NEUROSURGERY FOR TEMPORAL LOBE EPILEPSY: PSYCHIATRIC OUTCOME AND RELATIONSHIP TO COGNITIVE FUNCTION

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ABSTRACT

Temporal lobe epilepsy (TLE) is a chronic neurological disorder characterised by recurrent seizures arising from temporal lobe structures. Medical treatment is effective for the majority but for the remainder, seizure control remains difficult to achieve. Epilepsy surgery, however, has proved an effective treatment. Following TLE surgery psychiatric symptoms can develop for the first time (de novo), and pre-existing symptoms may worsen; having a detrimental impact on patients' quality of life. Yet, research data on psychiatric complications following TLE surgery is limited, in sharp contrast to the continuing emphasis on neuropsychological and neurological sequelae. The central aims of this thesis were to increase our understanding of the psychiatric status of patients with intractable TLE pre- and postoperatively, and to identify risk factors associated with poorer postoperative outcomes.

This thesis is divided into 2 main sections. Section 1 (Chapters 1-5) provide a literature review that demonstrates pre- and postoperative psychopathology in TLE is common, unrecognised, and under-treated. Emerging evidence suggests that pre-surgical psychiatric morbidity is associated with more widespread cerebral pathology, but striking, is the lack of attention to its relationship to cognitive variables. The central hypothesis formulated and explored here is that TLE patients with less localised cerebral dysfunction, as supported by electrophysiological, neuro-radiological and cognitive indicators will be at risk for psychiatric disturbance preoperatively and have poorer outcomes following TLE surgery.

Section 2 consists of 5 interlinked studies incorporating retrospective and prospective methodologies. In Study 1 (Chapter 7), the medical records of 280 TLE surgical cases were reviewed, and more than a third presented with significant psychiatric morbidity within 4 years following surgery. Fifty-one patients (18%) developed de novo psychopathology, half within 6 months of surgery and for the majority, persisted for more than 6 months. A

preoperative history of secondary generalised tonic-clonic seizures (SGTCS) was an independent predictor of de novo psychopathology, but cognitive variables were not. Patients with a history of SGTCS and those with a preoperative psychiatric diagnosis were significantly less likely to remain seizure free.

Using voxel based morphometry (VBM), Study 2 (Chapter 8) explored the preoperative neural correlates of de novo depression in a sub-group of patients (n=43) presented in Study 1. Grey matter (GM) reductions in the orbitofrontal cortices (OFC), ipsilateral cingulate gyrus and ipsilateral thalamus were associated with the development of de novo depression within 4 years postoperatively.

In Study 3 (Chapter 9), a sub-group of patients from Study 1, with a diagnosis of post-ictal psychosis (TLE+PIP), were compared to age-matched TLE patients without any psychiatric history (TLE-only; n=60), with respect to pre-surgical clinical and cognitive variables. TLE+PIP patients were significantly less likely to have localised ictal epileptiform activity and more likely to have a positive family psychiatric history than TLE controls. Other clinical and cognitive variables did not distinguish between the groups. Patients with two or more PIP episodes had significantly increased odds of developing de novo psychopathology within 4 years of surgery, after controlling for comorbid pre-surgical psychiatric status and a history of SGTCS. A history of PIP was not a predictor of seizure status or cognitive outcome.

Study 4 (Chapter 11) investigated the relationship between executive function and concurrent depression in TLE patients undergoing surgical evaluation. Depressed mood in TLE patients was *associated* with clinical, cognitive and behavioural indicators of more diffuse cerebral dysfunction.

Using multilevel modelling, Study 5 (Chapter 12) provides clinically relevant data confirming that psychiatric disturbance is a significant complication following TLE surgery, and is *predicted* by the presence of pre-surgical executive dysfunction.

The final chapter provides an overall summary of the findings, their implications, methodological limitations and directions for future research. It is argued that these studies have provided clinically relevant data that will aid the surgical decision-making process, and hopefully guide and improve post-surgical care and support.

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LIST OF ACRONYMS

^{18}FDG: ^{18}F-deoxyglucose

ACC: Anterior Cingulate Cortex

AEDs: Antiepileptic Drugs

AMIPB: Adult Memory and Information Processing Battery

ATLR: Anterior temporal lobe resection

B: Beta coefficient

B_0: Intercept

B_1: Gradient/slope

BADS: Behavioural Assessment of the Dysexecutive Syndrome Test Battery

BAI: Beck Anxiety Inventory

BDI-FS: BDI-Fast Screen for medical patients

BDI: Beck Depression Inventory

BDI: Beck Depression Inventory

BMIPB: BIRT Memory and Information Processing Battery

BOLD: Blood-Oxygen-Level-Dependent

CANTAB: Cambridge Automated Test Battery

CBF: Cerebral Blood Flow

CBT: Cognitive Behavioural Therapy

CI: Confidence Interval

CIDI: Composite International Diagnostic Interview

CNS: Central Nervous System

CSF: Cerebrospinal Fluid

DARTEL: Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra

DEX: Dysexecutive Questionnaire

DNETs: Dysembryoplastic Neuroepithelial Tumours

DSM: Diagnostic Statistical Manual

DTI: Diffusion Tensor Imaging

EEG: Electroencephalogram

FA: Fractional Anisotropy

FCD: Focal Cortical Dysplasia

FDA: Food and Drug Administration

FET: Fisher Exact Test

FLAIR: Fluid Attenuated Inversion Recovery

FLE: Frontal Lobe Epilepsy

fMRI: Functional Magnetic Resonance Imaging

GLM: generalised linear model

GM: Grey Matter

GMV: Grey Matter Volume

HS: Hippocampal Sclerosis

IAP: Intra-carotid Amobarbital Procedure

ICC: Interclass Correlation

ICD: International Classification of Diseases

IDD: Interictal Dysphoric Disorder

IGC: Individual Growth Curve Modeling

IGT: Iowa Gambling Task

ILAE: International League Against Epilepsy

IP: Interictal Psychosis

IQ: Intellectual Quotient

K-S test: Kolmogorov-Smirnov test

LFB/CV: Luxol Fast Blue/Cresyl Violet Stain

LOG: Logarithmic

MD: Mean Diffusivity

MDD: Major Depressive Disorder

MEG: Magnetoencephalography

MLE: Maximum Likelihood Estimation

MLM: Multilevel Modeling

MRI: Magnetic Resonance Imaging

mTLE: mesial Temporal Lobe Epilepsy

MTR: Magnetization Transfer Ratio

NAA: Creatine/*N*-acetylaspartate Metabolite Ratio

NART: Nelson Adult Reading Test

NES: Non-epileptic Seizures

NICE: National Institute for Clinical Excellence

OFC: Orbito-Frontal Cortex

OR: Odds Ratio

PET: Positron Emission Tomography

PFC: Pre-Frontal Cortex

PIP: Postictal Psychosis

PIQ: Performance Intellectual Quotient

rANOVA: repeated-measures analysis of variance

ROI: Region-of-Interest

r_s: Spearman's Correlation Coefficient

R_s^2: Coefficient of Determination

SCAN: Schedules for Clinical Assessment in Neuropsychiatry

SD: Standard Deviation

SEEG: Intracranial Electrode Implantation

SGTCS: Secondary Generalised Tonic-Clonic Seizures

SPECT: single photon emission computerised tomography

SSRIs: Serotonin Reuptake Inhibitors

SUDEP: Sudden Unexplained Death in Epilepsy Patients

SWM: Spatial Working Memory

TBI: Traumatic Brain Injury

TLE: Temporal Lobe Epilepsy

TMT (A/B): Trail Making Test

VBM: Voxel Based Morphometry

Video-EEG: Video electroencephalogram

VIQ: Verbal Intellectual Quotient

WAIS: Wechsler Adult Intelligence Scale

WCST: Wisconsin Card Sorting Task

WM: White Matter

X2:Chi-squared

DECLARATION OF OWN WORK

I, Rebecca Anne Pope (née Cleary) confirm that the work presented here is my own. All of the work is original and where information has been derived from other sources, I confirm that this has been indicated and referenced.

This thesis presents only scientific studies where I conducted all steps of the data analysis. The interpretations of the results are my own and were formed following discussions at supervision meetings. Drs Zoe Fox and Khadija Rantell, of the Education Unit at the Institute of Neurology, corroborated statistical techniques and output. I collabrated with Dr Maria Centeno who provided the data from the imaging analysis (Voxel Based Morphometry) described in Chapter 8. This data had been collected previously by Dr Dominique Flügel. Dr Thom, Consultant Neuropathologist, re-analysed the surgical specimens of TLE patients described in Chapter 9. Dr Mary-Anne Wright (Clinical Electro-physiologist, The National Hospital for Neurology and Neurosurgery) analysed and provided the EEG data used in the prospective chapters.

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"Life is not about finding yourself; life is about creating yourself"

George Bernard Shaw (1856-1950)

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SECTION 1:

LITERATURE REVIEW

Chapter 1. EPILEPSY: a common and severe neurological disorder

1.1 Definitions

According to the International League Against Epilepsy (ILAE), an **epileptic seizure** is *"a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain"* (Fisher et al., 2005, p. 471). The phenotype of each seizure is determined by the point of origin and the degree of propagation of this pathological activity (Elger & Schmidt, 2008).

Epilepsy is not one condition, but is a diverse family of disorders, having in common an alteration in the brain that increases the likelihood of future seizures. The ILAE defines epilepsy as a *"disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition"* (Fisher et al. 2005, p. 471).

1.2 Epidemiology, morbidity & mortality

Epilepsy is one of the most common and serious neurological disorders worldwide (Elger et al., 2008). The **incidence** of epilepsy in the UK is approximately 51 per 100,000 people per year (Joint Epilepsy Council, 2011). The incidence has a J-shaped curve as a function of age, with a higher incidence for infants and the elderly (Forsgren et al., 2005). Childhood incidence may be a result of abnormal brain development, metabolic disorders or perinatal insults, whereas acquired brain lesions, neurodegenerative disorders, head trauma or alcohol

abuse may increase the risk of epilepsy in the elderly (Duncan et al., 2006). Approximately 600,000 people in the UK have a diagnosis of epilepsy, which is equivalent to a **prevalence** rate of 9.7 per 1,000 people per year (Joint Epilepsy Council, 2011).

Stigma and prejudice demarcate epilepsy from most other neurological conditions (Jacoby, 2002). Epilepsy is associated with increased psychiatric morbidity, cognitive impairment, scholastic difficulties, unemployment, lower rates of marriage, reduced leisure opportunities and greater social isolation and family dysfunction than those without the condition (Baker, 2002). Furthermore, epilepsy patients have an increased risk of premature death that is two times higher than the general population, especially in the first few years after diagnosis (Lhatoo et al., 2001). Common causes of death include seizure-related death (e.g. status epilepticus, Sudden Unexplained Death in Epilepsy Patients, SUDEP) and accidents (e.g. drowning or burns) (Pati & Alexopoulos, 2010). Patients with epilepsy also have a higher risk of suicide, particularly in the first two years after onset (Hersdorffer et al., 2012).

1.3 Epileptic seizures & epileptic syndromes

Once a diagnosis of epilepsy has been established, the next step is seizure classification, and if possible, identification of the **epilepsy syndrome** (Brodie & French, 2000). The classification of epileptic seizures and syndromes is continually evolving (Olafsson et al., 2005) and is recognised as a "work in progress" (Engel, 2001, p. 796). For the last forty years the ILAE has been engaged in formulating an accepted system of classification (Gastaut, 1970; Commission, 1981; Commission, 1989; Berg et al., 2010). The main reason for this preoccupation is that a universally employed classification scheme would facilitate

communication among clinicians, but also establish a taxonomic foundation for consistent clinical research (Engel, 2001).

Until recently, the ILAE standardised classification and terminology for "epileptic seizures" of 1981 and "epilepsies and epileptic syndromes" of 1989 have been the prevailing framework for organising and differentiating the epilepsies (Panayiotopoulos, 2011). However, a revision of these classifications has been mandated by recent technological and scientific advances, particularly in neuroimaging and genetics (Berg et al., 2010). Since the new scheme was only published in 2010, and has met with dissent (see Panayiotopoulos, 2011; Luders et al., 2012, for discussion), the terminology employed in this thesis is based on the pre-existing nomenclature of the previous ILAE classifications that is still widely used.

1.3.1 1981 Classification of epileptic seizures

The 1981 classification scheme revised the 1970 proposal (Gastaut, 1970); and was based purposely on the observation of characteristic signs and symptoms during the seizure (ictal semiology), together with the associated EEG changes (Engel, 2001).

A seizure is first classified as **partial/focal**, whereby the clinical and EEG changes indicate activation of a system of neurons *limited* to part of *one* cerebral hemisphere, or **generalised** where clinical and EEG changes indicate initial involvement of *both* hemispheres. The second level of classification is based on the clinical manifestations of a seizure (seizure semiology): focal seizures are divided into **simple partial seizures** (awareness preserved) and **complex partial seizures** (awareness altered or lost), and further categorised as (1) motor, (2) somatosensory, (3) special-sensory (visual, auditory, olfactory, gustatory,

vertiginous), (4) autonomic or (5) psychic. A partial seizure may progress to a **"secondary generalised seizure"**.

Generalised seizures can be (1) absence, (2) tonic-clonic, (3) myoclonic, (4) clonic, (5) tonic or (6) atonic in type. For seizures that cannot be classified due to inadequate or incomplete data (e.g. neonatal seizures) a third seizure category "unclassified epileptic seizures" was included.

1.3.2 1989 Classification of epileptic syndromes

The revised classification of epilepsies and epileptic syndromes (1989) introduced two major classes: the first separated epilepsies with generalised seizures (generalised epilepsy) from epilepsies with partial or focal seizures (localisation-related, partial or focal epilepsies). The second divided epilepsies of known aetiology ("symptomatic" or secondary epilepsies) from those with no identified cause ("idiopathic") or whereby a focal origin is suspected but the cause is unknown ("cryptogenic").

