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Magnetic resonance imaging in epilepsy. Functional and structural imaging in frontal lobe epilepsy and language study in bilingual patients

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ABSTRACT

Imaging techniques have led to the discovery of key questions in the field of epileptology. In this thesis, functional and structural aspects of focal epilepsies are investigated through magnetic resonance imaging (MRI). In particular, functional MRI and voxel wise analysis are used as the tool to test the hypothesis posed in the different studies that conform this thesis.

The thesis is divided into three studies; two of them focus on frontal lobe epilepsy and the third one on language mapping of bilingual patients with epilepsy.

Frontal lobe epilepsy is the second most prevalent syndrome among the focal epilepsies after temporal lobe epilepsy. However, it has proved challenging to characterize cognitive dysfunction within this group. Furthermore, the functional anatomy correlates of dysfunction in FLE is still unknown. Understanding these changes may help to characterize better the cognitive profile of this group. It may also improve the understanding of the changes in cognitive function as the result of surgery. In particular one of the studies focuses in memory function in patients with FLE. This cognitive aspect has received little attention in this group of patients. However, there is a significant prevalence of memory deficits in patients with Frontal lobe epilepsy. Using functional MRI (fMRI) I investigated long term memory in patients with FLE in order to characterize the functional anatomy that underlies memory dysfunction in this group of patients. The second study on FLE explores the structural changes in this syndrome. It uses voxel wise quantitative MRI techniques to identify common structural changes across this heterogeneous group.

Language fMRI is widely used as part of the pre-surgical investigations of patients with drug resistant epilepsy. This is justified given the high prevalence of atypical language dominance in patients with epilepsy. The clinical validation of these tests have been performed using the subject's native language. However this is a problem when the evaluated subject has to perform the test in a secondary language as it is the case of immigrant population. Although there is a large

number of fMRI studies in bilingualism, these mainly focus in the differences in language networks between the different languages in bilinguals. The third study in this thesis investigates the differences in the language networks that support native and learned languages in bilingual patients with epilepsy and asses the clinical validity of mapping language using language paradigms in a subject's first and second languages.

RESUMEN

Gracias al desarrollo de las técnicas de neuroimagen en las últimas décadas se han conseguido avances importantes en el conocimiento de la epilepsia y sus mecanismos; descubriéndose cuestiones calves que han modificado conceptos clásicos y generado nuevas hipótesis en este campo. En los trabajos que componen esta tesis doctoral se utiliza como herramienta común la resonancia magnética para investigar varios aspectos que comprenden desde la función cognitiva a aspectos estructurales. En concreto se han empleado técnicas de resonancia magnética funcional y análisis cuantitativo de imagen estructural para responder a las hipótesis planteadas en los distintos trabajos que la conforman.

La tesis comprende tres estudios: los dos primeros se centran en la epilepsia frontal y el tercero en mapeo de lenguaje pacientes bilingües con epilepsia.

La epilepsia frontal (EF) es el segundo síndrome más prevalente dentro de las epilepsias focales, después de la epilepsia temporal. Sin embargo, debido a su complejidad como grupo, existen pocos estudios concluyentes a cerca de la función cognitiva en estos pacientes. Tampoco se conocen los cambios funcionales en las redes cognitivas que subyacen los déficits cognitivos en este grupo. Comprender estos aspectos contribuiría de manera importante a entender los déficits cognitivos en este grupo así como a comprender las alteraciones causadas por la cirugía. El primer trabajo de esta tesis estudia la memoria a largo plazo en pacientes con EF. Existen datos contradictorios sobre los déficits de memoria en pacientes con EF. Esta función ha sido poco explorada a pesar de la

prevalencia de problemas de memoria en este grupo. Utilizando un paradigma de memoria en resonancia magnética funcional se caracterizaron los cambios funcionales secundarios a la epilepsia frontal y las alteraciones que se asocian al deterioro de esta función. En el segundo trabajo sobre epilepsia frontal se explora la presencia de cambios estructurales en sustancia gris en pacientes con EF. A diferencia de los pacientes con epilepsia temporal, en este grupo no existen estudios que exploren de manera cuantitativa cambios comunes en la estructura de la sustancia gris. Para ello se han empleado técnicas cuantitativa voxel por voxel que son altamente sensibles a cambios no identificables con inspección visual.

La resonancia funcional (RMf) de lenguaje se ha integrado como parte importante de los estudios pre quirúrgicos en epilepsia. Esta necesidad se ve justificada por la alta incidencia de lateralización atípica del lenguaje en este grupo de pacientes. Este test se ha validado clínicamente en su mayoría utilizando la lengua nativa de los sujetos. Cuando el test se realiza en una segunda lengua como es el caso de población inmigrante se plantea la cuestión de la validez del test. Aunque existen un gran número de estudios de bilingüismo utilizando RMf, estos se han centrado en la búsqueda de diferencias en redes neuronales de las diferentes lenguas y no en el análisis de la validez clínica de estos mapas. En el tercer trabajo de la tesis se investiga las diferencias en los mapas de lenguajes obtenidos con RMf cuando se utiliza la lengua materna y cuando se utiliza una lengua secundaria. Con este estudio pretendemos evaluar la validez clínica de realizar mapeo de lenguaje con resonancia en una lengua secundaria.

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LIST OF ABREVIATIONS

ADNFLE	Autosomal dominant nocturnal frontal lobe epilepsy
AED	Antiepileptic drugs
AED	Anti-epileptic drugs
AI	Asymmetry Index
AOA	Age of acquisition of second language
ATLR	Anterior temporal lobe resection
BOLD signal	Blood-oxygen-level dependent signal
CPS	Complex partial seizure
CTR	Controls
DNET	Dysembryoplastic neuroepithelial tumour
DTI	Diffusion tensor imaging
ECoG	Electro corticography
EEG	Electroencephalography
EEG	Electroencephalogram
EPI	Echo planar imaging
EPI	Echo planar imaging
F	F-test
FCD	Focal cortical dysplasia
FLAIR	Fluid attenuated inversion recovery
FLE	Frontal lobe epilepsy
fMRI	Functional magnetic resonance imaging

FWE	Family wise error
FWE	Family wise error
GLM	General linear model
GMV	Grey matter volume
HRF	Haemodynamic response function
HS	Hippocampal sclerosis
IAT	Intracarotid amytal test
IFG	Inferior frontal gyrus
ILAE	International League against Epilepsy
L	Left
L1	Native language
L1	Native language
L2	Second language
L2	Second language
LI	Lateralization index
ME	Memory encoding
MFG	Middle Frontal gyrus
MFG	Middle frontal gyrus
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
PET	Positron emission tomography
PFC	Prefrontal cortex
R	Right

ROI	Region of interest
SMA	Supplementary motor area
SMG	Supramarginal gyrus
STG	Superior temporal gyrus
T	Tesla
TE	Echo time
TLE	Temporal lobe epilepsy
TR	Repetition time
VBM	Voxel based morphometry
VF	Verbal fluency
VG	Verb generation
WAIS-III	Wechsler Adult Intelligence Scale

1 INTRODUCTION

1.1 CONCEPTS IN EPILEPTOLOGY

1.1.1 Definition of seizure and epilepsy

An epileptic seizure is defined by the ILAE as “the transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (Fisher et al., 2005) and epilepsy as “disorder of the brain characterized by an enduring predisposition to generate epileptic seizures” (Berg et al., 2010). Later reports characterize in greater detail the concept of “enduring predisposition” and introduce concepts such as resolved epilepsy (Fisher et al., 2014).

1.1.2 Incidence and prevalence of epilepsy

Epilepsy is one of the most common serious neurological conditions affecting people of all ages. There are an estimated 50 million people with epilepsy in the world (Ngugi et al., 2011).

The incidence of a first unprovoked seizure is 61 per 100000 and the incidence of epilepsy is 44 per 100000 per year according to the Rochester study (Hauser et al., 1990). This varies according to the development level of the country, ranging from 100-190/100000/year in undeveloped countries to 50/100000/year in developed ones (Sander & Shorvon, 1996).

The lifetime prevalence of epilepsy is estimated to be 5.8 per 1000 in western countries (range 2.7- 12.4) (Ngugi et al., 2011), whereas the lifetime prevalence of seizures (the risk of having a non-febrile epileptic seizure at some point in a lifetime) is between 2 to 5%.

1.1.3 Aetiology of epilepsy

The most common aetiology of epilepsy is unknown or cryptogenic (presumed symptomatic) followed by idiopathic (presumed genetic). The rate of cryptogenic cases ranges from 44 to 67%, with the proportion of identified causes (symptomatic or localisation-related cases) increasing with age (Olafsson et al., 2005). Large community-based studies (Sander et al., 1990, Forsgren et al., 1996) show that the causes of epilepsy in the population vary with the age group. In adult population cerebrovascular diseases are the first cause (11-21%), followed by tumours (4-6%), head trauma (2-6%) and brain infections (0-3%) and cryptogenic (45-65%).

The advancements in imaging and genetic techniques have play a determinant role in the understanding of the aetiology of epilepsy. This has been reflected in the new epilepsy classification proposal (Berg et al., 2010).

1.1.4 Prognosis of epilepsy

The long term studies following up paediatric populations for ~40 years show that 67% of patients achieved seizure remission on or off medication in the long term. Early remission within the first year of treatment was achieved by 31% of the studied population. 14% showed a relapse-remitting pattern while in 19% seizures are persisting from the onset (Sillanpaa & Schmidt, 2006).

Poor seizure control is associated with symptomatic epileptic syndromes. In particular underlying pathology such as mesial temporal lobe epilepsy, focal cortical dysplasia; neurological or psychiatric comorbidity are associated with lower rates of seizure freedom. Other factors such as the type of seizures (complex-focal seizures, spasms); early age of epilepsy onset (< one year); status epilepticus before commencement of medical treatment; high number of seizures before commencement of medical treatment and no treatment response to initial therapy are markers of poor prognosis (Casetta et al., 1999, Kwan & Brodie, 2000). In

patients with poor seizure control, alternative treatment strategies such as epilepsy surgery are often considered.

The underlying epilepsy syndrome is a determinant factor in the prognosis of epilepsy: patients with a diagnosis of childhood absence epilepsy or juvenile absence epilepsy have an 80% chance of becoming seizure free with the appropriate medication. Similar rates are seen for the following syndromes: 86-90% of patients with juvenile myoclonic epilepsy; 60-80% of patients with idiopathic generalised epilepsy with generalised tonic-clonic seizures only; 40-60% of patients with focal epilepsies; 98% of patients with benign childhood focal seizures. The poorest prognosis are seen in syndromes such as Lennox-Gastaut syndrome and West-syndrome for which 20-40% of patients and 40-50% of patients would achieve seizure control respectively.

Failure to control seizures with the first or second AEDs is associated with a low probability of achieving seizure control with further AED. The probability of controlling seizures with subsequent drugs after the failure of two drug trials has been estimated approximately of a 10% (Kwan & Brodie, 2000). However, more recent reports suggest that subsequent medication changes may be having a greater effect in seizure control than that reported by Kwan and colleagues (Luciano & Shorvon, 2007). In a recent study the effect of 265 medication changes in 155 patients with uncontrolled seizures was measured in time. 16% of all patients achieved seizure freedom (>1 year) after a new drug was introduced and a further 21% had significant reduction in the number of seizures. Overall 28% were rendered seizure free by medication changes according to this retrospective study, which was subject to ascertainment bias (Luciano & Shorvon, 2007). Further studies of large cohorts have estimated that 4-5% a year of those with refractory epilepsy will achieve a remission of 1 year on medication and up to 50% of drug resistant patients in whom medication changes are attempted will obtain a significant benefit in terms of seizure control although the long term follow up demonstrates that the benefits may not be sustain in long term (Neligan et al., 2012).

1.1.5 Surgical treatment

Epilepsy surgery aims for the resection of the cortical area that generates seizures with the aim of rendering the patient free of seizures. Epilepsy surgery efficacy has been proved in two controlled trials where the outcomes of patients with temporal lobe epilepsy were compared after randomisation of the patients to either continued medical treatment or surgery (Wiebe et al., 2001, Engel et al., 2012). Both studies showed a superiority of surgery over continued medication for achieving seizure freedom and in quality of life measures.

The long term outcome of epilepsy surgery has been assessed in recent studies (de Tisi et al., 2011). The long term follow up of a cohort of 615 adult patients who underwent epilepsy surgery showed that 52% (95% CI 48-56) of patients remained seizure free after 5 years from surgery, and 47% continue seizure free at 10 years. The patients were followed up prospectively for a median of 8 years. From the 615 patients who underwent surgery, 497 had an anterior temporal resections, 40 had temporal lesionectomies, 40 had extratemporal lesionectomies, 20 underwent extratemporal resections, 11 hemispherectomies, and seven underwent palliative procedures (corpus callosotomy, subpial transection). Patients who had extratemporal resections were more likely to have seizure recurrence compared to those who had anterior temporal resections (ATLR) (hazard ratio [HR] 2·0, 1·1-3·6; p=0·02); whereas patients who underwent temporal lesionectomies did not have significantly different outcome from ATLR.

Longer periods of seizure remission were associated with less likelihood of relapse, while conversely, the longer seizures persisted post-operatively, the less likely it was that seizure freedom was achieved.

1.2 FRONTAL LOBE EPILEPSY

The frontal lobes are the largest lobes in the brain. They account for a third of the whole brain volume and are involved in majority of cognitive functions. Frontal lobe epilepsy (FLE) is the second most common type of focal epilepsy after temporal lobe epilepsy (TLE) (Engel & Williamson, 2008) . However, compared to TLE, FLE are less well characterized as a group from the clinical and neuropsychological perspective. This is in part due to the large heterogeneity of this group of patients which makes it difficult to draw conclusions applicable to the whole group. There is a large variability in seizure patterns, cognitive manifestations and disease progression within this group. The cortical regions that originate seizures within the frontal lobe can be located in areas with large spatial and functional differences and this may account for the observed variability (O'Muircheartaigh & Richardson, 2012).

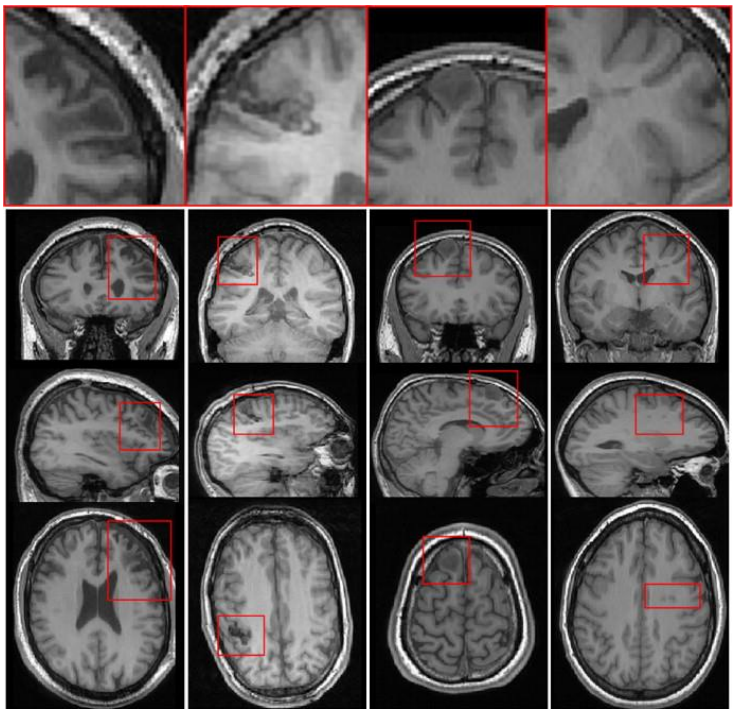

Figure 1-1. Lesion types and location of epileptic focus in frontal lobe epilepsy. *This figure illustrates the large variability in seizure onset location as well as in lesion type in FLE patients. Each column shows the location and a different type of lesion that can be found in patients with*

frontal lobe epilepsy. A: Abscess in frontal pole; B: DNET in Motor cortex; C: Glioma; D: Focal cortical dysplasia (FCD).This figure has been adapted from O'Muircheartaigh and Richardson 2012 Review (O'Muircheartaigh & Richardson, 2012).

1.2.1 Seizures in patients with Frontal lobe epilepsy

Frontal lobe seizures can present with a wide variety of semiological features and in occasions these can adopt bizarre forms. Seizures originating in the frontal lobes can often be mistaken for non-epileptic events, such as parasomnias, psychogenic behavioural episodes or movement disorders. The large variability in frontal lobe seizures reflects the functional heterogeneity of these brain lobes.

Localization of SOZ with EEG can be difficult as shown in the study of Foldvary and colleagues (Foldvary et al., 2001) who showed that ictal EEG is helpful in localize seizures with a lateral frontal onset in 63% of patients compared to a 95 % of patients with TLE. However when the seizure onset zone is located in the medial temporal lobe region, scalp EEG provides useful information only in 12% of the cases.

FLE seizures may share a number of common characteristics including : short duration, often with minimal or no postictal confusion, rapid secondary generalization, prominent motor manifestations which are tonic or postural, frequent falling when the discharge is bilateral (ILAE, 1989). However semiology may vary depending on the regions of the frontal lobes that are involved in the seizure generation as shown in Table 1.1.

Table 1-1. Seizure semiology associated to different frontal regions.(ILAE, 1989)

SITE INVOLVED IN SEIZURE	SEIZURE SEMIOLOGY
Motor cortex	Simple partial seizures. Contralateral tonic or clonic movements according to somatotopy, with frequent generalisation. Ipsilateral leg tonic movements in paracentral seizures may occur. Post ictal paralysis is frequent
SMA	Simple focal tonic and postural seizures with vocalisation, speech arrest, fencing postures, and complex focal motor activity.
Cingulate	Lose of awareness with focal automatisms. Autonomic features are common and changes in mood
Anterior Frontopolar	Force thinking and adversive head movements. Can be followed by subsequent contraversive movements of head and eyes. Axial clonic jerks, falls and autonomic signs with frequent generalised tonic-clonic seizures
Orbitofrontal	Complex focal motor seizures with initial automatisms or olfactory hallucinations, autonomic signs
Dorsolateral (premotor)	Simple focal tonic or less commonly clonic with versive eye/head movements and speech arrest.
Opercular	Laryngeal disturbances are typical. Mastication, salivation, swallowing and speech arrest with epigastric aura, fear and autonomic phenomena. Partial clonic facial seizures may be ipsilateral and gustatory hallucination is common

Several classifications have been proposed for categorizing the seizures arising from the frontal lobe. From the very early classification of Penfield and Jasper based on the anatomical division (Penfield & Jasper, 1954) and the IALE of FLE seizures (ILAE, 1989) based on frequent semiology related to different areas of frontal lobe to quantitative classifications based on cluster analysis of semiology recorded in VT (Salanova et al., 1995, Bonini et al., 2014). The classification proposed by Salanova et al. divided the seizures in 3 electroclincal patterns according to their semiology:

A) Supplementary motor seizures

These are characterized by the tonic posturing of one or both arms. Consciousness is characteristically preserved in these type of seizures.

B) Focal motor seizures

In these seizures consciousness is also preserved most of the time. Clonic movements would involve different parts of the body, and often a sequence starting in the face followed by arm involvement and contra version of the head would be observed.

C) Complex partial seizures (CPS).

These seizures typically begin with unresponsiveness at onset, followed by staring straight ahead. Head and eye contraversion may occur later in the seizure. Large amplitude movements such as bipedal movements are observed in this type of seizure. In contrast to CPS of temporal lobe origin, oroalimentary and repetitive hand automatism are less frequent in frontal lobe seizures.

Each seizure type is associated with certain core semiology as described in Table 1.2.

Table 1-2. Types of frontal lobe seizures. *The most common signs are described in the second column together with the proportion of cases in which each sign was evident. Table adapted from Salanova et al. study (Salanova et al., 1995).*

ELECTRO-CLINICAL SYNDROME	SEMIOLOGY	% CASES
Supplementary motor seizures	**Somatosensory auras**	**45**
	Unilateral tonic posture	**89**
	Bilateral tonic posture	**78**
	Vocalization	**33**
	Speech arrest	**61**
	Laughter	**22**
Focal motor seizures	**Conscious aversion**	**57**
	Speech arrest	**43**
	Unilateral clonic	**100**
	Tonic posturing	**43**
	Clonic eye movements	**29**
	Blinking	**43**
Complex partial seizures	**Cephalic auras**	**38**
	Staring or looking ahead	**63**
	Unconscious aversion	**38**
	Bilateral arm tonic	**50**
	Repetitive arm movements	**50**
	Bipedal movements	**25**
	Vocalizations	**50**

However, there is not a straightforward correlation between the seizure pattern and the anatomical location of the seizure onset zone. This may be in part explained due to the rich connectivity between regions in the frontal lobes. Rich connectivity would facilitate a rapid spread of epileptic activity and this in turn would result on the involvement of cortical regions remote from the seizure onset zone. Some

classic seizure patterns of SMA and focal motor do originate in SMA and primary motor cortex, but these patterns can also be seen when seizure onset regions are located elsewhere. Therefore localization of seizure onset zone cannot be reliably derived from seizure semiology in the frontal lobes (Salanova et al., 1995, Manford et al., 1996).

1.2.2 Cognitive function in frontal lobe epilepsy

Frontal lobe lesional studies have provided evidence about the cognitive impairment associated to damage to this region. The frontal lobes do not act as a unitary functional entity and damage to different regions within the frontal lobes may result in a range of different dysfunctions. Lesions located in the medial orbito-frontal cortex have been related to the disturbance of emotional processing and expression with associated dysfunction of the decision making process (Bechara et al., 2000). In contrast, lesions located in the dorsolateral frontal cortex are more related to deficits in working memory, attention, visuo-spatial functions learning and memory functions (Petrides, 1985, Fuster, 2001).

A number of studies have attempt to define the characteristics of the neuropsychological pattern of patients with FLE (Helmstaedter et al., 1996, Upton & Thompson, 1996, Upton & Thompson, 1997b, Exner et al., 2002) however this task as proof to be difficult. Some studies have identified specific deficits associated with FLE (and not present in other epilepsy groups such as TLE). These include significantly poorer performance in the domains of motor coordination, bimanual hand movements, motor sequencing and response inhibition (Helmstaedter et al., 1996). Some executive skills seem to be selectively impaired in FLE including the cost estimation, twenty questions and Stroop task (Upton & Thompson, 1996). Other domains such as social cognition seem also been affected in patients with FLE who perform poorly in humour appreciation (mental and physical state cartoons), recognition of facial emotion, and perception of eye

gaze expression. IQ is not affected in majority of patients with FLE (Farrant et al., 2005).

Age of onset of epilepsy seems to play a key role in the impairment of these functions with greater deficits associated to an early age of seizure onset, especially before the maturation of frontal lobe skills (Upton & Thompson, 1997a).

Studies in children with FLE have revealed similar deficits to those seen in adult Deficits seem to be more pronounced below the age of 13 suggesting that the epilepsy may delay the emergency of frontal lobe skills (Beaumanoir et al., 2003). The severity of these deficits is highly variable amongst patients and this is even more marked in children (Culhane-Shelburne et al., 2002).

However, there is a large overlap on the range of cognitive dysfunctions seen in FLE and TLE patients making it difficult to differentiate these groups based on the neuropsychological profile (Exner et al., 2002) (Upton & Thompson, 1996) (Helmstaedter et al., 1996). A relevant limitation to define an FLE neuropsychological profile is that there are not pure frontal functions as such. Instead, cognitive functions rely on the integrity of networks that involve several lobes (O'Muircheartaigh & Richardson, 2012). Additionally, the effects of epilepsy extend well beyond the limits of the frontal lobes as shown by functional and structural studies (Yasuda et al., 2010). These two factors increase the complexity of defining a neuropsychological profile exclusive to FLE.

Another relevant limitation of these studies is the coexistence of epilepsy and structural brain lesion in a large proportion of the patients included in the studies. This limits the interpretation of the data, making it difficult to disentangle whether the observed deficits are due to the lesion or to the effects of epilepsy. This question was addressed in two studies that lead to contradictory conclusions: while Helmstaedter et al. (Helmstaedter et al., 1996) did not find significant differences in cognitive performance between non lesional and lesional cases, Grafman et al. (Grafman et al., 1992) found greater deficits in patients with a similar extent of frontal lobe damage and epilepsy. Therefore further studies would be required to

separate the effect of lesion from the effect of epilepsy in the cognitive dysfunction seen in these patients.

1.2.2.1 Memory function in frontal lobe epilepsy

Memory dysfunction is a common finding in the neuropsychological evaluation of FLE patients (Helmstaedter et al., 1996) (Exner et al., 2002, Centeno et al., 2010) but the prevalence and the underlying mechanisms to this deficit remain poorly understood.

This chapter of the introduction is summarized in the review article that is indexed as annex 1.

1.2.3 Therapy and outcome

1.2.3.1 Drug therapy

There are no reported differences in the rate of response to treatment between patients with FLE and other focal epilepsies (Kellinghaus & Luders, 2004). Approximately two thirds of the patients become seizure free under antiepileptic drugs (AED) (Kwan & Brodie, 2000). Only one study (McCabe et al., 2001) has focused specifically on patients with FLE, showing that the combination of Valproate and Lamotrigine render seizure free 50% (11 out of 21) of patients who showed previous resistance to other AED. However, concerns regarding the design (open label not blinded) and the accuracy of the localization of epileptic focus suggest that results are considered with caution.

In frontal lobe epilepsies where the genetic and molecular abnormalities have been identified such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), specific drug treatments targeting the molecular basis of the disease are being developed (Yamada et al., 2013).

1.2.3.2 Surgical therapy

The benefits of epilepsy surgery were in first instance proven in patients with TLE (Wiebe et al., 2001). Given that no substantial differences in the mechanisms of action of surgical therapy are suspected between TLE and other locations of epilepsy, surgery is also the therapy of choice in drug resistant extra temporal lobe epilepsy when possible. The first case of surgery in a patient with FLE was performed in 1886 (Olivier, 1995) but the first large series of non-tumour FLE was not published until a century later by Rasmussen in 1983. In this study 24 (13%) out of 184 patients eventually became seizure-free (Rasmussen, 1983). Recent studies have reported better rates in the surgical outcome of these patients. Lazow et al (Lazow et al., 2012) showed that approximately 60% of patients with FLE become free of disabling seizures but may continue experiencing auras. Complete seizure freedom is achieved in a 30% of the patients. The long term follow up of epilepsy surgery case series shows that the surgical outcome of patients with FLE is poorer compared with those of TLE patients (de Tisi et al., 2011). In this long term follow up study of the London surgical cohort, patients with extra temporal resections achieved a seizure freedom in 30% of the cases compared to 60% of temporal cases at 10 years. However, even if seizure freedom was not achieved at 10 years, the most common pattern following surgery mixes prolonged periods of seizure freedom intermixed with recurrences.

The factors associated with a better surgical outcome across both temporal and extratemporal lobe epilepsy were the presence of an epileptogenic lesion in neuroimaging, the absence of febrile seizures, generalized or bilateral epileptiform activity on surface EEG and focal epileptiform activity in ECoG. Instead, residual epileptogenic tissue assessed by ECoG or MRI was a strong predictor for poor outcome after surgical resection (Wennberg et al., 1998, Ferrier et al., 1999, Kellinghaus & Luders, 2004).

