a response related to the goal of the memory task (Moscovitch and Winocur, 2002). In other words, our participants might have evaluated automatically whether the context required the retrieval of self-reference information or the fame judgment.

The influence of material

Turning now to the influence of the verbal/ nonverbal material, it selectively affected the semantic knowledge cerebral pattern. We observed that K faces were specifically associated with activation in left FG. Although the increased activity in FG was generally bilateral in previous neuroimaging studies using famous faces, it was stronger in the left

hemisphere that in the right hemisphere when conceptual knowledge was accessed (Bernard et al., 2004; Gobbini et al., 2004; Thompson-Schill, 2003, Turk et al., 2005). Hence, our results are in accordance with the aforementioned recent studies. We could speculate that the right FG is related to the perceptual processing of facial stimuli (either known or unknown), while the left FG is associated with retrieval of person identity knowledge. Likewise, the increased activation in the left insula associated with K names is in agreement with a person recognition study that attributed it to retrieval of verbal information about a person (Paller et al., 2003).

Turning back to autobiographically significant people, although we found left-sided MTL activation for R names and right-sided frontal activation for R faces, this apparent lateralisation could not be entirely accounted in terms of verbal / nonverbal stimulus effect *per se*. There are indeed inconsistencies concerning the side of MTL activation in studies using famous faces and/or names (for example, Leveroni et al, 2000 found right hemisphere activation when famous faces were compared to unfamiliar faces and left activation when they were contrasted with newly learned ones. Douville et al., 2005 reported bilateral activation for famous names). Given that our behavioural results showed more detailed recollections for R names than R faces and that autobiographical memory literature reports left MTL activation in relation to memory richness (Moscovitch et al., 2005 for review), we could argue that the increased activation of the left MTL may be attributed to the amount of remembered details associated with names rather that the famous names *per se*. Concerning faces of personally relevant people, they were associated with significantly increased activation in the right superior frontal gyrus (corresponding to BA 6) than their names were, which, to our knowledge, has never been documented in famous face recognition neuroimaging research and only rarely reported in autobiographical memory studies (Gilboa, 2004), and therefore its interpretation remains rather uncertain for the time being.

Pre- and post-scanning behavioural data

Although the emotional ratings for R items differ before and after the fMRI session, the pre-scanning emotion scores and the post-scanning ones cannot be directly compared: the former corresponds to the global apercu of a personal event, while the latter refers to the detailed recollections during the fMRI experiment. However, the low emotion debriefing scores are consistent with the hypothesis that fMRI environment inhibits the ability to fully relive the original emotion during recollections (Denkova et al., 2006; Raz et al., 2005).

Limitation and future directions

Some limitations of this study are worth mentioning. Firstly, the pre-scanning interview, which was used here and in several previous autobiographical studies (e.g., Addis et al., 2004a, b; Greenberg et al., 2005b; Maguire and Frith, 2003a, b) has been criticised because the refreshment of the memory trace could bias the results, particularly the MTL activation during the autobiographical retrieval. However, since subjects viewed all famous people (R and K) in the questionnaire before the fMRI experiment, it seems unlikely that this previous session would affect selectively the R condition. In the same vein, some authors demonstrated that the MTL involvement during remembering past events could not be due to the pre-scanning interview (Addis et al., 2004a; Greenberg et al., 2005b; Ryan et al., 2001). Importantly, in our study, this method has the advantage to ensure the equal proportion of R and K items and to warrant the subsequent statistical comparison. Secondly, due to the temporally-extended nature of autobiographical memory retrieval process, the R condition is associated with considerably longer RTs than the K condition. This difference of time could act, at least in part, as a confounding variable. Although it has been illustrated that it did not affect the general cerebral network (see above), further studies are needed to elucidate this issue using multivariate approach, such as the Partial Least Squares statistical method (Addis et al., 2004b). Finally, we did not observe activation within the hippocampus itself. As Levine et al. (2004) commented on, it seems possible that the frequently used EPI acquisition parameters are not sufficiently sensitive to detect variations in activity within the hippocampus, in which BOLD signal is reduced due to susceptibility artefact. On the one hand, retrieval of personal episodes associated with famous people might be less vivid than recollection of highly personally significant events. On the other hand, recent neuroimaging studies revealed that quality of the recollective experience, such as vividness and personal significance, determines the hippocampal activation (Addis et al., 2004a; Gilboa et al., 2004). Both these observations could account for enhanced activity in the parahippocampal gyrus rather than in hippocampus.

In conclusion, we provided neuroimaging evidence that autobiographically significant knowledge is mediated by a cerebral network different from that underlying semantic or generic information. The core difference between the two patterns of activation is the increased activity in the MTL associated with famous people relevant to one's personal experience. Moreover, our results demonstrated that although the verbal/ nonverbal nature

of material did not readily influence the left/ right lateralisation of the cerebral network, it differentially engaged some brain regions.

6. Study 1 and Study 3: some comparison notes

One could argue that the present experiment challenges, to some extent, our first study, in which we used famous faces recognition as a semantic memory task. We would like to specify, therefore, that in the functional neuroimaging experiments, the association of famous faces recognition with specific personal memories depends on different methodological factors. Firstly, the time allowed for the recognition could play an important role in retrieving autobiographical episodes in relation to some celebrities. Most authors, who observed MTL involvement during famous faces recognition allowed relatively long time periods (at about 4 s), while in our first experiment as well as in Gobbini et al.'s (2004) study that did not reveal activation in the medial temporal structures for famous faces, the recognition times were 1.46 s and 1 s, respectively. As already mentioned, in investigations using relatively long intervals between stimuli, it is not impossible that the subjects continued, beyond the simple identification processing of famous faces by retrieving personal incidents related to the face. Secondly, the experimental context could also influence the results, namely the MTL activation. Whereas the majority of the studies presented famous and non famous faces, both our first and Gobbini et al.'s (2004) works used faces of relatives and friends, in addition to faces of celebrities. It would be reasonable to assume that when famous and personally familiar faces, both associated with pre-existing biographical information, were studied in the same neuroimaging experiment, the former 'lost' their potential to elicit autobiographical episodes (Denkova, unpublished data).

Further studies using relatives' and friends' faces, famous faces associated with autobiographical episodes and non personally significant famous faces, will be critical in determining the involvement of MTL structures; specifically, whether the MTL will be differentially activated in relation to the degree of familiarity and the strength of episodic memories associated with faces. Likewise, such study will allow us to test the hypothesis that the absence of the MPFC activation in the comparison R *vs* K reflects the 'felt of rightness' assessment (see above) as well as to shed light on the relationship between MPFC and self-referential processing.

CHAPTER 7

THE INFLUENCE OF AUTOBIOGRAPHICAL SIGNIFICANCE ON SEMANTIC KNOWLEDGE IN

TEMPORAL LOBE EPILEPSY: EVIDENCE FROM fMRI IN TWO PATIENTS

Before describing the study carried out in a clinical framework, a brief overview of memory research in epileptic patients is provided below.

1. Memory research in temporal lobe epilepsy

Epilepsy, in general, is a frequent (~ 0.5% of the world's population, Kaneko et al., 2002) chronic neurological condition characterised by recurrent seizures due to excessive discharge of neurons. Epileptic seizures can be described as clinical manifestations of excessive and hypersynchronous abnormal neuronal activity predominantly located in the gray matter of the cerebral cortex (Engel, 1996). Seizure are divided into partial and generalised according to clinical and EEG data (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). Partial seizures are characterised by an initial activation of a system of neurons limited to one cerebral hemisphere only. They can occur as (i) simple partial seizures with preserved awareness of self and surrounding and as (ii) complex partial seizures with loss of awareness. Both simple and complex seizures can further progress into secondarily generalised seizures. The latter involve neuronal activity in both hemispheres.

The most common form of human epilepsy refers to the Temporal Lobe Epilepsy (TLE), which is described as a chronic condition characterised by partial epileptic seizures originating in the temporal lobe. Its underlying structural pathology is usually hippocampal sclerosis (Engel, 1996). The TLE with hippocampal sclerosis is typically resistant to antiepileptic drug treatment. The antiepileptic medication controls seizures in 11% of the patients with unilateral hippocampal sclerosis (Semah et al., 1998). However, complete surgical resection of the epileptogenic region leads to seizure freedom in up to 60-90% of patients with unilateral TLE (Engel, 2001; see also Koepp and Woermann, 2005 for review on refractory focal epilepsy).

Scoville and Milner's (1957) investigation in the case of the famous epileptic patient HM, who underwent bilateral MTL lobectomy and who subsequently exhibited severe anterograde amnesia, highlighted the critical importance of the MTL structures in the acquisition of explicit memory. This study opened an avenue in memory research in epileptic patients. In fact, TLE has provided an outstanding opportunity to enhance our

understanding of mechanisms underlying human memory and therefore it has been considered as a 'natural laboratory' for the study of human memory (Snyder, 1997). Moreover, patients with unilateral TLE have allowed neuroscientist to investigate the plasticity of memory functions (e.g., Jokeit and Markowitsch, 1999; Gleissner et al., 2002; Helmstaedter et al., 2004). For instance, Jokeit and Markowitsch (1999) demonstrated that the right hemisphere could compensate for deficit in early onset of left TLE. Additionally, postoperative improvement of nonverbal memory in adult patients with temporal lobe epilepsy was reported (Gleissner et al., 2002; Helmstaedter et al., 2004). However, plasticity appears to be greater in childhood (Gleissner et al., 2005).