In 2001, the ILAE Task Force recognised that these dichotomies were overly simplistic and often difficult to apply (Engel, 2006). Consequently, changes in terminology (e.g. *focal seizures and syndromes* replaced the terms *partial seizures* and *localisation-related syndromes*, respectively) and the introduction of a diagnostic scheme, across five hierarchical axes ((1) ictal semiology, (2) seizure type, (3) syndrome, (4) aetiology and (5) impairment) describing the available knowledge of the condition (Engel, 2001).

Focal epilepsies are further categorised according to the affected hemisphere (i.e. right/left) and lobe (frontal/temporal/parietal/occipital). Sub-lobar classification associated with specific ictal semiology and EEG abnormalities can be further detailed (e.g. medial and lateral temporal lobe epilepsy).

1.4 Temporal Lobe Epilepsy

Temporal lobe epilepsy is the most common form of focal epilepsy in adults, accounting for 60% of cases (Shorvon, 2010). A number of sub-classifications exist regarding the neuroanatomical origin of the seizures, with the distinction between mesial temporal and lateral temporal seizure onsets being one of the most widely used.

1.4.1 Mesial Temporal Lobe Epilepsy (mTLE)

The commonest pathology underlying mesial temporal lobe epilepsy is **hippocampal sclerosis** (Kim & Spencer, 2001). This condition is often associated with a history of febrile seizures in infancy. Other aetiologies include dysembryoplastic neuroepithelioma (DNETs) and other benign tumours, cavernous angiomas, glioma, malformations of cortical development, or gliosis as a result of encephalitis or meningitis.

Seizures originating in the mesial temporal lobe may be simple or complex partial in form. Secondary generalisation may occur. A simple partial seizure has a short duration, lasting for a matter of seconds. A complex partial seizure evolves gradually, developing over minutes.

More than 90% of patients with mesial temporal lobe epilepsy (mTLE) report a visceral aura, most commonly an epigastric sensation that has a rising character (Elger et al., 2008). Other auras maybe characterised by an abnormal sense of taste, an aversive smell, déjà vu or a dreamy sensation. Fear is the most reported affective symptom, although other complex emotional symptoms may also occur. Autonomic symptoms include changes in skin colour, blood pressure, heart rate and piloerection (Shorvon, 2010).

An aura can occur in isolation or it can be the initial manifestation of a complex partial seizure. The latter is characterised by prominent behavioural changes, often a motionless stare. Speech usually ceases or is severely disrupted if the seizure involves the language-dominant temporal lobe (normally the left). If the seizure onset is in the non-language dominant hemisphere, speech may be retained throughout the seizure, but is generally marked by meaningless repetitive vocalisations (Shorvon, 2010).

Behavioural automatisms which demarcate a seizure focus as originating in mesial temporal lobe structures are usually oroalimentary (e.g. lip-smacking, chewing, swallowing) or gestural (e.g. fumbling, fidgeting, repetitive motor action, undressing, walking, running or sexually directed actions), and are often prolonged (Shorvon, 2010). Limb automatisms are usually ipsilateral to the epileptogenic focus, with contralateral dystonic posturing. Following a temporal lobe complex partial seizure, confusion and headache are common. Post-ictal nose-rubbing may occur and most frequently occurs ipsilateral to the epileptogenic zone (Geyer et al., 1999).

EEG correlates of mTLE often show anterior and mid-temporal spikes. Further changes include intermittent or persisting slow activity over the temporal lobes, which can be unilateral or bilateral. With advances in magnetic resonance imaging (MRI), structural

abnormalities are often identified in mesial temporal brain structures (Shorvon, 2010).

1.4.2 Lateral (neocortical) Temporal Lobe Epilepsy

Lateral temporal lobe epilepsy is often associated with detectable underlying structural pathology, the most common being a glioma, angioma, cavernoma, hamartoma, DNET, neuronal migration defect and post-traumatic change. Unlike mTLE, this condition is not associated with febrile convulsions (Shorvon, 2010).

Unsurprisingly, there is considerable overlap between the clinical and electrophysiological features of mesial and lateral temporal lobe epilepsy, due presumably to the rapid spread of discharges between these two neighbouring anatomical areas. However, subtle differences between lateral and mesial temporal lobe epilepsies are discernible. For example, during a lateral temporal lobe seizure auras include hallucinations that are often structured with visual, auditory, gustatory or olfactory forms, which can be crude or elaborate in nature or with illusions of size, shape, weight, distance or sound. Compared to mTLE, affective, visceral or psychic auras are far less frequent. Moreover, lateral temporal lobe seizures typically involve more motor activity; automatisms are unilateral and have more prominent motor manifestations. However, from a post-ictal perspective, mesial and lateral temporal lobe epilepsies are difficult to distinguish.

The electrophysiological pattern between seizures (interictal pattern) shows spikes over the temporal region, maximal over the posterior or lateral temporal rather than inferomesial electrodes. In contrast to mTLE, hippocampal volumes and T_2 measures (fluid attenuated inversion recovery; FLAIR) on MRI are usually normal (Shorvon, 2010).

1.5 Management

1.5.1 Pharmacological therapy

Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment (Duncan et al., 2006). AEDs increase inhibition, decrease excitation or prevent the aberrant burst-firing of neurons. They are a symptomatic treatment, suppressing the seizures, and have no influence on the long-term natural course of the disease (epileptogenesis) (Duncan et al., 2006). At present, over 20 AEDs have been licensed worldwide, each associated with adverse side-effects (Table 1). The primary goals of pharmacological treatment are to achieve complete seizure freedom, ideally without adverse side effects, to reduce morbidity and mortality and to improve quality of life (Sisodiya & Sander, 2004).

Conventionally, AEDs are divided into new or old agents, depending upon whether they were available before or after the 1990s. Despite vigorous debate, there is no evidence that new drugs are more effective, although they may be better tolerated than old drugs (McCorry, Chadwick & Marson, 2004; Duncan et al., 2006). A number of agents are used as first-line treatment and are selected on the basis of their effectiveness for the seizure type (Table 2) or epileptic syndrome. In addition, the tolerability, safety, ease of use, pharmacokinetics and cost of AEDs are also considered before commencing treatment (Schmidt, 2009). This patient-tailored approach to treatment is strongly recommended in existing NICE guidelines (NICE, 2012).

Antiepileptic agent	Usual starting dose in adults (mg)	Recommended daily maintenance dose for adults (mg)	Side effects
Acetazolamide (1952)	250	500-1000	Idiosyncratic rash; rarely Stevens-Johnson syndrome and toxic epidermal necrolysis; aplastic anaemia
Carbamazepine (1963)	100-200	400-1800	Idiosyncratic reactions; rarely Stevens-Johnson syndrome; aplastic anaemia, hepatotoxicity
Clobazam (1986)	10	11232	Rarely idiosyncratic rash
Clonazepam (1975)	0.5	41426	Rarely idiosyncratic rash, thrombocytopenia
Diazepam (1965)	44105	N/A	Respiratory depression
Ethosuximide (1953)	250	500-1500	Rarely idiosyncratic rash, Stevens-Johnston syndrome, aplastic anaemia
Felbamate (1993)	400	1800-3600	Hepatic failure, aplastic anaemia
Gabapentin (1993)	300	1800-3600	Paradoxical increase in seizures
Lamotrigine (1991)	50 (10 if taking Valproate)	100-400	Idiosyncratic rashes, rarely Stevens-Johnson syndrome, toxic epidermal necrolysis, liver failure, aplastic anaemia, multi-organ failure
Levetiracetam (1991)	250	750-3000	Behavioural problems
Lorazepam (1972)	41366	N/A	Respiratory depression
Phenobarbital (1912)	30	30-180	Idiosyncratic rash; rarely toxic epidermal necrolysis; hepatotoxicity; osteomalacia; Dupuytren's contracture
Phenytoin (1938)	200	200-400	Idiosyncratic rash; rarely pseudolymphoma; peripheral neuropathy; Stevens-Johnson syndrome; Dupuytren's contracture; hepatotoxicity; Osteomalacia
Pregabalin (2004)	50	100-600	Weight gain; rarely increased seizures
Primidone (1952)	125	500-1500	Idiosyncratic rash; rarely agranulocytosis; thrombocytopenia; lupus-like syndrome
Oxcarbazepine (1990)	150-300	900-2400	Idiosyncratic rash; hyponatraemia
Tiagabine (1996)	5	30-45	Increased seizures; non-convulsive status
Topiramate (1995)	25	75-200	Weight loss; kidney stones; impaired Cognition
Valproic acid (1968)	200	400-2000	Teratogenicity; rarely acute pancreatitis; hepatotoxicity; thrombocytpenia; encephalopathy; polycystic ovarian syndrome
Vigabatrin (1989)	500	1000-2000	Visual fields defects, increased seizures
Zonisamide (1990)	50-100	200-600	Rash; rarely blood dyscrasias

Table 1. *Antiepileptic drugs in present use (year of introduction). Adapted from Duncan et al. (2006)*

Seizure Type	First-line drugs	Second-line drugs	Other drugs that can be considered	Drugs to be avoided (may worsen seizures)
Generalised tonic-clonic	Carbamazepine Lamotrigine Sodium Valproate Topiramate	Clobazam Levetiracetam Oxcarbazepine	Acetazolamide Clonazepam Phenobarbital Phenytoin Primidone	Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium Valproate	Clobazam Clonazepam Topiramate		Carbamazepine Gabapentin Oxcarbazepine Tiagabine Vigabatrin
Myoclonic	Sodium Valproate Topiramate	Clobazam Clonazepam Lamotrigine Levetiracetam Piracetam Topiramate		Carbamazepine Gabapentin Oxcarbazepine Tiagabine Vigabatrin
Tonic	Lamotrigine Sodium Valproate	Clobazam Clonazepam Levetiracetam Topiramate	Acetazolamide Phenobarbital Phenytoin Primidone	Carbamazepine Oxecarbazepine
Atonic	Lamotrigine Sodium Valproate	Clobazam Clonazepam Levetiracetam Topiramate	Acetazolamide Phenobarbital Primidone	Carbamazepine Oxcarbazepine Phenytoin
Focal with/without secondary generalisation	Carbamazepine Lamotrigine Oxcarbazepine Sodium Valproate Topiramate	Clobazam Gabapentin Levetiracetam Phenytoin Tiagabine	Acetazolamide Clonazepam Phenobarbital Primidone	

Table 2. *Antiepileptic drug options by seizure type. Adapted from NICE (2012)*

Monotherapy is the treatment of choice, as it avoids drug-interactions and reduces teratogenicity, long-term toxic effects, and provides a simpler regimen that may improve compliance (Leppik, 2000). Despite the good response to monotherapy in a large proportion of patients, up to 50% will be managed with combination therapy (Duncan et al., 2006). For example, in a Scottish epilepsy unit database, 21% of 1,617 seizure free patients were taking more than one drug, with 14% of those receiving three or more (Stephen & Brodie, 2002).

1.5.2 Pharmaco-resistance & epilepsy surgery

Despite the existence of numerous AED drugs, 30% of patients who develop epilepsy continue to experience seizures (Duncan et al., 2006). Kwan and Brodie (2000) demonstrated in a prospective study that 47% of patients with new-onset epilepsy became seizure-free on the first AED, 32% on the second AED, and 9% on the third AED. Forth and subsequent AEDs had at most a 5% chance of bringing seizure remission. Although there is no uniformly accepted definition of **pharmaco-resistance** (Pati et al., 2010), those continuing to have seizures after trying three different AEDs are recommended to be considered for surgical treatment (Duncan, 2007). In the UK, there is a median interval between diagnosis and surgical intervention of between 15 to 20 years (Duncan, 2007; Engel et al., 2012). This referral delay is sub-optimal for a number of reasons. First, throughout this period patients have an increased risk of mortality and severe disability due to unremitting seizure activity (Langfitt & Wiebe, 2008). Second, the earlier TLE surgery is performed the better the long-term surgical (seizure) outcome (Janszky et al., 2005). Finally, earlier surgical intervention may also reduce the deleterious psychological, cognitive and psychosocial consequences of pharmaco-resistant epilepsy (Hermann, Wyler & Somes, 1992).

1.5.3 Epilepsy surgery

For a subset of individuals with medically refractory epilepsy, neurosurgery represents the optimal treatment option (Spencer & Huh, 2008). A range of surgical techniques have been developed (see Table 3), which can be divided into two major categories: functional or resective surgeries.

It is beyond the scope of this work to review the variant forms of functional epilepsy surgery (for further details, see Spencer et al., 2008). The objective of **functional** surgery is to *palliate* rather than cure the epilepsy. Consequently, such procedures rarely result in seizure freedom (Elger et al., 2008).

Surgical Procedure	Method	Clinical Use
Functional:		
Corpus callosotomy	The corpus callosum is sectioned to prevent interhemispheric propagation of epileptic discharges and generalisation of seizure activity	Atonic drop attacks
Multiple subpial transection	Selective vertical incisions are made in grey matter of the eloquent cortex at 4mm intervals. Theoretically, this procedure prevents the propagation of epileptic activity within the eloquent cortex, without disturbing functional integrity	Epileptogenic zone lies in eloquent cortex (e.g. Motor cortex, speech area).
Vagal nerve stimulation	Pulse generator is placed subcutaneously in the left praecordium and connected to the left vagal nerve	For patients not suitable for resective surgery
Resective:		
Anterior temporal lobe resection	Resection of a large amount of the temporal neocortex, along with resection of the medial temporal structures	Mesial hippocampal sclerosis
Selective amygdalohippocampectomy	Limited neocortical resection of the anterior temporal lobe that allows access to the hippocampus	Mesial hippocampal sclerosis
Lesionectomy	Resection of small epileptogenic lesions	Cavernomas, focal cortical dysplasia, indolent tumours (e.g. Dysembryo-plastic neuroepithelial tumours)
Extratemporal resections	Comprise of single and multi-lobar resections. Chronic invasive EEG recording may be needed to determine the extent of resection	Diffuse epileptogenic zone (with no apparent lesion) or lesion resides outside of the temporal lobe
Functional hemispherectomy	Resection of the temporal lobe and central cortex followed by disconnection of frontal and occipital neocortex from the subcortical structures and corpus callosum	Diffuse cortical dysplasia Rasmussen's encephalitis Sturge-Weber syndrome

Table 3. *Surgical treatments for epilepsy. Adapted from Duncan et al. (2007)*

In contrast to palliative surgical treatments, the aim of **resective** surgery is to remove or disconnect the brain region identified as responsible for generating seizures (the epileptogenic zone) without creating a new unacceptable handicap; rendering a patient seizure free (Duncan, 2007). In order to satisfy this aim, a thorough and extensive pre-surgical evaluation is necessary.