1.3 MAGNETIC RESONANCE IMAGING (MRI) IN EPILEPSY

In 1937 the first study using electroencephalographic (EEG) showing the electrical correlates of seizures was published (Gibbs et al., 2002). For the first time the specific electrical patterns that characterize generalize tonic clonic seizures, absences and partial seizures were identified. This represented a crucial step in the diagnosis and classification of epilepsies. Brain imaging represented the second big step by contributing to the identification of the anatomical correlates of epileptic disorders. In particular, the development of MRI made a significant change to the diagnosis and aetiological filiation of epileptic syndromes and is currently used as the gold standard imaging technique in the routine study of the patient with epilepsy.

*In this chapter I will do an overview of the different MRI techniques with an emphasis on the techniques used in the studies of this thesis: functional MRI and voxel based morphometrical techniques.

1.3.1 Basic principles of MRI

The MR signal arises from the nucleus of the atom and it relies on the magnetic properties of all atoms that have “spin angular momentum” (Cascino & Jack, 1996). The magnetic properties of the atom vary and the one most commonly measured in human MRI is the hydrogen particle (H), which is a proton. Relaxation times after RF pulses and proton density vary among different tissues and different types of lesions. These differences in signal are transformed into images that enhance or contrast certain types of tissues depending on the sequence.

The concept of nuclear magnetic resonance was discovered by Block and Purcell in the 1940s but it was only in the late 1970s when the first MRI images of human body where obtained (Damadian et al., 1977). Over the following decades, there was a rapid development of MR imaging methods that has made its extended use in the medical field possible.

MR brain imaging created a revolution in the field of Neurology, changing the way many diseases were diagnosed and treated. Later developments such as functional MRI have brought light to understanding the functional processes of the brain.

Both structural and functional MRI techniques are currently used in the diagnosis and management of epilepsy (Duncan, 2010). In the following sections these will be discussed in greater detail.

1.3.2 Structural MRI. Aetiological diagnosis of epilepsy

Identifying the structural cause of epilepsy is crucially important for performing an accurate diagnosis and syndromic classification of the epilepsy, as well as for treatment planning. This aspect becomes even more crucial if the patient is being evaluated for epilepsy surgery. It is estimated that around 3% of patients are evaluated for surgery (Lhatoo et al., 2003). The removal of a clear-cut focal abnormality improves the chances of seizure freedom. Approximately 70% of patients who have such lesions removed can achieve seizure freedom after surgery (Spencer & Huh, 2008).

The development of new MRI sequences and the improvements in MRI technology have resulted in an increased yield for lesion detection in patients with epilepsy. In particular, the higher strength of the magnetic field (3Tesla MRI machines) and the use of epilepsy tailored sequences have demonstrated structural abnormality detection in up to 20% of patients with previously unremarkable or inconclusive MRI (Knake et al., 2005).

Dedicated protocols for epilepsy have been elaborated by the ILAE neuroimaging commission in order to optimize the detection of abnormalities in patients with epilepsy (Barkovich A. J., 1998). These protocols suggest that an MRI study in epilepsy should include the following sequences: volumetric T1-weighted sequence; Proton density, T2-weighted and fluid-attenuated inversion recovery sequences in oblique coronal and axial planes and Gradient-echo sequence.

Latest revisions of the protocols (Wellmer et al., 2013) recommend the addition of axial hemosiderin/calcification-sensitive sequences, the volumetric T1 to be isotropic 1mm cubic size voxels and the thickness of the slices in the T2-weighted and FLAIR sequences to be set at 3mm or less with an angulation both perpendicular and parallel to the hippocampus.

Despite these advances in 20-50% of patients referred to tertiary centres, structural abnormalities cannot be identified on MRI (Bernasconi et al., 2011). This is where advanced post processing analysis techniques come into play.

The lesions identified using structural MRI in patients with epilepsy vary depending on the age group. The most common lesion types can be classified in one of the following categories:

- Mesial temporal lobe sclerosis
- Malformations of cortical development such as focal cortical dysplasia, polymicrogyria heterotopia, and schizencephaly
- Low grade tumours
- Ischaemic or haemorrhagic strokes
- Arteriovenous malformations, cavernomas
- Post-traumatic brain injury
- Infectious-post infectious encephalitis
- Cortical tubers

Hippocampal sclerosis is the most common finding in adult patients with drug-resistant temporal lobe epilepsy (Armstrong, 1993). The radiological diagnosis of hippocampal sclerosis is characterized by loss of volume in the hippocampus and increased signal intensity on T2-weighted images. The volumes of the hippocampus are usually measured manually which is time consuming, however recent automatic methods based on multi-atlas segmentation propagation are showing accuracy similar to the manual-based method (Winston et al., 2013) (https://hipposeg.cs.ucl.ac.uk/).

1.3.3 Quantitative MRI-voxel based studies

Quantitative voxel-based methods are objective and unbiased techniques that allow identification of differences in brain structures. These analysis aim to identify abnormalities undetectable to visual inspection. These can be used to investigate differences at a group level, or to characterize individual abnormalities by comparing a case against a cohort of controls.

Voxel-based analysis of FLAIR images revealed that 14% of cases with a previous negative MRI study have subtle abnormalities at the voxel level. In half of these patients, the abnormalities in the FLAIR images were concordant with the irritative zone characterized from scalp EEG (Focke et al., 2009) (Figure 1-2).

Quantitative voxel based analysis of diffusion tensor imaging (DTI) has also shown a high sensitivity in the detection of subtle structural abnormalities. Diffusivity abnormalities are detected in 50% of patients with drug-resistant focal epilepsy. These abnormalities showed a significant degree of concordance with the findings from stereo-EEG recordings. (Thivard et al., 2006, Chen et al., 2008). However, the clinical utility of a voxel-based analysis of an individual patient is limited by the need to balance sensitivity with specificity, and the optimal balance will differ for various MRI contrasts. Overall, the yield of positive and helpful findings from such an analysis in individuals with unremarkable conventional MRI is 10–30% (Salmenpera et al., 2007).

Recent approaches have attempted to improve sensitivity and specificity in the detection of subtle lesions by incorporating not only signal intensity changes but other characteristics such as surface-based features. These include the degree of folding, depth of the sulcus and location of the finding (bottom of the sulcus versus surface), the detection of changes in the grey-white matter differentiation (Huppertz et al., 2005) or the use of novel sequences such as NODDI (Winston, 2015). The combination of several parameters holds the promises of increasing the yield for true positives of quantitative techniques. Recent studies combining different features have been reported to detect FCD with a sensitivity of 74% and specificity of 100% (Hong et al., 2014).

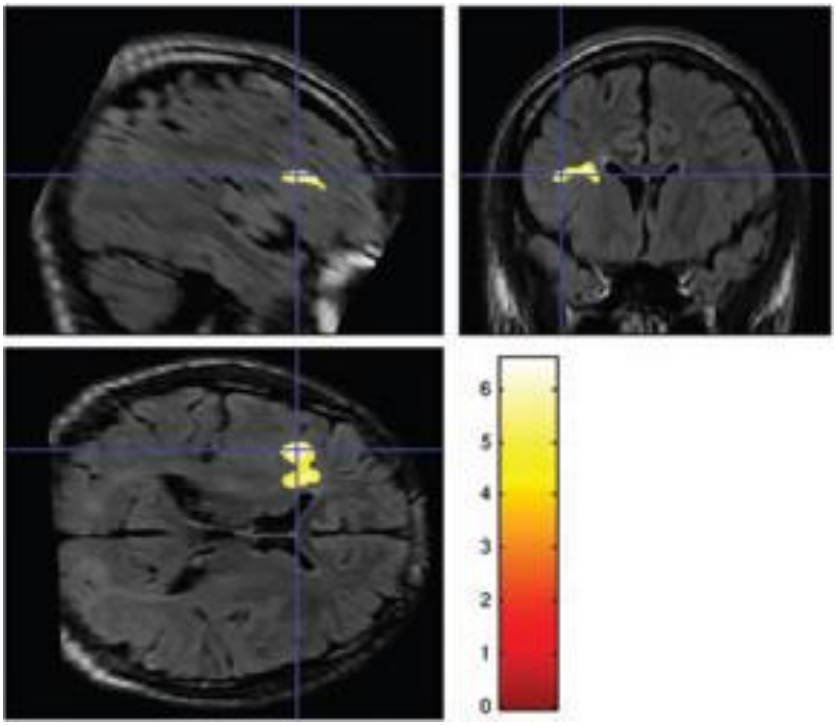

Figure 1-2. Voxel by voxel analysis of FLAIR. *Area of abnormal FLAIR signal of a single subject with normal MRI compared with a group of healthy controls. Postoperative analysis revealed FCD. Figure adapted from Focke et al. 2009 (Focke et al., 2009).*

1.3.3.1 Voxel based morphometry studies in epilepsy

Voxel-based morphometry (VBM) is a fully automated technique aiming to quantify concentration of grey and white matter at the voxel level. It detects differences in the local composition of the tissue between individuals.

It relies on normalising all the structural images to the same stereotactic space to account for macroscopic differences to then segment the normalised images into grey and white matter; after that signal intensity is calculated in each voxel and compared between groups of subjects (Mechelli et al., 2005).

VBM has been widely used in different neurological conditions to characterize brain tissue differences. It explores the whole brain as opposed to other quantifying MRI techniques such as volumetric studies that target pre-selected regions

(Yasuda et al., 2010) allowing for testing brain regions without an a priori spatial hypothesis.
Changes in grey matter volumes (GMV) have been reported in a number of epilepsy syndromes (Keller et al., 2002, Lawson et al., 2002, Bernasconi et al., 2004) (Woermann et al., 1999, Widjaja et al., 2011).

VBM studies in epilepsy have targeted mostly temporal lobe epilepsy (TLE). In this group, grey matter volume (GMV) reduction ipsilateral to hippocampal atrophy have been reported in areas within the temporal lobe (parahippocampal gyrus, superior temporal gyrus, amygdala and fusiform gyrus), in addition to the basal ganglia, thalamus, insula, and regions in the frontal, parietal and occipital lobes and cerebellum (Yasuda et al., 2010). Not only decreases, but also increases of grey matter have been reported in VBM studies across different epileptic syndromes. Atrophy secondary to neuronal loss is the common anatomo-pathological correlate of decreased GMV in the epileptogenic zone (Keller et al., 2002, Bernasconi et al., 2004) however the significance of areas of increased grey matter remains uncertain.

These studies highlight the fact that structural changes extend to brain regions well beyond the epileptogenic and seizure zones. These findings support the theories that suggest epileptic seizures are maintained and propagated by common cortico-subcortical circuits beyond the seizure onset regions (Norden & Blumenfeld, 2002).

In contrast with the well characterized abnormalities of TLE patients, other focal epilepsies have barely been investigated using voxel wise quantitative techniques. This has provided the motivation for one of the studies included in this thesis: the investigation of common regions of abnormality in patients with frontal lobe epilepsy with the aim of identifying common structural abnormalities in this group that help to characterize the epileptic network.

1.3.4 Functional MRI

Functional MRI (fMRI) allows for non-invasive assessment of brain activity and represents one of the biggest advances in recent decades to investigate brain function. The technique was introduced in the early nineties (Kwong et al., 1992) and since then has been widely applied in the neurosciences field to investigate different brain functions.

fMRI is an indirect measure of brain activity and relies on the fact that cerebral blood flow and neuronal activity are coupled. fMRI uses the blood-oxygen-level dependent (BOLD) contrast (Huettel et al., 2008), that is sensitive to the differential paramagnetic properties of oxy and deoxyhaemoglobin (Ogawa et al., 1990). The sequence used in fMRI is echo planar imaging (EPI) allowing excellent temporal resolution due to short repetition times (TR).

1.3.4.1 BOLD contrast

The paramagnetic properties of deoxygenated haemoglobin in red blood cells produce differential distortions of the local magnetic field and these can be detected using T2* sequences (Ogawa et al., 1990). This is known as blood-oxygen-level dependent (BOLD) contrast. Changes in the special distribution of blood oxygenation secondary to brain function across time are the basis of fMRI studies.

The BOLD signal is believed to represent synaptic activity, referred to as local field potentials (Logothetis, 2003). During neuronal activity there is a conversion from oxygenated to deoxygenated haemoglobin. A short initial decrease in oxygen concentration is followed by an increase in the supply of oxygenated haemoglobin that exceeds the neurons' demand due to the increased blood supply (Villringer & Dirnagl, 1995). This in turn results in a relative decrease in the concentration of deoxygenated haemoglobin, which suppresses the MR signal. The decrease in neuronal activity is followed by blood flow decreases; this may turn the balance between oxi and deoxyhaemoglobin in favour of deoxygenated haemoglobin for a

short period, which explains the so called “post-stimulus undershoot” when the overall fMRI signal falls below the baseline.

The haemodynamic response to neuronal activity occurs with a temporal delay with respect to electrical neuronal activity. BOLD signal peaks with a delay of 5 seconds from the neuronal activity onset and returns to the baseline after 20 seconds. The hemodynamic response function was characterized in primate studies(Logothetis, 2003) by plotting the BOLD signal of the visual cortex as a response to visual stimulus against time revealing what has been called the canonical haemodynamic response function” represented in Figure 1-3. This function is used in the analysis of functional images.

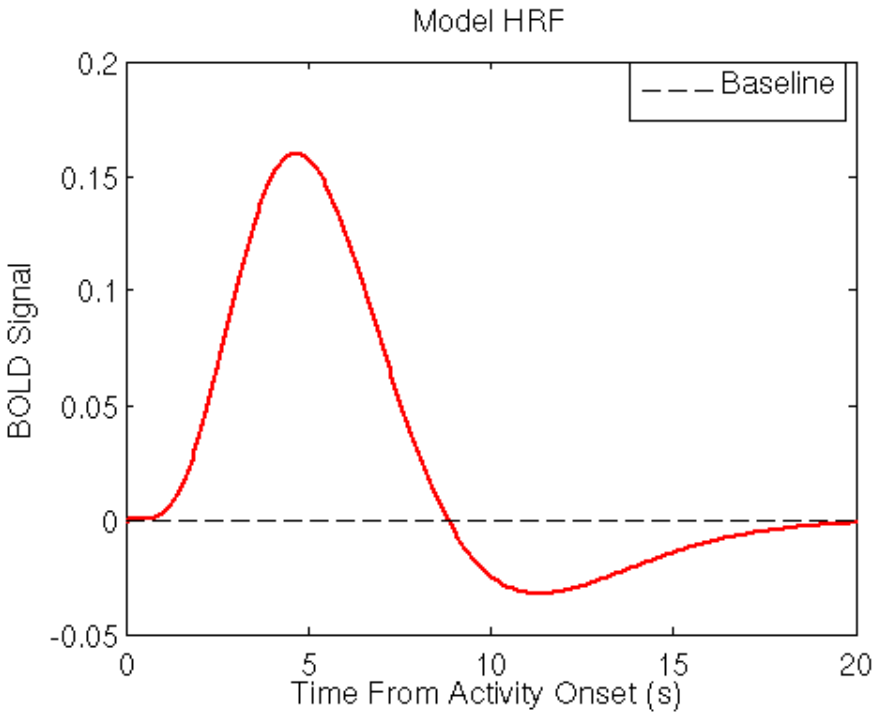

Figure 1-3. Canonical hemodynamic response function. *The function represents the change of BOLD signal (y axes) as a function of time (x axes) following neuronal activity. A gradual increase in signal occurs over time peaking at about 5 seconds with a complete recovery after 20 seconds.*

1.3.5 Cognitive functional MRI in epilepsy. Mapping of language and memory functions

Functional MRI has been used in the field of epilepsy with two main purposes: 1) as a clinical tool to map cognitive functions. This information is part of the presurgical evaluation process. 2) As a research tool to investigate cognitive dysfunction associated with different epilepsy syndromes. fMRI allows for non-invasive mapping of brain functions with good spatial resolution. The advantages of fMRI include its reproducibility, it does not involve radiation, and that it is universally available technology with robust and well established analysis techniques (Duncan, 2010).

Language and memory are the functions that have most often been explored in fMRI studies of patients with epilepsy. Both cognitive domains are known to be often impaired to different degrees in patients with epilepsy (Helmstaedter, 2002). Furthermore, these cognitive functions are at greater risk of decline following epilepsy surgery.

1.3.5.1 Language fMRI

Anterior temporal lobe resection in the language-dominant hemisphere may result in language deficit in up to 30% of patients (W.H. Pilcher, 1993). Assessment of language laterality in patients with epilepsy prior to surgery is helpful for estimating an individual's risk in suffering a decline in language functions.

Language is lateralized to the left hemisphere in approximately 95% of the healthy population. However, patients with epilepsy have up to a 30% increased chance of atypical language dominance (Woermann et al., 2003, Berl et al., 2014). Atypical lateralization can adopt different patterns with bilateral or right lateralization of either expressive, receptive language functions, or both. Recent studies in a large cohort of patients with epilepsy have shown that the atypical language patterns can be further subdivided in up to six different subtypes: a symmetrically bilateral,

two unilaterally crossed (frontal and temporal involvement in opposite hemispheres), and three right dominant patterns (Berl et al., 2014) (Figure 1-4). Several factors are associated to atypical language lateralization, these include: left handedness, vascular damage, early seizure onset and left seizure focus.

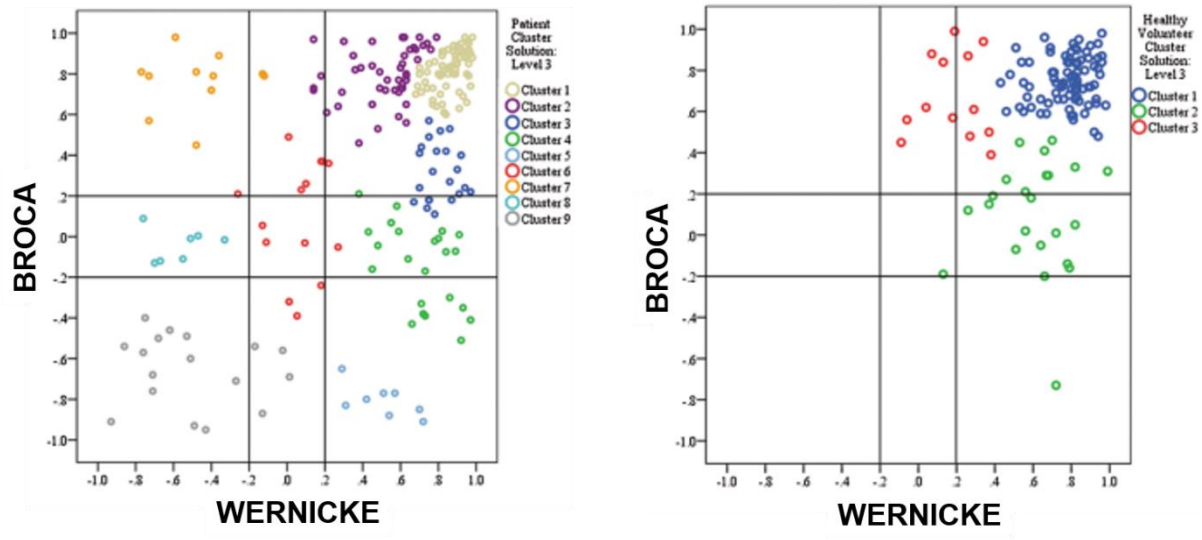

Figure 1-4. Distribution of language patterns derived from fMRI. *Distribution of language patterns derived from fMRI in patients with epilepsy (left) and controls (right). The lateralization indexes of activations in a language production task for the Wernicke and Broca area is plotted for each subject (dot). Left lateralization indexes are values between 2 to 10. Bilateral 2 and -2 and right lateralized -2 to -10. The majority of the controls are left lateralized for both areas with 5% that fall mainly in the bilateral ranges. Patients show a greater variability and a higher rate of atypical language dominance. Figure adapted from Berl et al 2014 (Berl et al., 2014).*

Classically, language lateralization and localization has been established through invasive methods: the Wada test or intracarotid amytal test (IAT) was the technique of choice in lateralized language function, whereas electro-cortical stimulation mapping is still the technique of choice to localize eloquent cortex. Large cohort studies have shown a high degree of correlation between fMRI maps and the invasive Wada test (Binder et al., 1996, Woermann et al., 2003, Janecek et al.,

2013a). Despite the good degree of concordance between methods there are between a 15-20% of discordant cases across studies. These cases of discordance correspond mainly to patients with atypical language (Bauer et al., 2014) (Janecek et al., 2013a) with more cases being reported atypical by fMRI rather than IAT suggesting fMRI may be more sensitive to right language processing. In only one study these discordant cases were further investigated and compared to the postsurgical outcome (Janecek et al., 2013b). The analysis showed that language surgical outcomes were more in agreement with the language lateralization obtained by fMRI test. However further research is granted to fully understand the clinical significance of these findings (Koepp, 2014).

At group level, language fMRI studies have allowed a greater understanding of the changes in language networks that underlie language deficits in epilepsy. In patients with temporal lobe epilepsy, the role of the hippocampus in language has been subject of great interest. fMRI studies show that the integrity of the hippocampus is required for maintaining language function (Bonelli et al., 2011) and the changes to the functional and structural networks that occur after surgery can predict the functional outcome (Yogarajah et al., 2010, Bonelli et al., 2012).

1.3.5.1.1 Language fMRI paradigms and language maps

Language networks can be explored through a number of fMRI paradigms. Language fMRI protocols usually combine expressive and receptive language tasks. Frontal language areas comprising IFG (Figure1- 5), corresponding to Brodmann's area 44 and 45 and middle frontal gyrus (MFG) as well as supplementary motor cortex (SMA) are activated by expressive language paradigms. Wernicke's area (supramarginal gyrus (SMG), superior temporal gyrus (STG)) corresponding to Brodmann's area 20, 21 and 39 activations are brought by more receptive tasks.

Initially, a panel of at least two language fMRI tasks was recommended in order to derive robust information about single subject's language dominance (Gaillard et al., 2004), however recent studies highlight the importance of the auditory

paradigms in detecting atypical language dominance and these should be part of the protocol (Berl et al., 2014).

Lateralization indexes (LI) are often used as a quantitative measure of language lateralization. These are calculated by counting the number of active voxels within the regions of interest in both hemispheres with the formula LI = (L – R) / (L+R). L and R represent the strength of activation for the left (L) and right (R) sides respectively (Adcock et al., 2003, Gaillard et al., 2004). Activations in the ROI vary for different thresholds of significance. Therefore bootstrap methods that weight the findings at the different thresholds are preferred in order to account for this (Wilke & Lidzba, 2007).

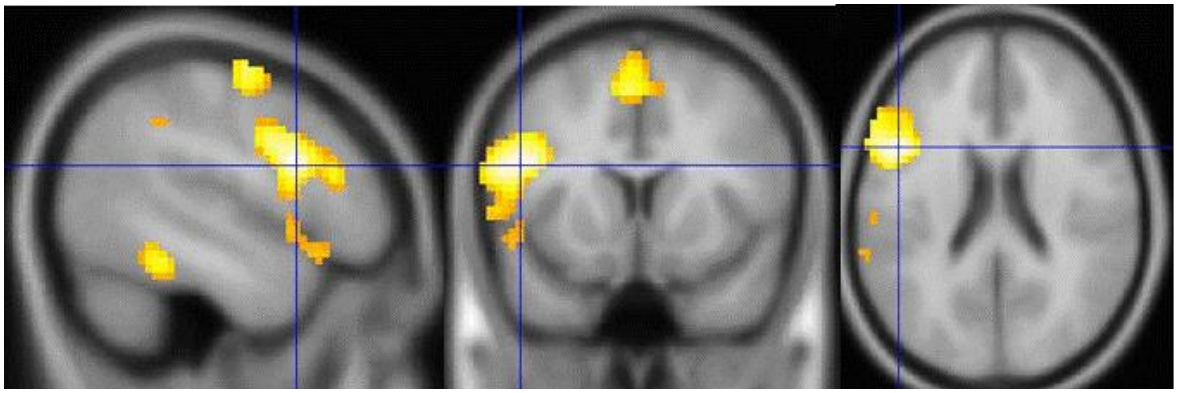

Figure 1-5. Regions significantly activated during a verbal fluency fMRI task. *Activations for a group of healthy controls in a verbal fluency task. A strong left sided activation in inferior and middle frontal gyrus (crosshair) is observed. Figure adapted from Bonelli et al 2012 (Bonelli et al., 2012).*

1.3.5.1.2 Bilingualism and language fMRI

The third study of this thesis addresses the problem of language lateralization assessment in bilingual patients. Language assessment is usually carried out in the country's language that for a proportion of the population is their second language. The validity of lateralizing language for clinical proposes using language

fMRI in the subject's secondary language has not been previously formally assessed.

Bilingualism varies between countries and is more prevalent in those countries with high rates of immigration. In Britain, up to 8% of the population has a mother tongue other than English. In large cities such as London the percentage of non-native English speakers can be as much as 20 %.(Office-for-National-Statistics, 2011).

fMRI studies for language lateralization have been primarily validated using native language speakers. In clinical practice however, these are sometimes performed in the subject's a secondary language (English for example would be secondary language to migrant population) posing the question towards the validity of language mapping in these cases.

A large number of fMRI studies have investigated bilingualism and the differences/similarities of the language networks involved in each of the languages (Hernandez et al., 2000, Hasegawa et al., 2002, Perani & Abutalebi, 2005, Parker Jones et al., 2012) . A majority of studies report that the networks for different languages largely overlap (Xue et al., 2004, Perani & Abutalebi, 2005) with differences in the extent or intensity of activations. These differences are reported to be associated to several factors: age of language acquisition (Mahendra et al., 2003, Perani & Abutalebi, 2005), proficiency (Hasegawa et al., 2002, Mahendra et al., 2003, Perani & Abutalebi, 2005) , and language-specific attributes such as orthographic characteristics (Meschyan & Hernandez, 2006).

Two opposed theories for language processing in bilinguals have been proposed by the researchers in the field: the existence of distinct networks versus a common network for the processing of different languages. Selective aphasias for one language have been reported after stroke (Green et al., 2010), epileptic seizures (Aladdin et al., 2008) or surgical resections (Gomez-Tortosa et al., 1995). There is also evidence from intra-operative language mapping suggesting the presence of distinct areas within the left hemisphere for native (L1) and secondary (L2) languages (Lucas et al., 2004, Cervenka et al., 2011). However, the majority of

research evidence supports the theory of a common network supporting the different languages in bilinguals, and explain the evidence of distinct networks in terms of modulation related to specific computational demands which vary according to the age of acquisition, the proficiency in the secondary language and the level of exposure to each language (Perani & Abutalebi, 2005).

Language fMRI studies have provided crucial insight for the characterization of language networks in bilinguals. Hernandez and colleagues showed that networks involved in reading words (Meschyan & Hernandez, 2006) and naming (Hernandez et al., 2000, Hernandez, 2009), as well as in comprehension (Hasegawa et al., 2002) largely overlap for the different languages. However, differences in the networks are seen in relation to language characteristics such as language-specific orthographic properties (Meschyan & Hernandez, 2006).