1.1 Clinical neuropsychological studies

Clinical neuropsychological studies have concentrated primarily on anterograde memory (i.e., acquisition of new information) in patients with unilateral TLE. They have usually investigated differential impairment of verbal and nonverbal memory according to the laterality of the seizure focus (see Milner, 1968 for an initial report of material-specific memory deficits in epileptic patients, who underwent unilateral temporal lobectomy). Several authors reported that patients with left TLE showed a memory deficit for verbal material, while patients with a right locus of seizures tended to be impaired on visual memory tasks (e.g., Baxendale et al., 1998; Gleissner et al., 1998; Moscovitch and McAndrews, 2002). Although there is a convincing evidence that left TLE can produce a verbal memory deficit, the respective relationship between the right TLE and nonverbal memory seems far less consistent.

A few studies have investigated very long-term anterograde amnesia manifesting as a severe forgetting after effective learning took place, in epileptic patients (example of case-reports: Kapur et al., 1997; Manning et al., 2006; O'Connor et al., 1997; example of group studies: Blake et al., 2000; Jones-Gotman et al., 1997; Mameniskiene et al., 2006). More precisely, they observed that people with TLE showed accelerated forgetting, i.e., an abnormal fast forgetting rate, of verbal and nonverbal material over a period of four or more weeks, despite the fact that they exhibited normal learning and retention after a short delay ($\leq$ 30 min). These findings suggested that failure in very-long-term memory consolidation might be contributing to the impaired remote memory in TLE patients; a deficit that is described in the next paragraph.

Little research has focused on memory for the past in patients with TLE. Remote memory is commonly divided into autobiographical memory and memory for famous people and

public events (i.e., semantic memory). In neuropsychological investigations, the former is usually accessed by means of verbal tests, such as the Crovitz Test and the AMI (see Chapter 2). The latter is assessed on public events questionnaires and on tests of famous faces and names identification (Kopelman, 2002a; Kopelman and Kapur, 2001). Examples of tests are: (i) the Dead/Alive Test (Kapur et al., 1992; adaptation for French population: Bindschaedler et al., unpublished; Manning, 2002), in which the subjects are presented with a written list of 45 names of celebrities and they indicated for each famous person if s/he is dead or alive, the nature and period of death; (ii) the Public Events Test (*EVE*, Thomas-Antérion, 1997, 2006), in which the subjects are presented with written questions about public events and they were asked to evoke spontaneously each event, to recognise it between two distractors, to answer two precise questions related to it, and to date the event to a single decade; (iii) the Famous Scenes Test (Thomas-Anterion, 1997, 2006) during which the subjects have to name or give as many details as possible concerning an event displayed on a photograph. On the one hand, a few case-reports have documented a selective memory deficit for either personal recollections (Manes et al., 2001) or knowledge of public events (Kapur et al., 1989; 1997; Manning et al., 2005). On the other hand, group studies of individuals with TLE have reported remote memory loss for autobiographical episodes (e.g., Lah et al., 2006; O'Connor et al., 1999; Viskontas et al., 2000; Voltzenlogel et al., 2006) and/or an impairment of memory for famous people and public events (e.g., Bergin et al., 2000; Lah et al., 2004; Viskontas et al., 2002; Voltzenlogel et al., 2006). Most of these group studies have attempted to investigate the pattern of memory deficit in relation to the side of epiletogenic region. Although the methodology (e.g., tests used to probe autobiographical memory) and, a fortiori, the results vary across the aforementioned investigations, they found that generally both right and left TLE patients are impaired in the recall of autobiographical incidents (O'Connor et al., 1999; Viskontas et al., 2000; Voltzenlogel et al., 2006) and also non personal information (Viskontas et al., 2002; Voltzenlogel et al., 2006). Moreover, Voltzenlogel et al. (2006, in revision) reported that patients with left TLE relative to right TLE patients were more impaired on remote memory tasks probably due to their greater anterograde memory deficit. However, to date, no clear explanation has been suggested to account for the remote memory deficits in right TLE patients. Importantly, the findings from group studies and those of single case-reports, although they cannot be directly compared, are apparently inconsistent due, at least partially, to group statistical analysis. While the former demonstrated autobiographical memory loss, together with memory loss for public events

and famous people in left and right epileptic patients, the latter usually found selective impairment on either personal recollections or public events knowledge in patients with unilateral TLE.

1.2. Functional neuroimaging studies

Over the past decade, the rapid development of functional neuroimaging techniques and experimental designs has made possible the investigation of high-order cognitive processes in people with TLE. For instance, the sensitivity for detecting brain activation in patients seems to be enhanced by using recently developed event-related and self-paced designs. The major application of fMRI has been in respect of presurgical assessment of language and memory functioning in medically refractory TLE patients. (Detre, 2004; Hwang and Golby, 2006; Powell and Duncan, 2005; Powell et al., 2004 for reviews). The aims of preoperative fMRI studies have been primarily to localise and lateralise language and memory functions and to use this information to predict potential cognitive decline following temporal lobectomy. Additionally, fMRI technique has begun to be employed to examine the postoperative plasticity (the number of studies dealing with this topic is, however, very small and limited to language functions; for example Noppeney et al., 2005).

Although the localisation and lateralisation of language functions have been most widely examined, there is a growing number of studies focusing on memory functions. Some of these investigations have examined the lateralisation of memory during encoding or retrieval of verbal and/or nonverbal material in TLE patients (e.g., Detre et al., 1998; Golby et al., 2002; Janszky et al., 2004; Jokeit et al., 2001; Richardson et al., 2003). In general, they have shown an asymmetrical pattern of MTL activation, i.e., greater activation in mesial temporal structures appears contralateral to the side of seizure focus. However, Dupont et al. (2002) found that right TLE patients showed impaired verbal memory performances and reduction of the left hemisphere activation, which has been interpreted as related to bilateral functional consequences of unilateral TLE on memory processing.

Concerning the preoperative prediction of memory impairment after temporal lobe resection, Richardson et al. (2004; 2006) reported that greater left MTL activity predicted the extent of verbal memory decline after temporal lobectomy in patients with left hippocampal sclerosis. Likewise, using complex scene encoding task, Rabin et al. (2004) found that increased activation ipsilateral to the seizure focus correlated with greater

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postoperative memory deficit. Overall, all these studies have demonstrated the feasibility and the utility of using fMRI to examine memory functions in patients with TLE. To date, no study has used neuroimaging technique to investigate brain activations sustaining remote memory in epileptic patients, although few case-reports have begun to examine neural correlates of remote memory in patients with developmental amnesia (Maguire et al., 2001b), adult-acquired hippocampal damage (Maguire et al., 2005) and functional amnesia (Botzung and Manning, submitted; Costello et al., 1998; Markowitsch et al., 1997). Because single-case reports demonstrated that TLE can selectively disrupt either autobiographical recollection or recall of non personal information, functional neuroimaging of appropriate epileptic patients should further our understanding of the neuronanatomical representations of both autobiographical and semantic remote memory. Moreover, this issue could provide important insights into the way autobiographical memory interacts with semantic memory in the human brain.

2. Neural correlates of remembering/knowing famous people in two epileptic patients: event-related fMRI investigation

2.1. Introduction

Single-case reports of epileptic patients have shown a double dissociation between memory for personally experienced events and memory for factual knowledge. For instance, loss of autobiographical memories with relative preservation of semantic knowledge has been reported by Manes et al. (2001), while impaired knowledge of famous people or/and public events with spared autobiographical memory has been documented by Kapur et al. (1989, 1997) and Manning et al. (2005, 2006). It is worth noting that the latter pattern of remote memory disorder is an infrequent dissociation. Kapur et al. (1997) and Manning et al. (2005, 2006) have suggested that the unusual selective loss of public events memory could be a consequence of accelerated forgetting observed in those cases. More importantly, Manning et al. (2005, 2006) have reported that the few public events recalled by their epileptic patient should be very likely integrated into his autobiographical memory, which appears to be well-preserved and probably mediated by the intact right MTL.

Westmacott and colleagues (2003, 2004) have investigated the interaction between autobiographical experience and semantic memory by means of the R/K paradigm applied to famous people knowledge. Especially, they have examined the contribution of personal

significance on semantic knowledge according to the lesion profile and severity of autobiographical memory deficit in individuals with different neuropathological profiles: semantic dementia (SD), Alzheimer's disease (AD) and MTL lesions. On the one hand, the authors demonstrated that personally significant knowledge was relatively preserved compared with 'purely' semantic knowledge in SD patients. On the other hand, amnesic and Alzheimer's disease patients exhibited reduced or impaired personally relevant knowledge. They showed, however, a performance advantage for the few concepts that they categorised as autobiographically relevant (see Chapter 1 for fuller description). This result highlighted the crucial role of personal significance on semantic knowledge; even thought AbM is impaired, the few autobiographical memories that are spared continue to influence the non personal knowledge.

The relationship between autobiographical experience and semantic memory has never been studied, to our knowledge, in patients with TLE. It represents a challenging field of memory research in that it bridges topics on the dissociation within remote memory and the interaction between autobiographical experience and semantic memory. Moreover, functional neuroimaging investigation in those patients should shed light on the neural correlates of remote memory.