1.6 Pre-surgical evaluation

Information from the investigations described below are utilised to formulate recommendations for surgical intervention.

1.6.1 Clinical history

The cornerstone of the pre-surgical evaluation involves a thorough review of the patient's epilepsy history, including details regarding past seizure frequency and current seizure semiology (Ryvlin & Rheims, 2008). Questions regarding birth history, febrile convulsions, head injuries, central nervous system infections and a family history of epilepsy may identify possible causes of the epilepsy (Morris, Najm & Kahane, 2008). A seizure description will yield clues as to the location of the symptomatogenic zone (see Table 4), and in addition, indicate whether there is evidence of multifocal or diffuse epileptogenicity.

Terminology	Definition
Symptomatogenic zone	The cortical area that produces the ictal symptoms of the individual patient when it is activated by the epileptic discharge. It is defined by history and video-EEG semiology.
Irritative zone	The cortical area that generates interictal epileptiform activity. It is estimated by scalp EEG, MEG or intracranial EEG.
Ictal onset zone	The zone capable to generate spontaneous seizures. It is a subset of the irritative zone. It can be estimated with the same tools as the irritative zone except that MEG rarely captures seizures due to recording sessions generally limited to less than one hour.
Epileptogenic zone	Area of brain tissue that is necessary to generate the seizures and which needs to be surgically removed to obtain seizure freedom. It is estimated by a combination of all the above zones estimated during pre-surgical evaluation.
Epileptogenic lesion	Structural brain abnormalities with the potential of generating interictal and ictal epileptic activity. It is identified by neuroimaging or by post-operative histological examination.
Eloquent cortex	Cortical region that is identified as crucial for neurological or cognitive functions (i.e. motor, sensory, visual, language cortex).

Table 4. *Terminology used in the description of focal epileptic activity. Adapted from Rosenow et al. (2001)*

1.6.2 Electrophysiological investigations

Video-EEG (VEEG) monitoring involves an inpatient stay with continuous EEG and simultaneous video monitoring over several days. The aim is to record ictal (seizure related) and interictal epileptic activity (from the irritative zone), and demonstrate the correlation between the signs and symptoms of seizures and their corresponding EEG pattern (Olson, 2002). Consistent electro-clinical patterns, over a number of habitual seizures, are deemed necessary to ensure that the seizure disorder is unifocal.

Ictal scalp recording also provides valuable information in lateralising the ictal onset zone (Kilpatric et al., 2003). Scalp EEG surface electrodes are located at a relatively large distance from the cortex and are separated from the brain by a series of barriers (scalp, bone, meninges) that interfere significantly with the transmission of the electrical signals, consequently the *localisation* of the ictal onset zone must be inferred with caution (Rosenow et al., 2001; Olson, 2002).

Intracranial electrode implantation (SEEG/depth electrodes) is indicated when there is a lack of a potentially epileptogenic structural lesion, multiple putative epileptogenic lesions (zones), scalp EEG with multifocal or no interictal epileptiform discharges, indeterminate or multifocal ictal onset zone(s), discordant non-invasive findings, or if the ictal onset zone is in close proximity or overlaps with eloquent cortex (Siegel, 2004).

Magnetoencephalography (MEG) is a non-invasive neurophysiological imaging technique that detects interictal epileptiform discharges and therefore aids in the identification of the irritative zone (Carreno & Luders, 2001). The advantage of MEG over scalp EEG is that it

has greater resolution owing to the lack of distortion of the magnetic signal by the meninges or skull. However, MEG also has notable limitations. Firstly, it has a small signal-to-noise ratio due to the low amplitude of the magnetic signal generated by electrical brain activity. Secondly, the static recording device limits the patient's mobility, which restricts the possibility of prolonged recordings (Carreno et al., 2001). Finally, the main shortcoming of MEG remains its lack of availability in the majority of epilepsy surgery centres (Ryvlin et al., 2008), such that its exact role and clinical potency in the evaluation of patients for epilepsy surgery remains undetermined (Morris et al., 2008).

1.6.3 Brain imaging

Crucial to the pre-surgical evaluation is the acquisition of a high quality **MRI brain scan** (Duncan, 2007). The principal pathologies identified are hippocampal sclerosis, malformations of cortical development such as focal cortical dysplasia (FCD), cavernomas, DNETs, low-grade tumours (gliomas), arteriovenous malformations and focal cerebral damage (Ryvlin et al., 2008).

Rapid advances in MRI resolution (3 Tesla) and techniques (e.g. FLAIR) have resulted in patients who were previously regarded as "MRI negative" being re-evaluated for surgical intervention as more subtle abnormalities become more easily detected (Duncan, 2010). The ILAE has published guidelines and technical recommendations to optimise MRI scanning for detecting focal epileptogenic abnormalities (ILAE, 2005).

Quantitative MRI assessment of the hippocampus (volumetry) can be helpful in determining uni- or bilateral hippocampal atrophy (Duncan, 2010). This can be achieved by visual

inspection and manual segmentation of the hippocampi by a trained radiologist or with automated segmentation techniques (Bonilha et al., 2009). Volumetry is particularly important in the pre-surgical work-up to ensure the contralateral hippocampus is intact.

Positron emission tomography (PET) is used to map regional cerebral glucose metabolism using the radioactive tracer ^{18}F-deoxyglucose (^{18}FDG) (Duncan, 1997). In the interictal state, the hallmark of an epileptogenic focus is an area of reduced glucose metabolism (hypometabolism). In contrast, focal seizures are associated with an increase in regional cerebral glucose metabolism (hypermetabolism) in the region of the epileptogenic focus (Duncan, 1997). The role of ^{18}FDG-PET as a tool for localising an epileptogenic focus in the pre-surgical workup is being replaced by newer MRI techniques. A recent meta-analysis has shown that ^{18}FDG-PET failed to have any additional preoperative decision making value in TLE patients with well localised ictal scalp EEG and concordant MRI (Willman et al., 2007). However, in the 20-25% of patients with refractory focal seizures with normal or non-definitive MRI scans, the findings of focal hypometabolism can provide useful data towards a decision to conduct an invasive intracranial EEG recording (Duncan, 2009).

For the pre-surgical assessment, **single photon emission computerised tomography (SPECT)** is employed to localise the ictal onset zone by administering a tracer during or immediately following a seizure (ictal SPECT). An injection of ^{99m}Tc-HMPAO at the time of a seizure results in an image of the distribution of CBF 1-2 minutes after tracer administration, which is then stable for several hours, permitting the patient to be imaged once the seizure has terminated (Duncan, 1997). During the ictal state, the general pattern is of localised ictal increased CBF (hyperperfusion), with surrounding decreased CBF (hypoperfusion), followed by accentuated hypoperfusion in the region of the focus, which gradually returns to the interictal state (Duncan, 1997). Simultaneous video-EEG is essential

to determine the relationship between the onset of a seizure and the tracer delivery; without this precaution, there is a risk of blurring the ictal and post-ictal data.

Functional MRI (fMRI) techniques detect changes in the blood oxygenation and flow that occur in response to neural activity (Duncan, 1997). During neuronal activity, there is an increase cerebral blood flow to the active area(s) of the cerebrum, resulting in higher concentrations of oxyhaemoglobin relative to deoxyhaemoglobin (Baxendale, 2002). The subtle blood-oxygen-level-dependent (BOLD) differences in magnetic state result in a larger BOLD signal from the active region. In order to infer whether the fMRI-derived activation is related to a particular mental function, it is necessary to compare the activation during two experimental conditions that are as similar as possible except for the mental function or process of interest (Desmond et al., 1995).

The main use of fMRI in pre-surgical evaluations is the delineation of brain substrates for specific functions, such as the motor cortex as well as receptive and expressive language areas, and the identification of their anatomical relation to areas of planned neurosurgical resection (Duncan, 1997).

A number of studies have demonstrated that lateralising hemispheric language dominance is achievable using fMRI (Desmond et al., 1995; Binder et al., 1996; Hertz-Pannier et al., 1997). Good concordance rates have been recorded with the **Intra-carotid Amobarbital Procedure (IAP, see below).**

1.6.4 Neuropsychological evaluation

Neuropsychological testing has become an integral part of the pre-surgical evaluation at most surgical centres (Helmstaedter, 2004). Assessments involve the testing of a broad range of cognitive domains with an emphasis on memory functions in TLE candidates. A neuropsychological assessment provides a means of establishing a patient's functional deficit zone and, in doing so, often provides supportive confirmatory information regarding the location of the epileptogenic zone. For example, impairment of verbal memory suggests involvement of the language-dominant hemisphere, while global memory deficits may be an indicator of bilateral temporal lobe pathology, and therefore a marker of poor outcome following focal resection (Malmgren et al., 2008). Increasingly, the assessment findings are used to estimate the risk of postoperative cognitive decline; knowledge that may prove crucial for patients deciding whether to elect for surgical therapy (Baxendale et al., 2006). Risk factors for postoperative cognitive deterioration include: intact preoperative verbal memory in left temporal lobe cases, older age at surgery and lower IQ (Baxendale et al., 2006). Despite seizure freedom being the obvious objective of epilepsy surgery, the gain of seizure control must be weighed against the attendant risks of cognitive deficits that may be associated with the procedure (Noachtar et al., 2009).

The **IAP** has been used to determine language dominance and to assess for the risk of a post-operative amnesic syndrome in TLE surgical candidates since its inception in the mid twentieth century (Baxendale, Thompson & Duncan, 2008). Indeed, in 1993 over 95% of epilepsy surgery centres worldwide reported using the IAP, primarily to assess language dominance (94%) and memory capacity (98%) (Rausch et al., 1993). However, in recent years the deployment of the IAP has decreased markedly. Baxendale et al. (2008) surveyed

the clinical practice of 92 epilepsy surgical centres in 31 countries and found that only 12% of centres performed an IAP on every TLE surgical candidate.

One explanation for the decreased reliance on the IAP is the development of high definition structural MRIs, allows detailed examination of ipsilateral and contralateral structures in pre-surgical candidates (Duncan, 1997). A number of surgical epilepsy centres use data from these images, coupled with detailed baseline neuropsychological data, to assess the structure and functional capacity of the contralateral mesial temporal lobe in surgical candidates. This affords an assessment of the risk of a post-operative amnesic syndrome and prediction of post-operative changes in memory function (Baxendale et al., 2008).

1.6 Psychiatric assessment

Until recently, psychiatric assessment has not been considered an integral part of the pre-surgical evaluation (Foong & Flugel, 2007). However, its importance and potential value is increasingly recognised. The evidence will be discussed in detail in Chapter 2.

1.7 Post-operative outcome

1.7.1 Seizure control

Anterior temporal lobe resection (ATLR) for mTLE is the most common resective surgical procedure in adult practice in the UK (Neligan et al., 2013), leading to seizure freedom in up to 70% of patients at two years follow-up (Engel, 1996). Longer follow-ups indicate that seizure outcomes are not static (Jette & Wiebe, 2013). Late seizure recurrence is not

uncommon (de Tisi et al., 2011), with seizure-freedom rates decreasing over time to approximately 41% at a 10 year follow-up (McIntosh et al., 2004). Two randomised control trials of surgery have established the short-term benefits (i.e. seizure freedom and enhanced quality of life) of ATLR compared with medical treatment for refractory TLE at 1 and 2 year follow-up, respectively (Wiebe et al., 2001; Engel et al., 2012).

1.7.2. Medical and Neurological

Hader et al. (2013) reported minor medical postoperative complications (lasting < 3 months) in 5.4% patients undergoing TLE resections and, major medical complaints in 1.6%. The most common minor medical complication was cerebrospinal fluid (CFS) leakage; with an intracranial hematoma being the most frequent major medical complication. Minor neurological sequelae occurred in 12% of TLE patients, whereas major complaints were recorded in 4.1%. The risk and seriousness of a neurological complication was dependent on the site and extent of the resection.

1.7.3. Neuropsychological

The neuropsychological complications of TLE surgery, particularly memory decline have been extensively researched and are well established (Bell et al., 2011). Up to 60% of patients who undergo a left (language dominant) ATLR experience a decline in verbal memory (Spencer et al., 2008; Bell et al., 2011). Non-verbal (figural) memory decline is associated with right ATLR, although this is not an invariable finding (Helmstaedter, 2004).

Determinants of better cognitive outcome include: surgery within the non-dominant hemisphere, younger age at surgery, better baseline performance/intellectual capacity, absence of FCD and successful seizure control (Helmstaedter, 2004; Baxendale et al., 2006). Studies with greater than 5 years follow-up suggest that, although memory deficits develop early after surgery, the degree of decline stabilises after 1-2 years (Helmstaedter et al., 2003); with *progressive* post-surgical declines in memory function associated with poorer seizure control (Baxendale, Thompson & Duncan, 2012).