Age of language acquisition (AOA) is a key factor in explaining the differences observed in language fMRI maps in bilinguals (Perani & Abutalebi, 2005). Subjects with a late AOA show greater fMRI activations in the language networks compared to those subjects where L2 was acquired early in life.

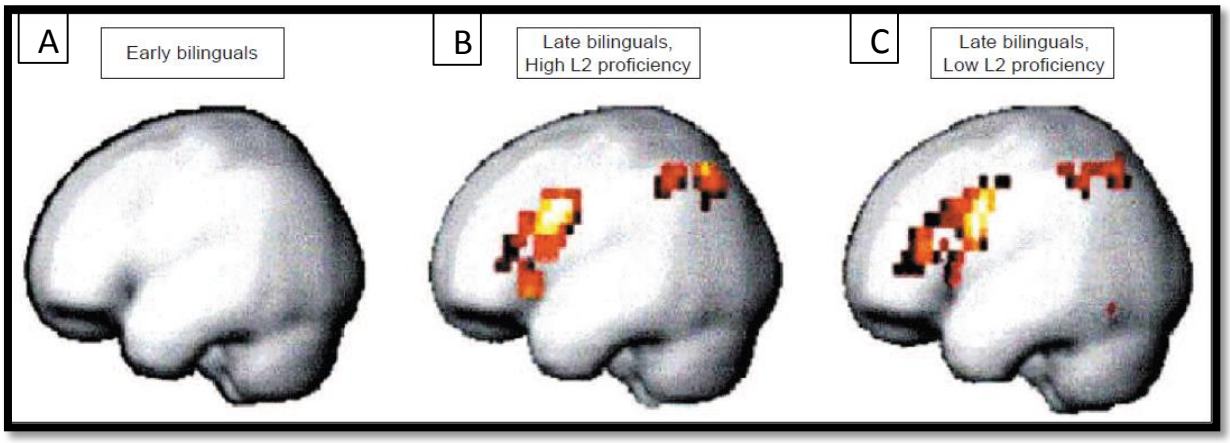

Figure 1-6. Effect of age of acquisition and proficiency in fMRI activations. *The three images show the differences between second and native language maps (Second language>Native language). No differences are seen for early bilinguals (A). In late bilinguals, greater activations are seen for the second language compared to the native language, regardless of whether the proficiency level (B-C). Figure adapted from Wartenburger et al. 2003 (Wartenburger et al., 2003)*

Proficiency in the secondary language is related to differences in the extent and significance level of the activations in language fMRI studies. The least proficient language would produce larger and more widespread BOLD signal changes in relation to language task compared with the more proficient one (Hasegawa et al., 2002, Perani & Abutalebi, 2005) and may involve additional areas such as supplementary motor cortex during reading words (Meschyan & Hernandez, 2006). However, this does not seem to be a consistent finding since other studies have not replicate this finding (Xue et al., 2004). Greater and more widespread activations for second language are interpreted as greater cognitive effort during language processing when using the less proficient language. Age of acquisition and proficiency may interact with other language characteristics. Grammatical processing in particular, has been shown to be specifically sensitive to the effect of age of acquisition, whereas semantic-lexical processes depend more on the level of proficiency (Wartenburger et al., 2003, Perani & Abutalebi, 2005).

1.3.5.2 Working memory fMRI

Working memory or short term memory dysfunction has been reported in patients with focal and generalized epilepsies (Helmstaedter, 2002, Stretton et al., 2012, Wandschneider et al., 2012). Epilepsy surgery can cause a worsening of this function especially when the frontal lobes are targeted during the surgery (Lendt et al., 2002, Helmstaedter, 2011). However, improvement on working memory function has been also reported after temporal lobe surgery (Stretton et al., 2014).

Research studies using fMRI have provide important insights in the understanding of the dysfunctional anatomy of working memory in the different epilepsy syndromes. Working memory paradigms such as the N-back paradigms allow for imaging the networks involved in working memory process (Stretton et al., 2012).

In patients with juvenile myoclonic epilepsy (JME) fMRI has shown evidence of working memory network abnormalities (Vollmar et al., 2011): while the fronto-parietal network activity seem to be spared in this group, the motor and

supplementary motor areas did not modulate their activity according the difficulty of the task (Vollmar et al., 2011). Furthermore the connectivity between the fronto-parietal networks and the motor regions seem to be abnormally high in these patients. This aberrant connectivity and abnormal modulation of activity may explain the dysfunction seen in these patients and offer an explanation to the myoclonic jerks triggered by cognitive effort. Similar findings have been found in siblings of JME suggesting the existence of an endophenotype (Wandschneider et al., 2014).

In patients with TLE Stretton el al. (Stretton et al., 2012) showed that patients with TLE failed in deactivating the diseased hippocampus during the task and this was in turn related to poorer performance working memory performance (Fig 1-7). Patients with TLE improved working memory function after resection (Stretton et al., 2014). This improvement was associated to the improvement on the deactivation of the medial temporal lobe structures and the increased activity in the parietal regions after surgery. Abnormalities in the connectivity of the fronto-parietal regions have also been found in patients with TLE (Huang et al., 2015).

In patients with FLE the whole extent of working memory network seem to be generally affected with a proportion of patients (~40%) showing focal deficits in the network related to the epileptic focus (Vollmar et al 2016 in preparation). The age of epilepsy onset is the factor more robustly related to the dysfunctional activation in verbal and visual working memory in patients with FLE (Centeno, 2011). Patients with epilepsy onset once the maturation of frontal lobes have been completed (>13 y.o.) showed significant greater activity in the WM network compared with those with an earlier onset.

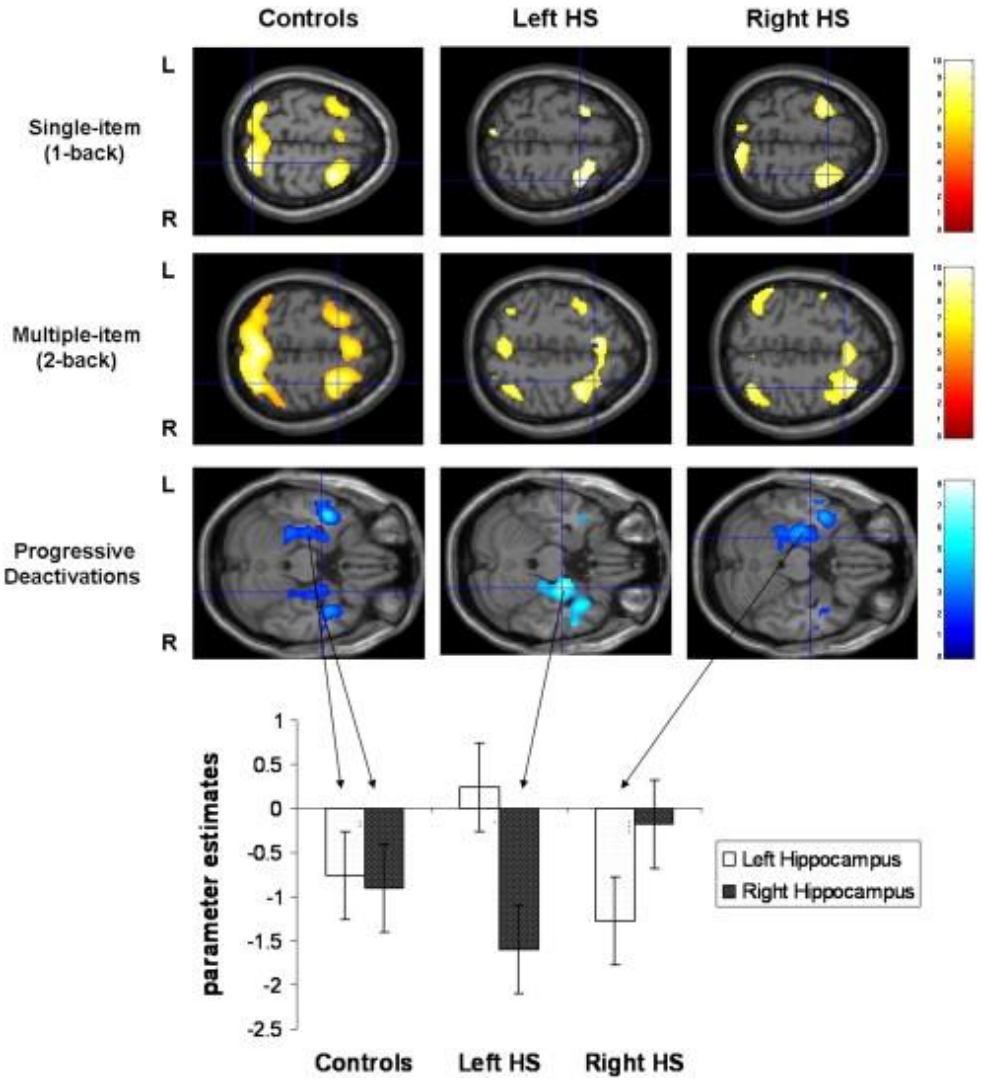

Figure 1-7. Group networks for working memory task. *Group results for different levels of WM single item, multiple-item and progressive deactivations. Each group shows significant bilateral fronto-parietal activations (yellow) Progressive deactivation (blue) of the hippocampus was observed bilaterally in controls, but only contralateral to the damaged hippocampus in HS groups ($p < 0.01$ uncorrected.). The graph depicts the parameter estimates ($p < 0.01$ unccorrected.) of the negative BOLD signal in the left and right hippocampus of each group. (HS = Hippocampal sclerosis, L = left, R = right). Figure adapted from Stretton et al. 2012 (Stretton et al., 2012).*

1.3.5.3 Memory fMRI

Memory dysfunction is a common complaint among patients with epilepsy. Neuropsychological studies show that the memory domain is affected in a large proportion of patients and the function declines with time in patients with chronic and active disease (Helmstaedter, 2002). Long term memory dysfunction (autobiographical, and episodic) is characteristically seen in the neuropsychological profile of patients with TLE. However, it has also been reported in patients with FLE (Helmstaedter et al., 1996), but memory function in this group of patients is still not well characterized (Centeno et al., 2010).

Episodic memory is defined as the cognitive process which enables the explicit recollection of events and their context (Baddeley, 2001) .The events are transformed into an enduring memory trace during a process known as the memory encoding process; these are subsequently recollected at a later time by a process known as memory retrieval.

The network involved in this process is composed by the medial temporal lobe (MTL) and prefrontal cortices (PFC) and can be characterized in healthy population using memory fMRI paradigms (Cabeza & Nyberg, 2000, Kim et al., 2010a). fMRI of memory functions has played a determinant role in the investigation of the different components of memory networks, as well as in the characterization of memory network changes as a result of disease.

In patients with TLE, fMRI studies have shown reduced activation in the temporal lobe ipsilateral to the seizure onset (Golby et al., 2001, Richardson et al., 2003). Additionally, reorganization changes with increases of activity in the contralateral mesial temporal lobe were seen in this group (Richardson et al., 2003, Powell et al., 2007). However, memory performance in these patients seem to rely on the activation of the damaged ipsilateral hippocampus (Powell et al., 2007).

The role of the hippocampus in memory encoding was established from early on (Scoville & Milner, 1957). However, the role of frontal lobes in memory has only been more recently acknowledged and investigated (Centeno et al., 2010).

Classically, a material specific memory dysfunction is seen in patients with TLE, with verbal memory impairment associated to TLE in the dominant hemisphere and visual memory impairment associated to epilepsy in the non-dominant hemisphere. Material specific memory fMRI paradigms are designed to capture the memory networks related specifically to each type of memory (verbal and visual). Using these paradigms, it has been possible to map the network changes related to the memory dysfunction (Bonelli et al., 2010) and understand the functional reorganization after anterior temporal lobe resection (ATLR) and the functional anatomy associated to memory outcome after surgery (Bonelli et al., 2013). More recently the role of frontal lobes has been shown to be relevant in these patients (Sidhu et al., 2013). Functional changes in these areas as the result of epilepsy contribute to the memory dysfunction in this group.

One of the greatest challenges of fMRI is to predict cognitive deficits that may occur as the result of surgery. In this regard Bonelli and colleagues (Bonelli et al., 2010) proposed an algorithm that included several factors and tested its ability of predicting memory outcome after surgery. Factors such as preoperative memory scores and hippocampal volume were included together with fMRI markers: language lateralization index and asymmetry of hippocampal activations during memory tasks. The algorithm predicted with a high level of sensitivity and specificity (100% and 86% respectively) significant memory decline after anterior temporal lobe resection. fMRI activations in the hippocampus were the strongest predictor of memory decline after surgery among those included in the algorithm (Figure1-8).

Furthermore memory fMRI has provide clinically relevant insight about the sub regions in the hippocampus related to memory preserved memory function after surgery. Posterior hippocampus activation prior to surgery was found to be related to a better memory outcome after surgery.

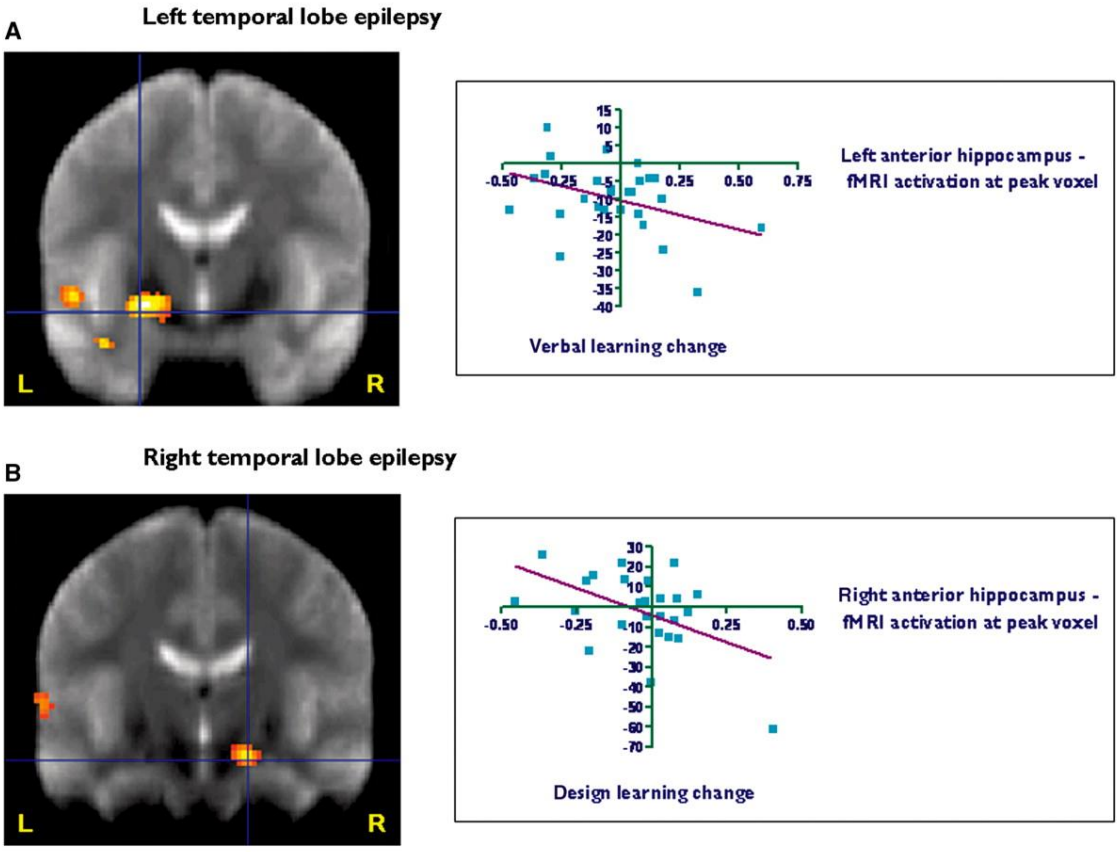

Figure 1-8. Prediction of verbal and visual memory decline using memory fMRI. *(A) Change in verbal learning scores after left anterior temporal lobe resection (ATLR) correlates with left anterior hippocampal activations during word encoding. Subjects with greater fMRI activation will suffer greater decline. (B) Likewise, the change in design learning scores after right ATLR correlates with activations in the right hippocampus during faces encoding. Those subjects with greater fMRI activation will experience greater visual memory decline. Figure adapted from Bonelli et al 2010 (Bonelli et al., 2010).*

Memory function and the brain networks abnormalities related to dysfunction have been explored in detail in patients with TLE. However very little is known about the memory network changes associated to memory dysfunction in patients with FLE. In the first study of this thesis memory function and the changes of memory networks in FLE are investigated.

2 PUBLICATIONS

2.1 MEMORY IN FRONTAL LOBE EPILEPSY: AN FMRI STUDY

Epilepsia, 53(10):1756–1764, 2012
doi: 10.1111/j.1528-1167.2012.03570.x

FULL-LENGTH ORIGINAL RESEARCH

Memory in frontal lobe epilepsy: An fMRI study

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[Correction added after online publication 5-Jul-2012: Dr. O'Muircheartaigh's name has been updated.]

Summary

Purpose: Focal epilepsies are often associated with structural and functional changes that may extend beyond the area of seizure onset. In this study we investigated the functional anatomy of memory in patients with frontal lobe epilepsy (FLE), focusing on the local and remote effects of FLE on the networks supporting memory encoding.

Methods: We studied 32 patients with drug-resistant FLE and 18 controls using a functional magnetic resonance imaging (fMRI) memory encoding paradigm.

Key Findings: During encoding of stimuli, patients with FLE recruited more widely distributed areas than healthy controls, in particular within the frontal lobe contralateral to the seizure onset. Normal memory performance was associated with increased recruitment of frontal areas, and conversely a poor performance was associated with an absence of this increased recruitment and decreased activation in mesial temporal lobe areas.

Significance: In patients with FLE, recruitment of wider areas, particularly in the contralateral frontal lobe, appears to be an effective compensatory mechanism to maintain memory function. Impaired hippocampal activation is relatively rare and, in turn, associated with poor recognition memory.

KEY WORDS: Frontal lobe epilepsy, Memory, Functional fMRI, Cognition.

Focal epilepsies are frequently accompanied by cognitive dysfunction, the causes of which are a matter of ongoing debate. Neuropsychological studies have shown that focal epilepsy may have both a local effect in the area of the seizure focus, and also remote effects on networks beyond the lobe containing the focus. A sizable proportion of temporal lobe epilepsy patients with temporal lobe epilepsy (TLE) have "frontal lobe dysfunction" on neuropsychological testing (Hermann & Seidenberg, 1995; Helmstaedter et al., 1996; Upton & Thompson, 1996; Martin et al., 2000; Bernhardt et al., 2008). Fluorodeoxyglucose–positron emission tomography studies have demonstrated reduced glucose metabolism in the frontal lobes of patients with drug-resistant TLE that correlates with cognitive dysfunction (Takaya et al., 2006), and this was reversible after successful epilepsy surgery (Spanaki et al., 2000). The rich interconnectivity between the temporal and frontal lobes may facilitate epileptic activity propagation and subsequent dysfunction in distant structures.

In contrast to the well-described cognitive profile of TLE, the cognitive profile in frontal lobe epilepsy (FLE) is less well characterized. Neuropsychological studies in FLE have focused on frontal lobe dysfunction (Helmstaedter et al., 1996; Upton & Thompson, 1996), but impairment of functions that are not typically "frontal," such as memory encoding, have not been assessed systematically. Some studies have reported long-term memory impairment in patients with FLE showing dysfunction during encoding, free recall, and retrieval (Exner et al., 2002; Nolan et al., 2004), and there is also evidence of memory dysfunction following frontal lobe resection for epilepsy (McDonald et al., 2001).

The role of the frontal lobes during memory process have gained attention recently, with several studies in the field showing that specific areas within the frontal cortex are involved in relevant processes for encoding and retrieving (Shimamura, 1995; Fletcher et al., 1998a,b; Blumenfeld & Ranganath, 2007; Blumenfeld et al., 2010).

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The prevalence of memory impairment in FLE and whether the underlying mechanism is a frontal lobe dysfunction "per se" or a remote effect of FLE on temporal lobe regions remain unclear.

Functional magnetic resonance imaging (fMRI) studies using memory encoding paradigms are useful tools to characterize the networks involved in the encoding process in healthy population (Cabeza & Nyberg, 2000; Kim et al., 2010). These paradigms have been used to study the integrity of these networks in patients with TLE (Richardson et al., 2003, 2004; Wagner et al., 2008; Bonelli et al., 2010). In this study we employed an fMRI memory encoding paradigm together with out-of-scanner recognition testing to investigate the following:

1 Memory encoding and recognition performance in patients with FLE.
2 Characterization of the brain regions involved in memory encoding in patients with FLE.
3 The effect of FLE on the frontotemporal brain networks involved in memory encoding, assessing the local effect of the epileptic focus in the frontal lobe and the remote effect on the medial temporal lobe.
4 The effect of seizure focus lateralization on changes observed due to FLE.
5 The functional brain correlates of memory impairment in FLE.

Methods

Subjects

We studied 32 patients (16 female) with a diagnosis of drug-refractory FLE recruited from the epilepsy clinics at the National Hospital for Neurology and Neurosurgery and King's College Hospital (London, United Kingdom). Diagnosis of the patients was based on prolonged video-electroencephalography (EEG) monitoring, seizure semiology, and MRI. In addition, some patients had FDG-PET and ictal/interictal single-photon emission computed tomography (SPECT). Epileptic focus was located on the left frontal lobe in 19 patients and on the right frontal lobe in the remaining 13. Clinical data regarding the age at seizure onset, duration of epilepsy, antiepileptic medication and number and type of seizures as well as etiology of epilepsy were collected for each patient. Etiology was cryptogenic in 75% of patients. Small areas of focal cortical dysplasia were found in six patients and a single area of MRI signal abnormality of unknown nature was found in two patients. Location of lesions was concordant with the presumed epileptic focus. See Table 1 for population details.

We recruited 18 healthy controls (12 female) with no history of neurologic disease, no family history of epilepsy, and normal structural MRI.

The study was approved by the Research Ethics Committee of the UCL Institute of Neurology and UCL Hospitals. Written informed consent was obtained from each subject.

fMRI acquisition

MRI was acquired on a 3T General Electric Excite HD scanner (General Electric, Milwaukee, WI, U.S.A.).

For the fMRI paradigm gradient-echo echo-planar T_2*-weighted images were acquired using the following parameters: Echo time (TE) of 25 msec and repetition time of 2.5 s. A total of 294 volumes were acquired. Each volume comprised 50 interleaved 2.4-mm slices with a 0.1-mm interslice gap, with an orientation parallel to the anterior to posterior cingulate (AC-PC) line. Images had a 64×64 matrix with a 24-cm field of view giving an in-plane pixel size of 3.75 mm. The scanner's body coil was used for radiofrequency transmission, and the manufacturer's standard eight-channel head coil was used for signal reception. An array spatial sensitivity encoding technique (ASSET) (parallel imaging) speed up factor of 2 was employed.

fMRI paradigm

We used a memory encoding paradigm containing visual stimuli of different types. A total of 210 items were presented inside the scanner grouped in 30 s blocks of 10 pictures (black and white nameable line drawn objects), 10 words (single concrete nouns), or 10 faces (photographs unfamiliar to the subjects). Items were presented every 3 s

Table 1. Sample characteristics

	N	Gender (F)	Age	IQ	Onset (years)	Duration (years)	Number AED	Seizures per month	Type of seizures		Epilepsy etiology	
Controls	18	12	31.5 (24–46)	111 (102–123)								
Left FLE	19	8	35 (18–53)	97 (80–120)	6 (3–19)	24 (7–47)	3 (1–4)	30 (0.1–752)	37%	SPS	16	Cryptogenic
									63%	SPS > SGTCS	2	FCD
											1	Unspecific lesion
Right FLE	13	8	29 (18–49)	101 (81–126)	10 (2–24)	20 (3–31)	2 (2–4)	90 (0.17–750)	38%	SPS	8	Cryptogenic
									62%	SPS > SGTCS	4	FCD
											1	Unspecific lesion

Median and mean values are shown for each variable. Full scale IQ was estimated with the National Adult Reading Test scale. SPS, simple partial seizures; SPS > SGTC, simple partial seizures progressing to secondary generalization; FCD, focal cortical dysplasia.

and encoding blocks were separated by 15 s of cross-hair fixation. Subjects were instructed to actively memorize the items and indicate whether each item was pleasant or unpleasant by a right hand joystick response.

Subjects underwent a recognition test 60 min after the scanning in which the 210 presented items were randomly mixed with an additional 50% novel items.

fMRI analysis

Images were analyzed using statistic parametric mapping (SPM5) (http://www.fil.ion.ucl.ac.uk/spm/). Each subject's images were realigned using the mean image as a reference, spatially normalized into Montreal Neurological Institute (MNI) space (using a scanner-specific template created from patient and control data) and smoothed with a Gaussian kernel of 8 mm full-width at half maximum.

Statistical fMRI analyses were performed first at the single subject level and then at the group level. In the single subject level analyses, trial-related activity was modeled by convolving a vector of block onsets with a canonical hemodynamic response function (HRF) to create regressors of interest. One regressor was modeled for each type of material (pictures, words and faces). Each subject's movement parameters were included as confounds, and parameter estimates pertaining to the height of the HRF for each regressor of interest were calculated for each voxel. Contrasts for the effect of encoding pictures, words, and faces were built for each subject.

Second level group analyses were carried out as random-effects analysis. Individual contrasts were entered into three different factorial designs models to test the following questions:

Effect of frontal lobe epilepsy

Individual contrasts were submitted to a 2 × 3 analysis of variance (ANOVA) within SPM5. Cells were specified as 2 (group: controls vs. all 32 FLE patients) ×3 (material type: pictures, words and faces). The effect of FLE was investigated collapsed across the different material types.

Effect of the laterality of the focus

Patients with frontal lobe epilepsy were subdivided according to the laterality of the focus: 19 left, 13 right). Individual contrasts were submitted to a 3 × 3 ANOVA. Cells were specified as 3 (group-laterality: controls vs. left FLE vs. right FLE) ×3 (material type: pictures, words, and faces).The effect of epileptic focus lateralization was assessed relative to controls.

Lateralization indices of the maps left FLE versus controls and right FLE versus controls were calculated using the Lateralization Index (LI) toolbox for SPM5 (Wilke & Lidzba, 2007), that follows the equation:

$$\frac{\text{Activity right} - \text{Activity left}}{\text{Activity right} + \text{Activity left}}$$

Functional correlates of performance

Patients were subdivided into those with and without memory impairment according to their performance on the recognition test after the scan. To determine the impairment in a patient we compared the recognition accuracy of each patient with FLE to the control group mean by calculating the modified *t*-test developed for single case studies (Crawford & Garthwaite, 2002; Crawford et al., 2003). A patient was classified as having recognition memory impairment if the performance was significantly poorer than that of the controls when the alpha level was set at 0.05 (two-tailed). The modified *t*-test has been proposed as an appropriate tool to establish the abnormality of a score when the control sample against which the patient is compared is modest in size.

Individual contrasts were submitted to a 3 × 3 ANOVA, with cells specified as 3 (performance-group: controls vs. FLE good-performers vs. FLE poor performers) × 3 (material type: pictures, words, and faces).