The aim of the present study was to investigate, using the fMRI technique, the effects of autobiographical significance on the semantic memory in two epileptic patients, JR and RF, who showed different patterns of remote memory loss. JR demonstrated a loss of memory for public events with well-preserved autobiographical memory, while RF exhibited impaired memory for personal episodes with relatively intact knowledge of public events and famous people. We adopted the experimental protocol of study 3. JR and RF signed informed written consent to participate in the fMRI study. The present experiment was approved by the local Ethics Committee (CCPPRB Alsace, April 2006).

2.2. PATIENT JR

2.2.1. Case history and neuropsychological assessment

JR, a right-handed man (d.o.b. 1950), working as an electrical technician, had a long-standing history of epilepsy. His medical history included viral meningitis and prolonged febrile seizures at 7 months of age. JR's first unprovoked seizure occurred at 13 years of age. After a secondarily generalised seizure in 1969, a diagnosis of epilepsy was given. Despite antiepileptic drug treatment, he continued to have four to five seizures per month.

Therefore, he was considered for surgical treatment. Extensive pre-operative (e.g., video-EEG telemetry, MRI and SPECT scanning) testing determined that the seizure origin was in the left temporal lobe. MR images prior to surgery revealed a left hippocampal volume loss, while the right MTL appeared normal. JR underwent a left anteromedial temporal lobectomy in May 2002. The hippocampus, amygdala and the anterior 5cm of the middle and inferior temporal gyri were removed (see Figure 17). Postoperatively, JR was seizure free (EEG data) and at the time of the fMRI scanning, he had stopped taking antiepileptic drugs.
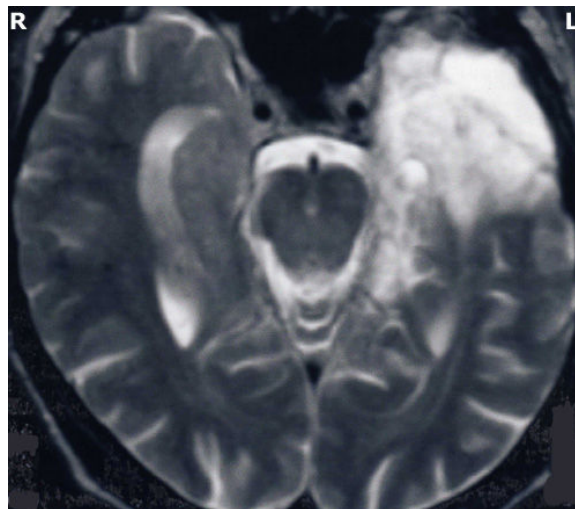
Figure 17. Postoperative horizontal MR image showing left resection of the hippocampus and temporal pole. L = left; R = right.

JR underwent neuropsychological testing during four different periods of time (preoperatively: May 2002; postoperatively: September 2002; May 2003 and June 2004). Full details of the JR's neuropsychological profile have been reported elsewhere (Manning et al., 2005; 2006). In short, pre and postoperatively, his IQ and general neuropsychological profile were relatively stable and normal (i.e., there were no major differences in JR's neuropsychological profile before and after surgery) (see Table 11; for more details see Manning et al., 2006). He performed within the normal range on standard either verbal or nonverbal anterograde memory tasks. Performances on the AMI and Modified Crovitz Test revealed well-preserved autobiographical memory. By contrast, JR showed impaired performances on non personal retrograde memory tasks (Public Events Test, Famous Scenes Test). Postoperatively, he was tested on the acquisition of new public events; one part of them was rehearsed by talking regularly about them with his wife. JR

performances on the rehearsed events were superior to the normal controls, while his score on unrehearsed events was impaired. Manning and colleagues have suggested that "His memory improvement on trained public events may have relied on his preserved autobiographical memory system" (Manning et al., 2006, p. 227). Postoperatively, JR's forgetting rate was also tested for verbal and nonverbal material, and it was markedly accelerated (see Manning et al., 2005, 2006 for more details).

Table 11. JR's performance on general abilities, anterograde and remote memory

Tests	Pre-op JR	Post-op JR	Controls
WAIS- R			
Verbal IQ	88	103	100 (15)
Performance IQ	84	90	100 (15)
Naming [a]			
Deno (100)	96	97	97 (6)
Frontal tests			
MCST	6	6	6
Stroop	1	9	0 (8)
Letter fluency	15	14	14 (5)
Category fluency	22	21	25 (7)
Anterograde memory			
CVLT			
- first recall	7	9	7.5 (2.0)
- last recall	15	15	12.4 (3.0)
- total recall	56	64	53.4 (9.2)
- DFR	10	11	11.6 (2.7)
RMTW	82nd Pc	49th Pc	
RMTF	25th Pc	47th Pc	
RMTT	67th Pc	67th Pc	
Remote memory			
Public Event Test			
- standard	*18%*	*40%*	79%
- rehearsed	-	*89%*	80%
- unrehearsed	-	*37%*	77%
Famous Scenes	*20%*	*31%*	70%
Famous Faces	*45%*	*39%*	97%
Modified Crovitz Test	284.5/400	283/400	267.5/400

WAIS-R = Wechsler Adult Intelligence Scale-Revised (Wechsler, 1989); [a]Kremin (unpublished); MCST = Modified Cart Sorting Test (Nelson, 1976); Stroop = Stroop Test (Stroop, 1935); CVLT = California Verbal Learning Test (Delis, 1987), DFR = Delayed Free Recall; RMTW / F / T = Recognition Memory Test for Words / Faces / Topography (Warrington, 1984; 1996); Pc: Percentile.

2.2.2. Functional neuroimaging investigation

Pre-scanning interview

We used the R/K paradigm as described in Study 3 (see Chapter 6). Four days before the fMRI experiment, JR was presented with a list of 130 famous personalities names. He was asked to indicate for every item if he associated the name with an autobiographical episode (R response) or possessed only semantic information without any personal significance (K response) about it. Examples of autobiographical events were provided in order to ensure that he understood the instructions and made the R/K distinction. Additionally, JR rated on a 5-point scale each name for familiarity (0 = *barely familiar* and 4 = *extremely familiar*) and emotion (0 = *no emotional reaction* and 4 = *intense emotion*). R responses were rated also for memory vividness (0 = *very vague* and 4 = *extremely detailed*). JR provided 11 R responses (8.46%), 28 K responses (21.54%), and he did not recognise 70% of the famous persons presented in the list (see Table 12). It is worth noting that R and K celebrities differ not only in terms of autobiographical significance, but also according to the familiarity and emotion. The mean score for familiarity was 2.36 for R celebrities and 0.96 for K famous people. The corresponding emotional mean scores were 2.36 and 0.18, respectively (see Table 13). Not surprisingly, R responses were vivid and associated with very specific personal events, while K responses were naturally, devoid of specific details. We used all R and K responses in the subsequent fMRI experiment.

Table 12. JR's, RF's and control group's percentages of R, K and 'unknown' responses on the pre-scanning R/K questionnaire.

R/K questionnaire	JR	RF	Control group
R responses	8.46	10.53	36.51
K responses	21.54	70.68	60.03
'Unknown' responses	70.00	18.79	3.46

Table 13. JR's, RF's and control group's ratings on the pre-scanning scales for items used in the fMRI session (mean ± standard deviation).

Scales	JR	RF	Control group
R responses			
- vividness	2.64 ± 1.03	2.21 ± 0.70	2.61 ± 0.77
- familiarity	2.36 ± 1.43	2.07 ± 0.92	2.04 ± 0.63
- emotion	2.36 ± 0.92	2.57 ± 0.85	2.75 ± 0.44
K responses			
- familiarity	0.94 ± 0.51	1.4 ± 0.81	1.78 ± 0.85
- emotion	0.18 ± 0.55	1.73 ± 0.64	1.71 ± 0.69

fMRI procedure (stimuli, tasks, design)

The fMRI procedure used in Study 3 was adapted for JR according to his performances on R/K task. Whereas our normal subjects underwent successively a 'verbal fMRI session' where stimuli were 15 full names of celebrities and a 'nonverbal fMRI session' composed by 15 faces of famous people different from those presented in the verbal one, JR underwent only a verbal fMRI session since he did not provided a sufficient number of R (only 11 R responses). The presentation of less than 10 events enables the statistical analysis. Our decision to show famous names rather than famous faces was driven by the two following reasons: (i) JR did not show a material-dependent memory remote impairment and (ii) because it has been suggested that the name of celebrities is more closely linked to their identity than is their face. Presenting JR with famous names might avoid a potential difficulty related to faces. Thus, our patient performed only a verbal fMRI session, which included 3 conditions: (i) In the autobiographical memory condition (R responses), specific episodes had to be retrieved after the presentation of personally significant famous names. The 11 R items given by JR during the pre-scanning interview were presented twice in order to increase statistical power (Greenberg et al., 2005b). (ii) The semantic memory condition (K responses) consisted of the recognition of the 28 famous names that were previously judged as not autobiographically significant. (iii) In the baseline (B) condition, which was designed to control for perceptual, decision, and motor demands, JR had to make a gender judgment. In all conditions, unknown names were used as foils to control the JR's attention.

Prior to the scanning session, we gave detailed instructions about the three types of tasks. JR was asked to press the *yes* key once the original recollection associated with the famous person was evoked (R condition), when the celebrity was identified (K condition), when a male name was presented (B condition). The *no* button was to be pressed otherwise.