1.8 Conclusion

Epilepsy surgery can be a life changing intervention in patients with pharmaco-resistant epilepsy, but it remains underutilised. Great advances are being achieved in the pre-surgical evaluation and planning for epilepsy surgery, including fundamental progress in neuroimaging and neurophysiology. The majority of complications (medical/neurologic) after TLE surgery are minor or transient, and mortality in the modern era is rare. Neuropsychological outcome and predictors of memory decline have been well researched. Less studied are the psychiatric complications. These are considered in the next chapter and are the subject of this thesis.

Chapter 2. PSYCHOPATHOLOGY IN TLE

2.1 Temporal relationship with seizures

Psychiatric symptoms can be classified according to their temporal relationship with seizure occurrence into peri-ictal (related to the seizure itself) or interictal (independent of the seizure) symptoms. As demonstrated in Figure 1, peri-ictal symptoms may precede the seizure (pre-ictal), be clinical manifestations of the seizure itself (ictal state) and may follow the seizure directly (post-ictal) (Swinkels et al., 2005). Most research has focussed on interictal psychiatric morbidity.

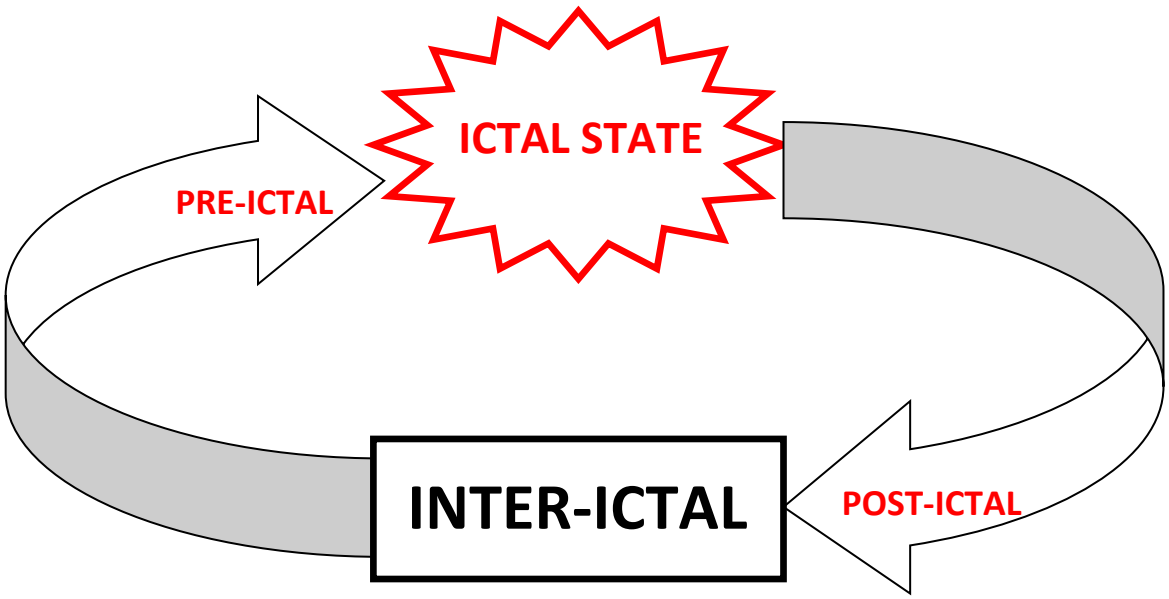

Figure 1. *Timing of psychiatric disturbances in epilepsy.*

2.2 Common, undertreated and multifactorial

Rates of psychiatric comorbidity in epilepsy have been varied and in a review article ranged from 19-80% (Swinkels et al., 2005). Higher rates of psychopathology are observed in people with epilepsy compared with the general population, other neurological control groups and people with chronic non-neurological disorders (Torta & Keller, 1999; Tellez-Zenteno et al., 2007; Rai et al., 2012). A recent population-based study in England found that almost one-third of people with epilepsy had a psychiatric condition compared to one in six people without epilepsy, according to the International Classification of Diseases (ICD-10) (Rai et al., 2012). Psychiatric comorbidity has been related to the chronicity and severity of epilepsy. In highly selected clinical populations, including those with medically refractory TLE the prevalence is highest, compared to community-based and primary care cohorts (see Gaitatzis, Trimble & Sander, 2004, for review). Mood disorders are the most common psychiatric diagnoses, particularly depression, followed by anxiety disorders and psychoses (Gaitatzis et al., 2004).

Individuals with epilepsy must endure sudden, unpredictable seizures, which significantly impair their psychosocial functioning and publically disclose the presence of their disorder. Consequently interictal psychiatric symptoms, namely mood disturbance, have been regarded as an 'understandable' reaction to difficult life circumstances (Marsh & Rao, 2002; Kanner & Balabanov, 2002). Accordingly, patients may not disclose these symptoms and clinicians do not inquire or screen for them. Thus, psychiatric morbidity in epilepsy is often unrecognised or overlooked in routine neurological consultations and remains undertreated (Kanner, Kozak & Frey, 2000; Paradiso et al., 2001; Boylan et al., 2004; Kanner, 2012a; Rai et al., 2012).

Although interictal psychiatric disturbances have been conceptualised as a complication of the underlying seizure disorder (Kanner, 2008), recent epidemiological studies suggest a more complex bidirectional relationship. Forsgren and Nyström (1990) in a population-based study found that a history of depression *preceding the onset of epilepsy* was seven times more common among an epilepsy group than age- and gender-matched controls. When analyses were limited to cases with focal epilepsy, a history of depression was 17 times more common than among the controls. Hesdorffer et al. (2000) in a study carried out among adults aged 55 or over with new-onset epilepsy, found that compared to controls, those with epilepsy were almost 4 times more likely to have a diagnosis of depression *preceding* their initial seizure. A third population-based study included 324 patients aged 10 years and older with a first unprovoked seizure/newly diagnosed epilepsy and 647 controls (Hesdorffer et al., 2006). They found that a major depressive episode, according to DSM-IV criteria, was associated with a 1.7-fold *increased odds* for developing epilepsy.

More recently, a longitudinal cohort study conducted on the UK General Practice Research Database reported a *two-way relationship* between psychiatric disorders (depression, anxiety and psychosis), suicidality and epilepsy (Hesdorffer et al., 2012). These findings indicate that epilepsy is associated with an increased likelihood psychiatric disorders and suicide present both *before and after* epilepsy diagnosis (Hesdorffer et al., 2012). Adelöw and co-workers (2012) investigated the risk of developing unprovoked seizures/epilepsy among patients who had been hospitalised for psychiatric disorders (n=1,885). Compared to matched control individuals who were selected randomly from the Stockholm County population register (n=15,080), the age-adjusted odds ratio (OR) for the development of unprovoked seizures was significantly *increased* for patients with any psychiatric disorder (OR: 2.7, 95%CI: 2.0-3.6). Specifically, 2.5 (95%CI: 1.7-3.7) for depression, 2.7 (95%CI:

1.4-5.3) for bipolar disorder, 2.3 (95%CI: 1.5-3.5) for psychosis, 2.7 (95%CI: 1.6-4.8) for anxiety disorders, and 2.6 (95%CI: 1.7-4.1) for suicide attempts. The odds of developing unprovoked epileptic seizures was highest in less than two years before and up to two years after a first psychiatric diagnosis, particularly for depression and psychosis (Adelöw et al., 2012). Psychiatric morbidity has also been reported as predictive of seizure recurrence in *newly* treated patients (Petrovski et al., 2010) and has been associated with a poorer response to anti-epileptic medication (Hitiris et al., 2007) and epilepsy surgery (Anhoury et al., 2000; Guarnieri et al., 2009; Kanner et al., 2009).

The relationship between epilepsy and interictal psychopathology is complex. Psychosocial stressors including stigma, unemployment, loss of control, lower rates of marriage and greater social isolation are relevant (see, Baker, 2002; Wrench et al., 2011a, for reviews). However, the aforementioned epidemiologic and clinical research has led to the hypothesis that *common neurobiological pathogenic mechanisms* both lower seizure threshold and increase the risk for psychiatric disorders (Kanner, 2012).

2.3 Psychopathology and TLE

A wide range of risk factors have been proposed to explain the high incidence of psychiatric disorder in epilepsy, and can be categorised into clinical, biological and psychosocial factors (see Table 5).

Table 5. Factors related to the risk for psychiatric disorders
Clinical factors
Age at onset of epilepsy
Duration of disorder
Type and frequency of seizures
Hemisphere of cerebral dysfunction (if present)
Interictal and ictal EEG abnormalities
Family history of epilepsy or psychiatric disorder
Psychosocial factors
Chronic nature of disease
Low socio-economic status
Low educational level
Negative cultural approach to epilepsy
Difficulties in adjustment to the consequences of the illness
Fear of seizures
Social stigma
Overprotection by families
Legal limitations (i.e. driving regulations)
Low self-esteem
Biological factors
Neuropathological damage to areas connected with psychiatric functioning (i.e. amygdala, limbic system, frontal cortex)
Emotional and cognitive side effects of antiepileptic drugs

Adapted from Torta et al. (1999)

There is general agreement within the literature that patients with TLE are at increased risk of developing psychiatric disorders (Gaitatzis, et al., 2004). Several investigators have reported that psychiatric disturbance is more prevalent in TLE compared to extra-TLE and/or primary generalised epilepsies (Pond & Bidwell, 1960; Gureje, 1991; Perini et al., 1996). Perini et al. (1996) reported that patients with TLE (n=20) had higher rates of psychiatric disorders (80%) than patients with juvenile myoclonic epilepsy (22%) and patients with Type I diabetes (10%). These findings suggest that psychopathology in TLE is not only an adjustment reaction to a chronic disease, but rather may be related to limbic dysfunction.

The limbic system is situated in the medial parts of the temporal lobes and is involved in the regulation of emotional/psychiatric function. It has been hypothesised that psychiatric disturbances, in particular mood disorders, are more likely to be found in patients with an epileptic focus in these parts of the brain (i.e. TLE), especially in the context of concomitant frontal lobe dysfunction. Other potentially important determinants of psychiatric comorbidity in TLE are presented in Table 5.

The psychiatric outcome of TLE surgery is of particular interest given the high overall prevalence of psychiatric conditions in persons with TLE (Perini et al., 1996; Altshuler et al., 1999; Quiske et al., 2000; Glosser et al., 2000; Gaitatzis et al., 2004; Tellez-Zenteno & Wiebe, 2008; García-Morales, de la Peña Mayor & Kanner, 2008; Ertekin et al., 2009; Bragatti et al, 2010; de Oliveira et al., 2010; Wrench, Rayner & Wilson, 2011; Adams et al., 2012; Filho et al., 2012; Engman & Malmgren, 2012; da Conceição et al., 2013).

2.4 Psychiatric morbidity in TLE: Surgical Impact

For many temporal lobe surgical patients, the long-term psychosocial gains are significantly more favourable than those medically treated (Jones et al., 2002; Mikati, Comair & Rahi, 2006). Following TLE surgery however, psychiatric symptoms can develop for the first time (de novo) or pre-existing symptoms may worsen. Accordingly, psychiatric complications may tarnish an otherwise good surgical outcome, resulting in significant distress for patients and their families (Moss et al., 2009). Research data on psychiatric complications following TLE surgery is limited, in sharp contrast to the continuing emphasis on neuropsychological and neurological sequelae. Although recognition of psychiatric complications following TLE surgery can be traced back to the 1950s (Hill et al., 1953; Hill et al., 1957), it is only in the

last 15 years that there has been increased research into this topic (Kanner et al, 2002). The focus of recent studies has been to clarify pre- and postoperative psychopathology and importantly, to identify risk factors for poor psychiatric outcome.

2.5 Systematic literature review

A literature search was conducted using Medline, Embase and PsychINFO until July 2013 with the following search terms: temporal lobe epilepsy, neurosurgical procedures and mental disorders (e.g., mood and anxiety disorders, psychosis, adjustment disorders, non-epileptic seizures and personality disorders) (see Figure 2). Previous literature reviews were excluded (Foong et al., 2007; Macrodimitris et al., 2011), although reference lists were checked to ensure no additional studies had been missed. The search yielded 4,191 articles relating to TLE surgery. Of these, less that 4% (n=139) reported psychiatric comorbidity as an outcome of surgery. Studies on palliative neurosurgical procedures, stimulation studies, case reports, child/adolescent-only and studies not published in peer reviewed English language journals were excluded. Forty-six studies met the inclusion criteria. These studies are summarised in Table 6.