Activations at the group level were reported as significant at a threshold of $p < 0.05$ corrected for multiple comparisons (family-wise error correction) in a whole brain analysis.

Because of the low signal-to-noise ratio in the anterior temporal lobe, activations in medial temporal lobe structures were reported as significant at a threshold of $p < 0.001$ uncorrected for multiple comparisons.

Hippocampal volumes

Hippocampal volumes were measured manually for each subject on T_1-weighted scans. Volumes were estimated by measuring the area of the hippocampus on contiguous 1.5-mm–thick coronal slices throughout the whole anterior-posterior extent by using manually drawn boundaries (Woermann et al., 1998). Normal range of hippocampal volume measures was defined as control mean ± 2 standard deviations (SDs).

Behavioral data

Responses of the recognition test were classified as remembered (hits), forgotten, and false alarms for the falsely recognized items. Recognition accuracy (RA) rates were calculated for each subject as: hit rate minus false alarm rate.

To investigate whether there was evidence of material specificity on memory dysfunction related to the side of epileptic focus in patients with FLE we performed a mixed-design ANOVA analysis. For this purpose we used the RA scores for words and faces as measures of verbal and non-verbal recognition as the within-subject factor and laterality of epileptic focus (left and right) as the between-subject factor.

We investigated the distribution of recognition memory performance in patients with FLE by comparing each patient's mean RA across the three type of stimuli with the controls mean RA calculating z-scores. Patients were

classified as significantly impaired when the alpha level was set at 0.05 (two-tailed).

Correlations of RA with the different clinical variables and IQ were investigated using Pearson's correlation test.

Results

Behavioral performance

Recognition accuracy (RA) was significantly lower in patients with FLE than in controls for all the items: Pictures ($F_{1,46} = 4.5$, $p < 0.038$), Words ($F_{1,46} = 5.4$, $p < 0.024$), Faces ($F_{1,46} = 12.53$ $p < 0.001$) (Fig. 1).

We observed a main effect of the material type ($F_{1,28} = 115.96$, $p < 0.0001$). Words RA (Mean [M] RA = 65.8) was better than faces (M RA = 24.2) in both patient with left and patients with right FLE. However, there was no significant interaction between material type and the side of epilepsy ($F_{1,28} = 2.81$ $p < 0.14$) (Fig. 2).

Seven (22%) of the 32 patients with FLE had significantly impaired RA scores compared to controls: three had a left-sided and four had a right-sided focus. There was no correlation with the side of epilepsy.

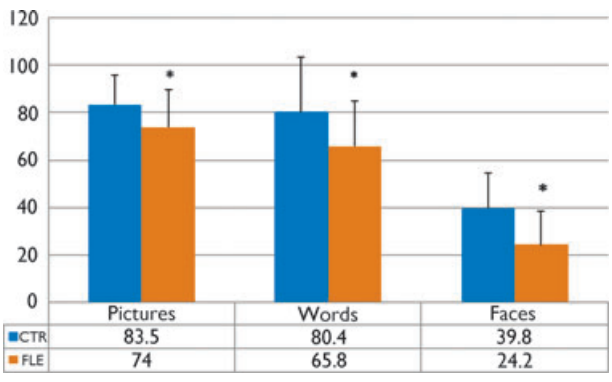

Figure 1.
Recognition accuracy. Recognition accuracy measures the proportion of correctly remembered items minus proportion of falsely recognized items. Patients with FLE have a significantly decreased recognition accuracy compared to controls for all categories. Mean RA = average of recognition accuracy for the three type of stimuli. Error bars represent 1 standard deviation. CTR = healthy controls. FLE = patients with frontal lobe epilepsy. *Significant difference of means at a p-value < 0.05.
Epilepsia © ILAE

Functional MRI results

Group maps

Consistent with previous memory encoding fMRI studies (Cabeza & Nyberg, 2000; Kim et al., 2010), activation maps for the effect of encoding items involved a number of frontal lobe areas and medial temporal structures comprising dorsolateral and ventrolateral prefrontal cortex, amygdala, hippocampus, and parahippocampal gyrus (Fig. 3, Table S1).

Activations in frontal lobe areas and medial temporal lobes were greater on the left during the encoding of words and pictures. Conversely, during faces encoding, the activation in the frontal and medial temporal lobe was greater on the right. This pattern was observed in controls and for both left and right FLE.

Effect of frontal lobe epilepsy

Patients with FLE demonstrated greater areas of activation within the frontal lobes relative to controls during the encoding across different types of stimuli. Bilateral clusters of increased activation were located in the middle frontal gyrus, perisylvian cortex, inferior frontal gyrus, and supplementary motor area (SMA) (Fig. 4, Table S2). No areas of greater activation were identified in the control group across the whole brain when compared to the FLE group.

Effect of epileptic focus laterality

We explored whether lateralization of the epileptic foci may affect functional activations.

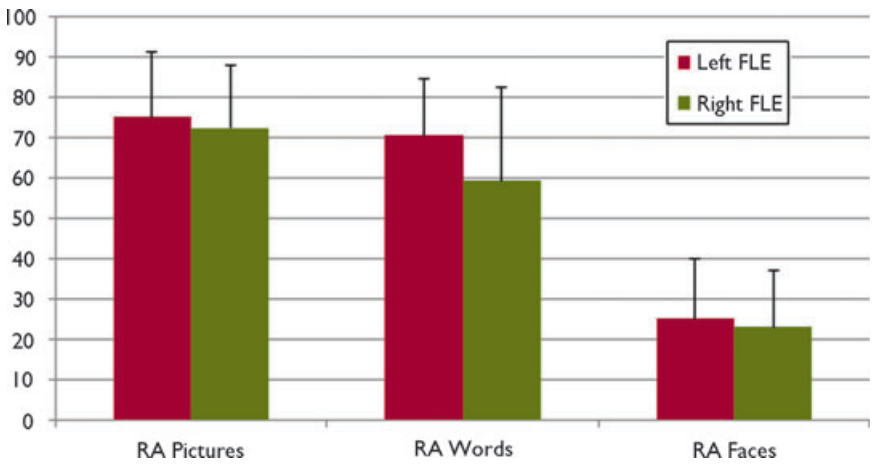

Figure 2.
Verbal/nonverbal performance and laterality of seizure focus. Side of epileptic focus does not have an effect on the recognition accuracy of verbal and nonverbal material. Patients with right FLE show a tendency to perform poorer on the recognition and learning tasks for verbal and nonverbal items. Error bars represent 1 standard deviation.
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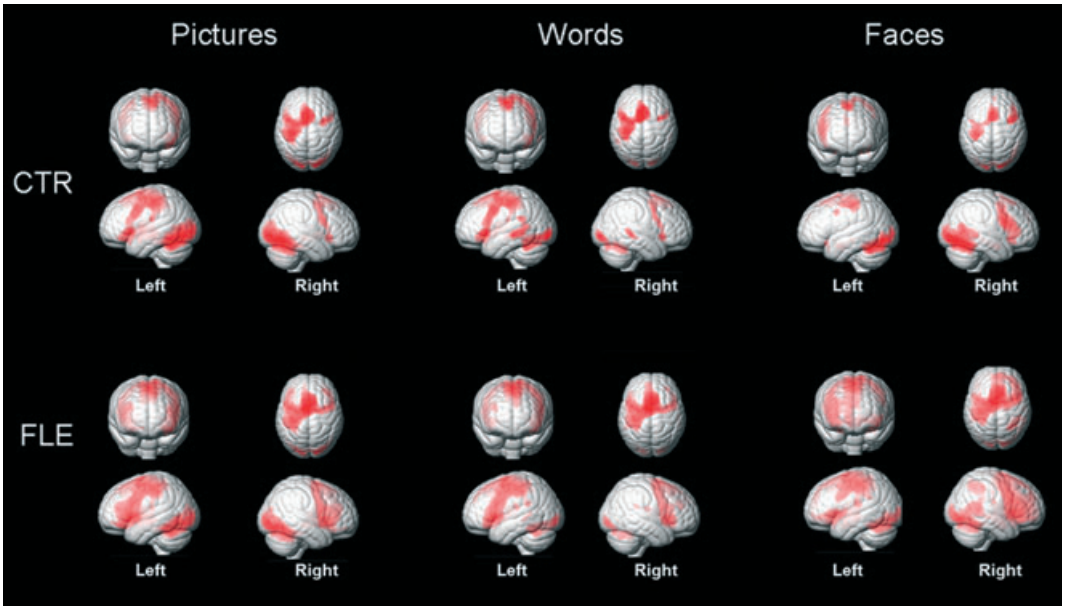

Figure 3.
Activation maps for the effect of encoding the different stimuli in controls and patients with FLE. Activations are located in dorsolateral and ventrolateral prefrontal cortex, visual areas, and mesial temporal lobe areas (not shown). Lateralization of activations in frontal lobes is dependent on the stimuli type. Activations are right lateralized for faces and left lateralized for words and pictures in both patients and controls. Left central and bilateral medial supplementary motor area activation is induced by joystick response and similar for all stimuli. CTR = healthy controls. FLE = patients with frontal lobe epilepsy.

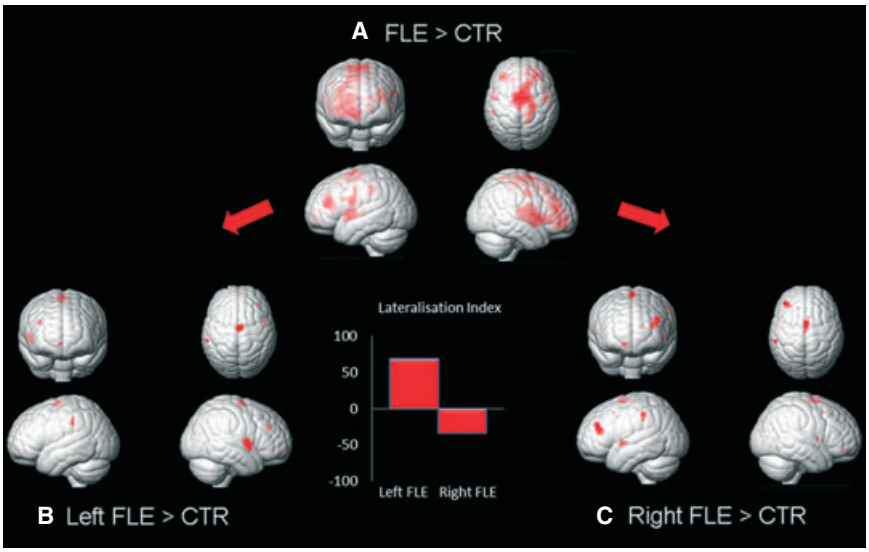

Figure 4.
Effect of frontal lobe epilepsy and focus lateralization. (**A**) Areas of increased activation in patients with FLE relative to controls (FLE > CTR) collapsed for all item types are located within the frontal lobe areas involved in the task. Increased activation was lateralized differently for patients with left FLE and patients with right FLE (patients with left FLE showed increased activations in the right hemisphere (**B**) and patients with right in the left hemisphere (**C**). Bar chart shows the values of lateralization index (LI) of the maps (**B**,**C**). LI values range from 1 to −1; positive values indicate a right hemispheric lateralization, whereas negative values indicate a left lateralization. In left FLE, increased activations are lateralized to the right and the inverse for right FLE.

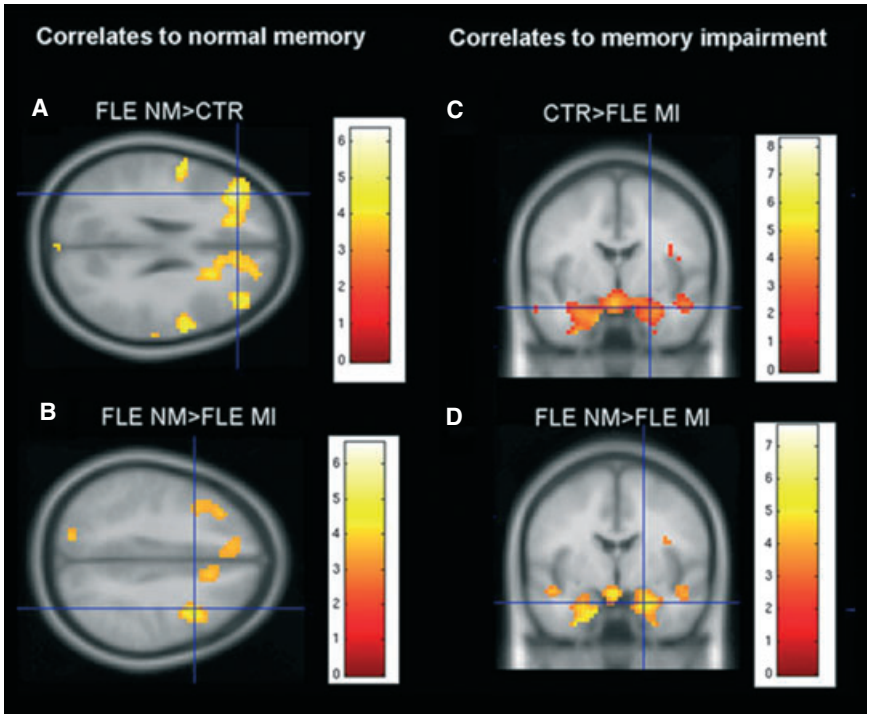

Figure 5.
Functional correlates of different performances. (**A**,**B**) Patients with FLE with normal memory (FLE NM) showed increased frontal activation when compared to controls (CTR) (FLE NM > CTR) and to patients with memory impairment (FLE MI) (FLE NM > FLE MI). (**C**,**D**) Patients with FLE with impaired memory showed decreased amygdala and hippocampal activation when compared to CTR (CTR > FLE MI) and to patients with normal memory (FLE NM > FLE MI). Scaling bars show T scores for the activations. *Epilepsia* © ILAE

Both left and right FLE showed greater frontal lobe activation than controls. Lateralization of these activations was contralateral to the side of epileptic focus on both groups of patients (Fig. 4B,C). No areas of lesser activation were found in left or right FLE groups relative to controls (Table S3).

Functional correlates of performance

There was a high variability in memory performance among patients with FLE: 7 of 32 patients with FLE had a mean RA score within the impaired range, whereas 25 patients with FLE had mean RA scores within normal limits.

Comparing different performance groups showed the following:

1. Patients with FLE with normal memory showed greater activations compared to controls and to FLE patients with impaired memory in the middle and inferior frontal gyrus, bilaterally (Fig. 5A,B, Table S4).
2. Patients with impaired performance had decreased amygdala-hippocampal activation compared to controls and to FLE patients with normal recognition scores (Fig. 5C,D).
3. There was no difference in the frontal activations between controls and those patients with memory impairment.

Hippocampal volumes

Patients with left and right FLE had hippocampal volumes measurements within normal limits. Left FLE: mean left hippocampal volumes (SD) 2.67 cm^3 (0.28), right hippocampal volumes 2.78 cm^3 (0.28). Right FLE: left hippocampal volumes 2.77 cm^3 (0.24), right hippocampal volumes 2.89 cm^3, (0.3). There was no interaction between the side of epilepsy and the hippocampal volumes $F_{30,1} = 0.46$ (n.s.). Hippocampal volumes from FLE patients with impaired recognition memory were not significantly different from those patients with normal memory.

Memory performance and clinical variables

No significant correlations were found between RA scores and age at seizure onset, duration of epilepsy, number of antiepileptic drugs, etiology (cryptogenic vs. lesional), and frequency of seizures.

There was no correlation between IQ scores and RA for neither left nor right FLE patients.

Discussion

Memory is a highly complex cognitive function and cannot be assigned to a circumscribed structure in the brain. It is known that the medial temporal structures are crucial for long term encoding, but the process of encoding as well as memory retrieval largely depend on a network involving temporal and frontal lobes.

In this study we explored the functional anatomy of memory in patients with FLE and how FLE affects memory networks. In particular, we analyzed the local effect of FLE on the frontal lobe component of the memory network and whether there was evidence for remote dysfunction in the temporal lobe.

Performance scores show that patients with FLE as a group are impaired compared to controls; however, there was high performance variability among patients, with only one fifth of patients with FLE showing significantly impaired recognition. We did not observe material-specific effects related to the lateralization of the epileptic focus.

We showed that patients with FLE recruit wider areas within the frontal lobes during the encoding process compared to controls, suggesting compensatory mechanisms. Effective compensation in patients can only be assessed if there are no differences in in-scanner task performance. The observed increases in activations are likely to represent compensatory mechanisms for two reasons. First analysis subdivided by side of seizure onset revealed that activations are more prominent in the hemisphere contralateral to the epileptic focus. A similar pattern has been reported in the side contralateral to the epileptic focus in patients with TLE in correlation with a maintained memory performance with and without memory impairment (Richardson et al., 2003, 2004; Bonelli et al., 2010). Secondly, increased frontal activations were present in the group of FLE patients with normal memory relative to controls and to FLE patients with memory impairment. The areas of increased activation comprise dorsolateral and ventrolateral prefrontal cortex. These areas have been implicated in successful memory formation, since they are involved in encoding item-specific information and relational processing during the encoding (Blumenfeld et al., 2010).

Medial temporal lobe activation was preserved in the majority of patients with FLE; however, the subgroup of patients with recognition memory impairments showed decreased amygdalar and hippocampal activation, suggesting a possible remote dysfunction in these areas in this subgroup of patients.

Patients with FLE may have a large range of cognitive dysfunction, ranging from severe impairment of attention, executive, and motor coordination skills to subtle personality traits (Helmstaedter, 2011). This heterogeneity has being attributed to the variability in seizure focus localization or differences in etiology or in the course of epilepsy observed among patients. Neuropsychological studies in this population (Helmstaedter et al., 1996; Upton & Thompson, 1996; Exner et al., 2002) have focused on testing frontal lobe functions, showing that patients with FLE are impaired on these domains. Of interest, these deficits have been found not to be specific to FLE, being also present in various degrees in other epilepsy syndromes such as TLE (Helmstaedter et al., 1996; Upton & Thompson, 1996; Exner et al., 2002). In a similar way, some studies reported patients with FLE to be impaired in learning and recall, functions that are supported by temporal lobes (Exner et al., 2002; Nolan et al., 2004; Helmstaedter, 2011).

Evidence for memory dysfunction in FLE patients varies widely between studies. Delaney et al. (1980) and Riva et al. (2002) found no memory impairment in adult subjects with FLE, whereas Nolan et al. (2004) found memory impairment in verbal and nonverbal domains in children with FLE but to a lesser degree than in patients with TLE. Exner et al. (2002) reported memory impairment in patients with FLE of a comparable severity to that in patients with TLE for immediate and delayed recall of visual and verbal items. Memory impairment has also been reported in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) where all but one patient were found to be impaired on at least one memory measure, and for four patients the memory impairment was found to be more severe than executive dysfunction (Cho et al., 2008; Picard et al., 2009).

In our FLE sample we found impaired recognition performance in 22% of patients. This indicates that memory dysfunction is not a widespread deficit in this group and offers an explanation to the variable findings of the aforementioned studies. This high variability on memory performance among patients has also been reported in studies on subjects with lesions to the frontal lobes, suggesting that the different location of lesions may play a relevant role for developing memory impairment after damage to the frontal lobes (Bastin et al., 2006). Recent neuropsychological research has raised awareness about the role of the frontal lobes in the long-term memory process. The prefrontal cortex may deal with the organization and control of memory storage that takes place in medial temporal lobe structures (Shimamura, 1995) that contributes to successful memory. Distinct areas within the prefrontal cortex have subspecialized functions during the encoding process: the more ventral areas are the ones involved in processing item-specific information, whereas the dorsal areas deal with the relational memory (Blumenfeld & Ranganath, 2007; Long et al., 2010).

Our fMRI data provide evidence for the involvement of both the frontal and the medial temporal lobe areas in the impairment of memory function in patients with FLE. Normal recognition memory was associated with increased recruitment of frontal areas, contralateral to the epileptic focus, and, conversely, a poor performance was associated with an absence of this increased recruitment and decreased activation in mesial temporal lobe areas.

Frontal lobe activations in patients with FLE with poor memory performance were not significantly different from that in healthy controls, despite the decreased activation observed in the mesial temporal lobe structures. Decreased activations in the epileptogenic area have been reported as a group effect in patients with mesial TLE during memory tasks (Bonelli et al., 2010); however, our analysis did not revealed common areas of decreased activation within the frontal lobes across the whole FLE group or for the subgroup of patients with memory impairment. Activations during memory encoding task are seen within the lateral prefrontal cortex, The great interindividual variability on

the location of the epileptogenic focus within the frontal lobes compared to patients with TLE may offer an explanation for this difference. The lack of common areas of decreased activation does not rule out the presence of individual dysfunctional regions that are not captured as group effects. Whereas the medial temporal lobe structures seem to be commonly dysfunctional in FLE patients with memory impairment, there is no common area of dysfunction in the frontal lobes of these patients.

Remote functional and structural changes have been widely reported in patients with TLE (Martin et al., 2000; Bernhardt et al., 2008; Keller et al., 2009). However, only two recent studies have included patients with FLE when exploring the remote effect of focal epilepsies. Vlooswijk et al. (2010) showed dysfunction in the frontotemporal connectivity for verbal tasks in both frontal and temporal focal epilepsy syndromes. Everts et al. (2010) correlated the atypical patterns of language lateralization in focal epilepsy syndromes (frontal and/or temporal epileptic focus), with temporal lobe function finding a correlation between the representation of language and memory performance regardless of the location of epileptic focus. In our study, the decreased activity in medial temporal lobes seen in patients with poor memory provides further evidence of remote dysfunction in FLE.

The impairment in function was not associated with a decrease in the hippocampal volumes. This suggests that the observed decrease of activation is not the result of structural damage but a remote functional effect in the mesial temporal lobe areas of these patients. We hypothesize that different locations of epileptic focus within the frontal lobe may explain why there is a decreased activation in only a subgroup of patients with FLE. It is possible that patients with epileptic foci located in areas with greater connectivity to the limbic system may have a greater degree of remote dysfunction in the medial temporal lobe structures. However, this hypothesis could not be further tested in our patients, since epileptic focus could only be lateralized but not further localized for the majority of the patients.

One limitation of our study is the effect of patient's motivation and capacity to cope with on-line task demands. Although attention is monitored via the responses during the scanning process, we cannot rule out differences in their attention to and concentration on the task. Decreased fMRI signal has been reported in relation with poor engagement with the task in patients (Price & Friston, 1999), and this may play a role in the observed signal variability.

Our findings provide evidence for functional reorganizational changes in FLE. Frontal lobes are recruited during encoding processes, and compensatory activations within the frontal lobes, contralateral to the epileptic focus, are observed in patients with FLE. This functional reorganization is likely to be effective in the maintenance of memory function in this group.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Group maps.

Table S2. Areas of difference between patients and controls.

Table S3. Areas of difference between left and right FLE and controls.

Table S4. Areas of difference between the FLE patients with normal and impaired recognition performance and controls.

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2.2 STRUCTURAL CHANGES IN THE TEMPORAL LOBE AND PIRIFORM CORTEX IN FRONTAL LOBE EPILEPSY

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SHORT COMMUNICATION

Structural changes in the temporal lobe and piriform cortex in frontal lobe epilepsy

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KEYWORDS
Frontal lobe epilepsy;
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Voxel based morphometry;
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Summary
Background: Neuronal networks involved in seizure generation, maintenance and spread of epileptic activity comprise cortico-subcortical circuits. Although epileptic foci vary in location across focal epilepsy syndromes, there is evidence for common structures in the epileptogenic networks. We recently reported evidence from functional neuroimaging for a unique area in the piriform cortex, common to focal epilepsies in humans, which might play a role in modulating seizure activity.

In this study, we aimed to identify common areas of structural abnormalities in patients with frontal lobe epilepsy (FLE).
Methods: T1-weighted MRI scans of 43 FLE patients and 25 healthy controls were analysed using voxel based morphometry. Differences in regional grey matter volume were examined across the whole brain, and correlated with age at epilepsy onset, duration and frequency of seizures.
Results: We detected areas of increased grey matter volume in the piriform cortex, amygdala and parahippocampal gyrus bilaterally, as well as left mid temporal gyrus of patients relative to controls, which did not correlate with any of the clinical variables tested. No common areas of atrophy were detected across the FLE group.

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Conclusions: Structural abnormalities within the piriform cortex and adjacent structures of patients with FLE provide further evidence for the involvement of this area in the epileptogenic network of focal epilepsies. Lack of correlation with duration or age of onset of epilepsy suggests that this area of abnormality is not a consequence of seizure activity.

Introduction

Changes in grey matter volumes (GMV) have been reported in a number of epilepsy syndromes (Bernasconi et al., 2004; Keller et al., 2002; Lawson et al., 2002; Widjaja et al., 2011; Woermann et al., 1999). Regional increases and decreases of GMV have been identified within the epileptogenic region but also extending to brain areas distant from the seizure onset zone. Atrophy secondary to neuronal loss is the common pathological correlate of decreased GMV in the epileptogenic zone (Bernasconi et al., 2004; Keller et al., 2002). However, the biological significance of changes remote from the epileptic focus remains unclear.

In focal epilepsies, the network involved in the generation, modulation and spread of seizures may encompass not only the seizure onset zone but a number of areas believed to be involved in seizure modulation (Norden and Blumenfeld, 2002). Although seizure onset zones vary across different focal epilepsies, there is evidence for common cortico-subcortical circuits that underlie the maintenance and propagation of seizures. Animal and human studies have shown that areas comprising the nigro-striatial pathways, thalamus (Norden and Blumenfeld, 2002) are key parts of the epileptogenic network in both focal and generalised epilepsies. We recently reported evidence from functional neuroimaging for a unique area in the piriform cortex, common to focal epilepsies in humans, which might play a role in modulating seizure activity (Laufs et al., 2011).

Structural changes in patients with TLE have been widely studied using region and voxel-based morphometry (VBM) analysis (Bernasconi et al., 2004; Keller et al., 2002); however, these studies are usually dominated by areas of atrophy in the hippocampus and ipsilateral temporal lobe, which affects the accuracy of the normalisation process involved in this type of analysis. Only few studies have assessed structural abnormalities in patients with frontal lobe epilepsies (FLE) (Lawson et al., 2002; Widjaja et al., 2011). In this study we used whole brain VBM analysis of grey matter to explore common structural changes in a population with FLE.

Materials and methods

We recruited 43 patients with drug resistant FLE (26 left FLE and 17 right FLE). Diagnosis and lateralisation of seizure focus was performed by experienced neurologists based on video-EEG, seizure semiology, MRI imaging and FDG-PET/Ictal SPECT when available. The aetiology was cryptogenic in 32 patients. Small areas of focal cortical dysplasia in concordance with the suspected seizure onset zone were identified in 11 patients. Additionally, we scanned 25 healthy controls with no history of neurological or psychiatric disorders. Population characteristics are reported in Table 1.

The study was approved by the Research Ethics Committee of the UCL Institute of Neurology and UCL Hospitals.