We used the self-paced event-related design described in Study 3 (see Chapter 6). It appeared to be a suitable approach to study patients (Daselaar et al, 2003; Tieleman et al., 2005). R condition encompassed 5 sequences and K and B conditions were composed of 6 sequences. Each sequence consisted of targets and foils that were randomly displayed on the screen for 2 s. The sequences were alternated and were separated by a short instruction on the screen that lasted for 15 s (*recollection: yes key* for R condition; *famous: yes key* for K condition; *a man: yes key* for B condition). Once the subject's response was given, the post-trial interval started. This interval varied from 2.0 to 5.0 s in R condition and from 1.5 to 4.5 s in K and B conditions. Inquisit 1.33 software (see above) was used to set the timing of stimulus presentation and to record the responses.

Post- scanning debriefing

Immediately after scanning, we carried out a debriefing session to access successful autobiographical recollections cued with R names and correct recognition of K names during the scanning session. JR retrospectively rated on a same 5-point scale each R response for vividness and emotion and he dated approximately his memories.

fMRI scanning parameters

We used the same scanning parameters as in the previous experiment described in see Chapter 4.

fMRI data analysis

All fMRI data were processed and analysed using the SPM2 software (Wellcome Department of Imaging Neurosciences, London, UK; Friston et al., 1995) implemented in Matlab6 (The MathWorks, Inc.). Time-series were realigned to the first volume. Because JR's left mesial temporal structures were removed, the functional images were normalised by using his anatomical image as a mask to prevent the lesion influencing normalisation. The normalised images were spatially smoothed with an isotropic 8-mm full width at half maximum (FWHM) Gaussian kernel. The haemodynamic response to each stimulus event

(stimulus presentation plus motor response) was modelled using a canonical haemodynamic response function (Friston et al., 1998). We took into account the stimulus events corresponding to *yes* responses only (i.e., recollections of autobiographical episodes, correct famous person recognition and male judgement). We constructed the following contrasts: R *vs* K, R *vs* B and K *vs* B. We did not fix a threshold *a priori* because in functional neuroimaging of patients the threshold used may vary on an individual basis (Powell and Duncan, 2005).

To ascertain that the repetition of R names did not affect the cerebral network, we undertook an additional statistical analysis, in which only the first presentation of R items was taken into account. In terms of locations of activity, this analysis made no appreciable difference (i.e., the same regions were found but using a less conservative threshold).

Concerning healthy subjects' cerebral networks, we performed a random effect analysis, in which only the responses of the verbal fMRI session of Study 3 were taken into account. Thus, for each normal subject, we calculated the following contrasts: R *vs* K, R *vs* B and K *vs* B. The, we performed one-sample t tests for each of the comparisons. We adopted a threshold of $p < 0.001$ uncorrected and a minimum cluster size of 10 contiguously activated voxels. This threshold is less conservative than that used in Study 3 since only a half of the items were analysed here (verbal responses only).

For the time being, we have not compared directly JR and the younger control subjects (M = 32.7 yr) by means of statistical test. We shall obtain a normal group data with healthy subjects matched for age and education to carry out direct contrasts. At this stage, our primary focus of interest was our patient's profile. We have indeed adopted the clinical approach, in which the priority is to identify brain regions sustaining 'preserved' and 'impaired' tasks and to test for differences between them.

Results

A section of Table 14 shows JR's behavioural results (behavioural results of the control group comprising healthy subjects from Study 3 are also displayed on Table 14).

Table 14. JR's, RF's and control group's behavioural performance in the fMRI verbal tasks (mean ± standard deviation).

fMRI verbal tasks	JR	RF	Control group
R task			
- *yes* responses (%)	63.64	64.28	81
- reaction time (s)	3.43 ± 1.29	4.46 ± 1.23	7.61 ± 3.51
- vividness	3.14 ± 0.38	2.11 ± 0.93	2.66 ± 0.57
K task			
- *yes* responses (%)	100	100	98
- reaction time (s)	1.76 ± 0.44	1.46 ± 0.64	1.21 ± 0.30
B task			
- *yes* responses (%)	100	100	99.17
- reaction time (s)	1.61 ± 0.50	1.28 ± 0.45	1.29 ± 0.37

JR's R *vs* B contrast yielded bilateral but predominantly right-sided posterior pattern of brain activations ($p < 0.001$ uncorrected and $k \geq 10$ voxels; see Figure 18 and Table 15). It included the temporo- occipital junction (BA 19, 39), the posterior cingulate cortex (BA 23, 31), the precuneus (BA 19, 31), the fusiform gyrus (BA 20), the parahippocampal gyrus (BA 36), the thalamus and the superior (BA 11) and medial (BA 6, 11) frontal gyri. Conversely, K *vs* B comparison did not reveal significant increased activation in any brain region, even when a less conservative threshold ($p < 0.01$ uncorrected) was used. Thus, the R *vs* K contrast did not seem appropriated in accordance with the above mentioned result for K *vs* B.

Table 15. JR's regions of significant activation for the R *vs* B contrast (p < 0.001 uncorrected, k ≥ 10 voxels).

Brain region (BA)	x, y, z	Z score	Cluster size
R temporo-occipital junction (BA 19, 39)	40 -78 26	4.95	244
L Cingulate (BA 23)	-2 -24 26	4.25	386
R Posterior Cingulate (BA 23, 31)	6 -26 22	4.10	
R Parahippocampal (BA 36)	26 -28 -18	3.90	32
R Middle Temporal (BA 31)	70 -2 -10	3.89	26
R Precuneus (BA 31)	20 -50 34	3.86	23
L Precuneus (BA 19)	-24 -76 34	3.86	86
R Precuneus (BA 31)	10 -62 20	3.81	43
R Superior Frontal (BA 11)	18 46 -26	3.72	76
R Thalamus	28 -32 4	3.69	23
L Occipital (BA 19)	-34 -44 -4	3.58	17
R Medial Frontal (BA 11)	8 66 -18	3.53	28
L Fusiform (BA 20)	-46 -22 -12	3.43	11
L Medial Frontal (BA 6)	0 -14 54	3.34	20

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right.
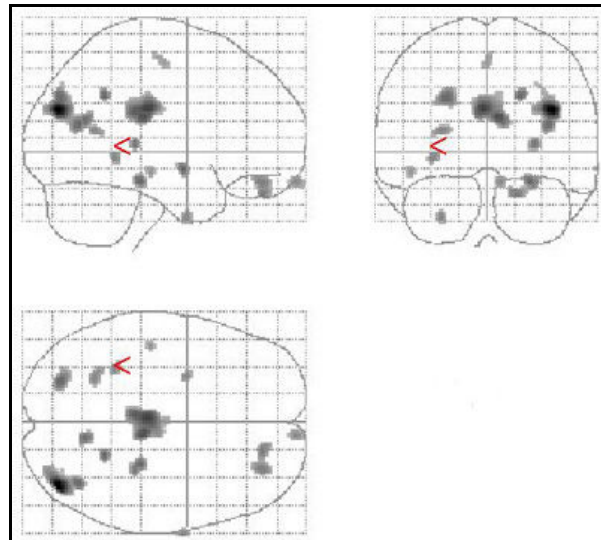
Figure 18. JR's Statistical Parametric Maps showing significant signal increases for the R *vs* B contrast (p < 0.001 uncorrected, k ≥ 10 voxels).

The cerebral networks underlying R famous names and K famous names in normal subjects are shown in Figure 19. Although we used a less conservative threshold, we found similar patterns of brain activations as in Study 3.
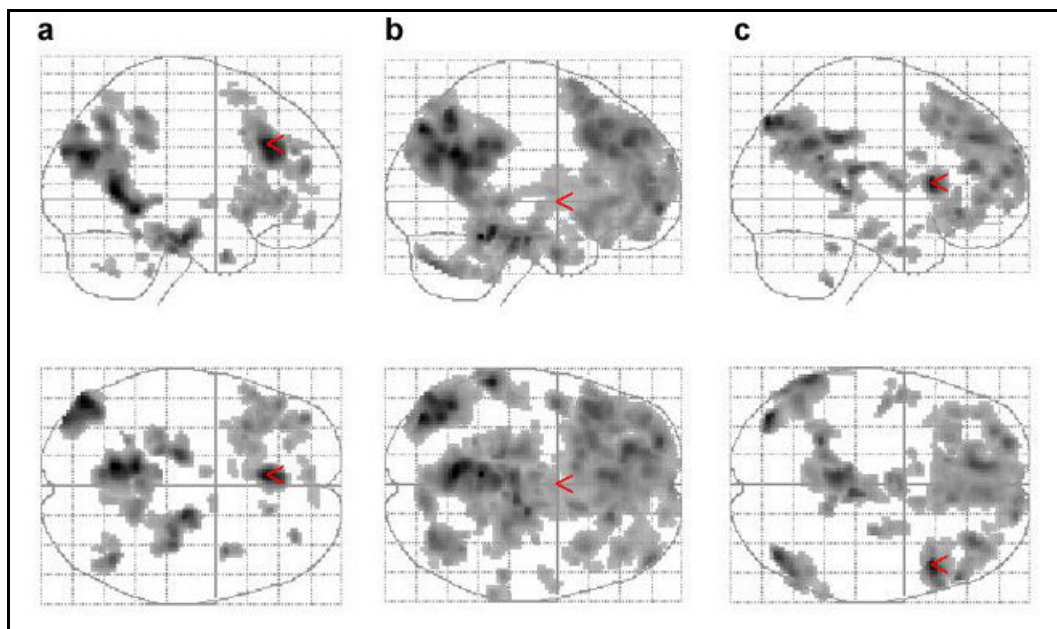
Figure 19. Control group's Statistical Parametric Maps showing significant signal increases for the following contrasts: (a) R *vs* K; (b) R *vs* B; (c) K *vs* B of the verbal experiment (p < 0.001 uncorrected, k ≥ 10 voxels).