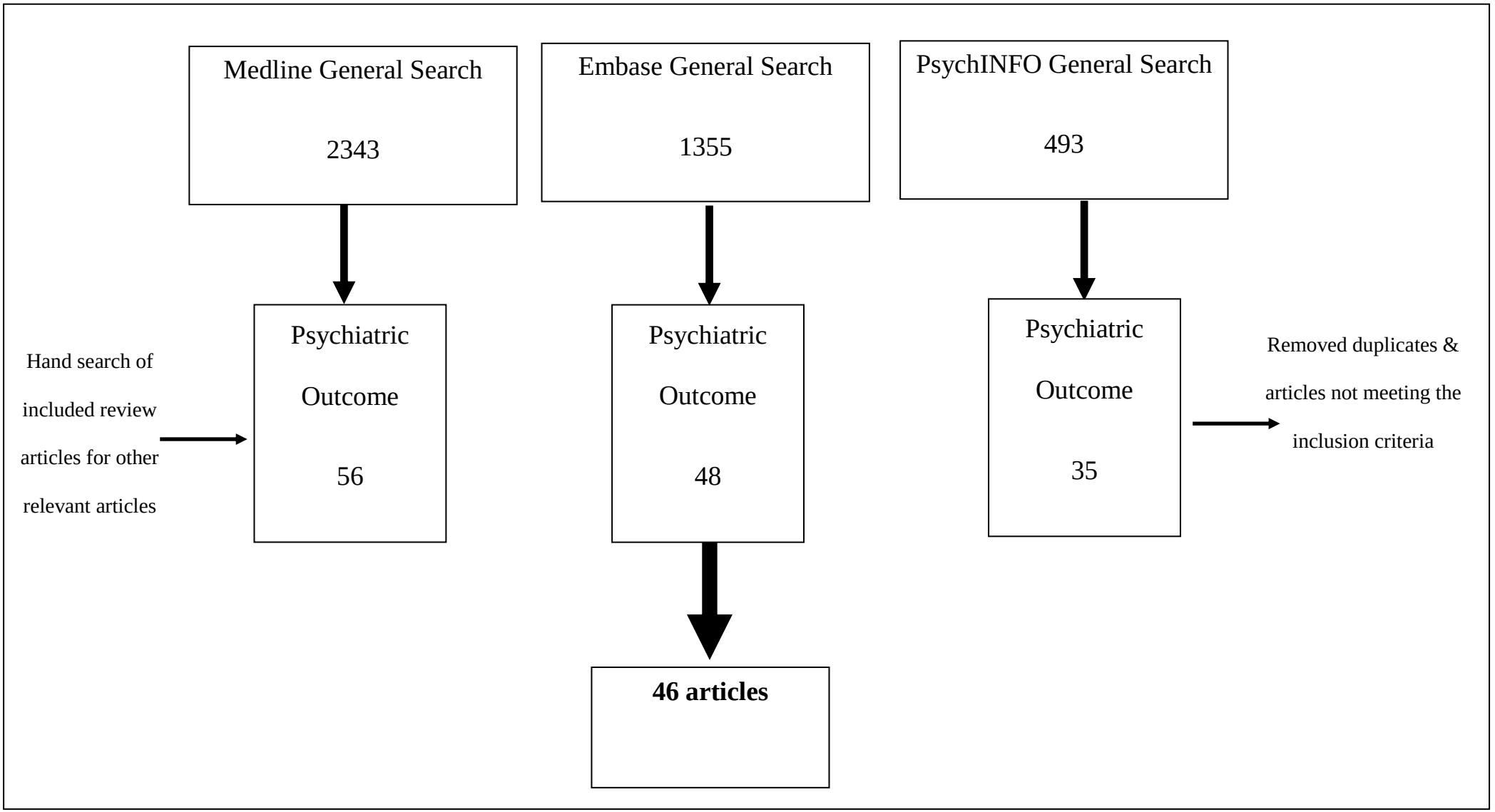

Figure 2. *Literature review search results – General Search refers to terms "temporal lobe epilepsy", "neurosurgical procedures" and "mental disorders". Adapted from Macrodimitris et al (2011).*

Table 6. Summary of psychiatric outcomes of TLE surgery

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Taylor (1972)	Retrospective; uncontrolled	100 temporal 9 pts <15yrs	2-12 yrs	Preop: case-notes Postop: 84 pts had semi-structured interview	Psychopathy - 48/33 Neurosis - 30/19 SLP - 16/19 37 pts admitted to a mental hospital during F/U; 5 pts committed suicide	-	-	Psychopathy: 4 (4%) Neuroses: 3 (3%) SLP: Unclear
Jensen et al. (1979)	Retrospective; uncontrolled	74 temporal Age range: 4-54 yrs 14 pts <15yrs	1 yr	Preop: case-notes Postop: clinical assessment, based on Mayer-Gross criteria	Behavioural disturbance - 54/33 SLP - 11/20 Neurosis - 7/5 6 pts attempted suicide on ≥1 occasion during F/U	-	-	SLP: 9 (12%) 6/9 *de novo* SLP pts pts were seizure free prior to the onset of SLP
Stevens (1990)	Retrospective; uncontrolled	14 temporal (1 pt had a re-resection) Age range: 20-47 yrs	20-30 yrs	Case-notes	Normal - 9/6 Paranoid personality: 3/0 SLP: 0/5 Suspicious: 1/0 Severe irritability: 1 preop, showed significant improvement postop 2 pts psychiatrically "normal" preop had "memory defects" postop	-	-	SLP: 2 (14%) (onset 6-12m)
Roberts et al. (1990)	Retrospective; uncontrolled	249 temporal Mean age: 26.1 yrs	Unknown	Clinical diagnosis of SLP derived from pt case-notes; pathological data	SLP: 16/25	-	1. Gangliogliomas were associated with *de novo* SLP	SLP: 9 (4%)
Manchanda et al. (1993)	Retrospective; uncontrolled	298 temporal Age range: 24-44 yrs	3-15 yrs	Review of case-notes using Syndrome Check List	PIP: 0/4 (mean onset: 45 months)	Not statistically analysed. However, 2 pts had 2 focal szs in a 24hr period. The remaining 2 pts' PIP occurred after a flurry of CPS szs, progressing to secondary generalisation	-	PIP: 4 (1.3%)

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Naylor et al. (1994)	Retrospective; uncontrolled	47 = 38 SAH/9 "other" **9 "other":** 2 pts: intially treated with SAH underwent ATLRs 1 pt: intially treated with SAH had an extra-TL resection 3 pts: TL lesionectomy 2 pts: ATLR 1 pt: previous ATLR had a frontal & re-tailored TL resection Mean age: 29.0 ± 8.9 yrs	Mean: 1.9 yrs	Structured clinical interview (PSE) & review of case-notes; ICD 10 diagnosis	**38 SAH** Mood disorder: 2/5 Anxiety disorder: 0/2 Personality disorder: 2/5 SLP: 1/1 Organic delusional disorder: 2/2 Delirium: 1/0 Eating disorder: 1/1 Cannabis dependent syndrome: 1/0 Alcohol dependent syndrome: 2/1 **9 "other"** Mood disorder: 1/1 Acute & transcient psychosis: 1/0	-	-	**38 SAH:** Mood disorder: 5 (13%) Anxiety disorder: 2 (5%) Personality disorder: 1 (3%) **9 "other"** Mood disorder: 1 (11%)
Kanemoto et al. (1998)	Retrospective; controlled	38 TLE pts who underwent TLE surgery MD mean age range: 26.8 ± 3.8 yrs Non MD mean age range: 26.1 ± 6.5 yrs	24 months	Case-notes; DSM-IV	1. Higher frequency (5x) of preop PIP pts in the postop MD (38%) than the non-MD (7%) group	-	PIP & L-sided surgery	Unclear
Altshuler et al. (1999)	Retrospective; controlled	62 = 49 ATLR (2/49 had two TL surgeries; the second were lateral neocortical extensions of a previous ATLR); 13 non-surgical group **Mean age:** Surgical group: 40.0 ± 5.3 yrs Non-surgical group: 38.9 ± 9.9 yrs	Mean: 10.9 yrs	Structured interview (SCID); DSM-III-R diagnosis	Depression: 17/14	Yes - 7/8 (88%) pts without depression recurrence postsurgery were sz free	1. Surgical group had a higher lifetime history of depression than controls	Depression: 5 (10%) 4/5 *de novo* cases developed within 1 yr
Lendt et al. (2000)	Retrospective; controlled	56 = 28 surgical/28 medical (13 temporal resections, 11 extra-TL, 2 hemispherectomies, 2 callosotomies) Age range: 4-16 yrs	3m	Child Behaviour Checklist (CBCL)	Behavioural problems in surgical group (%): 39/25. Behavioural changes significantly worsened in the medical group	Yes - better seizure outcome predicted significant improvement in postop behaviour problems	-	-

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Anhoury et al. (2000)	Retrospective; uncontrolled	109 temporal Mean age: 30.1 ± 7.4 yrs	12m	Case-notes	Mood disorder: 16/35 Anxiety disorder: 12/17 SLP: 3/3 Emotional lability: 5/12 NES: 0/4 31 (28.4%) had treatment for their psychopathology. 10 (9.2%) required psychiatric admission	No, but seizure freedom was *significantly reduced* by the presence of a preop diag of anxiety	1. Poor psychiatric outcome was associated with preop psychiatric history & bilateral interictal EEG discharges 2. Bilateral interictal EEG abnormalities related to *de novo* psychopathology 3. Postop emotional lability positively related to size of resection 4. History of affective disorders associated with postop anxiety	Mood disorder: 19 (17%) Anxiety disorder: 5 (5%) Emotional lability: 7 (6%) NES: 4 (4%)
Kohler et al. (2001)	Retrospective; uncontrolled	59 temporal (22 fear aura; 22 other aura; 15 no aura) Mean age: 33.0 ± 10.6 yrs	1-3 & 12m	Case-notes; DSM-IV diagnosis	**Fear aura (preop/1-3m/12m)** Mood disorder: 13/15/13 Anxiety disorder: 2/3/5 **Psychiatric meds (preop/12m)** Fear: 5/16 Other aura: 2/6 No aura: 2/2	Yes - mood & anxiety disorders more common in pts with persistence of szs	1. Fear aura preoperatively associated with mood & anxiety disorders 12 months after surgery 2. In the sz free sample at 12 months, mood & anxiety disorders were more common in the preoperative fear aura group	Not specified, despite clear occurrence of *de novo* cases
Inoue et al. (2001)	Retrospective; uncontrolled	226 = 196 temporal (166 ATLR; 25 SAH); 20 FLE; 10 other Age range: 15-55 yrs (mean: 26.9 yrs)	>2 yrs	Case-notes; ICD-10 diagnosis	78 (74 TLE) pts had a psychiatric diagnosis before &/ after surgery; 22 preop psychiatric diagnosis only; 39 psychiatric disorders persisted after surgery; 17 *de novo* psychiatric disorders	-	-	Affective disorder: 9 (4%) - resolved within 1-2 months. SLP: 5 (2%) - onset within 2 2 postoperative years PIP: 1 (0.4%) Adjustment disorder: 1 (0.4%) Personality disorder: 1 (0.4%)
Kanner et al. (2009)	Retrospective; uncontrolled	100 temporal (ATLR) Mean age: 31.2 ± 3.1 yrs	Mean: 8.3 yrs Range: 2-14 yrs	Structured clinical interview (SCID); DSM-IV diagn.	**Preop/2 yrs postop (n)** Axis I diagnosis: 56/24 Mood disorder: 46/18 Anxiety disorder: 25/8 Comorbid mood & anxiety: 21/7 PIP: 2/0 NES: 0/7 2 yrs postop: 44% = psychiatric medication	N/A focus of this study was identifying predictors of seizure outcome: seizure freedom at 2yrs was *significantly reduced* by the presence of a lifetime preoperative psychiatric diagnosis	-	*De novo* mood/anxiety disorders not reported; NES: 7 (7%)

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Metternich et al. (2009)	Retrospective; uncontrolled	113 = 95 temporal; 18 FLE surgical procedures: SAH/LesX Mean age: 38.5 ± 13.2 yrs	12m	Self report: BDI Overall BDI scores used in analysis, rather than clinical cut-offs	Pre- & postop BDI data not reported. The focus of this paper was identifying predictors of seizure outcome 1 yr postop: 11% = anti-depressant medication; unrelated to sz outcome	1. Yes - sz free pts had significantly lower BDI scores 2. Low preop BDI scores predicted sz freedom		-
Guarnieri et al. (2009)	Retrospective; uncontrolled	186 = TLE+HS Mean age: 35.8 yrs (8 (4%): bilateral HS)	1-10.5 yrs (Mean F/U: 6.1 yrs)	Clinical interview; DSM-IV diagnosis	**Preop (%) only reported:** Axis I diagnosis: 41 Mood disorder: 19/ Anxiety disorder: 5/ IDD: 6/ IP: 8% PIP: 3% Axis II diag: 12	N/A focus of this study was identifying predictors of seizure outcome: seizure freedom during F/U was *not* associated with preop Axis I disorders. However, pts with preop anxiety disorder or Axis II disorders were significantly less likely to be rendered seizure free	-	-
Adams et al. (2012)	Retrospective; uncontrolled	72 = TLE+HS Age range: 16-71 yrs Mean age: 37 yrs	12m	Clinical interview; DSM-IV-TR	**Preop (%) only reported:** Lifetime MD: 15 Lifetime psychosis: 4 Lifetime diag: 38 (inc. anxiety, personality disorders & substance abuse)	N/A focus of this study was identifying predictors of seizure outcome: seizure freedom at 12m was *not* significantly reduced by the presence of a lifetime preoperative psychiatric diagnosis in TLE+HS pts	-	-
Lackmayer et al. (2013)	Retrospective; uncontrolled	45 TLE+MTS Age range: 25-49 yrs	12, 24, 36m	BDI (adapted German version) (BDI < 11 = non-depressed; BDI ≥ 11 = depressed). Further analysis: BDI ≥ 18 (moderate depression) was used to assess prognostic impact of moderate depressive symptoms on seizure outcome	**Preop (%) only reported:** BDI ≥ 11: 44% BDI ≥ 18: 22%	N/A focus of this study was identifying predictors of seizure outcome: seizure freedom at 12, 24 or 36m was *not* significantly reduced by the presence of preoperative depressive symptoms (BDI ≥ 11 or 18) in TLE+MTS pts	-	-

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Hermann et al. (1989)	Prospective; uncontrolled	41 temporal Mean age: 31.4 ± 8.9 yrs	1, 3 & 6m	Self report: MHI	Specific data for pre- & post-surgery MHI scores not given.	Yes - no change in psychopathology for pts with continued szs (despite sig. reduction ≥ 75%); whereas pts with improved mental health were sz free at at 3 months F/U	-	-
Hermann et al. (1992)	Prospective; uncontrolled	97 temporal Mean age: 30.5 ± 9.4 yrs	6-8m	Self report: MMPI, WPSI & GHQ	N/A - The focus of this study was on the predictors of psychosocial adjustment	Yes - total sz freedom predicted overall postoperative psychological adjustment	Preoperative total psychological adjustment	-
Leinonen et al. (1994)	Prospective; uncontrolled	57 = 54 temporal/3 temporal & extra-TL Age range: 17-52 yrs (mean: 33.5 yrs)	2 wks, 3 & 12m	Clinical interview; DSM-III-R diagnosis & GHQ	SLP: 0/3 PIP: 4/2	Not statistically analysed. However, the 2 pts with postoperative cessation of PIP had a marked improvement in their postop sz frequency	-	SLP: 3 (5%) (mean onset: 3.8 months)
Blumer et al. (1998)	Prospective; uncontrolled	50 = 44 temporal & 6 frontal **Age Range (mean):** TLE pts: 12-59 yrs (36 yrs) FLE pts: 37-46 yrs (41 yrs)	3m & 6 monthly thereafter; mean: 2 yrs	Semi-structured interview; epilepsy questionnaire & neurobehavioural inventory	IDD: 25/28 28 (64%) pts required psychiatric medication SLP: unclear/6	Yes - poor seizure outcome associated with psychiatric morbidity	-	IDD: 8 (18%) 2/8 with concomitant psychotic features; onset within 8 months SLP: 6 (12%) - all TLE pts; onset within 6 months postop
Ring et al. (1998)	Prospective; uncontrolled	60 temporal Age range: 16-48 yrs (mean: 27 ± 7.4 yrs)	6 wks & 3m	Structured clinical interview; DSM-IV diagnosis	**Preop/6wks/3m (n)** Depression: 13/14/20 Anxiety: 11/25/5 Emotional lability: ?/27/5	-	Left-sided pathology associated with *de novo* anxiety	Unclear, although authors report that at 6 wks after surgery 50% of pts with no psychopathology at baseline had developed symptoms of anxiety or depression.