Subjects were scanned with a 3 T General Electric Excite HD scanner. A 3-dimensional T1-weighted fast spoiled gradient echo (FSPGR) volumetric scan was obtained for each subject. Matrix size was $256 \times 256 \times 196$ voxels, with an isotropic voxel size of 1.1 mm (echo time/repetition time/inversion time 2.8/6.6/450 ms, flip angle 20°).

T1 images were processed and analysed using Statistical Parametric Mapping software (SPM8) (http://www.fil.ion.ucl.ac.uk/spm8).

Segmentation of the T1 images was performed using the ''New segmentation'' algorithm of SPM8. The grey matter, white matter and CSF tissue maps where normalised to MNI space using the *DARTEL* toolbox. The resulting tissue classification GM images were modulated by the Jacobian determinants derived from the registration step, in order to preserve subject's tissue volume after warping. Finally, images were smoothed by an 8-mm full width at half maximum isotropic Gaussian kernel.

Voxel-wise GMV differences between FLE patients and controls were examined using independent-sample *t*-tests. To account for differences in brain sizes, images were globally normalised using each subject's whole brain volume. Age and gender were used as regressors of no interest in the model.

Differences were considered significant at a threshold of $p < 0.05$ corrected for multiple comparisons (family wise error correction).

Correlation of structural changes with epilepsy duration, age of onset and monthly seizure frequency at the time of scan were explored by regressing the grey matter maps against these variables.

Results

FLE patients showed bilaterally, predominantly right-sided increases of grey matter volumes compared to controls in the piriform cortex, amygdala and parahippocampal gyrus as well as in the left mid temporal lobe gyrus (Fig. 1). Changes in medial temporal lobes were similarly distributed in patients with left and right FLE (Supplementary Fig. 1).

Supplementary Fig. 1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2014.03.001.

Regression analysis did not reveal any significant correlation of GMV changes with age at seizure onset, duration of epilepsy, or seizure frequency.

Table 1 Population demographics. Values displayed represent the mean (range) FCD: focal cortical dysplasia. AED: number of antiepileptic drugs.

	N	Gender (F)	Age	Age at epilepsy onset	Duration epilepsy	Aetiology	Seizures/month	AED
Controls	25	15	31 (23—55)					
Left FLE	26	10	35 (18—59)	10.6 (3—31)	24.6 (7—47)	5 FCD, 21 cryptogenic	61 (1—720)	3 (2—5)
Right FLE	17	9	31.8 (18—49)	11.3 (2—25)	19 (3—37)	6 FCD, 11 cryptogenic	138 (1—750)	3 (2—5)

There were no common areas of decreased GMV across all FLE patients, or within the left or right FLE subgroup.

Discussion

Our study provides evidence for common cerebral structural abnormalities in patients with FLE. VBM analysis showed increased grey matter in the anterior medial temporal lobe and orbitofrontal cortex, comprising piriform cortex (temporal and frontal portion), amygdala and parahippocamapal gyrus. These findings provide further evidence for the involvement of the piriform cortex in the epileptogenic network in patients with focal epilepsies of temporal and frontal lobe origin (Laufs et al., 2011). EEG-fMRI showed that this area was commonly activated during interictal epileptic activity regardless of the location of seizure focus. Additionally, [^{11}C]-flumazenil PET analysis found decreased benzodiazepine-GABAA receptor density correlated with seizure frequency in the same area. Using dynamic causal modelling, we reported recently that this structure is the driving input in an epileptogenic network supporting reading-induced foal seizures (Vaudano et al., 2012). This converging evidence from different functional imaging techniques in different focal epilepsy populations suggest that this area may have a seizure-modulating role in man, similarly to what has been observed in animals models (Piredda and Gale, 1985).

The piriform cortex and amygdalar nuclei are known to play a crucial role acting as a seizure generator in response to chemical and electrical stimulation and as an amplifier of epileptic activity when seizures are generated elsewhere. Animals studies have shown structural chronic inflammatory changes such as astrogliosis occurs in response to seizure activity in these areas (Loscher and Ebert, 1996).

Decreases and increases in GMV have been reported in different epilepsy syndromes. Volumetric measures of piriform cortex and periamygdalar cortex on autopsy specimens of TLE patients have shown atrophy in the ipsilateral side to the epileptic focus and a bilateral atrophy in up to 18% of the cases (Goncalves Pereira et al., 2005). Increases of GMV have been identified in the frontal lobes, cingulate, insula,

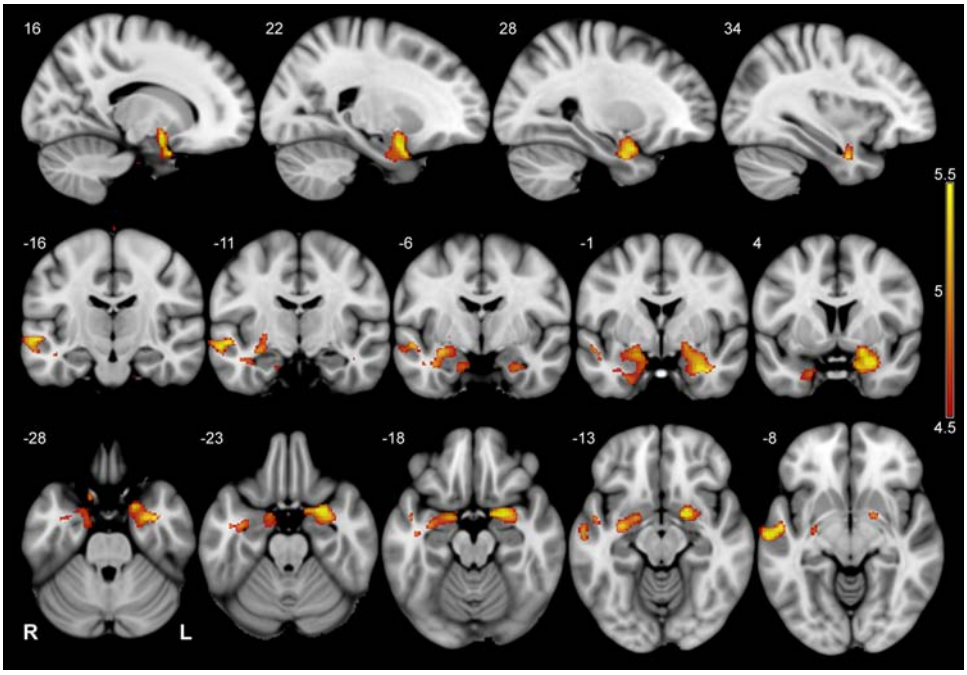

Figure 1 Grey matter abnormalities in patients with FLE. Greater grey matter regional volumes in FLE patients relative to controls are seen in piriform cortex and amygdala bilaterally, and on the left mid temporal lobe gyrus. Statistic maps are overlaid on an average T1 MNI template. For display proposes, maps have been thresholded at $p < 0.005$ (FDR corrected). Scale bar represent *t*-values. Numbers indicate *X*, *Z* and *Y*-coordinates in MNI space.

lateral temporal lobe cortex and amygdala contralateral to the seizure focus in TLE patients (Keller et al., 2002).

In our study, VBM analysis did not detected common areas of atrophy, or decreased GMV in FLE patients. Given the high variability of seizure focus location in patients with FLE, it is not surprising that a voxel wise analysis does not identify a common area of atrophy in this population, in the way it is seen in TLE patients with hippocampal sclerosis (Bernasconi et al., 2004; Keller et al., 2002). Cortical thickness (Widjaja et al., 2011) and frontal lobe volume measures (Lawson et al., 2002) were reduced in the frontal lobes of paediatric FLE patients indicating a more widespread effect of FLE on the developing paediatric brain.

Areas of GMV decrease are generally interpreted as consequence of seizure propagation (Bernasconi et al., 2004; Keller et al., 2002), but the neuropathological correlates and biological meaning of increased volumes remote to the epileptic focus is unclear. Anatomo-pathological studies revealed the presence of mild abnormalities in the layering and cellularity of grey and white matter tissue of patients with epilepsy (Eriksson et al., 2005). These areas of microscopic dysplastic changes may offer an explanation for increased GMV detected in VBM studies (Keller et al., 2002; Woermann et al., 1999). Further studies investigating the anatomo-pathological correlates of VBM findings are needed to in order to understand the pathological role of these changes.

Our analysis did not reveal significant correlations with age at seizure onset, duration or number of seizures. The observed changes in the piriform cortex and adjacent areas are therefore, unlikely to be consequence of seizure activity but may instead represent a common node in the intrinsic epileptogenic network.

Conclusions

Structural abnormalities shown using voxel wise analysis in patients with FLE suggest the presence for common underlying major hubs in the epileptogenic networks in focal epilepsies and add further evidence for the involvement of the piriform cortex and adjacent structures in the epileptogenic circuit of focal epilepsies.

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2.3 LANGUAGE DOMINANCE ASSESSMENT IN A BILINGUAL POPULATION: VALIDITY OF FMRI IN THE SECOND LANGUAGE

FULL-LENGTH ORIGINAL RESEARCH

Language dominance assessment in a bilingual population: Validity of fMRI in the second language

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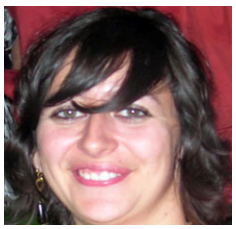

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Summary

Objective: **Assessment of language dominance using functional magnetic resonance imaging (fMRI) is a standard tool to estimate the risk of language function decline after epilepsy surgery. Although there has been considerable research in the characterization of language networks in bilingual individuals; little is known about the clinical usefulness of language mapping in a secondary language in patients with epilepsy, and how language lateralization assessed by fMRI may differ by the use of native or a secondary language paradigms. In this study we investigate language representation in a population of nonnative English speakers to assess differences in fMRI language lateralization between the first (native) and second language (English).**

Methods: **Sixteen nonnative English-speaking patients with focal drug-resistant epilepsy underwent language fMRI in their first (native) language (L1) and in English (L2). Differences between language maps using L1 and L2 paradigms were examined at the single subject level by comparing within-subject lateralization indexes obtained for each language. Differences at the group level were examined for each of the tasks and languages.**

Results: **Group maps for the second language (English) showed overlapping areas of activation with the native language, but with larger clusters, and more bilaterally distributed than for the first language. However, at the individual level, lateralization indexes were concordant between the two languages, except for one patient with bilateral hippocampal sclerosis who was left dominant in English and showed bilateral dominance for verb generation and right dominance for verbal fluency in his native tongue.**

Significance: **Language lateralization can generally be reliably derived from fMRI tasks in a second language provided that the subject can follow the task. Subjects with greater likelihood of atypical language representation should be evaluated more carefully, using more than one language paradigm.**

KEY WORDS: **Language fMRI, Epilepsy surgery, Second language, Bilingualism.**

Anterior temporal lobe resection in the language-dominant hemisphere may result in language deficit in up to 30% of patients.[1] Assessment of language dominance is part of the presurgical investigation to reduce this risk.

Patients with temporal epilepsy have up to a 30% increased chance of atypical language dominance,[2] with bilateral or right lateralization of either expressive or receptive language functions, or both.[3]

Functional magnetic resonance imaging (fMRI) is a robust tool for imaging brain networks involved in language,[4] with the advantage of being noninvasive and

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economical, and with good intrasubject reproducibility.[2] Large cohort studies have shown a high degree of correlation with the invasive Wada test.[2,5]

Language networks in bilingual subjects have been investigated extensively using fMRI.[6–13] The majority of studies report that the networks for different languages largely overlap,[6,12] but with differences in the extent or intensity of activations due to several factors: age of language acquisition,[6,13] proficiency,[6,11,13] and language-specific attributes such as orthographic characteristics.[10]

Bilingualism is prevalent in countries like the United States and the United Kingdom, with a high degree of ethnic diversity. Furthermore, it is an increasing phenomenon in many countries due to immigration. In Britain, up to 8% of the population has a mother tongue other than English. In large cities such as London the percentage of nonnative English speakers can be as high as 20%.[14]

Language fMRI studies for language lateralization in patients have been validated primarily using mother tongues. In clinical practice, however, these studies are often performed in a secondary language such as English. To our knowledge, the clinical efficacy of language fMRI mapping in a second language has not previously been formally evaluated.

We investigated fMRI language representation in a population of nonnative English speakers in each subject's native language (L1) and in English (L2).

We addressed the following questions:

1 What is the concordance in language lateralization when assessed in L1 and L2 fMRI for each subject?
2 What are the differences at the group level of acquired second (English) language on fMRI language and the effect of age of language acquisition?

Methods

Subjects

Sixteen consecutive patients (age range 24–50 years), speaking 11 different native languages, with drug-resistant focal epilepsy underwent language fMRI as part of their presurgical investigations. All patients were nonnative English speakers, with 31% self-rated as low level of English proficiency, 37% as medium, and 32% as highly proficient. The age of English acquisition varied across subjects and ranged from 3 to 35.

Clinical and language data are summarized in Table 1.

fMRI paradigms

Language fMRI was obtained as part of the presurgical evaluation. All subjects gave written consent to participate in the tests.

Two language paradigms (verbal fluency [VF] and verb generation [VG]) were presented to each subject in two sessions: native language (L1) and English (L2), in total four

Table 1. Patient's demographics and language lateralization

N	Gen	Age (year)	LI	Age L2 acquisition	L2 proficiency	Hand	Age seizure onset (year)	Duration (year)	Focus location	Aetiology	L2 VF	LI VF	L2 VG	LI VG
1	M	50	Eritrean	Early	High	R	27	22	L TL	Left HS	L	L	L	L
2	M	26	Shona	Early	High	R	10	15	L FL	FCD	L	L	L	L
3	M	32	Urdu	Early	High	R	13	17	R TL	Cryptogenic	R	R	R	R
4	M	24	Urdu	Early	High	R	17	8	Unknown	Dual pathology	L	L	L	–
5	M	32	Welsh	Early	Medium	R	2	30	R TL	Bilateral HS	L	R	L	B
6	M	34	Farsi	Late	Medium	R	31	3	R FL	Cavernoma	L	L	L	L
7	M	47	Greek	Late	Low	R	2	48	L TL	HS	–	L	L	L
8	M	29	Polish	Late	Medium	R	8	21	L OC	Tumoral vs. vascular	L	L	L	L
9	M	31	Polish	Late	Medium	R	27	4	L TL	Cryptogenic	L	L	L	L
10	F	29	Russian	Late	Low	L	10	17	TL	Cryptogenic	L	L	L	L
11	M	33	Spanish	Late	Low	R	7	26	R TL	HS	L	L	L	L
12	M	32	Turkish	Late	Medium	R	20	11	L TL	Cavernoma	L	L	L	L
13	M	35	Turkish	Late	Low	R	7	28	L hemisph	Multiple cavernomas	L	L	–	L
14	M	34	Portuguese	Late	High	R	25	9	L TL	HS	L	L	L	L
15	F	50	Portuguese	Late	Low	R	0.4	60	TL	Bilateral HS	L	L	L	L
16	F	32	Portuguese	Late	Medium	L	15	17	L FL	Cryptogenic	R	R	R	R

LI, native language; L2, English; TL, temporal lobe; FL, frontal lobe; OC, occipital cortex; FCD, focal cortical dysplasia; HS, hippocampal sclerosis; Early, before 6 years; Late, after 6 years. Last four columns contain categorical lateralization for M, male; F, female; each of the tasks: VF, verbal fluency; VG, verb generation; L, left; R, right; B, bilateral representation. Highlighted in pink is the case of LI –L2 discordant representation.

paradigms. The order of sessions was allocated randomly to account for the effect of habituation.

The verbal fluency paradigm consisted of a blocked experimental design with 30-s activation blocks alternating with 30-s of cross-hair fixation over 5 min.[15] Subjects were instructed to covertly generate different words beginning with a visually presented letter. Letters for L1 were taken from tables of relative frequencies of first letters of a word for each language, for L2 we used letters A, S, W, D, and E. If the language did not use Roman script, the equivalent letter was presented in the script of their native language.

In the VG paradigm, concrete nouns were presented visually every 3 s in blocks of 10, contrasted by 30 s of crosshair fixation as rest. Subjects were instructed to either covertly generate verbs associated with these nouns (indicated by the letter "G" preceding the noun) or silently repeat the nouns presented (indicated by the letter "R" preceding the noun).

Translation of the VG paradigm was carried out by a native speaker of each of the languages.

fMRI acquisition

We used a 3T General Electric Excite HDx scanner (General Electric, Milwaukee, WI, U.S.A.). Standard imaging gradients with a maximum strength of 40 mT/m and slew rate 150 T/m/s were used.

All data was acquired using an eight-channel array head coil for reception and the body coil for transmission. During fMRI task, gradient-echo planar T_2*-weighted images were acquired, providing blood oxygenation level–dependent (BOLD) contrast. Each volume comprised 50 interleaved 2.4 mm slices with a 0.1 mm interslice gap, with an orientation parallel to the anterior to posterior commisure (AC-PC) line, 64 × 64 matrix with a 24 cm field of view giving an in-plane pixel size of 3.75 mm. Echo time (TE) was 25 msec and repetition time 2.5 s.

fMRI analysis

Images were analysed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Each subject's images were realigned using the mean image as a reference, spatially normalized into Montreal Neurological Institute (MNI) space (using a scanner specific template created from patient and control data) and smoothed with a Gaussian kernel of 8 mm full-width at half maximum.

Statistical fMRI analyses were performed first at the single subject level and then at the group level. In the single subject level analyses, trial-related activity was modeled by convolving a vector of block onsets for each condition with a canonical hemodynamic response function (HRF) to create regressors of interest. In VF task one single condition (VF) was modeled and in VG task two conditions were modeled: "verb generation" and "word repetition." Each subject's movement parameters were included as confounds. Parameter estimates pertaining to the height of the HRF for VF and for "verb generation-VG" condition in VG task were calculated for each voxel.

Language dominance

Language dominance was quantitatively measured using lateralization indices (LIs) of statistic parametric maps (spmT) maps.[16] LIs were calculated for each subject's four spmT maps (corresponding to VF and VG tasks in L1 and L2) using the bootstrap method of the lateralization index toolbox implemented in SPM.[16,17] Activated voxels within the inferior and mid-frontal gyrus[15] were computed using the formula [LI = (R − L)/(L + R)]. A negative LI indicates a left hemispheric lateralization and a positive index indicates right lateralization. LIs were subsequently classified as left-hemisphere language dominant (defined as LI <-0.2) and atypical dominance, comprising bilateral distribution ($-0.2 \geq$ LI $\leq +0.2$) or right hemisphere dominant (LI $>+0.2$).[3]

Concordance of LI was investigated between the two languages within each task for each subject. Correlations between LI were also quantitatively measured with Pearson's test.

Group differences between L1 and L2 maps

Individual spmT maps of VF and VG were taken to a second level random-effects analysis. Group maps for L1 and L2 were created for each of the tasks using one-sample *t*-test, and thresholded at $p < 0.001$ (uncorrected for multiple comparisons) with a minimum cluster size of 20 voxels. Number of active clusters and extension of clusters (i.e., number of active voxels within a cluster) were compared between L1 and L2 tasks.

Effect of age of L2 acquisition

Subjects were divided according to their age of L2 acquisition (AOA) into early[18] (<6 years) and late acquisition (>6 years). We investigated the effect of age of acquisition in fMRI maps by creating a second-level regression model, where maps for intra-individual language differences L1 > L2 and L2 > L1 were regressed against the variable AOA.

Activations in the regression analysis were considered significant at a threshold of $p < 0.001$ (uncorrected for multiple comparisons) with a minimum cluster size of 20 voxels.

Results

All individual language fMRI maps were inspected visually to assess their validity. One of the four tasks had to be discarded in three subjects due to the images being corrupted by movement artifact. For these subjects, the comparison between L1 and L2 was performed only for the tasks where the two languages were available.

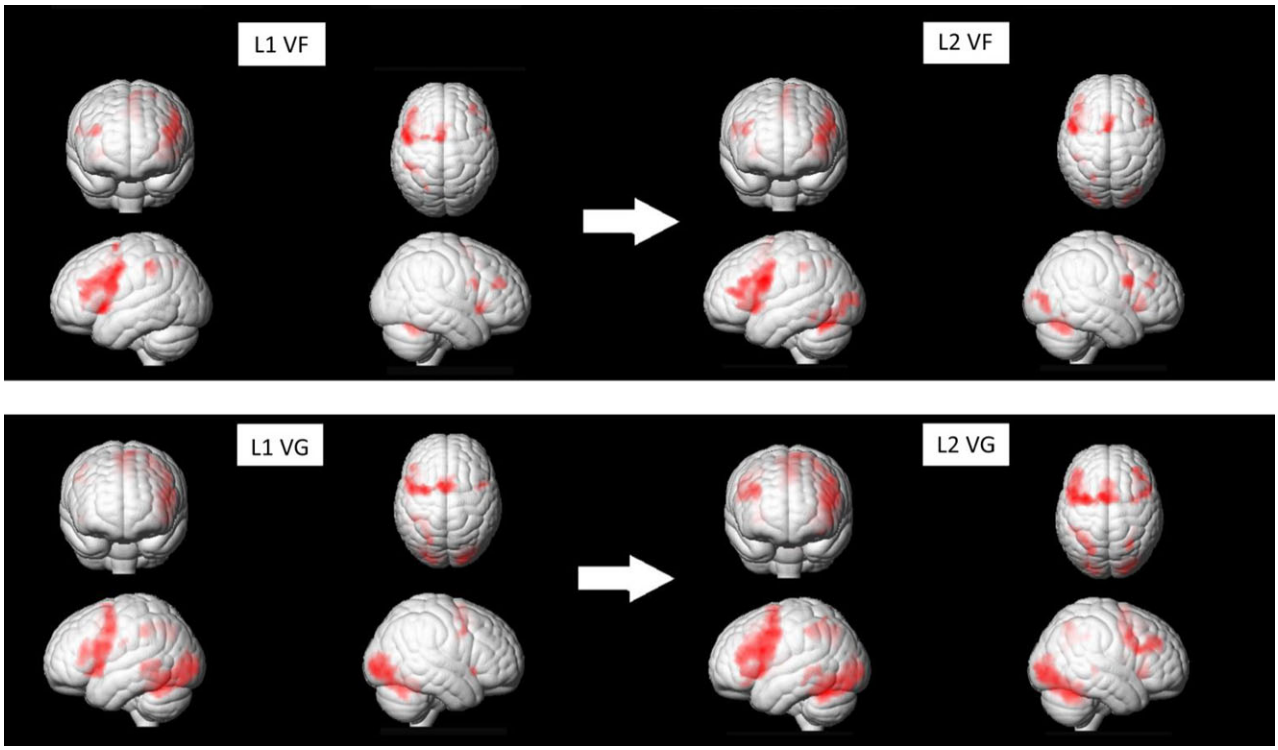

Figure 1.
Group activations. Upper row shows VF (verbal fluency) activations in L1 (Native) and L2 (English). Lower row corresponds to VG (verb generation) tasks. A larger number of clusters and total number of voxels are active during L2 tasks. Quantification and location of activations are described in Tables 2 and 3.

Areas of significant activation in VF and VG tasks for both languages were observed in the middle and inferior frontal gyrus, the medial aspect of superior frontal gyrus, angular gyrus, and cerebellum (Fig. 1; Tables 2 and 3).

Single subject results: language dominance derived from L1 and L2 tasks

Despite different levels of L2 proficiency across subjects, all participants showed significant activations in language-related areas in each of the four fMRI maps.

We observed "atypical," either bilateral or right-lateralized language representation in 3 of 16 patients for L1 and 2 for L2.

There was good concordance between the lateralization indexes (LIs) derived from L1 and L2 tasks (Table 1; Fig. 2). Language representation (left/right or bilateral) was concordant for all tasks in 15/16 (94%).

Only one subject (subject 5, right temporal lobe epilepsy [TLE] with bilateral hippocampal sclerosis) showed discordant language representation between L1 and L2 VF maps (Fig. 2), with right dominance in L1 VF (LI 0.48) and bilateral dominance in L1 VG (LI −0.2) as opposed to left dominance for L2 (LI VF −0.53; VG −0.7).

Across all subjects, Pearson's correlations of LIs between L1 and L2 were 0.81 for the VF tasks and 0.93 for VG tasks.

Group effects of L1 and L2

At a group level, patients activated a larger number of clusters and total voxels during L2 sessions in both, VF and VG tasks compared to their native language (L1) (Fig. 1; Tables 2 and 3). Activations showed left hemispheric lateralization for both VF and VG tasks in both languages across the group.

The majority of areas activated overlap for L1 and L2 (Tables 2 and 3). Common clusters for both languages include the lateral frontal areas involving the left superior, mid- and inferior frontal gyrus, left superior parietal gyrus, and right cerebellum, and to a lesser extent on the right inferior frontal gyrus.

However, specific activations were also seen for L1 and L2 maps. Left thalamus was active only during L1 tasks; for L2 we found additional activations comprising right parietal, right thalamus, (VG), and extra activations in right mid- and inferior frontal gyri, and both fusiform gyri (VF).

Effect of age of acquisition

Late English (L2) acquisition (after 6 years of age) was associated with increased activation within the right frontal cortex (middle frontal gyrus) relative to L1 in the VF task (Fig. S1). There was not a significant effect of age of acquisition on VG task activation patterns.

Table 2. Activations in verbal fluency (VF) tasks

Location clusters	Number voxels L1	Number voxels L2	T values L1	T values L2	Coordinates L1 x	Coordinates L1 y	Coordinates L1 z	Coordinates L2 x	Coordinates L2 y	Coordinates L2 z
Frontal										
Left MFG/SFG/IFG	1,146	1,082	10.68	9.87	−51	6	33	−51	6	30
Left SFG	262	267	6.84	6.7	−6	15	42	−6	9	51
Left SFG	30		6.53		−24	3	72			
Right IFG	79	116	5.9	7.76	45	18	−6	33	27	0
Right MFG	34	112	4.68	7.41	60	15	24	51	12	27
Right MFG/IFG		42		5.44				42	39	21
Parietal										
Left parietal	102	79	6.54	6.72	−48	−42	42	−48	−39	45
Left parietal		31		6.64				−21	−72	48
Occipital										
Right cerebellum	192	321	6.19	7.43	36	−51	−30	36	−63	−27
Left occipital/left cerebellum		287		6.76				−42	−66	−24
Right occipital		143		6.06				30	−93	9
Thalamus										
Left thalamus	27		4.87		−18	3	0			
Total activated voxels/ Number of clusters	1,872/8	2,480/10								

Coordinates are given in MNI space. Clusters highlighted in blue are specific to L1 (Native) tasks, clusters highlighted in pink are only seen during L2 (English) tasks.

MNI, Montreal Neurological Institute; IFG, inferior frontal gyrus; MFG, mid-frontal gyrus; SFG, superior frontal gyrus.

Discussion

We compared fMRI language mapping in nonnative English patients using English and native languages paradigms. Lateralization of language representation was concordant for both languages in the majority (15/16) of patients, suggesting that language mapping can generally be reliably performed in the second (acquired) language, even if there is a different proficiency for this language. In only one case (6%) was there a clear discrepancy between languages in both tasks. LI in this patient suggests that he has atypical language dominance for his native language (VF 0.48/VG −0.2) and left dominance for his secondary language (VF −0.53/VG −0.7).