2.2.3. Comment

The central finding of the JR's neuroimaging investigation was the absence of activation for K celebrities, while R famous persons were mostly associated with posterior right-sided cerebral network. Differently stated, fMRI results of our patient revealed that there are no differences between celebrities devoid of personal significance and unknown people, whereas autobiographically relevant famous people involved a cerebral network, which was similar, although less extended, to that of the control subjects.

The absence of increased brain activation while JR performed the semantic memory task (K condition) was totally coherent with his altered non personal remote memory. It seemed very likely that JR's K responses were based on a mere perceptual familiarity rather that on a familiarity based on semantic identity information. In fact, qualitatively, his K responses were quite blurred and incomplete (e.g., Jean Paul Belmondo: 'I think he is an actor; Serge Gainsbourg: 'He has always a cigarette on photographs' but JR did not know if Serge Gainsbourg was still alive or not). We would like to suggest that his semantic memory network underlying famous people knowledge is severely impoverished or roughly existent at all.

By contrast, knowledge of famous people, which were related to his autobiography, seemed to be preserved (see neuropsychological assessment). This spared knowledge involved cerebral activations in the undamaged MTL structures and posterior neocortical regions. The former have been associated with retrieval of autobiographical memories. The latter were considered as the sites of multimodal representations, specifically sensory-perceptual details linked to personal memories (e.g., Conway et al., 2003). It is in accord with JR's results on the scale of vividness (see Table 14). He stated indeed that he had detailed visual images of the autobiographical events associated with celebrities during the fMRI task. It seemed that JR's autobiographical memories linked to famous people were remarkably vivid and recalled without effort. These recollections could be viewed as 'flashbulb memories' (Brown and Kulik, 1977). Interestingly, the four R names that failed to evoke a specific personal episode during the fMRI session were those rated as less detailed and less emotional in the pre-scanning interview. These observations could account for the 'paucity' of prefrontal activations. Because memories were vivid and directly retrieved, perhaps they did not need the involvement of regions sustaining effortful and control processes.

Most importantly, our finding provided functional support for the hypothesis that the few public events recalled by JR and the increased performance on rehearsed public event reflected his well-preserved autobiographical memory, i.e., they were preserved because they have personal significance (Manning et al., 2005; 2006).

2.3. PATIENT RF

2.3.1. Case history and neuropsychological assessment

RF, a right-handed man (d.o.b. 1944), was retired from his job as engineer. His medical history included brief paroxystic phenomena at 35 years of age and night secondarily generalised seizure at 39 years of age. He did not suffer from febrile seizures, meningitis or traumatic brain injury. Following extensive neurological and radiological assessments, RF was diagnosed with probable left temporal lobe epilepsy. EEG epileptic activity was detected in anterior temporal lobe. MR imaging showed vascular lesions in the white matter of the brain and in the cerebellum, few lesions in the orbitofrontal cortex and compression of mammilary bodies resulting from a dolicho basilar artery. By contrast, temporal lobes, including hippocampi, appeared normal. However, a hypersignal was detected in temporal lobe using a FLAIR sequence (FLAIR: fluid-attenuated inversion recovery). He was on antiepileptic drug treatment. After a test to stop the medication, a secondarily generalised seizure occurred. At the time of fMRI experiment, RF was on antiepileptic medication.

RF was examined in our Neuropsychological Unit in March and November 2005 (by L Manning and V Voltzenlogel) because he complained of memory difficulties. The neuropsychological assessment comprised general abilities, language, executive functions and memory functions. The results of general testing are summarised in Table 16. RF's IQ was superior. He demonstrated neither language nor attentional deficits. With the exception of impaired performance on the Tower of London test, the remaining frontal/executive functions tasks were normal. RF performed within the normal range on standard anterograde memory tasks, except for the recognition memory test for faces, which was impaired. RF's performances were normal on semantic remote memory tasks, while he showed an impaired retrieval of autobiographical episodes. The Modified Crovitz Test was shortened because the patient exhibited a severe difficulty in providing specific autobiographical episodes.

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Table 16. RF's performance on general abilities, anterograde and remote memory.

Tests	RF
WAIS- R	
Verbal IQ	121; superior
Performance IQ	123; superior
Speed AMIPB	
Motor	70-90th Pc
IP	95th Pc
Language	
Images naming	100%
Vocabulary (WAIS-R)	17; very superior
Spontaneous speech	good
Frontal tests	
MCST	6/6
Stroop	3.5; average
Hayling	
- time score	33 s; good: cut-off = 96 s
- number of correct items	13/15; good
Tower of London	
- time score	21; fail: cut-off = 25
- number of correct items	7/12; fail: cut-off = 8
Letter fluency	14; average
Category fluency	25; average
Anterograde memory	
CVLT	
- first recall	7; matched controls: 5.15 ± 1.28
- last recall	13; matched controls: 12.61 ± 1.94
- total recall	49; matched controls: 49.31 ± 5.39
- DFR	11; matched controls: 10.69 ± 3.06
RCF IR	55th Pc
RMTW	75th Pc
RMTF	< 5th Pc
RMTT	75th Pc
Remote memory	
Dead/Alive Test	86/115; good: cut-off = 78/115
Public Event Test	
- spontaneous	24/30; good
- recognition	15/15; good
Famous Scenes	10/10
Famous Faces	17/20
Modified Crovitz Test	*22/50 (for 10 memories); impaired**

AMIPB = Adult Memory Information Processing Battery (Coughlan and Hollows, 1985), IP = Information processing; Hayling: Hayling test (Burgess and Shallice, 1996); Tower of London Test (Shallice, 1982, personal communication to Lilianne Manning); RCF IR = Rey Complex Figure immediate recall (Osterrieth, 1944); Public Event Test and Famous Scenes Test adapted from Thomas-Antérion, 1997 with permission; Pc: Percentile.

2.3.2. Functional neuroimaging investigation 1

Pre-scanning interview

Three days before the fMRI experiment, RF performed the R/K questionnaire as previously described in the case of JR and Study 3 (see Chapter 6). He was presented with a list of 130 famous personalities. He was asked to indicate for every item if he associated the name with an autobiographical episode (R response) or possessed only semantic information without any personal significance (K response) about it. RF rated on a 5-point scale each name for familiarity (0 = *barely familiar* and 4 = *extremely familiar*) and emotion (0 = *no emotional reaction* and 4 = *intense emotion*). R responses were rated also for memory vividness (0 = *very vague* and 4 = *extremely detailed*). RF provided 14 R responses (10.53%), 94 K responses (70.68%). Only 18.79% of the famous persons presented in the list were not recognised (see Table 12). It is noteworthy stating that qualitatively, his R responses did not correspond to genuine autobiographical recollections, they were in form of dispatched images and devoid of precise temporal and spatial context (e.g., Barbara: "It is my favourite singer, I remember seeing her for the first time, and hearing her first song, I felt in love" but FR cannot say if he was alone or with friends, if he was at home or somewhere else. He was unable to say when that happened). Although R famous people were associated with autobiographical episodes that were not specific and precise, they were integrated to the patient's own history.

All RF's R responses and the 30 K responses that were the most closed matched to R famous persons in terms of familiarity (K mean = 1.40; R mean = 2.07) were used in the subsequent fMRI experiment (see Table 13).

fMRI procedure (stimuli, tasks, design)

Like JR, RF was tested only in a verbal task during the fMRI session because he did not provide a sufficient number of R responses. As already mentioned, it included 3 conditions: (i) an autobiographical memory condition (R responses), in which the patient's R items were presented twice in order to increase statistical power; (ii) a semantic memory condition (K responses) during which RF was asked to recognise 30 famous names; and (iii) a baseline (B) condition. In all conditions, unknown names were used as foils to control the RF's attention. Prior to the scanning session, we gave detailed instructions about the three types of tasks. The *yes* button was to be pressed for personal recollections

(R task), correct famous names recognition (K task) and male names (B task), while the *no* button was to be pressed for foils.

We used a self-paced event-related design as described in the case of JR (see also Chapter 6). Inquisit 1.33 software (see above) was used to set the timing of stimulus presentation and to record the responses.

Post- scanning debriefing

Immediately after scanning, we carried out a debriefing session to access successful autobiographical recollections cued with R names and correct recognition of K names during the scanning session. RF retrospectively rated on a same 5-point scale each R response for vividness and emotion and he dated approximately his memories.

fMRI scanning parameters

We used the same scanning parameters as in our previous experiments (see Chapter 4).

fMRI data analysis

All fMRI data were processed and analysed using the SPM2 software (Wellcome Department of Imaging Neurosciences, London, UK; Friston et al., 1995). RF's functional data were realigned, normalised and smoothed with a Gaussian kernel (FWHM = 8 mm). The haemodynamic response to each stimulus event was modelled using a canonical haemodynamic response function (Friston et al., 1998). We took into account the stimulus events corresponding to *yes* responses only (i.e., recollections of autobiographical episodes, correct famous person recognition and male judgement). We constructed the three following contrasts: R *vs* K, R *vs* B and K *vs* B. We did not fix a threshold *a priori*.

Results

The behavioural results for RF are shown in a section of Table 14.