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Derry et al. (2000)	Prospective; uncontrolled	39 temporal Age range: 18-51 yrs (mean: 31.2 ± 1.0 yrs)	2 yrs	Self report: psychosocial (WPSI) & depression (CES-D) scales	Depression: 16/11	Yes - poor seizure outcome predicted poor postop depression score	Poor preop emotional adjustment (particularly for older pts, with neurological deficit(s), preop history of generalised szs, family history of psychiatric illness &/ szs) predicted higher postop depression scores	Depression: 4 (10%)
Suchy et al. (2001)	Prospective; uncontrolled	60 = 30 temporal & 30 frontal **Mean age:** TLE pts: 28.3 ± 6.3 yrs FLE pts: 27.9 ± 8.9 yrs	Mean: 7.3m	Self report: BDI (≥ 10 BDI = depressed)	**Temporal pts:** Mean BDI: 8.80/6.07 **Frontal pts:** Mean BDI: 8.80/7.47	No - change in BDI scores *unrelated* to postoperative sz status	1. Males reported lower postsurgical BDI scores 2. Frontal pts were more likely to experience *extreme* changes in mood compared to temporal pts	-
Koch-Stoecker (2002)	Prospective; uncontrolled	100 temporal Age range: 24.3-43.1 yrs (mean: 33.7 yrs) At least 4 pts: ≥ 1 TL resection	24m	Structured clinical interview (SCID); DSM-III-R diagn. The defining outcome in this study relates to the number of pts requiring psychaitric admission postoperatively	**Preop/24m (%)** Axis I diagn. only: 11/11 Axis I & II diag: 32/32 Axis II diag. only: 29/29 14% (all with preop PDs) were hospitalised	Not statistically analysed.	1. Pts with a preop PD & axis I diagn. were more likely to require postop psychiatric hospitalisation 1. Pts with a preop PD *without* an axis I diagn. were more likely to require postop psychiatric hospitalisation	-
Malmgren et al. (2002)	Prospective; uncontrolled	70 = 54 temporal; 16 extra-TL Age range: 18.3-62.2 yrs (mean: 35.1 yrs)	3, 12 & 24m	Clinical interview; DSM-III-R & Linqvist-Malmgren diagnosis	**Preop/within 24m postop** Affective disorder: 4/16 Anxiety disorder: 1/12 SLP: 1/1 AE disorder: 16/34 Frontal lobe syndrome: 11/11	-	Postop anxiety/depression associated with preop history of anxiety/depression or AE disorder	Not specified, despite clear occurrence of *de novo* cases
Spencer et al. (2003)	Prospective; uncontrolled	396 (temporal & extra-TL, no further details provided). Age range: 14-66 yrs (mean: 36.6 ± 11.3 yrs)	3, 12 & 24m	Self report: BDI & BAI (BDI & BAI ≥ 16 = moderate-severe symptoms)	**Preop/3m/12m/24m (%)** BAI ≥ 16 : 26/10/10/13 BDI ≥ 16: 24/10/13/13	No	-	-
Quigg et al. (2003)	Prospective; uncontrolled	107 = 90 temporal; 17 extra-TL Mean age: 32.5 ± 1.4 yrs	12m	Clinical interview (CDI) & MMPI-2	Depression (%): 33/44 4 pts attempted suicide within 12m of F/U; 3/4 pts completed suicide; all patients were *sz free*	-	1. Presurgical depressive morbidity predicted higher postop depression scores 2. Right sided surgery associated with increased postop depression scores	Not specified, despite clear occurrence of *de novo* cases

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Wrench et al. (2004)	Prospective; uncontrolled	60 = 43 temporal, 17 extra-TL **Mean age:** TLE pts: 35 ± 10 yrs extra TL pts: 37 ± 10 yrs	1 & 3m	Semi-structured interview (Austin CEP); DSM-IV diagnosis	**Preop/1m/3m (%)** Depression (TL group): 33/26/30 Depression (ETL group): 53/0/17 Anxiety (TL group): 23/42/24 Anxiety (ETL group): 18/6/17	No	1. Site of surgery (temporal) associated with increased depression & anxiety at 1 month F/U 2. Poor psychosocial adjustment associated with postop depression (particulary in the TL group at 1m F/U)	**Depression (TL group; 1m/3m)** 5 (13%)/4 (13%) **Anxiety (TL group; 1m/3m)** 10 (26%)/5 (15%) **Anxiety (ETL group; 1m/3m)** 0/2 (17%)
Reuber et al. (2004)	Prospective; controlled	94 = 76 surgical (60% SAH, 15% ATLR & 25% extended temporal lesionectomy); 18 medical treatment; **Mean age:** Surgical group: 35.0 ± 9.0 yrs Medical group: 35.8 ± 10.1 yrs	12m (surgical) 16m (medical)	Self report: BDI & SRAS (> 12 BDI = probably depressed; > 35 SRAS = abnormal anxiety)	**Surgical group: Preop/12m (%)** BDI > 12: 29/16 SRAS > 35: 48/39 Started antidepressant therapy postop: 3 Started anxiolytic therapy postop: 17 **Medical group: Preop/16m (%)** BDI > 12: 18/41 SRAS > 35: 39/56 Started antidepressant therapy postop: 5 Started anxiolytic therapy postop: 5	Yes - improved symptoms of depression with better sz control regardless of treatment (surgical/medical) mode	1. Pts with higher presurgical depression scores demonstrated most improvement in depression if they were sz free postsurgery 2. Increase in anxiety scores only for pts that experienced <50% improvement in sz frequency	**Depression (surgical group):** 3 (4%) **Anxiety (surgical group):** 10 (13%) **Depression (medical group):** 6 (35%) **Anxiety (medical group):** 4 (22%)
Devinsky et al. (2005)	Prospective; uncontrolled	360 = 322 temporal, 38 extra-TL Mean age: 37.6 ± 11.1 yrs	3, 12 & 24m	Clinical interview (CIDI) ICD-10 & DSM-IV diagnosis; Self-report: BDI & BAI: (scores ≥ 16 = moderate - severe)	**Preop/24m (%)** BDI ≥ 16: 22.1/11.7 BAI ≥ 16: 24.7/13 **CIDI diagnosis: preop/24m (n)** Anxiety disorder: 59/29 Depression: 75/26 SLP: 6/3 Of note, authors state at 24m F/U, pts with preop SLP were lost to FU	Yes - moderate to severe depressive symptoms were reported in 17.6% with continued seizures vs 8.2% who were sz free at 24 months	Presurgical depressive symptoms strongest predictor of postop depression (i.e. ≥ 16 BDI score)	Depression: 16 (6.1%) Anxiety: 18 (6.9%) SLP: 3 (1.1%)
Cankurtaran et al. (2005)	Prospective; uncontrolled	22 temporal Age range: 18-49 yrs (mean: 30.0 ± 9.1 yrs)	3 & 6m	Clinical interview (SCID-I); DSM - IV diagnosis; BPRS, HDRS & HARS	**Preop/3m/6m** **Psychiatric dignosis (SCID-I):** **6 (27%)/7 (32%)/2 (9%):** Depression: 2/4/2 Anxiety: 4/2/0 Adjustment disorder: 0/1/0 **Self-report measures: Preop/3m/6m (mean)** BPRS: 6.0/8.3/4.0 HDRS: 5.3/8.0/4.1 HARS: 6.5/9.5/4.7 Psychiatric meds required in 4 (18%) pts at 3m F/U and 7 (32%) at 6m F/U	-	-	**3 months** Depression: 4 (18.2%) Anxiety: 2 (9%) Adjustment disorder: 1 (5%) **6 months** Depression: 1 (5%)

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Mattsson et al. (2005)	Prospective; uncontrolled	57 = 47 temporal; 10 extra-TL Mean age: 39.0 ± 10.0 yrs	2-8 yrs	Anxiety scale (KSP)	Specific data for pre- & postsurgery KSP scores not reported. However, somatic & psychic trait anxiety normalised in pts with Engel I outcome	No significant differences in KSP scores between Engel I (sz free/auras) & Engel II-IV (CPS ± secondary generalisation) groups	-	-
Pintor et al. (2007)	Prospective; uncontrolled	70 = 59 ATLR/11 SAH Mean age: 31.1 ± 8.3 yrs	1, 6 & 12m	Clinical interview (SCID-IV); DSM - IV diagnosis	**Preop/1m/6m/12m (%)** Psychiatric disorder: 47/43/32/25	No (Additionally, no significant difference in sz outcome & presence of a preop psychiatric diagnosis)	1. Any (lifetime/during presurgical evaluation) psychiatric history related to psychiatric disorders post-surgery 2. Gender: females more likely to have postoperative psychiatric diagnoses	Psychiatric diagnosis: 3 (4.3%) (no further details given)
Meldolesi et al. (2007)	Prospective; uncontrolled	52 temporal Mean age: 33.0 ± 9.4 yrs	12 & 24m	Self report: BDI, STAI, MMPI & STAXI (BDI ≥ 16 = clinical depression)	Specific data for pre- & post-surgery psychiatric prevalence rates not reported. However, anxiety & anger significantly improved; depression reduced, but not significantly	No	Both (1) younger age and (2) shorter duration of epilepsy were related to improved postoperative anger scores	-
Witt et al. (2008)	Prospective; uncontrolled	151 = 125 temporal; 26 extra-TL **Mean age:** TLE pts: 37.9 ± 12.2 yrs extra-TL pts: 33 ± 9.9 yrs	12m	Self report: BDI, FPZ (BDI ≥ 17= clinical depression)	**Mean score: Preop/12m** BDI: 9.4/7.9 **FPZ:** Extraversion: 52.7/52.5 Neuroticism: 80.6/74.2 Organic Psycho-Syndrome: 71.4/65.5 Addiction: 17.1/16.6	Yes - significantly lower neuroticism, organic psych-syndrome & BDI scores in sz free group	Right sided surgery associated with decreased postop depression scores	Depression: 13 (8.6%), of which 6 pts were sz free
Salgado et al. (2009)	Prospective; uncontrolled	36 temporal Age range: 22.9-41.1 yrs (mean: 32 ± 9.1 yrs)	6 &12m	Self report: QOLiE-31; STAI; BDI; PEQ; PLCQ	**Mean score: Preop/6m/12m** QOLiE-31: 63.7/84.3/82.7 STAI: 45.9/37.1/37.3 BDI: 9.6/5.8/4.2 PEQ: 36.1/-/- PLCQ: -/51.6/58.8	-	-	-

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Guangming et al. (2009)	Prospective; uncontrolled	62 temporal (all CAH) Age range: 16-46 yrs (mean: 28.8 ± 7.6 yrs)	12 & 24m	Self report: SCL-90-R	**Preop/12m/24m (mean score)** SCL-90-R: 2.18/1.95/1.79	Yes - significantly lower SCL-90-R scores attained at 12m & 24m F/U for pts with Engel I outcome	-	-
Wrench et al. (2011)	Prospective; uncontrolled	60 = 38 MTR/22 NMTR = 9 lateral TL corticectomies 10 frontal; 2 occipital; 1 temporoparietal corticectomy. Age range: 18-60 yrs (mean: 35 ± 10.9 yrs)	1, 3, 6 & 12m	Clincal interview (MSE); DSM-IV diagnosis; semi-structured interview (Austin CEP)	**MTR group: Preop/1m/3m/6m/12m (%)** Depression: 40/16/20/26/38 **NMTR group: Preop/1m/3m/6m/12m (%)** Depression: 50/14/20/25/24 Irrespective of surgical intervention, 13 (22%) on SSRI therapy postoperatively	No - postoperative depression was *unrelated* to sz outcome for the sample as a whole or at post-surgical time-point	1. History of preoperative depression associated with post-surgical depression 2. Poor postoperative family dynamics associated with postoperative depression 3. Type of surgical intervention (MTR) associated with *de novo* depression: 13% MTR vs 0% NMTR	Depression: 5 (8.3%); all pts had a MTR (4/5 pts onset within 3m)
Barbieri et al. (2011)	Prospective; uncontrolled	12 = 8 temporal; 2 FLE; 1 occipital; 1 temporo-frontal Mean age: 36.3 ± 8.2 yrs	6 &12m	Clinical interview; DSM-IV-TR diagn. SANS; SAPS	**Mean preop/6m/12m scores** SANS: 33/39/34.4 SAPS: 31/34/28.5	Small n precluded statistical analysis	-	-
Hamid et al (2011)	Prospective; uncontrolled	256 = temporal and extra-TL surgeries Age range: 27.3-48.1 yrs (mean: 37.7 ± 10.4 yrs)	3, 12, 24, 48 & 60m	Self report: BDI (BDI ≥ 15= moderate - severe depression)	**Preop/60m (%)** not depressed: 64.1/77.3 mild depression: 13.3/7.8 moderate-severe: 22.7/14.8	Yes, only pts with excellent (vs. fair/poor) or good (vs. poor) sz control had significant reduced mean change in BDI BDI scores at 60m	-	Depression: 10 (4%) Notably, 6/10 pts *did* have a previous history of affective disorders
Hellwig et al. (2011)	Prospective; uncontrolled	84 = 55 temporal; 21 extra-TL; 8 temporal & extra-TL Age range: 23.8-49.2 yrs Mean age: 36.5 ± 12.7 yrs	3 & 12m (N.B. 12m F/U data was only avaliable on 67pts which is not clearly reported)	Clinical interview; ICD-10 & ILAE neuropsychiatric classification	**Preop/3m (n)** Psychiatric diag: 48/46 Affective disorder: 29/27 Irrespective of surgical intervention, 9 (11%) were prescribed psychotrophic medication.	Yes, significant association between the remission of affective disorder and Engel I or II seiuzre outcome at 3m. However, no sigificant difference between Engel I and II-IV were observed at 3 or 12m	-	**3 month F/U** Psychiatric diag: 14 (17%) Affective disorder: 12 (14%) 3 pts (25%) had a preoperative personality disorder diagnosis. 6 pts showed remission of affective disorder within 12m