Studies in bilingual subjects question the existence of distinct networks versus a common network for the processing of different languages. Although there are reports of selective aphasias for one language after stroke,[19] epileptic seizures,[20] or surgical resections[21] and evidence from intraoperative language mapping suggesting the presence of distinct areas within the left hemisphere for L1 and L2 languages,[22,23] the majority of neuropsychological models suggest a common network supporting the different languages, and explain the evidence of distinct networks in terms of modulation related to specific computational demands, which vary according to the age of acquisition, the degree of mastery, and the level of exposure to each language.[6] This may translate into differences observed in language maps obtained by fMRI.

Our results are in keeping with the assumption of a common network processing different languages in bilinguals. This is supported by the overlapping of the majority of clusters of activations (Fig. 1; Tables 2 and 3) between the two languages. The difference in the extent of activations may reflect increased processing demands for L2 as opposed to distinct networks.

Language fMRI studies have contributed greatly to the investigation of differences and similarities between the networks used for each language. In several studies, Hernandez et al. have shown that networks involved in reading words[10] and naming,[8,9] as well as in comprehension,[11] largely overlap for the different languages in bilinguals. However, differences in the networks are seen in relation to language characteristics such as language-specific orthographic properties.[10]

Age of language acquisition (AOA) is a relevant factor that accounts for a relevant proportion of differences in the languages maps in bilinguals.[6] A late AOA is related to greater fMRI activations in the language networks compared to those subjects for whom L2 was acquired early in life.

Proficiency in the secondary language has also been associated with differences in the extent and significance of activations defined by fMRI studies. Activations associated with the less proficient language in bilinguals are more significant and widespread,[6,11] and may involve additional areas such as supplementary motor cortex during reading words[10]; however, some studies have not found significant differences associated with low proficiency.[12] These findings have been interpreted in relation to a greater effort when using the less proficient language. Age of onset and proficiency may interact with other language characteristics. In particular, grammatical processing has been shown

Table 3. Activations in verb generation tasks

Location clusters	Number voxels L1	Number voxels L2	T values L1	T values L2	Coordinates L1 x	Coordinates L1 y	Coordinates L1 z	Coordinates L2 x	Coordinates L2 y	Coordinates L2 z
Frontal										
Left MFG	1,612	3,476	9.97	10.17	−51	0	42	−42	15	24
Right SFG/MFG/IFG	36	709	4.76	6.31	48	3	36	39	45	33
Parietal										
Left parietal	341	595	7.52	9.26	−24	−75	42	−24	−66	45
Right parietal		218		5.97				30	−66	48
Occipital										
Left occipital	1,521	2,265	11.22	11.24	−21	−90	−15	−15	−99	−12
Right occipital	1,127	1,510	14.28	11.82	18	−96	−3	21	−93	−9
Thalamus										
Left thalamus	26		4.94		−18	−9	15			
Right thalamus		50		4.83				12	−12	15
Total activated voxels/ Number of clusters	4,663/6	8,823/7								

Coordinates are given in MNI space. Clusters highlighted in blue are specific to L1 (Native) tasks, clusters highlighted in pink are only seen during L2 (English) tasks.

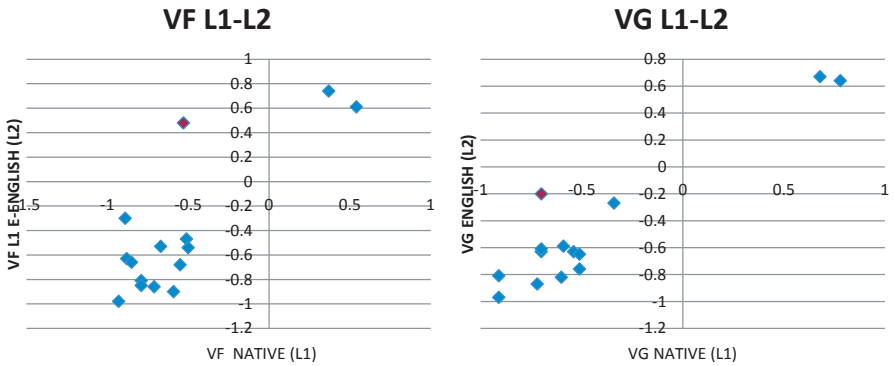

Figure 2.
Correspondence between LIs in VF (left) and VG (right) in L1 and L2 languages. Vertical axes represent the values of L1 and horizontal axes represent the values of L2. There is a high correlation between LI values for L1 and L2 (Pearson's correlation VF = 0.81, Pearson's correlation VG = 0.93). In red, subject number 5 with discordant language representation.

to be specifically sensitive to the effect of age of acquisition, whereas semantic-lexical processes depend more on the level of proficiency.[6,18]

Our data, in accordance with those of previous studies, show that late AOA is associated with more widespread activations, in particular, in the right MFG, as compared to an early AOA. However, the large range of AOA in our sample may be a limitation for the interpretation of this effect.

Despite the differences in the extent of activations between L1 and L2 observed at the group level, language lateralization as measured by LIs is not generally influenced by the use of different languages. Language dominance can be reliable inferred from one of the two languages in bilingual subjects. LIs are commonly used in the clinical settings to quantify language dominance. Language-dominance categorization is based on arbitrary limits to discriminate between categories, although LIs derived from fMRI are on a continuum.[3] For a more accurate interpretation of language maps, visual inspection of language maps, as well as the use of more than one fMRI paradigm,[24] is always advisable.

Differences between first and second language mapping become relevant clinically if there are intraindividual differences in the dominance between L1 and L2. We found a case of discordance in a patient. The patient had bilateral hippocampal sclerosis with seizures arising from right temporal lobe. Onset of seizures was at the age of two. The overall picture suggests that, in a patient with bilateral temporal lobe damage and atypical language dominance for his native tongue, the less proficient language had a greater representation in the hemisphere contralateral to the seizure onset. This is an unusual case due to its

complex underlying condition, but it emphasizes the fact that different languages can have different lateralization patterns in a small proportion of cases. Visual inspection of the languages maps (Fig. S2) showing an atypical distribution for L1 and left dominance for L2, in accordance with the LI, provides a more global vision of the distribution of the activations.

The mechanisms underlying atypical language dominance in epilepsy are not completely understood. Factors such as early epilepsy onset and the presence of a structural lesion have been correlated with atypical dominance.[25] Further investigation in larger patient samples is required to assess how representation of second (acquired) languages is affected by age of onset of the epilepsy, side of focus, and age of second language acquisition.

In conclusion, language lateralization can be reliably derived from fMRI tasks undertaken in a second language. Subjects with a greater likelihood of atypical language representation need more careful evaluation, using more than one language paradigm. Incorporating visual, as well as quantitative measures of laterality may be considered in these cases.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Late L2 acquisition: Areas related to late age of L2 acquisition in VF. Right mid-frontal gyrus activation is greater in VF in L2 compared to L1 in those patients with a late age of L2 acquisition.

Figure S2. Discordant L1/L2 case. Patient with discordant lateralization of L1/L2 maps. The maps show atypical language lateralization for L1 (first column); VF and VG lateralization indexes fall in the atypical range (0.48 and −0.2, respectively), as opposed to a left predominance for both L2 tasks.

3 SUMMARY OF RESULTS AND DISCUSSION

This section is organized in three parts. Each part summarizes the results of a study and discusses the particular findings.

3.1 MEMORY DYSFUNCTION IN FRONTAL LOBE EPILEPSY

In this study both memory function in patients with FLE and changes in memory networks associated with memory dysfunction are investigated using fMRI.

3.1.1 Results

3.1.1.1 Memory performance in a delayed recognition task

- Recognition accuracy (RA) was significantly lower in patients with FLE compared to controls for the three types of encoded material: pictures, words and faces (Figure 3-1).
- The type of material was a significant factor in the recognition accuracy scores ($F(1,28) = 115.96$, $p<0.0001$). Words were significantly better recognized than faces in patients with FLE.
- There was a high variability in memory performance amongst FLE patients. Seven out of 32 (22%) patients with FLE fell within the impaired range (2 standard deviations below the RA control range)

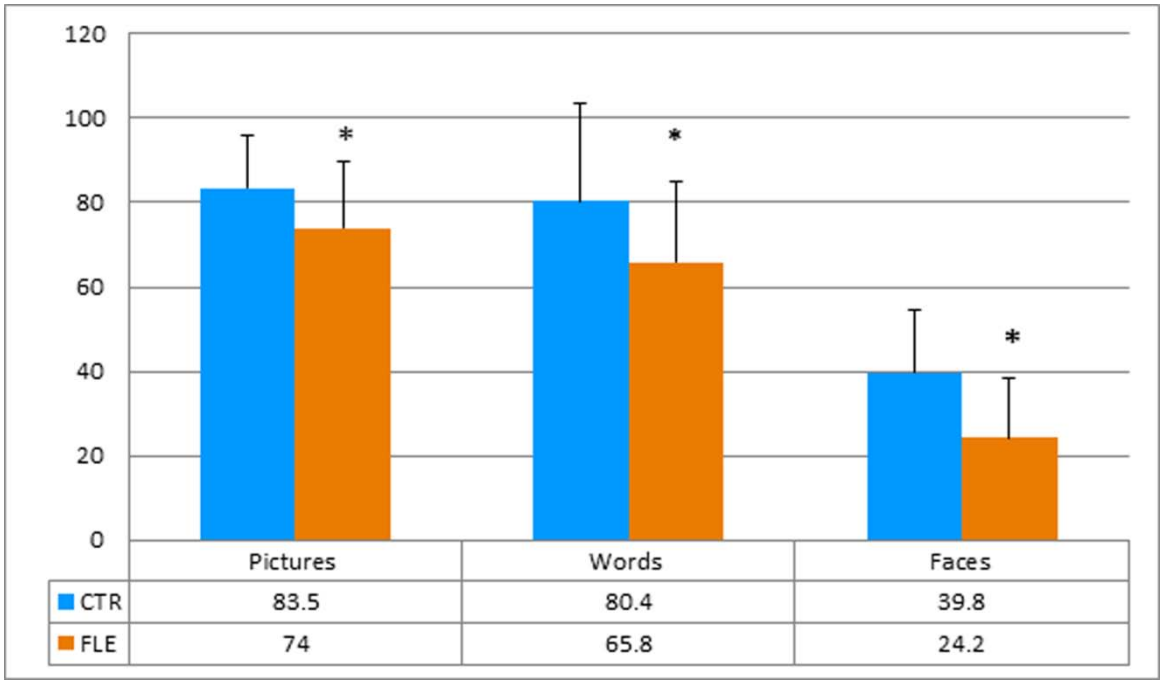

Figure 3-1. Recognition accuracy. *Recognition accuracy measures the proportion of correctly remembered items minus the proportion of falsely recognized items. FLE patients have a significantly decreased recognition accuracy (RA) compared to control group in all categories. Mean RA = average of recognition accuracy for the three type of stimuli is represented in the Y axis. Error bars represent 1 standard deviation. CTR= healthy controls. FLE= frontal lobe epilepsy patients *= significant difference of means at a p value <0.05*

3.1.1.2 Functional MRI results.

- Fronto-temporal regions were significantly activated during the encoding of pictures, words and faces. This network involved dorso and ventro-lateral prefrontal cortices, amygdala, hippocampus and parahippocampal gyrus
- Patients with FLE engaged larger regions within the frontal lobes relative to controls (Figure 3-2 A)
- Both left and right FLE showed greater frontal lobe activation than controls. Lateralization of these increased activations was contralateral to the side of epileptic focus on both groups of patients (Figure 3-2 B-C).

- Patients with impaired memory performance had decreased amygdala-hippocampal activation compared to controls and to FLE patients with normal recognition scores (Figure 3-3).

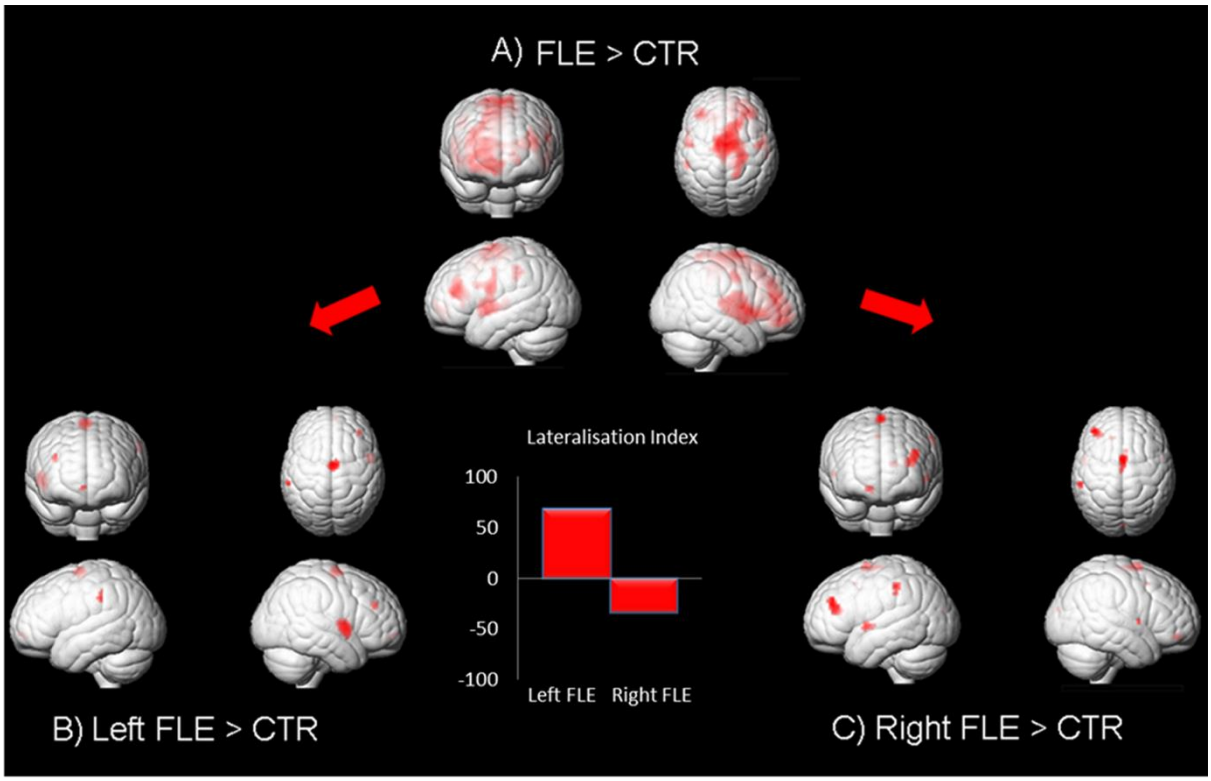

Figure 3-2. Effect of frontal lobe epilepsy and focus lateralization. *A) Areas of increased activation in FLE patients relative to controls (FLE>CTR) collapsed for all item types are located within the frontal lobe areas involved in the task. Increased activation was lateralized differently for left and right FLE patients (Left FLE patients showed increased activations in the right hemisphere (B) and right FLE patients in the left hemisphere (C). The bar chart shows the values of the lateralisation index (LI) of the maps B) and C). LI values range from 1 to -1, positive values indicate a right hemispheric lateralisation whereas negative values indicate a left lateralisation.*

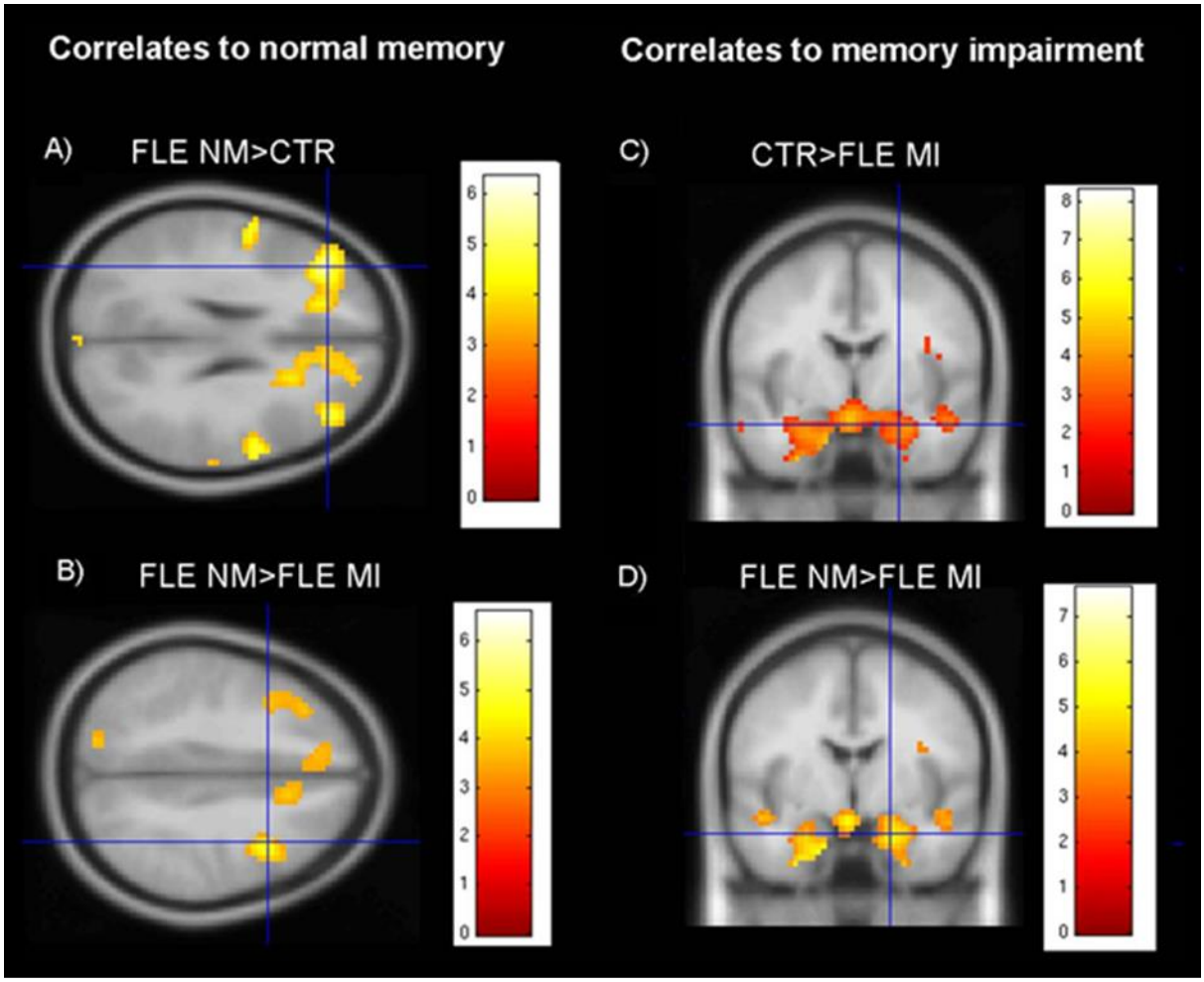

Figure 3-3. Functional correlates of different performances. *A) and B) FLE patients with normal memory (FLE NM) showed increased activations in the frontal lobes when compared to controls (CTR) (FLE NM>CTR) and to patients with memory impairment (FLE MI) (FLE NM>FLE MI). C) and D) FLE patients with impaired memory showed decreased amygdala and hippocampal activation when compared to CTR (CTR>FLE MI) and to patients with normal memory (FLE NM>FLE MI). Scaling bars show T scores for the activations.*

3.1.2 Discussion

3.1.2.1 Memory performance in patients with FLE

Patients with FLE as a group are impaired in long term memory retrieval compared to controls. However, there is a high variability in performance among patients with FLE. About a fifth of the patients were found to perform within the significant impaired range (2 standard deviation below the control mean) while the other four fifths fell within the normative range.

Evidence for memory dysfunction in FLE patients varies widely between studies. Delaney et al.(Delaney et al., 1980) and Riva et al.(Riva et al., 2002) found no memory impairment in adult subjects with FLE, whereas Nolan et al. (Nolan et al., 2004) found memory impairment in verbal and nonverbal memory domains in children with FLE, although this was to a lesser degree than in patients with TLE. Exner et al. (Exner et al., 2002) reported the severest memory deficits: in their study patients with FLE had memory dysfunction of a comparable severity to that seen in patients with TLE. This was found in immediate and delayed recall tasks of visual and verbal items. Memory impairment has also been reported in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) where all but one patient out of 11 were found to be impaired on at least one memory measure, and in four patients the memory function was found to be more severely disrupted than executive functions (Cho et al., 2008, Picard et al., 2009). The findings in our study support the hypothesis that memory deficit is patchy in this group of patients and offers an explanation to the variability seen between the aforementioned studies. This variability in memory performance is not only found in patients with FLE but also in subjects with lesions to the frontal lobes, suggesting that the different location of lesions and epileptic focuses may be a relevant factor in causing memory impairment (Bastin et al., 2006).

In contrast to what has been reported in patients with TLE, we did not observe material-specific deficits related to the lateralization of the epileptic focus.

3.1.2.2 Neurobiological implications

3.1.2.2.1 Network abnormalities related to memory dysfunction

The role of the frontal lobes in long term memory is not well established. The prefrontal cortex is thought to deal with the organization and control of memory storage that takes place in medial temporal lobe structures (Shimamura, 1995) contributing to successful memory. Distinct areas within the prefrontal cortex are thought to have subspecialized functions during the encoding process: the more ventral areas are involved in processing item specific information, whereas the dorsal areas deal with the relational memory (Blumenfeld & Ranganath, 2007, Long et al., 2010). Recent studies have demonstrated the importance of frontal lobes functions in successful memory encoding and in maintaining memory function after surgery in patients with temporal lobe epilepsy (Sidhu et al., 2013, Sidhu et al., 2015). Our fMRI results provide support for the hypothesis that both the frontal and the medial temporal lobe areas are involved in the impairment of memory function in patients with FLE. Normal recognition memory was associated with increased recruitment of frontal areas, contralateral to the epileptic focus, and, conversely, a poor performance was associated with an absence of the increased recruitment as well as with decreased activation in mesial temporal lobe areas.

A) Medial temporal lobe involvement

Medial temporal lobe activation was preserved in the majority of patients with FLE. However, the subgroup of patients with recognition memory impairments showed significant decreased activation in amygdala and hippocampus, suggesting a dysfunction in these areas remote from seizure focus in the patients with impaired memory.

We hypothesize that the localization of epileptic focus within the frontal lobe may explain why there is a decreased activation in only a subgroup of patients with FLE. We suggest that patients with epileptic foci located in areas with greater connectivity to the limbic system may have a greater degree of remote dysfunction in the medial temporal lobe structures and in turn a greater memory dysfunction. However, to prove this hypothesis further studies should be carried out in patients with a greater accurate localization of the epileptic focus within the frontal lobes.

B) Compensatory frontal activations

We showed that patients with FLE recruit wider areas within the frontal lobes during the encoding process compared to controls, suggesting the presence of compensatory mechanisms. Effective compensation in patients can only be assessed if there are no differences in in-scanner task performance.

The observed increases in activations are likely to represent compensatory mechanisms for two reasons. Firstly, the analysis subdivided by side of seizure onset revealed that activations are more prominent in the hemisphere contralateral to the epileptic focus. A similar pattern has been reported in the side contralateral to the epileptic focus in patients with TLE in correlation with a maintained memory performance with and without memory impairment (Richardson et al., 2003, Richardson et al., 2004, Bonelli et al., 2010).

Secondly, increased frontal activations were present in the group of FLE patients with normal memory relative to controls and to FLE patients with memory impairment suggesting these activations are associated with a maintained memory function

3.1.2.3 Strengths and limitations

This is the first study to examine memory networks in patients with FLE. Our cohort of patients were well characterized from the clinical point of view, having all undergone detailed neuroimaging and ictal and interictal video-EEG recording. However the accurate localization of the epileptogenic region within the frontal lobes was unknown in a large proportion of these patients making it difficult to extract further conclusions about the correlation of epileptic focus and memory function/network changes.

Memory performance scores were extracted from in-scanner tasks. In scanner performance can be influenced by motivation and compliance with the task. Decreased fMRI signal has been reported in relation with poor engagement with the task in patients (Price & Friston, 1999) and this may play a role in the observed signal variability. These factors may result in differences in BOLD signal changes patterns, thereby acting as confounding factors of performance.

3.1.2.4 Future perspectives

This study was limited to the investigation of the memory. However, in order to fully characterize memory function in patients with FLE, future studies should target the rest of memory domains. Frontal lobes have been reported to be involved in the different aspects of memory being of particular relevance to memory retrieval and prospective memory. The investigation of these memory domains would provide valuable information for understanding memory dysfunction in these patients

3.2 LANGUAGE DOMINANCE ASSESSMENT IN A BILINGUAL POPULATION: VALIDITY OF FMRI IN THE SECOND LANGUAGE.

In this study language representation in native and second languages was investigated in a bilingual population of patients with epilepsy. The main aim of the study was to test the validity of language fMRI studies in a second language for the lateralization of language used for presurgical evaluation. Comparison between language maps in both native and second language (English) were performed both, at the subject and at group level. Laterality indexes derived from both languages were compared for each of the subjects.

3.2.1 Results

3.2.1.1 Group results

- Group maps for the second language (L2) showed overlapping areas of activation with the native language (L1), but with larger clusters, and more bilaterally distributed than for the native language.
- Patients activated a larger number of clusters and total number of voxels for the second language in both, VF and VG tasks compared to their native

language (Figure 3-4). Activations showed left hemispheric lateralization for both languages in the two tasks.

- Late second language (L2) acquisition (after 6 years of age) was associated with increased activation within the right frontal cortex (middle frontal gyrus) relative to L1 in the VF task (Figure 3-5). There was not a significant effect of age of acquisition on VG task activation patterns.