RF's contrast of R *vs* K revealed increased activation only in one brain region centred on medial prefrontal cortex (BA 10, 11) (see Figure 20a and Table 17a). Apart from medial PFC activity, R *vs* B comparison led to bilateral activation in the occipital regions, namely lingual and fusiform gyri and cuneus (see Figure 20b and Table 17b). We did not observe MTL activation. Surprisingly, the K *vs* B yielded very few and not extended activations.

These activations were localised in the right superior temporal region (BA 22) and the left superior frontal area (BA 6) (see Figure 20c and Table 17c).

Table 17. RF's regions of significant activation for the following contrasts: (a) R *vs* K, (b) R vs B and (c) K vs B of the verbal experiment (p < 0.01 uncorrected, k ≥ 10 voxels).

Brain region (BA)	x, y, z	Z score	Cluster size
a. R *vs* K			
R Medial Frontal (BA 10)	8 66 4	3.99	249
R Superior Frontal (BA 11)	6 64 -14	3.64	
L Medial Frontal (BA 10)	-12 56 -14	3.41	
b. R *vs* B			
R Medial Frontal (BA 10)	6 66 6	3.00	16
L Medial Frontal (BA 10)	-14 64 4	2.89	13
L Superior Frontal (BA 11)	-12 56 -14	2.80	16
L Lentiform Nucleus	-16 -4 2	2.79	57
R Lingual (BA 18)	16 -90 -14	2.77	53
L Fusiform (BA 18)	-16 -84 -20	2.53	65
R Cuneus (BA 17)	20 -94 0	2.58	57
R Medial/Superior Frontal (BA 11)	14 54 -16	2.58	18
R Medial Frontal (BA 9)	26 38 14	2.52	11
L Inferior Occipital (BA 17)	-22 -96 -10	2.40	26
c. K *vs* B			
R Superior Temporal (BA 22)	68 -10 2	2.85	26
L Superior Frontal (BA 6)	-8 24 52	2.68	10

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right.
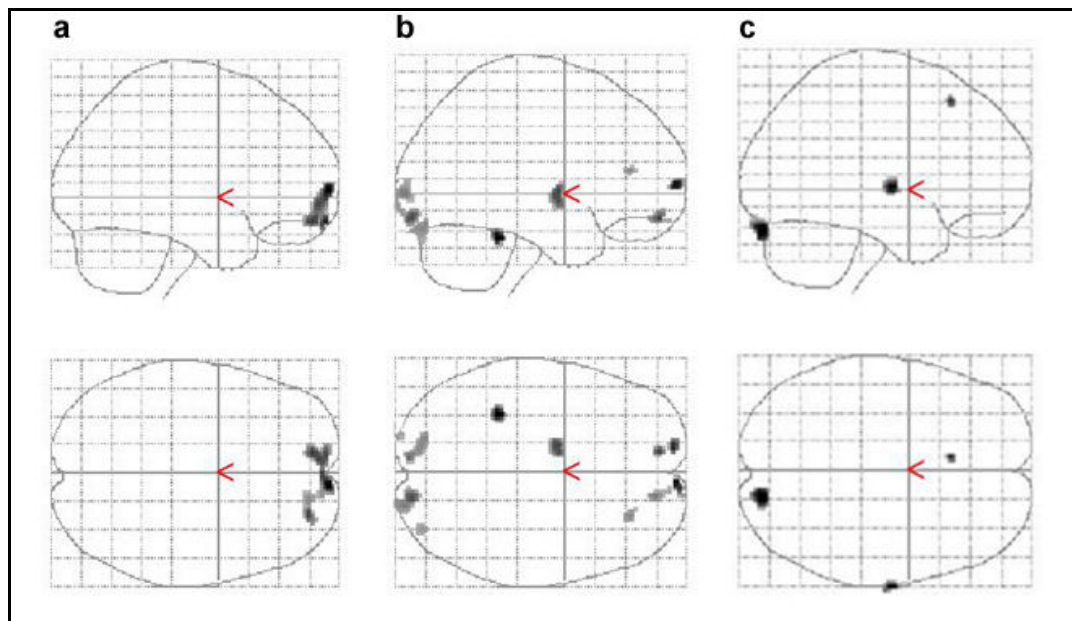
Figure 20. RF's Statistical Parametric Maps showing significant signal increases for the following contrasts: (a) R *vs* K; (b) R *vs* B; (c) K *vs* B of the verbal experiment (p < 0.01 uncorrected, k ≥ 10 voxels).

For all RF's contrasts, we adopted the less conservative threshold of p < 0.01 because we did not find any brain activations using a more stringent threshold. This was very likely due at least at part, to his age and probable vascular dysfunction (see the patient's neurological profile). Although fMRI technique can be used in normal ageing and vascular pathology, the BOLD signal could be reduced in those cases and differences between young and older adults must interpret with caution (D'Esposito et al., 2003).

2.3.3. Comment 1

The present experiment revealed that RF could provide a few famous people names associated with personal events, although his autobiographical memory was impaired. These few R responses seemed to be sustained by the medial prefrontal cortex, which has been frequently associated with self-referential processing (see Northoff et al., 2006). We could suggest with caution that what remained intact in his autobiographical memory was the self-relevant information. RF's R responses were closely linked to his autobiography, even if they were vague and devoid of a specific and precise temporo-spatial context. This observation could account for the increased activity in MPFC and the absence of medial temporal lobe activation.

Most surprisingly, we failed to observe a specific pattern of brain activation for K famous people, despite the fact that RF's performance on targeted tests demonstrated a preserved

semantic memory. How can we explain the discrepancy between the behavioural and neuroimaging data of our patient? We can suggest that our fMRI experiment based on verbal material is not appropriate to study this particular patient. Specifically, since we used only famous names to probe semantic knowledge, it could be the case that in some neurological pathologies, names do not provide a suitable means of testing semantic memory. Thus, for instance, Snowden et al. (2004) found that semantic dementia patients with bilateral but predominantly left-sided temporal atrophy identified faces better than names. More to the point, Viskontas et al. (2002) reported that left-sided TLE patients can provide semantic identity information about famous people from their faces but not from their names. Concerning RF, it could be possible that the names did not automatically activate semantic information about celebrities in fMRI condition. The pre-scanning presentation of names differed from the fMRI presentation in terms of quality of conditions to access the semantic system, i.e., the names were visually as well as auditory presented as they were written and spoken by the examiner, and there were no constraints of time. Concerning the latter point, it has been documented that the access to 'verbal' semantic memory could be temporary unavailable according to temporal factors; that is called semantic refractory access disorder (Warrington and McCarthy, 1983, see also Crutch and Warrington, 2004 for refractoriness in identification of person names). Refractoriness is described as the inability to access semantic knowledge for a period of time following activation. Longer intervals between stimuli (10 s compared with 1 s) facilitate the access to the semantic information. Importantly, Warrington and Crutch (2004) demonstrated that "access to verbal semantics becomes refractory whereas access to visual semantics does not" (p. 313). Thus, we would argue that in the case of RF, the link between famous names and related semantic knowledge might be vulnerable and that the fMRI condition exacting short inter-stimuli intervals could hinder normal access to verbal semantic information about famous people. Consequently, to test this hypothesis, RF was asked to perform a nonverbal fMRI session, in which he was presented with famous faces.

2.3.4. Functional neuroimaging investigation 2

fMRI procedure (stimuli, tasks, design)

One month after the verbal scanning session, RF was tested in a nonverbal task during a second fMRI session. The famous people previously presented in the form of names (verbal fMRI investigation) were presented in the form of faces. Thus, the nonverbal

session includes the same 3 conditions. (i) (i) In the autobiographical memory condition (R responses) 28 faces (14 faces repeated twice) of personally significant famous people were used to probe specific self-related episodes. (ii) The semantic memory condition (K responses) consisted of 30 non-personally significant famous faces that have to be recognised. (iii) In the baseline (B) condition, RF was presented with male and female unknown face and had to make a gender judgment. In all conditions, unknown faces were used as foils to control the RF's attention.

Prior to the scanning session, we gave detailed instructions about the three types of tasks. The *yes* button was to be pressed for personal recollections (R task), correct famous names recognition (K task) and male names (B task), while the *no* button was to be pressed for foils.

We used the same self-paced event-related design.

RF had virtually forgotten the previous fMRI session (for example, he had forgotten that there were 3 conditions; he did not remember how he saw the stimuli in the scanner, etc).

Post- scanning debriefing

Immediately after scanning, we carried out a debriefing session. RF was presented with every faces. He was asked to verbalise the autobiographical 'episodes' evoked during the fMRI session (for R famous faces) and to provide semantic information and to name K faces.

fMRI scanning parameters and data analysis

We used the same scanning parameters and SPM2 software (Wellcome Department of Imaging Neurosciences, London, UK; Friston et al., 1995) as in the previous experiment. We took into account the stimulus events corresponding to *yes* responses only (i.e., recollections of autobiographical episodes, correct famous faces recognition and male judgement). We constructed the three following contrasts: R *vs* K, R *vs* B and K *vs* B.

Results

RF's behavioural results are shown in Table 18. During the post-scanning debriefing interview, he recognised and provided semantic information about 28 K famous faces (93%). Four of these faces were not spontaneously named, however, the first name, spoken by the examiner, helped RF to retrieve the surname. The non recognition of 2 faces was

very likely due to the material, because when the examiner gave their name, RF provide semantic information.

Table 18. RF's behavioural performance in the fMRI nonverbal tasks (mean ± standard deviation).