Table 6 (continued)

Study	Study type	Sample (n)[a,b]	Follow-up	Assessment type	Overall outcome (preop/postop)	Outcome related to seizure freedom?	Other predictors of psychiatric outcome[c]	Number of *de novo* cases
Filho et al. (2012)	Prospective; uncontrolled	115 = TLE+MTS Mean age: 36.9 ± 10.7 yrs	Within the first year following surgery	Clinical interview; DSM-IV (Axis I & II were considered)	**Lifetime preop/postop (%)** Psychiatric diag: 41/27 MD: 23/12 Anxiety: 10/9 PIP: 3/? IP: 3/7	N/A The preop psychiatric group had significantly more pts with an *unfavourable* sz outcome	1. De novo psychosis (type: PIP/ IP unspecified) was associated with L MTS 2. Preop MDD and IP were associated with the continuance of postop psychopathology 3. Contralateral epileptiform discharges were associated with continued postop psychiatric morbidity 4. Older age at surgery related to de novo psych	Psychiatric diag: 11 (10%) MD: 3 (4%) Anxiety: 3 (4%) Psychosis: 5 (7%); type (PIP/IP) unspecified. 27 (54%) of preop cases reported complete remission of psychopathology postop
Filho et al. (2012a)	Prospective; uncontrolled	115 = TLE+MTS Mean age: 36.9 ± 10.7 yrs (same sample as 2012 paper)	Within the first year following surgery	Clinical interview; DSM-IV (Axis I)	**Lifetime preop/postop (%)** Psychiatric diag: 41/27 MD: 23/12 Anxiety: 10/9 PIP: 3/? IP: 3/7	N/A The preop psychiatric & MDD groups had significantly *poorer* postop sz outcome	-	- 27 (54%) of preop cases reported complete remission of psychopathology postop
Engman et al. (2012)	Prospective; uncontrolled	50 = 39 TLE & 11 FLE	24m	KSP & HADS	**Lifetime preop/postop (%)** Psychiatric diag: 24/? Specific data for KSP & HADS were not reported. Statistical analyses were based on *change* from baseline (preop) to 24m F/U	No - there were no significant associations between change in KSP/HADS & seizure outcome for either the TLE/FLE groups	-	-
da Conceição et al. (2013)	Prospective; controlled	145 TLE+MTS (8 (6%) = bilateral MTS) Age range: 18-63 yrs Mean age: 37.8 ± 10.3 yrs	≥ 24m	Clinical interview; DSM-IV	**Preop (%) only reported:** Psychiatric diag: 42 MD: 61 Anxiety: 13 PIP: 12 IP: 8	N/A focus of this study was identifying the surgical outcome of pts with a lifetime psych history: Seizure outcome did not significantly differ between pts with/without preoperative psychiatric morbidity (n=94)	-	-

ATLR, anterior temporal lobe resection; AE disorder, Astheno-Emotional disorder; Austin CEP, Austin Comprehensive Epilepsy Program; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; CAH, corticoamygdalohippocampectomy; CDI, clinical depression index; CES-D, Centre for Epidemiological Studies Depression Scale; CIDI, Composite International Diagnostic Interview; Diagn, diagnosis; DSM, Diagnostic and Statistical Manual for Mental Disorders; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders - Text Revision; ETL, extra-temporal; F/U, follow-up; FLE, frontal lobe epilepsy; FPZ, Fragebogen zur Persönlichkeit bei zerebralen Erkrankungen; GHQ, General Health Questionnaire; HADS, Hospital anxiety and depression scale; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; HS, hippocampal sclerosis; ICD, International Classification of Disease; IDD, interictal dysphoric disorder; IP, interictal psychosis; KSP, Karolinska Scales of Personality; LesX, lesionectomies; m, months; MD, mood disorder; MHI, Mental Health Inventory; MMPI, Minnesota Multiphasic Personality Inventory; MMPI-2, Minnesota Multiphasic Personality Inventory, scale 2; MSE, mental state examination; MTR, mesial temporal resection; MTS, mesial temporal sclerosis; n, sample size; NMTR, nonmesial temporal resection; PD, personality disorder; PEQ, Preoperative Expectations Questionnaire; PIP, postictal psychosis; PSE, Present State Examination; PLCQ, Postoperative Life Changing Questionnaire; Pts, patients; QOLiE-31, quality of life questionnaire; RCI, reliable change index; SAH, selective amygdalohippocampectomy; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SCID, Structured Clinical Interview for DSM; SCL-90-R, Self-Report Symptom Inventory; SLP, schizophrenia-like psychosis; SRAS, Self-Rating Anxiety Scale; STAI, Spielberger State-Trait Anxiety Inventory; STAXI, Spielberger State-Trait Anger Expression Inventory; Sz(s), seizures; TL, temporal lobe; TLE, temporal lobe epilepsy; WPSI, Washington Psychosocial Seizure Inventory. ([a] = sample size that was used in statistical analysis. Thus, sample size may not always equal the size reported in research article; [b] = age data as reported in article; [c] = only listed if statistically significant predictor).

Twenty-seven studies were prospective but uncontrolled; fourteen were retrospective but uncontrolled; three were retrospective and controlled and two prospective and controlled. Control groups consisted of patients deemed not eligible for surgery (Altshuler et al., 1999; da Conceição et al., 2013), continued on medical treatment (Lendt et al., 2000; Reuber et al., 2004) or who did not develop a postoperative mood disorder (Kanemoto, Kawasaki & Mori, 1998). The majority of retrospective studies (n=10) had a follow-up of more than 1 year (range 3 months – 30 years). However, one retrospective study did not report their follow-up duration (Roberts et al., 1990). Unsurprisingly, prospective studies in comparison had a shorter follow-up ranging from 2 weeks to 8 years.

Depression (twenty-nine studies), anxiety (twenty-three studies) and interictal psychosis (seventeen studies) were the most frequent outcomes explored. These outcomes were assessed mainly through reviewing case-notes, via structured clinical interview and/or self-report measures. Other outcomes received less attention: postictal psychosis (nine studies), personality disorders (seven studies), non-epileptic seizures (three studies), psychosocial adjustment (one study), behavioural problems (one study) and interictal dysphoric disorder (IDD; one study).

2.5 Depression

The prevalence of preoperative depressive symptoms in TLE patients was highly variable owing to divergent methodologies and diagnostic classifications (range 5-61%) (Naylor, et al., 1994; Ring, Moriarty & Trimble, 1998; Altshuler et al., 1999; Derry, Rose & McLachlan, 2000; Kohler et al., 2001; Wrench, Wilson & Bladin, 2004; Cankurtaran et al., 2005; Kanner et al., 2009; Guarnieri et al., 2009; Wrench et al., 2011; Adams et al., 2012; Filho et al., 2012;

da Conceição et al., 2013; Lackmayer et al., 2013). Cases of attempted and completed suicide have been reported, paradoxically in patients who have been rendered seizure free (Jensen & Larsen, 1979; Quigg et al., 2003).

There were inconsistent findings comparing depression before and after temporal lobe surgery. A number of studies reported improvements in depression after surgery, defined either as a reduction in the number of patients meeting the clinical criteria for depression (Ring et al., 1998; Altshuler et al., 1999; Kanner et al., 2009; Wrench et al., 2011; Filho et al., 2012), or significant improvements in rating scales measuring depressive symptomatology (Derry et al., 2000; Reuber et al., 2004; Hamid et al., 2011).

In contrast, Anhoury and colleagues (2000) found no change in prevalence rates of mood disorders pre- and post-surgery. In two studies it was unclear whether depression prevalence rates had improved or worsened after surgery, as the frequency of patients that developed de novo depression was not reported (Ring et al., 1998; Kohler et al., 2001).

Although depression improved in some patients, de novo cases (including IDD) were reported in a minority of cases (Naylor et al., 1994; Blumer et al., 1998; Altshuler et al., 1999; Anhoury et al., 2000; Derry et al., 2000; Reuber et al., 2004; Wrench et al., 2004; Cankurtaran et al., 2005; Devinsky et al., 2005; Witt, Hollmann & Helmstaedter, 2008; Wrench et al., 2011; Hamid et al., 2011; Filho et al., 2012).

In studies that only included temporal lobe surgical patients, de novo depression prevalence rates ranged from 4% (Reuber et al., 2004) to 18% (Cankurtaran et al., 2005). The research findings reviewed suggest that de novo depression frequently occurs within 3-12 months after surgery (Altshuler et al., 1999; Cankurtaran et al., 2005) and tends to persist (range 1-11

months; Wrench et al., 2011). However, determining the evolution of depression is challenging, owing to the varied and limited time frames in which psychiatric symptoms have been assessed.

Regarding predictors of post-surgical depression, ten studies demonstrated that improvements in depression after surgery were related to significant gains in seizure control (Blumer et al., 1998; Altshuler et al., 1999; Derry et al., 2000; Kohler et al., 2001; Reuber et al., 2004; Devinsky et al., 2005; Witt et al., 2008; Metternich et al., 2009; Hamid et al., 2011). This, however, was not a consistent finding (Suchy & Chelune, 2001; Spencer et al., 2003; Wrench et al., 2004; Meldolesi et al., 2007; Wrench et al., 2011; Engman et al., 2012).

There is little evidence to suggest that post-surgical depression is associated with the laterality of the surgical resection. Only one study found that patients undergoing a right temporal lobe resection were at greater risk (Quigg et al., 2003), but this has not been confirmed by others (Ring et al., 1998; Blumer et al., 1998; Altshuler et al., 1999; Derry et al., 2000; Kohler et al., 2001; Wrench et al., 2004; Devinsky et al., 2005; Wrench et al., 2011; Hamid et al., 2011).

Significant preoperative risk factors for postoperative depression include: pre-existing history of affective disorders (depression or anxiety) (Malmgren et al., 2002; Quigg et al., 2003; Devinsky et al., 2005; Wrench et al., 2011; Filho et al., 2012); fear auras (Kohler et al., 2001); temporal versus extra-temporal surgery (Wrench et al., 2004) and within this group, mesial versus lateral resections (Wrench et al., 2011). Female gender (Suchy et al., 2001), poor psychosocial adjustment (Derry et al., 2000; Wrench et al., 2004) and negative family dynamics (Wrench et al., 2011) have also been found to place patients at higher risk.

2.6 Anxiety

The prevalence of preoperative anxiety symptoms was also extremely variable, ranging from 0-48% (Naylor et al., 1994; Ring et al., 1998; Anhoury et al., 2000; Kohler et al., 2001; Malmgren et al., 2002; Spencer et al., 2003; Reuber et al., 2004; Wrench et al., 2004; Cankurtaran et al., 2005; Devinsky et al., 2005; Kanner et al., 2009; Guarnieri et al., 2009; Salgado & Cendes, 2009; Filho et al., 2012; da Conceição et al., 2013), and as for depression, this is likely to be due to different diagnostic and psychopathological measures used. For instance, Devinsky et al. (2005) reported that preoperatively a quarter of patients had moderate to severe anxiety according to rating scale data, whereas 17% met the clinical criteria for an anxiety disorder following a structured clinical interview (Composite International Diagnostic Interview, CIDI).

The majority of studies demonstrated reduced prevalence of anxiety postoperatively when assessed between 3 months – 12 years after surgery (Taylor, 1972; Jensen et al., 1979; Spencer et al., 2003; Cankurtaran et al., 2005; Devinsky et al., 2005; Kanner et al., 2009; Salgado et al., 2009). Two studies however have suggested that anxiety symptoms may present early and resolve within the first few weeks following surgery (Ring et al., 1998; Kohler et al., 2001). Ring and co-workers (1998) reported that anxiety symptoms rose 6 weeks after TLE surgery in their surgical cohort, and reduced to about half the pre-surgical prevalence rate by 3 months. Similarly, Wrench et al. (2004) found anxiety diagnoses peaked 4 weeks after temporal lobe surgery, remitting to pre-surgical levels 3 months later.

Four studies found an increase in the prevalence of anxiety disorders postoperatively (Naylor et al., 1994; Anhoury et al., 2000; Kohler et al., 2001; Malmgren et al., 2002) and one study demonstrated no significant change in self-reported anxiety symptoms (Reuber et al., 2004).