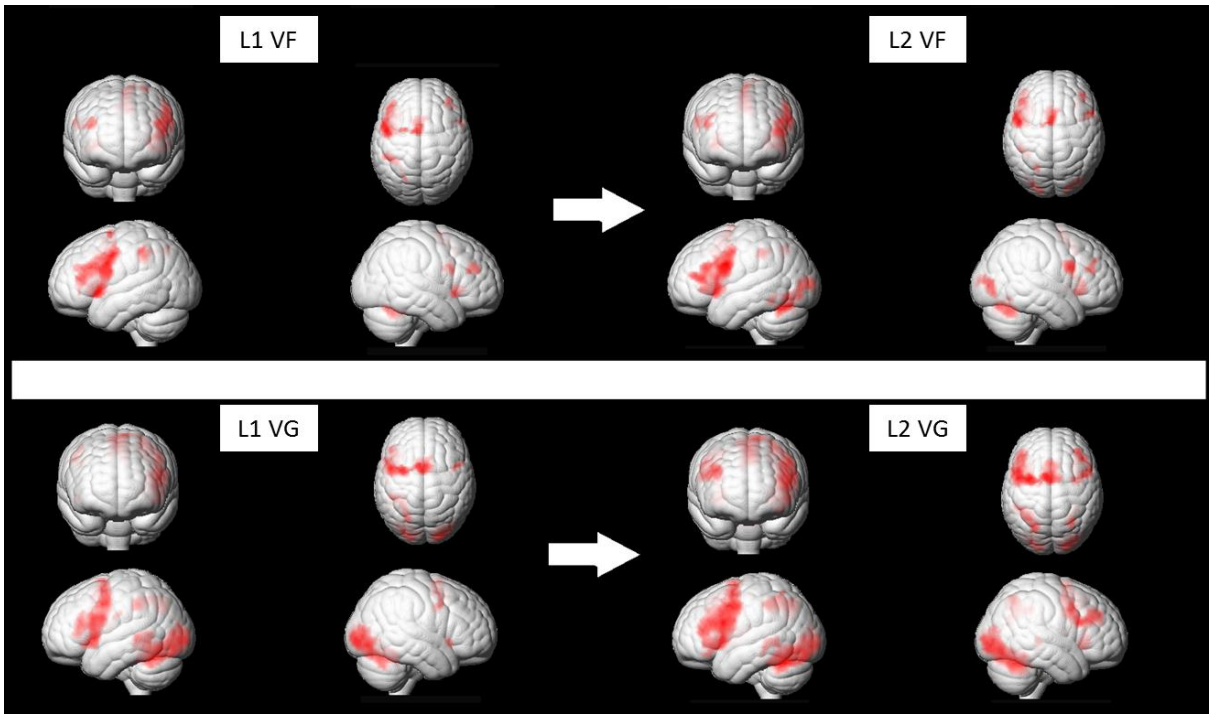

Figure 3-4. Memory encoding group activations. *Upper row shows VF (verbal fluency) activations in L1 (Native) and L2 (English). Lower row corresponds to VG (verb generation) tasks. A larger number of clusters and total number of voxels are active during tasks performed in L2.*

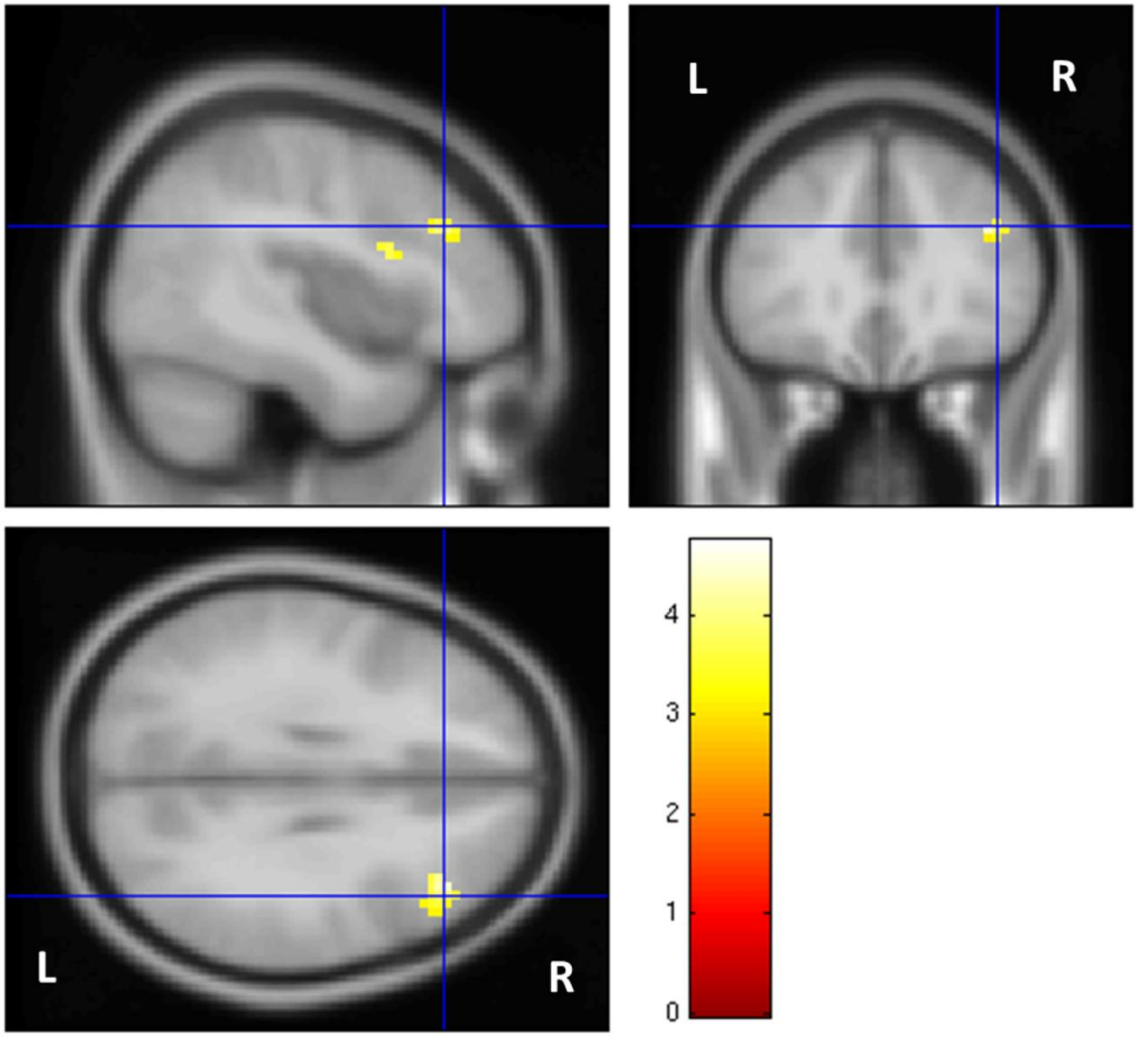

Figure 3-5. Late secondary language acquisition. *Areas related to late age of L2 acquisition in VF. Right mid frontal gyrus activation is greater in VF in L2 compared to L1 in those patients with a late age of L2 acquisition.*

3.2.1.2 Single subject results

Despite the differences in extent of activations at the group level; lateralization indexes were concordant between the two languages at individual level:

- Language representation (left/right or bilateral) was concordant for all tasks in 15 out of 16 patients (94%). (Figure 3-6).

- Only one subject (subject 5, right temporal lobe epilepsy [TLE] with bilateral hippocampal sclerosis) showed discordant language representation between L1 and L2 VF maps, with right dominance in L1 VF (LI 0.48) and bilateral dominance in L1 VG (LI -0.2) as opposed to left dominance for L2 (LI VF -0.53; VG -0.7).

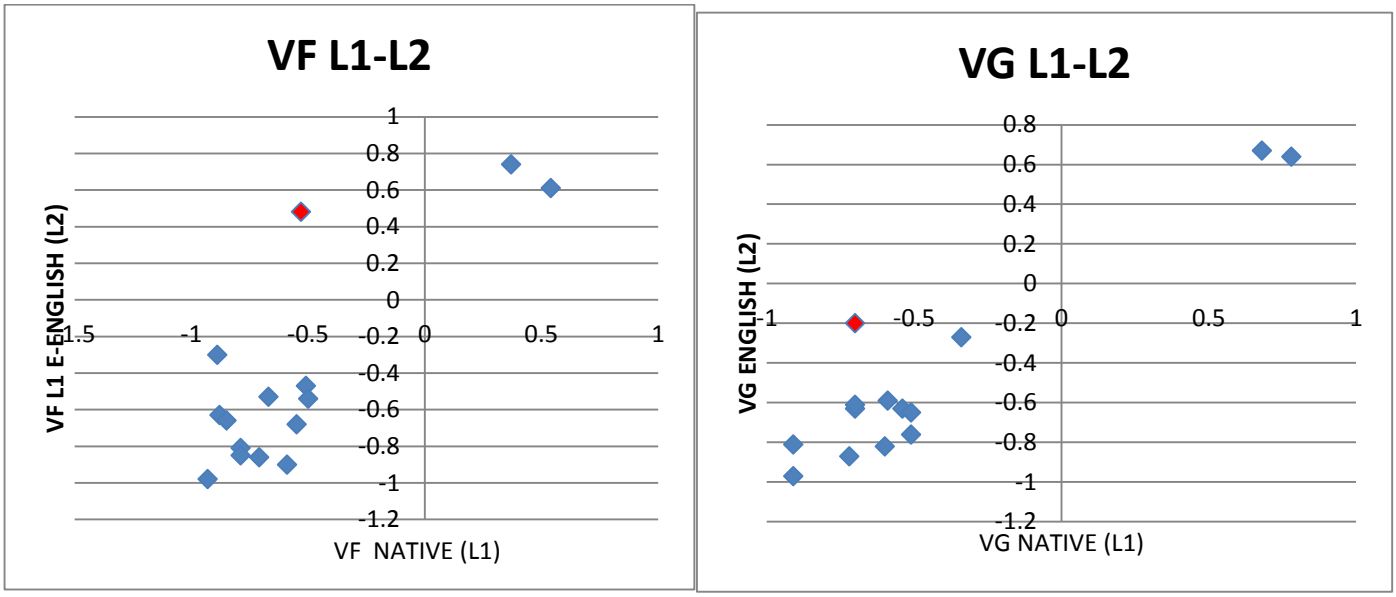

Figure 3-6. Correspondence between LIs in VF (Left) and VG (right) in L1 and L2 languages. *Vertical axes represent the values of L1 and horizontal axes represent the values of L2. Subject number 5 with discordant language representation is in red. LI values for L1 and L2 have high correspondence.*

3.2.2 Discussion

3.2.2.1 Common versus distinct language networks in bilinguals

Two psychological models at the language network level have been proposed to explain bilingualism: distinct networks versus a common network for the processing of different languages. Evidence in support of both models has been

reported previously in the literature. Single and small case series have described selective aphasias for one language after stroke (Green et al., 2010), epileptic seizures (Aladdin et al., 2008), or surgical resections (Gomez-Tortosa et al., 1995) as well as evidence from intraoperative language mapping suggesting the presence of distinct areas within the left hemisphere for L1 and L2 languages (Lucas et al., 2004, Cervenka et al., 2011). However, the majority of studies performed in bilingualism support the existence of a common network supporting the different languages, and explain the evidence of distinct networks in terms of modulation related to specific computational demands, which vary according to the age of acquisition, the degree of mastery, and the level of exposure to each language (Perani & Abutalebi, 2005). Variability in these factors may translate into differences observed in language maps obtained by fMRI.

Our results are in keeping with the assumption of a common network processing different languages in bilinguals. This is supported by the overlapping of the majority of clusters of activations (Figure 3-4) between the two languages. The difference in the extent of activations may reflect increased processing demands for L2 as opposed to distinct networks.

3.2.2.2 Group Effect of age of language acquisition

The main difference observed at the group level was more widespread activations related to language tasks when these are performed in English (L2) relative to the native language (L1). This finding has been reported previously and has been correlated with some factors such as the age of language acquisition (AOA) and the proficiency in L2. AOA is a relevant factor that accounts for a significant proportion of differences observed in the languages maps in bilinguals (Perani & Abutalebi, 2005). A late AOA is related to greater fMRI activations in the language networks compared to those subjects for whom L2 was acquired early in life. Proficiency in the secondary language has also been associated with differences in the extent and significance of activations defined by fMRI studies. Activations associated with the less proficient language in bilinguals are more significant and

widespread (Hasegawa et al., 2002, Perani & Abutalebi, 2005), and may involve additional areas such as the supplementary motor cortex during reading words (Meschyan & Hernandez, 2006). However, some studies have not found significant differences associated with low proficiency (Xue et al., 2004) suggesting that this may be a less significant contributory factor to the differences found between languages. These findings have been interpreted as signifying the requirement to a greater effort when using the less proficient language. Age of onset and proficiency may interact with other language characteristics.

In particular, grammatical processing has been shown to be specifically sensitive to the effect of age of acquisition, whereas semantic-lexical processes depend more on the level of proficiency (Wartenburger et al., 2003, Perani & Abutalebi, 2005). Our data, in accordance with those of previous studies, show that late AOA is associated with more widespread activations, in particular, in the right MFG, as compared to an early AOA (Figure 3-5). However, the large range of AOA in our sample may be a limitation for the interpretation of this effect.

3.2.2.3 Neurobiological significance

The mechanisms underlying atypical language dominance in epilepsy are not completely understood. Factors such as early epilepsy onset and the presence of a structural lesion have been correlated with atypical dominance (Moddel et al., 2009). Further investigation in larger patient samples is required to assess how representation of second (acquired) languages is affected by factors such as age of onset of the epilepsy, side of focus, and age of second language acquisition.

3.2.2.4 Clinical implications

The results of this study show that language dominance can be derived from fMRI in a second language for clinical purposes. Despite the differences in the extent of activations between L1 and L2 observed at group level, language lateralization is

not generally influenced by the use of different languages. Language dominance can be reliably inferred from one of the two languages in bilingual subjects.
LIs are commonly used in clinical settings to quantify language dominance. Language-dominance categorization is based on arbitrary limits to discriminate between categories, although LIs derived from fMRI are on a continuum (Berl et al., 2014). For a more accurate interpretation of language maps, visual inspection of language maps, as well as the use of more than one fMRI paradigm (Gaillard et al., 2004) is always advisable.

3.2.2.4.1 Case of discordance

Differences between first and second language mapping become relevant from the clinical point of view if L1 and L2 dominance differ within a subject. We found a case of discordance in a patient. The patient had bilateral hippocampal sclerosis with seizures arising from the right temporal lobe. Onset of seizures was at the age of two. The overall picture suggests that, in a patient with bilateral temporal lobe damage and an atypical language dominance of his native tongue, the less proficient language had a greater representation in the hemisphere contralateral to the seizure onset. This is an unusual case due to its complex underlying condition, but it emphasizes the fact that different languages can have different lateralization patterns in a small proportion of cases. Visual inspection of the languages maps showing an atypical distribution for L1 and left dominance for L2, in accordance with the LI, provides a more global vision of the distribution of activations.

Subjects with a greater likelihood of atypical language representation need more careful evaluation, using more than one language paradigm. Incorporating visual, as well as quantitative measures of laterality should be considered in these cases

3.2.2.5 Strengths and limitations

This study investigates for the first time the clinical validity of using language fMRI test in a second language for language lateralization in patients with epilepsy. There is a large number of studies investigating bilingualism using fMRI, however there is very little data in the comparability of different language mapping for clinical purposes. Furthermore we have shown this in a population with a greater rate of language atypical dominance such as patients with epilepsy. This study was timely in patients with epilepsy in whom language fMRI is frequently used and often acquired in a secondary language.

The evaluation of language proficiency of the participants was limited in this study. Scores of proficiency were self-reported by patients as high medium or low limiting the accuracy of this measure and therefore interpretation of the results. Further studies investigating deeper the effect of this factor should be performed.

3.3 STRUCTURAL CHANGES IN THE TEMPORAL LOBE AND PIRIFORM CORTEX IN FRONTAL LOBE EPILEPSY

The aim of this study was to investigate the presence of subtle structural abnormalities in patients with frontal lobe epilepsy. Additionally, we aimed to investigate the relationship between these abnormalities and the clinical factors. For this purpose, we use voxel-based morphometry that analyses the concentration of grey matter in a voxel-wise fashion.

3.3.1 Results

- Patients with FLE had bilateral, predominantly right-sided increases of grey matter volumes in the piriform cortex, amygdala and parahippocampal

gyrus as well as in the left mid temporal lobe gyrus when compared to controls (Figure 3-7).

- Changes in medial temporal lobes were similarly distributed in patients with left and right FLE.
- Regression analysis did not reveal any significant correlation of GMV changes with age at seizure onset, duration of epilepsy, or seizure frequency.

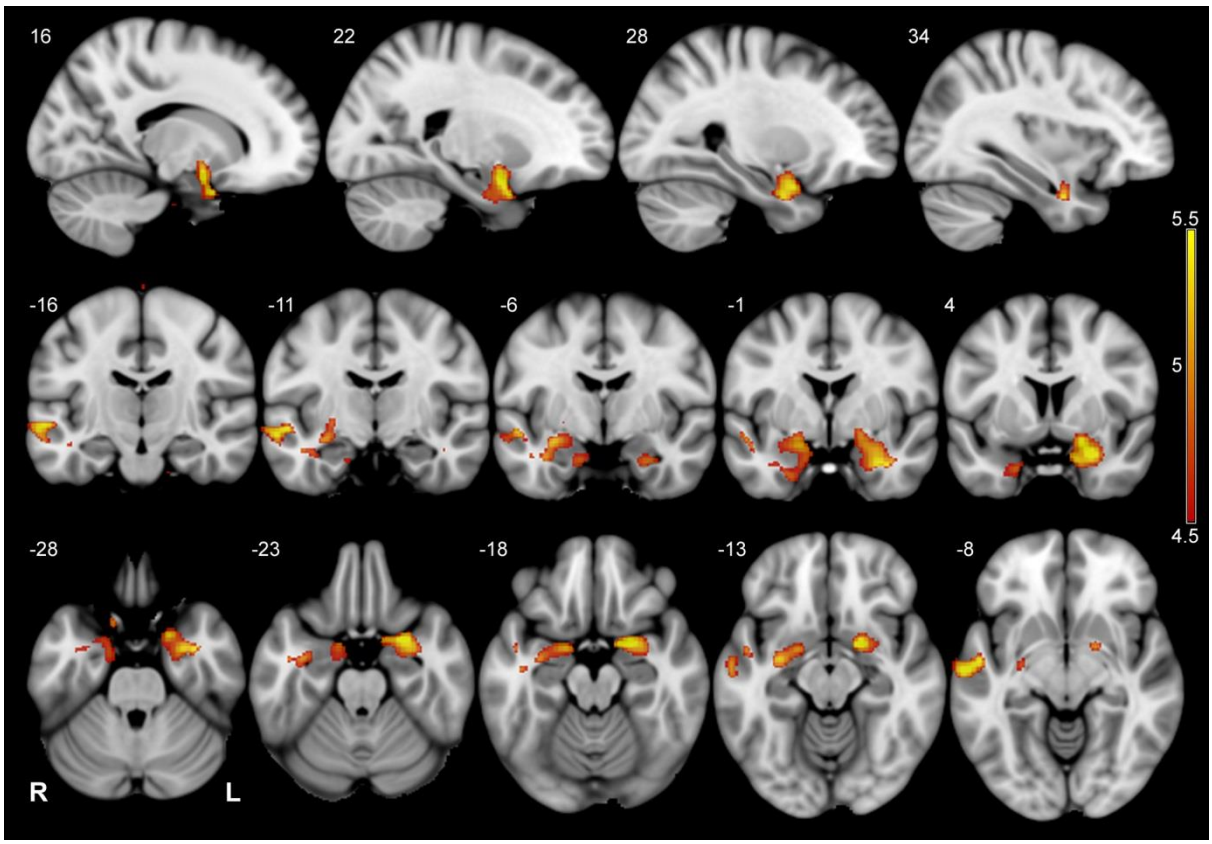

Figure 3-7. Grey matter abnormalities in patients with FLE. *Greater grey matter regional volumes in FLE patients in relation to controls are seen bilaterally in the piriform cortex and amygdala, and on the left mid temporal lobe gyrus. Statistic maps are overlaid on an average T1 MNI template. For display proposes, maps have been thresholded at p<0.005 (FDR corrected). Scale bar represent T values. Numbers indicate X, Z and Y-coordinates in MNI space.*

3.3.2 Discussion

We showed increases in grey matter volume in the anterior medial temporal lobe and orbitofrontal cortex, comprising piriform cortex (temporal and frontal portion), and amygdala and parahippocampal gyrus of patients with FLE, compared to controls. This suggests that there are common cerebral structural abnormalities in patients with FLE.

Previous studies have reported decreases and increases in GMV in the different epilepsy syndromes (Woermann et al., 1999, Keller et al., 2002, Bernasconi et al., 2004). While regions of GMV decrease are generally interpreted as atrophy, (Keller et al., 2002, Bernasconi et al., 2004), there is not a clear consensus about the meaning of areas of increased GMV. In patients with TLE, VBM studies have identified decreased GMV in the hippocampus and thalamus. Pathology studies have shown these regions experience cellular loss and it is suggested that this loss correlates with the generation and spread of epileptic activity (Bernasconi et al., 2004).

Areas of increased GMV indicate increase cellularity within that particular region. Anatomo-pathological studies have revealed the presence of mild abnormalities in the layering and cellularity of grey and white matter tissue of patients with epilepsy (Eriksson et al., 2005). Other authors have proposed that these areas of microscopic dysplastic changes may explain the increases of GMV detected in VBM studies (Woermann et al., 1999, Keller et al., 2002). However, further studies investigating the link between the VBM findings and the anatomo-pathological correlates are needed in order to understand the imaging results.

We did not detect common areas of atrophy, or decreased GMV in patients with FLE. Given the high variability of seizure focus location within the frontal lobes of patients with FLE, it is not surprising that no common area of atrophy related to seizure focus was identified in the way it is seen in TLE patients with hippocampal sclerosis (Keller et al., 2002, Bernasconi et al., 2004). However, other techniques such as analysis of cortical thickness (Widjaja et al., 2011) and measures of the whole frontal lobe volumes (Lawson et al., 2002) have found areas of atrophy in the frontal lobes of paediatric patients with FLE. This may indicate a more

widespread effect of FLE on the developing paediatric brain as compared to the adult brain, resulting in measureable common volume reductions.

3.3.2.1 Neurobiological significance

From animal models we have learned that the piriform cortex and amygdalar nuclei play a crucial role in the generation, spread and maintenance of seizures (Piredda & Gale, 1985, Loscher & Ebert, 1996, Vaughan & Jackson, 2014) . The piriform-amygdalar complex forms a functional unit that processes smell-related stimuli and shares a common layering organisation as the limbic system (Gottfried et al., 2002).

This is an area that is highly epileptogenic in animals; when chemical and electrical stimulation are delivered to the piriform cortex, it responds by acting as a seizure generator and plays the role of an amplifier of epileptic activity when seizures are generated elsewhere (Piredda & Gale, 1985, Loscher & Ebert, 1996, Vaughan & Jackson, 2014).

Epileptic activity and in particular status epilepticus induce changes in piriform cortex, amygdala and adjacent structures that change over time; these can be detected using MRI (Choy et al., 2010, Kim et al., 2010b). These changes in animals have been proven to be mainly inflammatory responses such as astrogliosis (Loscher & Ebert, 1996).

More recent human studies using functional imaging have found evidence for the involvement of the piriform cortex in the epileptogenic network in patients with focal epilepsies of different locations (Laufs et al., 2011). The piriform cortex and in particular the frontal sub regions are activated during interictal epileptic activity, regardless of the location of seizure focuses. Additionally, [^{11}C]-flumazenil PET analysis found a decreased benzodiazepine-GABAA receptor density correlating with seizure frequency in the same area. Independent studies have corroborated this finding using EEG-fMRI (Fahoum et al., 2012) and Flanagan (Flanagan et al., 2014) found that the piriform cortex ipsilateral at the side of seizure onset was

active during interictal discharges in patients with TLE and also for those with extra temporal lobe foci.

Our study adds further evidence to the involvement of the piriform cortex and adjacent structures in the epileptogenic circuit in focal epilepsies.

3.3.2.2 Clinical implications

The identification of common structures involved in the epileptic activity of patients with frontal lobe epilepsy adds relevant information towards the characterization of the epileptogenic network. The findings of this and previous studies point towards the piriform cortex playing a relevant role in the epileptic network and aim to investigate further its function in human epilepsy. This may open the doors to it being considered as a prospective target for stimulation in the treatment of epilepsy.

3.3.2.3 Strengths and limitations

This is the first study to apply VBM techniques in FLE to the investigation of structural abnormalities in this group. The size of the group and the chosen threshold of significance (FWE corrected) chosen for the study make the finding a robust result.

The main limitation of the study regards the interpretation of the areas of increased GMV. Structural changes of diverse aetiology can lead to differences in the segmentation and quantification of MRI signal in a cortical area without necessarily signifying an increase in GM. The lack of anatomo-pathological correlates to these findings limits the interpretation of these results.

3.3.2.4 Future perspectives

New acquisition MRI techniques that allow the investigation of different brain tissue properties in a quantitative fashion should the next step in order to further investigate the aetiology of the findings identified in this study.

4 CONCLUSIONS

The main conclusions derived from each of the study are summarized below.

4.1 MEMORY DYSFUNCTION IN FRONTAL LOBE EPILEPSY

4.1.1 Memory encoding dysfunction in patients with frontal lobe epilepsy is not an uncommon phenomenon. Significant impairment is observed in about a quarter of patients.

4.1.2 This dysfunction is in turn associated with dysfunction of hippocampal-amygdala areas without changes in the volumes of these structures suggesting epilepsy activity involving these areas probably by propagation.

4.1.3 Recruitment of wider areas, particularly in the contralateral frontal lobe, appears to be an effective compensatory mechanism to maintain memory function in this group of patients.

4.2 STRUCTURAL CHANGES IN THE TEMPORAL LOBE AND PIRIFORM CORTEX IN FRONTAL LOBE EPILEPSY

4.2.1 Patients with frontal lobe epilepsy have common structural abnormalities in the grey matter in patients with normal structural MRI.

4.2.2 Areas of abnormality are located in piriform cortex and amygdala bilaterally as well as in temporal lateral cortex. These changes are independent of the side of the epileptic focus, disease duration or age of onset. These areas may represent major hubs in the epileptogenic networks in frontal lobe epilepsy.

4.2.3 This study adds further evidence for the involvement of the piriform cortex and adjacent structures in the epileptogenic circuit of focal epilepsies.

4.3 LANGUAGE DOMINANCE ASSESSMENT IN A BILINGUAL POPULATION: VALIDITY OF FMRI IN THE SECOND LANGUAGE.

4.3.1 Language lateralization can generally be reliably derived from language fMRI tasks in a second language provided that the subject can follow the task.

4.3.2 Subjects with a greater likelihood of atypical language representation need more careful evaluation, using more than one language paradigm. Incorporating visual, as well as quantitative measures of laterality may be considered in these cases.

5 ANNEX 1

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REVIEW

Memory in frontal lobe epilepsy

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KEYWORDS
Frontal lobe epilepsy;
Memory;
Cognition;
Functional neuroimaging

Summary In contrast to the well studied long-term memory dysfunction of temporal lobe epilepsy (TLE) syndromes, data on memory performance of frontal lobe epilepsy (FLE) patients are limited and controversial. Behavioural and functional neuroimaging findings suggest that different regions within the frontal lobes contribute to long-term memory functioning, offering an explanation for the variability on memory function observed on patients with frontal lobe damage. Available evidence suggests memory dysfunction is a common finding on neuropsychological evaluation of FLE patients but prevalence and underlying mechanisms remain poorly understood. Variability on memory performance reported in FLE studies suggest this deficit may be dependant on the areas involved in seizure generation and spread. Recent research findings and the application of cognitive fMRI paradigms to FLE patients holds the promise of increasing understanding further.

Contents

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Introduction

Memory deficits are commonly reported by individuals with epilepsy, particularly by those with temporal lobe epilepsy (TLE). Whether frontal lobe epilepsy (FLE) is associated with specific memory deficits is the subject of current debate.

It is accepted that the frontal lobes play a crucial role in memory, but contrary to the traditional view, this is not limited to working memory; neuronal networks involving frontal regions contribute to longer term memories and damage to the frontal lobes can cause a range of more subtle memory impairments, although frontal lobe damage does not lead to a severe amnesic syndrome as is the case for medial temporal lobe structures.