Scores	R task	K task	B task
- *yes* responses (%)	71.43	93	100
- reaction times (s)	2.29 ± 0.39	1.68 ± 0.40	0.94 ± 0.27
- vividness	1.6 ± 0.69	-	-

RF's contrast of R *vs* K did not lead to any increased brain activation. R *vs* B comparison revealed bilateral but predominantly right-sided cerebral network (p < 0.01; k ≥ 10 voxels). It included medial (BA 10) and anterior cingulate (BA 32) regions, the superior (BA 11) and inferior (BA 47) frontal gyri, the temporal regions (BA 22, 29, 42), the fusiform (BA 20) and lingual (BA 17) gyri, and the striatum (see Figure 21a and Table 19). We did not observe MTL activation. RF's contrast of K *vs* B yielded a bilateral distributed cerebral network (p < 0.01; k ≥ 10 voxels), including large medial (BA 10) and lateral (BA 8, 9, 10, 11, 45) frontal regions, temporal and occipital areas (BA 19, 20, 21, 22), posterior cingulate cortex (BA 29) and precuneus (BA 31) (see Figure 21b and Table 20).

As in RF's verbal experiment, we adopted the less conservative threshold of p < 0.01 because we did not find any brain activations using a more stringent threshold.
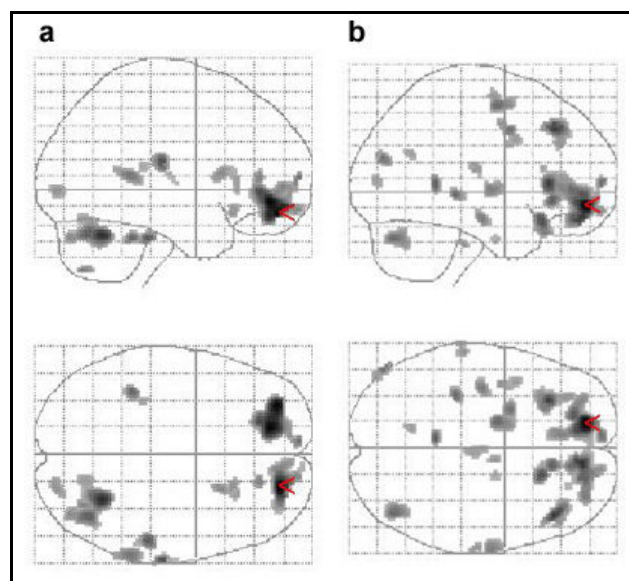
Figure 21. RF's Statistical Parametric Maps showing significant signal increases for the (a) R *vs* B contrast and (b) K *vs* B contrast of the nonverbal experiment (p < 0.01 uncorrected, k ≥ 10 voxels).

Table 19. RF's regions of significant activation for the R vs B contrast of the nonverbal experiment (p < 0.01 uncorrected, k ≥ 10 voxels).

Brain region (BA)	x, y, z	Z score	Cluster size
R Superior Frontal (BA 11)	20 52 -14	3.69	295
R Medial Frontal (BA 10)	10 50 -4	2.71	
L Superior Frontal (BA 11)	-30 50 -14	3.58	638
L Medial Frontal (BA 10)	-16 46 -8	3.58	
R Postcentral (BA 40)	66 -20 18	3.05	39
R Transverse Temporal (BA 42)	66 -16 10	2.43	
R Fusiform (BA 20)	54 -30 -30	2.98	51
R Superior Temporal (BA 22)	62 -42 10	2.78	85
R Anterior Cingulate (BA 32)	18 40 8	2.72	32
R Putamen	22 16 10	2.67	70
R Claustrum	26 26 6	2.50	
R Inferior Frontal (BA 47)	20 22 -14	2.60	24
R Lingual (BA 17)	22 -86 0	2.60	36
L Superior Temporal (BA 29)	-32 -34 14	2.46	10

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right.

Table 20. RF's regions of significant activation for the K vs B contrast of the nonverbal experiment (p < 0.01 uncorrected, k ≥ 10 voxels).

Brain region (BA)	x, y, z	Z score	Cluster size
L Medial Frontal (BA 10)	-16 52 -8	3.76	1140
R Superior Frontal (BA 11)	10 50 -16	3.29	
R Middle Frontal (BA 8, 9)	44 32 40	3.24	109
L Middle/Inferior Frontal (BA 10, 45)	-30 28 6	3.23	144
R Inferior Frontal (BA 11)	18 24 -18	3.11	76
L Posterior Cingulate (BA 29)	-6 -44 4	2.98	45
L Frontal (BA 6)	-16 -4 56	2.92	110
R Cerebellum	42 -72 -30	2.90	121
L Middle Temporal (BA 19)	-50 -78 22	2.85	28
L Middle Frontal (BA 6)	-24 4 40	2.84	41
L Inferior Frontal (BA 11)	-26 26 -26	2.79	88
L Temporal (BA 20)	-38 -14 -18	2.78	54
R Superior Temporal (BA 22)	66 -8 2	2.77	61
L Precentral (BA 6)	-42 -2 44	2.59	56
L Middle Frontal (BA 9)	-42 8 34	2.55	
L Middle Temporal (BA 21)	-70 -30 -2	2.59	20
R Medial Frontal (BA 6)	8 -6 62	2.59	19
R Postcentral (BA 40)	64 -18 16	2.59	19
L Precuneus (BA 31)	-14 -60 24	2.54	17
L Middle Occipital (BA 19)	-46 -82 8	2.53	23
R Caudate (body)	12 24 16	2.51	14

Listed are neuroanatomical regions with associated Brodmann areas (BA), Talairach's coordinates (x, y, z), Z score and cluster size. L = left; R = right.

2.3.5. Comment 2

We decided to conduct a nonverbal fMRI investigation in the case of RF, because the recognition of K famous names did not yield a specific pattern of brain activation, despite the fact that RF possessed semantic information about these celebrities. Thus, using nonverbal material, we observed a distributed cerebral network during the recognition of K famous faces. This finding provided support for the hypothesis that our patient did not activate automatically semantic knowledge about famous people from their name in fMRI condition. When RF was presented with the names of celebrities during the scanning session, his responses might be very likely based on familiarity without accessing specific biographical information (e.g., occupation) about famous individuals, which could confirm their identity. It seemed possible that the link between famous name and identity information could be selectively and temporally 'disturbed' according to the experimental condition. Therefore, the absence of specific brain activation during recognition of famous names could reflect failure to access the verbal stored semantic information under time limited conditions. On the basis of our second fMRI investigation, we would like to argue that temporary failure appeared to depend not only on the experimental conditions (out- and inside the scanner), but also on the material. We observed a specific cerebral pattern of brain activation while RF recognised the faces of the same famous people during the scanning session. In other words, presented with famous faces, RF activated the cerebral circuitry underpinning semantic knowledge about celebrities.

From a neuroanatomical point of view, the reasons why only the link between proper names and semantic information is vulnerable to the experimental condition, appears to be the left anterior temporal lobe epileptic activity. Some reports in the literature confort this suggestion. On the one hand, left anterior temporal lobectomy for refractory epilepsy has been associated with difficulties in retrieval of person names, but spared ability to provide semantic information from famous faces (e.g., Fukatsu et al., 1999; Glosser et al., 2003). On the other hand, although our patient did not exhibit a clear-cut naming deficit, his performance was not flawless. Moreover, epileptic activity together with a hypersignal was observed in his left temporal lobe. Thus, dysfunction, rather than a large structural damage, in the anterior temporal lobe could render vulnerable the link between names and semantic information without causing severe naming impairment. It is possible that the normal functioning of the cerebral pathway sustaining the link name-semantic knowledge could be disturbed by epileptic activity and takes longer to be activated. We have to wait for

semantic refractory disorder to be documented in epileptic patients to confirm this suggestion. Moreover, we cannot rule out that epileptic activity together with vascular lesions could account for the RF's results. For the time being, the question of what neurological factors could better account for the global picture of impaired verbal access and preserved nonverbal access remains open.

Concerning R famous faces, unsurprisingly, they did not reveal a specific pattern of brain activation when they were compared to K famous faces. Indeed, RF's performance on autobiographical memory showed a marked deficit. However, in the verbal fMRI investigation, we observed medial prefrontal activation for R *vs* K contrast. The absence of MPFC activity in the nonverbal session could be due to the fact that K famous faces engage this region (see Table 20) probably for the intuitive assessment of the 'felt of rightness' (see discussion Study 3, Chapter 6), while K famous names were not normally processed, and therefore did not yield specific brain activations (see above). However, MPFC was activated in the contrast R *vs* B in both verbal and nonverbal testing, which is in accord with our interpretation that the self-relevance appeared to be the unique preserved process in RF's autobiographical memory. The fact that in the verbal fMRI study, RF accessed personal significance without accessing semantic knowledge for famous persons is in accord with JR' results and other patients' reports, which demonstrated that "the semantic and episodic aspects of concept knowledge can exist independently of one another" (Westmacott et al., 2004, p. 19).

2.4. Discussion

We examined the neural correlates of autobiographically significant and non personally relevant semantic knowledge in two epileptic patients with different neuropsychological profiles. More specifically, our aim was to investigate the influence of autobiographical significance on semantic memory in patients who showed dissociation within remote memory (i.e., autobiographical memory *vs* semantic memory).