Here, we review the current evidence for the role of the frontal lobes in memory systems and evidence for memory dysfunction in FLE.

For this purpose we searched PubMed for original and review articles in English Spanish and German languages in the period 1980—2010 using the keywords frontal; epilep* and memory. We also followed up relevant citations in these papers.

Memory and the frontal lobes

The role of medial temporal lobe structures in the memory process is well established, damage to these areas disrupts memory formation by preventing the construction of a novel memory. In contrast, frontal lobe injury does not result in a classic amnesic syndrome, instead some more subtle but well documented memory impairments have observed in these cases (Hirst and Volpe, 1988; Wheeler et al., 1995; Ward, 2003; Turner et al., 2007). Due to the functional complexity of the frontal lobes, however, their role in memory processes is still poorly understood.

Research from human brain functional neuroimaging and animal behaviour provides strong evidence for a relevant role of the frontal lobes in long-term memory. On the other hand, studies carried out in patients with frontal lobe damage do not always support these findings, and there are some discrepancies among studies.

In general, the role of the frontal lobes in the memory process can be defined as a strategic action, whereas the medial temporal structures play an associative role in memory formation. In other words the frontal lobes exercise control of memory by coordinating, elaborating and interpreting the associations that take place in the medial temporal lobe (Stuss and Levine, 2002).

Before considering research on memory function in FLE we review the evidence of frontal lobe involvement in the formation and retrieval of long-term memories. The frontal lobes are thought to be involved not in one but in several of the processes that contribute to long-term memory.

Encoding

The manipulation of to be remembered material by making associations or by taking semantic decisions has been demonstrated to promote deeper levels of encoding, and to result in better memory performance (Craik et al., 1996). This ability to form and retrieve memories containing relationships between elements and the context in which those elements occurred has been defined as the relational memory. The application of relational memory processes is likely to be mediated by fronto-temporal networks. Neuroimaging studies with fMRI (Wagner et al., 2001; Prince et al., 2005) and PET (Fletcher et al., 1998) provide evidence of activation of frontal brain areas associated with the organization of material during encoding.

Some studies have suggested a lateralized specialization of the frontal cortex related to encoding tasks showing the left prefrontal cortex (PFC) is predominantly involved (Shallice et al., 1994; Fletcher et al., 1998; Habib et al., 2003). Activation of the left lateral PFC is a predictor of successful encoding as measured by event-related fMRI experiments (Wagner et al., 1998; Garoff et al., 2005; Dickerson et al., 2007) and PET studies (Fletcher et al., 1998). Networks involved during encoding processes include the inferior frontal gyrus and the medial temporal lobe. Connectivity within these areas has been found to vary accordingly to the success in encoding showing greater activations and coordination when items are successfully encoded (Dickerson et al., 2007). Within the lateral PFC the ventral area is most frequently reported as being involved in the encoding process (Blumenfeld and Ranganath, 2007).

In addition to task-related lateralization for encoding, there is also evidence for material-specific lateralization within the frontal lobes during the encoding process. fMRI studies have shown left-lateralized activation of Ventral PFC during the encoding of verbalizable material, in contrast to a right-lateralized activation of the same area for visual, stimuli that are less verbalizable (Wagner et al., 1998; Golby et al., 2001).

Retrieval

Functional neuroimaging studies have shown that lateral PFC activation is a consistent finding during memory retrieval tasks with the majority of studies reporting right-lateralized involvement of the PFC (Fletcher et al., 1998; Rugg et al., 1998, 1999). These findings have lead to neuropsychological theories that attribute to the right frontal lobe the role of integrating retrieved material into an episodic representation, and the monitoring of the relevance of retrieved information according to the task-related goal (Fletcher et al., 1996; Rugg et al., 1996; Cabeza et al., 2003). Detection of errors is among the monitoring tasks that frontal lobes exercise during material retrieval. Studies show a characteristic increase of false recognitions in the performance of patients with frontal lobe damage.

Paramnestic disorders described in psychiatric and lesional patients have also been explained in terms of faulty monitoring. The misidentification and delusional syndromes have as the main characteristic the incorrect identification (of the physical or psychical identity) of familiar persons, places or the patient themselves. The underlying problem seems to be an inability to correlate a specific sensory stimulus (image, sound) to previous memories and the inability to integrate the sensation of familiarity to these memories. Capgras syndrome is characterized by the misidentification of familiar persons as impostors or doubles with different psychic identity, that have adopted their relative's physical appearance. The same phenomenon can occur with regard to places, causing reduplicative paramnesia: the patient thinks a familiar place is a duplicate of the real place in a different location. Patients with delusions often have lesions in the right hemisphere and/or bifrontal areas (Devinsky, 2009). Capgras syndrome and reduplicative paramnesia in patients with unilateral lesions strongly implicate the right frontal lobe. For a successful retrieval process memories need to be placed into a coherent context. Cognitive processes of monitoring reality, familiarity and context retrieval seem to be mediated by the right PFC.

Prospective memory

Prospective memory (PM) was first defined by Ingvar (1985). PM allows us to imagine and simulate forthcoming events. The term has been also used to define our ability to remember to do things in the future, in other words, the process by which we ''remember to remember''. The integration of external clues that triggers the retrieval of these memories is very likely to be mediated by the frontal lobes.

Impaired PM was first described in amnesic patients with bilateral hippocampal damage and in those with Korsakov's Syndrome. When patients were asked to imagine possible scenarios their attempts were significantly impoverished in terms of richness and spatio-temporal coherence compared to controls. Their scenarios tended to consist of isolated fragments of information rather than connected scenes (Hassabis et al., 2007). More recently medial temporal and frontal lobe structures have been implicated as part of the network underlying this process. Depressed and schizophrenic patients have been found to have dissociations between retrospective and prospective memory, with a disproportionate difficulty imagining future situations rather than remembering past events. For schizophrenic patients this difficulty correlates with the presence of positive symptoms (D'Argembeau et al., 2008). Furthermore, structural abnormalities disrupting fronto-temporal connections have been correlated to positive symptoms in schizophrenia. This raises the possibility that disrupted fronto-temporal connections form the basis of impaired PM in this patient group.

It has been postulated that prospective memory depends on shared networks that code and retrieve retrospective memories requiring a system that flexibly recombines characteristics of past events. Neuroimaging experiments provide some insight into the identification of the networks involved in remembering the past, and imagining the future. The networks involved in these tasks overlap considerably and include both areas of prefrontal cortex and medial temporal lobe structures (Szpunar et al., 2007).

PM has been observed to decline with age. There is some evidence this occurs only when there is age-dependant impairment of frontal lobe functions, and PM has been shown to remain intact in those elderly adults with preserved frontal lobe functions (McFarland and Glisky, 2009).

Sequential memory

Sequential memory is the capacity to chronologically organize memories. Developmental neuropsychological theories indicate the frontal lobes are regulators of this process. Sequential memory develops in parallel with the maturation of frontal lobe functioning during childhood and adolescence (Romine and Reynolds, 2004). Clinical studies have found the functioning of this memory to be altered in patients with frontal lobe damage: patients can perform normally on memory tests compared to amnesic patients with damage to the diencephalic structures, but fail specifically in attributing a temporal order to acquired memories (Shimamura et al., 1990).

A degree of lateralization for sequential memory has been reported in lesional studies: patients with right and bilateral pre frontal damage perform less well than those with left prefrontal damage when chronological organization of memories was specifically tested (Kesner et al., 1994).

Contextual (source) memory

Episodic memory is composed of memory of the event and memory of the temporo-spatial context in which the memory occurred. Memory loss for context has been reported in relation to dysfunction of the PFC and that this can arise in the presence of preserved episodic fact memory (Dywan and Jacoby, 1990; Dywan et al., 1993). It has been hypothesised that the frontal lobes process retrieved information and place it in an adequate context. Damage to the frontal lobes results in faulty connections that can disrupt contextual memory retrieval (Janowsky et al., 1989). Some

argue that the attentional deficit caused by frontal lobe damage is responsible for this form of memory loss as the result of a poor contextual encoding (Dywan and Jacoby, 1990).

In an fMRI study, Rugg et al. (1999) showed the involvement of the left lateral PFC when the task required retrieval of contextual information in addition to factual details of the event. The recording of event-related potentials associated to context retrieval on the prefrontal cortex have complemented fMRI findings (Vallesi and Shallice, 2006). Converging evidence is indicating a crucial role of the frontal lobes in remembering the context.

Frontal lobe damage and memory

Classical studies of frontal lobe damage did not emphasize memory impairment as part of the syndrome. Indeed, patients with frontal lobe damage were reported to perform normally on routine memory tests such as item recognition (Janowsky et al., 1989; Kesner et al., 1994).

There are several reasons that may be considered for understanding the failure of earlier neuropsychological cognitive studies to identify memory problems in association with frontal lobe damage.

Firstly, the neuropsychological tests employed may not have been sensitive enough to detect deficits of the specific memory processes carried out by the frontal lobes. The majority of tests employed have focused on episodic memory assessing mainly ''what'' is remembered instead of ''how'' things are remembered. Patients with frontal lobe damage often perform well on simple recognition tests but fail on tests that require the use of tactical aspects of memory. Studies that have focused on testing strategic processes have found impairments on this population. Memory deficits found in lesional frontal lobe patients include a wide range of dysfunction involving processes such memory of the source (Dywan et al., 1993), memory for temporal order (Romine and Reynolds, 2004), estimation of frequency occurrence of the encoded material (Milner et al., 1985; Jurado et al., 2001), associative recall strategies (Incisa della Rocchetta and Milner, 1993), cued recall (Bastin et al., 2006) and prospective memory (McFarland and Glisky, 2009). These deficits are frequently accompanied by confabulation and reduplication (Ruff and Volpe, 1981; Turner et al., 2008).

Secondly, the majority of patients assessed have unilateral lesions, but frontal lobe involvement in memory seems to be mediated by bilateral networks, thus function may be maintained when lesions are circumscribed to one hemisphere.

Thirdly, patients with specific language processing difficulties are likely to have been excluded from studies due to anticipated problems complying with task demands; understanding or executing the necessary verbal responses. Patients with damage to the left lateral PFC, an area of particular interest during encoding may present with significant language problems. Such exclusions will introduce a bias towards participants with better memory functions. In support of this, Riege et al. (1980) and Whitehouse (1981) noted aphasic patients with damage to the language cortex had impaired performance on a recognition memory test for verbal material whereas patients with damage to a homologous area in the non-dominant hemisphere were impaired on recognition test for non-verbal material. Stuss et al. (1994) also found the greater impairment on verbal learning tasks within the lesional subjects with language processing deficits. Exclusion of dysphasic patients from studies has probably also resulted in an underestimate of the prevalence of memory deficits in patients with frontal lobe damage.

Most clinical studies have considered damage to the frontal lobe as a single entity. More recent studies have characterized damage within the frontal cortex by attempting to correlate patterns of memory deficits with the location of the lesion. Different memory functions would be expected to be impaired with lesions in different locations. In support of this, Turner et al. (2007) addressed the effect of lesion location within the prefrontal cortex on encoding, retrieval and retrieval monitoring. Left lateral and orbital subgroups did not show an impairment of these processes compared to controls. The right lateral frontal subgroup showed impairment on recall tasks but with improved performance following the manipulation of retrieval, indicating a strategic retrieval deficit. The medial frontal subgroup also showed impaired recall but this was not modified by encoding and retrieval manipulations, indicating memory deficits arising from disruption of the limbo-thalamic system and similar to the pattern observed on mesial temporal lobe damage. The left lateral group did not show recall impairments. Previous studies with less precise topographical localization of lesions have found different results. In the studies by Alexander et al. (2003) and Stuss et al. (1994) the left prefrontal group was the most impaired on recall tasks. These divergent results may be explained on the basis of lesion extension and the language areas involved. For the three studies, no significant memory deficits were found in patients with spared language processing, those subjects correspond to the group with damage to the more ventral portions of LPFC. The majority of the patients on left LPFC group in Turner's study had lesions in areas located more ventrally in the left frontal lobe.

Frontal lobe epilepsy and memory

Numerous studies have assessed the cognitive features of TLE populations, in contrast only a few studies have systematically evaluated cognition of FLE patients. The majority of studies have focused attention on executive skills rather than memory function (Helmstaedter et al., 1996; Upton and Thompson, 1996) and have provided support for impaired executive functions. Memory function has generally been neglected and therefore knowledge regarding this cognitive aspect in frontal lobe epilepsy is limited.

Surgical FLE

Early evidence of memory impairment in frontal lobe epilepsy comes from post-surgical case series. Studies published by the Montreal Neurological Institute group identified memory deficits in patients following frontal lobe resections. Table 1 summarizes main findings from these studies. For some memory deficits there was an overlap with findings from patients undergoing TLE surgery whose hippocampal

Table 1 Memory studies on post-surgical FLE patients.

Study	Memory function evaluated	Groups (*n*)	Findings FLE	Findings TLE	Comments
Smith and Milner (1988)	Estimation of frequency of occurrence of abstract designs	FLE 23 (15R/8L) TLE 47 (29R/18L) CTR 22	Impairment on R—L-FLE	No impairment	FLE normal design recognition rate R-FLE impaired design recognition
McAndrews and Milner (1991)	Temporal order of presented verbal items	FLE 16 (8R/8L) TLE 36 (18R/18L) CTR 20	Impairment R—L-FLE	No impairment	FLE improve memory for temporal order by using multimodal cues
Leonard and Milner (1991)	Kinaesthetic memory: (peripherical feedback dependant) 1. Encoding 2. Retrieval immediate/delayed	FLE 26 (18R/8R) TLE 36 (20R/16L) CTR 16	Impairment R-FLE (large resections): 1. Encoding 2. Delayed retrieval	No impairment	In a similar study where encoding of kinaesthetic information was not dependant on peripherical feedback, both Right FLE and TLE were impaired
Incisa della Rocchetta and Milner (1993)	Verbal memory: 1. Free recall 2. Cue utilization 3. Interference inhibition	FLE 20 (8R/12L) TLE 51 (25R/26L) CTR 12	Impairment L-FLE: 1. Free recall 2. Cue utilization 3. Interference inhibition	L-TLE (large hippocampal excision): 1. Free recall	
Petrides (1985)	Associative learning: 1. Arbitrary spatial pairs 2. Arbitrary non-spatial pairs	FLE 29 (14R/15L) TLE 55 (26R/29L) CTR 20	Impairment R—L-FLE	R-TLE (large hippocampal excision): 1. Spatial pairs L-TLE (large hippocampal excision): 1. Non-spatial pairs	
Smith and Milner (1984)	Visual memory: 1. Location recall immediate/delayed 2. Scene recall	FLE 20 (13R/7L) TLE 34 (17R/17L) CTR 17	No impairment	R-TLE (large hippocampal excision): 1. Location recall immediate/delayed 2. Scene recall delayed	
Pigott and Milner (1993)	Visual memory: 1. Figurative detail 2. Spatial composition	FLE 12 (7R/5L) TLE 53 (25R/28L) CTR 15	No impairment	R-TLE (large hippocampal excision): 1. Recall of figurative details 2. Spatial composition	

TLE: temporal lobe epilepsy patients after surgical resection; FLE: frontal lobe epilepsy patients after surgical resection; CTR: healthy controls; L: left; R: right.

excisions were extensive. Petrides (1985) reported impairment in post-surgical FLE patients on learning arbitrary associations of spatial and non-spatial content, irrespective of the side of surgery, the same problem was also observed in TLE patients but with a material-specific pattern dependant on the side of surgery. Incisa della Rocchetta and Milner (1993) found left FLE and TLE patients were both impaired on free verbal recall but probably due to different underlying mechanisms. The performance of FLE patients improved when encoding and retrieval strategies were supplied, an effect not observed in TLE patients. They proposed that the FLE group's poor performance was the result of the absence of retrieval strategies and the incapacity to suppress interfering stimuli.

Other memory deficits have been found to be specific to post-operative FLE patients including skills such as the estimation of frequency occurrence (Smith and Milner, 1988), the ability to suppress interference during encoding (Incisa della Rocchetta and Milner, 1993), memorizing the temporal order of named items (McAndrews and Milner, 1991) and learning and retrieving kinaesthetic information (Leonard and Milner, 1991). These difficulties in FLE post-surgical patients were independent of the side of the surgery, with the exception of the memory for kinaesthetic information that was clearly associated with right FLE excisions. Other aspects of memory have been assessed to be intact in post-surgical FLE patients, including long-term memory for complex visual stimuli, location recall and recognition of designs (Smith and Milner, 1984, 1988; Pigott and Milner, 1993).

Non-surgical FLE

Non-surgical FLE studies have provided some evidence of memory dysfunction. The number of investigations is small and the results divergent, such that the prevalence and severity of memory problems in FLE patients remains uncertain. These studies are summarized in Table 2.

Delaney et al. (1980) published one of the first studies evaluating memory performance in non-surgical FLE cases. A group of fifteen FLE, thirty TLE and fifteen healthy controls were assessed using two verbal and two non-verbal recall tasks. The Logical Memory and Visual Reproduction tests were taken from the Wechsler Memory Scale and word and visual learning tasks were also administered. The memory performance of the FLE group was comparable to the control group and significantly better than the TLE group.

In contrast, Exner et al. (2002) found memory impairments in FLE. Sixteen FLE (seven of whom were reported to have an structural brain lesion identifiable on MRI) sixteen TLE and ten controls were assessed on eight subtests from the Wechsler Memory Scale and two additional memory tests for associative learning and learning of emotional expressions. The FLE and TLE groups performed significantly worse than the controls on five of the WMS tests including Digit Span forward and backwards, immediate and delayed verbal recall and delayed visual reproduction and the associative learning tasks. Administered tests did not discriminate between the frontal lobe and temporal lobe groups and the authors proposed the use of more specialized cognitive measures in order to elicit differences. The authors performed a comparison between FLE patients and a group of post-surgical cases with frontal lobe tumours and concluded the FLE patients performed similarly to the post-surgical patients on memory measures.

These two studies used a similar approach and neuropsychological measures but there were some differences in the groups' IQ. In Exner's study both TLE and FLE patients had IQ scores significantly lower than controls whereas no IQ difference existed in the Delaney study. Although this difference may account for the divergent results, it does not explain adequately the absence of memory dysfunction found on one of them. Discrepant findings are more likely to be due to the greater heterogeneity of memory functions of the FLE group, possibly dependant on the location and area of spread of epileptic activity within the frontal lobe.

Using a different methodology, memory dysfunction in FLE has been highlighted in a recent study by Cahn-Weiner et al. (2009). They investigated the impact of memory dysfunction on the daily life of TLE and FLE group using five subtests of daily living from a neuropsychological assessment battery. They hypothesised that TLE patients would demonstrate relatively more impairment on a test of everyday memory than FLE patients. Contrary to the initial prediction, they found both groups scored in the impaired range for daily life memory measurements with no significant differences between groups.

Additional evidence of memory dysfunction in FLE syndromes has been reported in children. Nolan et al. (2004) compared the performance on memory tasks, five verbal and six non-verbal, of a group of seventy children with TLE, FLE and childhood absence epilepsy. Memory deficits were recorded in all three groups but to a different degree. Children with TLE were significantly impaired on all memory subtests. FLE children were impaired for two verbal (story recall delayed and sentence memory) and two non-verbal subtests (visual learning and finger windows). Absolute scores positioned the performance of FLE between CAE and TLE. Riva et al. (2002) studied the cognitive profile of eight children with FLE and found left FLE patients were impaired for delayed free recall on a verbal learning task. Again a common finding from children studies is the heterogeneity of memory functions of FLE in contrast to TLE patients. These findings suggest that memory dysfunction in frontal lobe epilepsy may vary depending on the localization of the seizure focus and/or the spread of seizure activity.

A few studies have reported memory disturbance in genetically characterized frontal lobe epilepsy syndromes. Recent studies have reported moderate to severe memory disturbances. Picard et al. (2009) studied executive and memory functions on eleven genetically confirmed ADNFLE patients. They found that memory performance was below average for ten out of the eleven cases, and surprisingly memory deficit was more prevalent than the dysexecutive syndrome. Smaller studies on family cases have also reported memory functions to be impaired more than executive functions (Bertrand et al., 2005; Cho et al., 2008).

Finally we present data on the memory performance of two large FLE cohorts from two major epilepsy centres in Europe. This data has been revisited due to the shortage of large population studies in the literature, and it provides valuable information regarding the scope of memory dysfunction in FLE.

Table 2 Memory studies on non-surgical FLE.

Study	Group (*n*)	Analysis	IQ	Memory tests	FLE findings	TLE findings	Comments
Adult FLE studies							
Delaney et al. (1980)	15 FLE 30 TLE 15 CTR	Comparisons: FLE/TLE vs CTR	Normal IQ	*Verbal*: 1. Logical memory (WMS) 2. Word List learning *Visual*: 1. Visual reproduction (WMS) 2. Recurring figures	*Verbal*: No impairment *Visual*: No impairment	*Verbal*: Left TLE 1. Logical memory immediate/retention 2. Free recall of word list *Visual*: Right TLE 1. Visual reproduction figural percentage retained 2. Recurring figures	
Exner et al. (2002)	16 FLE 16 TLE 10 CTR 5 TUM	Comparisons: FLE/TLE vs CTR FLE vs TUM	FLE IQ mean 81 (SD16) TLE IQ mean 81 (SD14)	*Verbal*: 1. Logical memory immediate/delayed (WMS-R) *Visual*: 1. Visual reproduction immediate/delayed (WMS-R) 2. Associative learning of facial identities 3. Associative learning of emotional expressions	*Verbal*: 1. Logical memory immediate/delayed *Visual*: 1. Delayed visual reproduction 2. Associative identity learning 3. Associative emotional learning	*Verbal*: 1. Logical memory immediate/delayed *Visual*: 1. Delayed visual reproduction 2. Associative emotional learning	• FLE patients compared to patients with frontal lobe resections have same pattern of memory impairment
Children FLE studies							
Nolan et al. (2004)	25 FLE 32 TLE 13 CAE	Comparisons: FLE/TLE/CAE vs ND FLE vs TLE vs CAE	No IQ differences within groups	*Verbal*: 1. Verbal learning (WRAML) 2. Verbal retention (WRAML) 3. Story recall immediate/delayed (WRAML) 4. Sentence memory (WRAML) *Visual*: 1. Visual learning (WRAML) 2. Visual retention (WRAML) 3. Picture memory (WRAML) 4. Design memory (WRAML) 5. Finguer windows (WRAML) 6. Rey complex figure	*Verbal*: 1. Delayed history recall 2. Sentence memory *Visual*: 1. Visual learning 2. Finguer window	*Verbal*: 1. Verbal learning 2. Verbal retention 3. Story recall immediate/delayed 4. Sentence memory *Visual*: 1. Visual learning 2. Visual retention 3. Design memory 4. Finguer windows 5. Rey complex figure	• Group comparisons showed FLE tended to function at a level between children with CAE (similar to normative mean) and TLE (function lower than normative data for all subtests)
Riva et al. (2002)	8 FLE	Comparisons: FLE vs ND	Normal IQ 7/8 patients	*Verbal*: 1. Californian verbal learning test immediate/delayed	*Verbal*: 1. Left FLE delayed free recall		• Seizure frequency and epilepsy duration correlated with attention deficit and inability to inhibit impulses
Nocturnal FLE studies							
Picard et al. (2009)	11 ADNFLE	Comparisons: FLE vs ND	IQ below normal on 5/11 patients	*Verbal*: 1. Rey auditory-verbal learning Test delay recall/recognition *Visual*: 1. Rey's visual design test delay recall/recognition	*Verbal*: 1. Rey auditory-verbal learning Test delay recall/recognition *Visual*: 1. Rey's visual design test delay recall/recognition		• 91% of patients showed a memory deficit in at least one measure • 36% memory impairment was more severe than executive impairment • 27% memory and executive functions were equally impaired • a4-S248F mutation associated to increased probability of memory and executive dysfunction
Cho et al. (2008)	2 ADNFLE	Comparisons: FLE vs ND	Normal	*Verbal*: 1. Verbal memory subtest K-MAS *Visual*: 1. Visual memory subtest K-MAS	*Verbal*: 1. Verbal memory subtest K-MAS. Moderate in one subject/severe one subject *Visual*: 1. Visual memory subtest K-MAS. Moderate in one subject/severe in one subject		• Working memory preserved

FLE: frontal lobe epilepsy; TLE: temporal lobe epilepsy; CTR: controls; TUM: surgical excision of frontal lobe tumours; CAE: childhood absence epilepsy; ADNFLE: autosomal dominant nocturnal frontal lobe epilepsy; ND: normative data; WRAML: wide range assessment of memory and learning tool; K-MAS Korean version of memory assessment scales; IQ: intelligence quotient.

Upton and Thompson (1996) studied seventy-four FLE patients and fifty-seven TLE patients. The study assessed several cognitive domains but the published data did not focus on memory. Memory was assessed using three verbal and two visual tasks. Verbal memory tests included word list learning, story recall and verbal recognition, and visual tests included design learning and a visual recognition task. The FLE group was impaired on all tests compared to normative data but there was a significant difference between the TLE and FLE patients only on the word recognition test, performance being poorer for the TLE group.

The second dataset comes from the University Clinic for Epilepsy in Bonn (Helmstaedter et al., 2007; Helmstaedter, 2010). A group of 119 FLE patients, 398 patients with medial TLE and 334 neocortical TLE patients were assessed on two memory measures, a verbal learning test and a figural design test. Although the memory performance of each group was impaired compared to normative data the authors found significant differences in the degree of impairment. Medial TLE patients performed significantly poorer than FLE and neocortical TLE patients.

Verbal learning and memory functions were tested with the German version of Rey auditory-verbal learning test (VLMT). A detailed analysis of the groups' performance on the VLMT provided relevant insights on the different mechanisms that may underlie memory dysfunction of temporal and frontal lobes epilepsies. In contrast to the material specificity that characterizes medial TLE memory impairment, FLE patients showed similar impairment for the verbal learning task regardless the laterality of epileptic focus. Performance across different sections of the task differs between FLE and TLE. Left medial TLE showed a greater impairment on the delayed recall and recognition sections compared to both groups of FLE. These differences suggest FLE memory problems may be predominantly secondary to faulty retrieval and accessing to information rather than a dysfunctional encoding. Performance of AVLT was correlated to attention and receptive language functioning. The strength of this correlation was greater for FLE patients than in those with medial TLE. Attention and language functions must be taken into account when interpreting memory results, especially in FLE patients.

Conclusions

The available evidence indicates the frontal lobes are vital structures underpinning efficient memory and in particular influence how well material is encoded and retrieved. Cognitive fMRI and lesional studies reveal different patterns of memory performance that seem to depend on different regions within the frontal lobes and these have contributed to the definition of specific characteristics of frontal lobe memory impairment. Research involving FLE syndromes are few but indicate memory difficulties, although much variability exists. Questions regarding the nature of memory problems, the prevalence and the underlying neuronal mechanisms remain largely unanswered. The application of cognitive fMRI paradigms to FLE patients holds the promise of increasing our understanding further.

Conflicts of interest

The authors report no conflicts of interest.

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