Although our patients suffered from left-sided TLE, JR showed relatively preserved autobiographical recollection with impaired memory for public events and famous people, while RF's autobiographical memory was markedly affected in the context of relatively intact, although dependent on the time factor and the material, semantic knowledge. There are several important differences between JR and RF. While JR underwent surgical resection of the left anterior temporal lobe for the treatment of TLE, RF was not surgically treated for epilepsy. Moreover, RF was diagnosed with *probable* left temporal lobe

epilepsy. Another crucial difference between JR and RF was the age at which epilepsy occurred. On the one hand, as suggested by Manning et al. (2006), JR's epilepsy onset at age 13 might have prevented the accurate building for memory of public events and famous people; the acquisition of public knowledge starting in adolescence. Moreover, epileptic activity could functionally have affected beyond the MTL, the left temporal pole, which has been associated with semantic knowledge of famous persons. For instance, in epileptic patients, Griffith et al. (2006) have demonstrated that the resting metabolism of the left temporal lobe is correlated with performance on access to semantic information about celebrities. Concerning autobiographical memory, which begins to develop in childhood, appeared to be relatively normally acquired and retrieved. These processes were relied in part, on the intact mesial temporal structures. This account was supported by the increased activity in the right MTL while JR remembered personal events associated with famous people. On the other hand, RF's epilepsy onset at age 39 might have disrupted the acquisition of new personal events and the retrieval of old autobiographical memories, which were probably normally acquired. His visual semantic knowledge appeared to be relatively normal because it did not depend on medial temporal regions once it was normally acquired and consolidated in the neocortical regions. This interpretation is in line with the multiple trace theory, i.e., retrieval of personal events needs life-long involvement of MTL, while retrieval of semantic knowledge does not depend on it after long-term consolidation has taken place (Nadel and Moscovich, 1997). However, RF demonstrated a semantic refractory like disorder concerning verbal knowledge about famous people. This is probably due to a dysfunction in the left anterior temporal lobe. It should be noted that RF's neuropsychological profile could result from a super additive effect of temporal lobe epilepsy, inferior frontal lesion and vascular lesions. In fact, both TLE and damage to the right inferior frontal cortex has been associated with autobiographical memory impairment (Viskontas et al., 2000; Voltzenlogel et al., 2006 for TLE; Markowitsch, 1995; Kroll et al., 1997 for inferior frontal lesion).

We reported two main findings concerning the functional neuroanatomy of remote memory. Firstly, we provided evidence that the autobiographically significant semantic knowledge appears to be preserved in the context of impaired semantic memory for public events and famous people and sustained, among others, by the controlesional mesial temporal structures. To this point, the fact that the right-sided MTL might be sufficient to mediate autobiographical memory seems to be dependent on the age at which the epilepsy occurred. Secondly, RF's fMRI investigations provide evidence of material specificity of

the semantic systems. Specifically, our patient showed a semantic refractory like deficit that is only present in the verbal task (famous names) while visual semantics, i.e., the access to semantic information about famous people from their faces, appeared to be spared.

CONCLUSIONS

OVERVIEW

The main aim of the present thesis has to help improving our understanding of neural mechanisms underlying autobiographical memory. On the one hand, we have documented how emotion influences the cerebral network sustaining personal recollections in healthy subjects. On the other hand, we have reported the contribution of autobiographical significance on the neural correlates of semantic memory in neurologically intact individuals as well as in two temporal lobe epileptic patients. Additionally, across all experiments, we questioned the influence of verbal/nonverbal material on the pattern of brain activations sustaining autobiographical and semantic memory.

Our first study investigated the neural correlates of spontaneous re-living of emotion during recollection of personal events. We presented directly in the scanner personally known faces (next of kin, other relatives and friends) because they might be *spontaneously* associated, beyond the facial recognition, with personal memories and an emotional response. In fact, their view elicits a unique and characteristic set of emotions. The behavioural data together with the neuroimaging data provided evidence that emotional aspects were implicitly involved during recollections. Our findings suggested that the use of highly self-relevant stimuli and the collection of data with no previous refreshment of the memory trace (i) influenced the right lateralisation of the activation in the medial temporal lobe activation, and (ii) involved increased activity in the cortical midline structures and subcortical circuits, known to sustain the self-generated emotion, even though no emotion was explicitly acknowledged.

In our second study, the aforementioned nonverbal experiment was compared with a verbal one involving pre-scanning testing. This comparison was performed in order to clarify whether the left lateralisation of the general network sustaining autobiographical memory retrieval, which was found in the majority of the previous neuroimaging studies, depended on methodological factors, the nature of the stimuli (verbal/nonverbal) and the time of testing (prior/directly in the scanner). Our finding of a predominantly left-lateralized cerebral network in both experiments suggested that left-sided pattern of brain activations is associated with AbM retrieval *per se* in healthy subjects.

The third experimental work of the present thesis focused on the interaction between autobiographical and semantic memory. We investigated the influence of autobiographical

significance to the cerebral network of semantic memory. In particular, we examined whether the semantic knowledge associated with specific personal episodes and the 'purely' semantic knowledge devoid of personal significance are mediated by different patterns of brain activation. Additionally, the influence of the nature of material on both the autobiographical significance and the 'purely' semantic cerebral networks has been studied. (i) Our result provided functional neuroimaging evidence that in healthy people, the autobiographically significant knowledge is mediated by a cerebral network different from that underlying semantic or generic information, with the core difference between the two patterns of activation being the increased activity in the MTL associated with personally significant famous people only. (ii) Moreover, we observed that although the verbal/ nonverbal nature of material did not readily influence the left/ right lateralisation of the cerebral network, it did play a role in engaging different cerebral regions.

The last study investigated the neuronanatomical representations of both autobiographical and semantic remote memory in two patients, JR and RF, with left temporal lobe epilepsy. Whereas JR demonstrated a loss of memory for public events with well-preserved autobiographical memory; RF exhibited the opposite pattern: impaired memory for personal episodes with relatively intact knowledge of public events and famous people. Two main findings rose from this study. (i) We provided functional neuroimaging evidence of the dissociation within remote memory (autobiographical *vs* semantic). On the one hand, JR showed a predominantly right-sided cerebral network for autobiographically significant semantic knowledge and the absence of brain activation for purely semantic knowledge about famous people. This finding confirm the hypothesis that the semantic information that was integrated to his preserved autobiographical memory appeared to be spared and sustained by the right-lateralised pattern of brain activation, including the MTL. On the other hand, RF's autobiographically significant semantic knowledge relied exclusively on the medial prefrontal cortex involved in self-relevant processing; this is in accord with his poor autobiographical recollections (devoid of specific temporo-spatial context). (ii) Importantly, we documented dissociation within semantic memory for famous people according to the nature of material (verbal *vs* nonverbal). RF exhibited a refractory-like deficit in accessing semantic information about famous people from their name in the context of relatively spared visual semantics. This neuropsychological profile reflected on the pattern of brain activation observed while RF was presented with famous names and famous faces during the scanning sessions. Thus, our data provide functional

neuroanatomical support for the multiple semantics hypothesis. Our last experimental work confirms the importance of combining neuropsychological and neuroimaging methods in appropriate patients order to better understand human memory functions.

CONCLUSIONS AND PERSPECTIVES

Several general conclusions could be drawn from the present thesis:

(i) Emotion, being embedded in autobiographical memory, contributes to the activation of the right-sided medial temporal lobe during personal recollections, even though it is not explicitly acknowledged. The observation that subjects are unaware of the emotional re-living of an autobiographical incident questions, at face value, the fMRI environment. The use of the electro-galvanic skin response together with questionnaires might help addressing the issue of implicit *vs* explicit emotional state accompanying personal recollections cued with the type of stimuli we used in experiment 1.

(ii) Although autobiographical memory seems to be sustained predominantly by the left-sided cerebral network in healthy subjects, the right hemisphere appears to be sufficient to mediate personal recollections in left-side brain-damaged patient depending on to the period at which the injury occurred. Our findings illustrate the concern pointed out by several authors, i.e., the inconsistencies between neuroimaging studies in the healthy individual and those carried out in clinical neuropsychological setting: while the former demonstrate left lateralised cerebral activations during recollections, the latter indicate the contribution of right hemisphere. To address this point, selected patients with autobiographical amnesia should be examined through fMRI procedures, which were validated in healthy subjects. Ideally, future clinical neuroimaging research could indicate patterns of functional reorganisation depending on the aetiology, the brain region affected by the lesion, the age at onset, the patient's age, among other variables.

(iii) Autobiographically significant semantic knowledge relies on a cerebral network different from that underlying 'purely' semantic knowledge, with the core difference being located at the MTL. Thus, personally relevant concepts appear to have a distinct status in the neural architecture of remote memory.

(iv) In one of our patients, the dissociation and the interaction between autobiographical and semantic memory were clearly detected at the functional neuroanatomical level. The

semantic knowledge integrated within the autobiographical memory is preserved in the case of brain injury and sustained by a pattern of brain activations, which are contralateral to the side of damage. Moreover, semantic knowledge devoid of personal significance is severely affected and apparently with no specific neural representations. In future studies, greater emphasis needs to be placed on the combined use of neuropsychological and neuroimaging approaches in carefully selected patients.

(v) The verbal and visual semantics appeared to be functionally separated in our patient FR. This observation leads to advocate for the application of functional neuroimaging in brain-damaged patients, whenever it is viable. This would provide a challenge and a powerful tool to better understand the dissociations and reorganisation of human memory functions. The use of appropriate neuroimaging procedure in neurological individuals could help, at least in some selected cases, to answer some questions, optimally.

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