Seven studies reported de novo anxiety cases, ranging from 3-26% (Taylor, 1972; Naylor et al., 1994; Anhoury et al., 2000; Reuber et al., 2004; Wrench et al., 2004; Cankurtaran et al., 2005; Hamid et al., 2011; Filho et al., 2012). The highest prevalence rate was noted one month after temporal lobe surgery (26%) (Wrench et al., 2004).

Evidence for predictors of post-surgical anxiety indicates patients with a previous history of affective disorders (depression/anxiety) (Anhoury et al., 2000; Malmgren et al., 2002) are more susceptible to postoperative anxiety. As with depression, TLE patients with preoperative fear auras were identified in one study as at greater risk of post-surgical anxiety disorders despite becoming seizure free (Kohler et al., 2001).

Data relating to the predictive value of other clinical characteristics is unconvincing. Some authors have reported an association between temporal lobe (versus extra-temporal lobe) surgery and postoperative anxiety (Wrench et al., 2004), but this has not been replicated (Devinsky et al., 2005). There is conflicting evidence as to whether postoperative anxiety is influenced by seizure outcome. Two studies reported that anxiety disorders/symptoms were more common in patients with persistent seizures (Kohler et al., 2001), or less than 50% reduction (Kanemoto et al., 1998), but another did not support such an association (Devinsky et al., 2005). Of those studies considering surgical laterality, only one reported an association between left temporal lobe resection and the development of de novo postoperative anxiety (Ring et al., 1998).

2.7 Interictal psychosis

Reported preoperative prevalence rates are widely divergent (0-16%) (Taylor, 1972; Jensen et al., 1979; Roberts et al., 1990; Leinonen, Tuunainen & Lepola, 1994; Naylor et al., 1994; Anhoury et al., 2000; Guarnieri et al., 2009; Malmgren et al., 2002; Barbieri et al., 2011; Filho et al., 2012; da Conceição et al., 2013). Arguably, the high baseline prevalence of interictal psychosis may have been inflated by earlier retrospective studies that included patients directly referred for surgery from psychiatric institutions (Taylor, 1972; Jensen et al., 1979).

Patients with pre-existing interictal psychosis are often unlikely to be considered for surgical intervention for their seizures (Taylor, 1972; Jensen et al., 1979; Roberts et al., 1990; Anhoury et al., 2000; Malmgren et al., 2002; Foong et al., 2007). However, a recent small prospective study, but the largest reported, (Barbieri et al., 2011) found that positive symptoms (hallucinations/delusions) worsened for a subgroup of patients (n=4/12) in the first 6 months and later improved to preoperative levels at 12 month follow-up. Negative symptoms (social withdrawal/emotional blunting) either persisted or remained unchanged in the majority of their patients at one year follow-up. No patients with worsening psychotic symptoms required hospitalisation.

There are a number of reports of an interictal psychosis presenting for the first time following TLE surgery (Jensen et al., 1979; Roberts et al., 1990; Stevens et al., 1990; Leinonen et al., 1994; Blumer et al., 1998; Inoue & Mihara, 2001; Devinsky et al., 2005). Two prospective studies reviewed reported de novo interictal psychosis cases (Blumer et al., 1998; Devinsky et al., 2005). Blumer et al.'s (1998) study of temporal and frontal lobe resections

demonstrated a 12% prevalence rate of de novo interictal psychosis at 6 months post-surgery. Notably, all de novo cases had undergone a temporal lobe resection. Devinsky et al.'s (2005) uncontrolled study of temporal and frontal resections reported a much lower rate of de novo interictal psychosis (1.1%) at 24 months follow-up. It is possible that the de novo interictal psychosis prevalence rate may have been underestimated due to the high attrition rate of this study.

There is no clear evidence of a relationship between the development of psychotic symptoms and postoperative seizure control (Jensen et al., 1979; Leinonen et al., 1994; Blumer et al., 1998; Inoue et al., 2001), or that surgical laterality is a risk factor. The pathological mechanisms mediating the development of de novo psychotic symptoms have not been clarified. Stevens (1990) proposes that aberrant reinnervation with axonal sprouting in the projection sites of the surgical area explains the latency (2-24 months) between surgical resection and the development of de novo cases. However, a histopathological study (Roberts et al., 1990) found a significant association between developmental lesions (gangliogliomas) in the temporal lobe and de novo interictal psychosis. In contrast, Anhoury et al. (2000) failed to find that de novo interictal psychosis patients had developmental pathological abnormalities. The authors highlight, however, that very few patients included in the 'developmental pathology' group had gangliogliomas.

2.8 Postictal psychosis (PIP)

Given the limited research on PIP, case studies will be reviewed, although they are not presented in Table 6.

PIP is a recognised psychiatric complication of temporal lobe epilepsy (TLE); usually manifesting after a cluster of complex partial or generalised seizures (Logsdail & Toone, 1988). Psychotic symptoms tend to emerge following a symptom-free (lucid) period ranging from 12 to 72 hours (Kanner et al., 1996) and are transient; typically lasting several days (Leutmezer et al., 2003), but may be up to weeks (Devinsky et al., 1995).

Incidence rates of PIP in studies of patients undergoing video-electroencephalography recordings (VEEG) are ~7% (Kanner et al., 1996; Alper et al., 2001). Patients who have a recurrent PIP may be at risk of developing chronic interictal psychosis (Tarulli, Devinsky & Alper, 2001). The clinical risk factors reported are diverse, although widespread cerebral disturbance has been consistently reported (Ferguson et al., 1969; So et al., 1990; Devinsky et al., 1995; Mathern et al., 1995; Kanemoto, Kawasaki & Kawai, 1996; Kanner et al., 1996; Seeck et al., 1999; Takeda et al., 2001; Christodoulou et al., 2002; Alper et al., 2008; Kanner & Ostrovskaya, 2008; Falip et al., 2009; Schulze-Bonhage & van Elst, 2010; Oshima, Motooka & Kanemoto et al., 2011; Kuba, Brázdil & Rektor et al., 2012)

There is limited data of post-surgical outcome of patients with PIP in relation to psychiatric status (Kanemoto et al, 1998; Kanemoto et al., 2001) or seizure outcome (Alper et al., 2008; Kanner et al., 2008; Falip et al., 2009). Two studies suggest that a history of PIP is associated with postsurgical de novo psychopathology, particularly mood disorders (Kanemoto et al., 1998; Kanemoto et al., 2001).

2.9 Methodological limitations

The literature review highlights a number of methodological problems that make it difficult to draw definite conclusions and undoubtedly contribute to the conflicting findings. Firstly, many studies provide little or no information regarding pre-surgical psychiatric status (Chovaz et al., 1994; Kanemoto et al., 1998; Kanemoto et al., 2001; Mayanagi et al., 2001; Moss et al., 2009). Even when reported, pre-surgical psychiatric evaluations are usually only sought if there is a positive psychiatric history or if patients report peri-operative psychiatric symptoms (Malmgren et al., 2002; Metternich et al., 2009). If a neuropsychiatric assessment is not part of the pre-surgical evaluation, cases and symptoms may be missed (Boylan et al., 2004; Kanner et al., 2008). Patients and families often under-report psychiatric symptomatology, viewing this as a "natural reaction" to difficult life circumstances (Kanner, 2008). Some surgical candidates may not disclose past or current psychopathology in the fear that it would disqualify them from surgical consideration (Kanner et al., 2000). Moreover, psychiatric comorbidities in TLE patients are often unrecognised or overlooked in routine neurological consultations and go untreated despite persisting symptoms severe enough to warrant pharmacotherapy (Kanner et al., 2000; Boylan et al., 2004). The lack of a psychiatric evaluation preoperatively, as part of standard clinical care, may in turn inflate the reporting of de novo figures postoperatively (type I error).

Another important consideration is the time-frame during which mental health is assessed. Psychiatric comorbidity rates may differ depending on whether the evaluation focuses on lifetime prevalence of psychiatric dysfunction (Anhoury et al., 2000; Guarnieri et al., 2009; Kanner et al., 2009; Adams et al., 2012; Filho et al., 2012) or sets a specific period (e.g. the 6 months immediately before surgery). Conceivably, psychiatric status in the months

preceding surgery, when patients are undergoing complicated assessments that include anxiety-provoking measures (sleep deprivation, medication reduction, continuous video-EEG recording) that could lead to life-altering neurosurgery may not represent stable mood states (Glosser et al., 2000).

Several studies had short follow-up periods (≤ 6 months) which may distort the profiling of postoperative psychopathology. It may be erroneously concluded that patients are no longer at risk of de novo psychiatric morbidity or an exacerbation of symptoms after this time-frame (Herman et al., 1989; Ring et al., 1998; Lendt et al., 2000; Wrench et al., 2004; Cankurtaran et al., 2005). Conversely, other studies where follow-up commenced after 6 months (Hermann et al., 1992; Anhoury et al., 2000; Metternich et al., 2009; Salgado et al., 2009), or even several years after surgery (Taylor et al., 1972; Stevens 1990; Naylor et al., 1994; Altshuler et al., 1999; Derry et al., 2000; Suchy et al., 2001; Inoue et al., 2001; Mattsson et al., 2005), will miss the emergence of early psychiatric complications. For example, Wrench et al. (2011) found the majority of clinically depressed patients (70%) were diagnosed within 3 months postoperatively and in 65% of diagnosed cases, the depression persisted for at least 6 months.

The application of diverse diagnostic criteria, instruments and clinical cut offs in assessing psychiatric status complicates comparison across studies. Self-reported measures are not comparable with results of psychiatric diagnostic procedures using semi-structured interviews of patients and families, or rating scales completed by a neuropsychiatrist (Glosser et al., 2000). A thorough psychiatric evaluation does not only consider transient mood states reflected by self-reported indices, but the full context of the presenting symptoms; including the history, other behavioural characteristics, and corroborative information from the family or carer(s). Although no single method is ideal to assess psychiatric functioning pre- or post-

surgery (Guangming et al., 2009), a composite of measures may be the best approach. Even when standardised classification systems are adopted, for example the DSM or ICD, many argue that neither has been validated on patients with neurological conditions (Glosser et al., 2000; Anhoury et al., 2000). Furthermore, the clinical constellation of symptoms evident in patients with epilepsy may not conform to a single diagnostic category (Glosser et al., 2000; Meldolesi et al., 2007).

Few studies had a control group (Kanemoto et al., 1998; Altshuler et al., 1999; Lendt et al., 2000; Reuber et al., 2004; da Conceição et al., 2013) and given the high psychiatric morbidity in patients with epilepsy, it is difficult to determine whether surgery per se is a risk factor. Control groups were restricted to patients who were denied surgery (Altshuler et al., 1999; Lendt et al., 2000; da Conceição et al., 2013), did not develop a postoperative mood disorder (Kanemoto et al., 1998) or who did not go on to have surgery; presumably due to high risks of neuropsychological impairment and low odds of seizure freedom (Reuber et al., 2004). Furthermore, a number of studies used heterogeneous samples that included temporal, extra-temporal and palliative procedures yielding limited data regarding temporal lobe surgery.

Regarding postictal psychosis, few studies have investigated the relationship between PIP and post-surgical psychiatric outcome. Of these, the relationship between the number of PIP episodes (i.e. PIP severity) and postoperative psychiatric morbidity has not been examined. No study has systematically explored the association of PIP with neuropsychological test performance, apart from studies reporting unspecified bi-temporal memory dysfunction (So et al., 1990; Mathern et al., 1995; Christodoulou et al., 2002; Falip et al., 2009), or the relationship with postoperative neuropsychological/seizure outcome.

2.10 Statistical analysis

Statistical approaches employed are also open to criticism. Research on the predictors of postoperative psychopathology is dominated by Chi-squared (X^2) or Fisher exact analyses (see, Naylor et al., 1994; Kanemoto et al., 1998; Ring et al., 1998; Kohler et al., 2001; Malmgren et al., 2002; Wrench et al., 2004; Devinsky et al., 2005; Pintor et al., 2007; Witt et al., 2008, for examples) as the outcome variables are normally categorical (i.e. presence/absence of psychopathology).

Although exploratory univariable analyses (i.e. multiple X^2 tests) are sufficient for identifying *possible* preoperative predictors of postoperative psychiatric morbidity, they fail to *quantify* or *adjust* for the association between variables of interest in the presence of *other* preoperative factors. Moreover, the performance of numerous univariable analyses also increases the chance of finding significant results purely by chance (type I error). A further disadvantage of this non-parametric test is that all predictor(s) variables are required to be *categorical*.

These difficulties can be avoided by using multivariable analyses and some studies have adopted this approach (Blumer et al., 1998; Anhoury et al., 2000; Wrench et al., 2011; Filho et al., 2012; Filho et al., 2012a, for examples). Logistic regression is a multivariable statistical technique with the advantage that predictor variables can be continuous *or* categorical. Therefore, the relationship between a continuous independent variable (e.g. *years* of epilepsy) and the outcome (e.g. de novo psychopathology) does not need to be partitioned into arbitrary categories (*'per 10 year'* increase in epilepsy duration). This approach also enables the *quantification* of associations between variables and examines the

odds of the outcome (de novo psychopathology) *per unit* increase/decrease in the predictor (*per year* of epilepsy duration).

Following the identification of significant univariable associations in the primary analysis, a multivariable logistic regression analysis can be performed to identify any *independent* associations, whilst controlling for other preoperative factors; thereby minimising the risk of a type I error.

Reducing the chance of a type I error can also be achieved by including the *fewest* possible predictors in a multivariable model. The suggested guideline is a ratio of 1 predictor per 10 positive cases (of postoperative psychopathology) (Field, 2009). Apart from the number of predictors, the *method* (e.g. hierarchical/forced/stepwise) in which predictors are entered into a model can also reduce the type I error rate. However, some investigators have exceeded this ratio and not specified the method used in their predictive analysis (see Filho et al., 2012, for example).

The majority of self-report longitudinal data collected in psychiatric research has some form of *hierarchical* structure, with repeated measurements (at Level 1) *nested/clustered within individuals* (at Level 2) (see Figure 3).

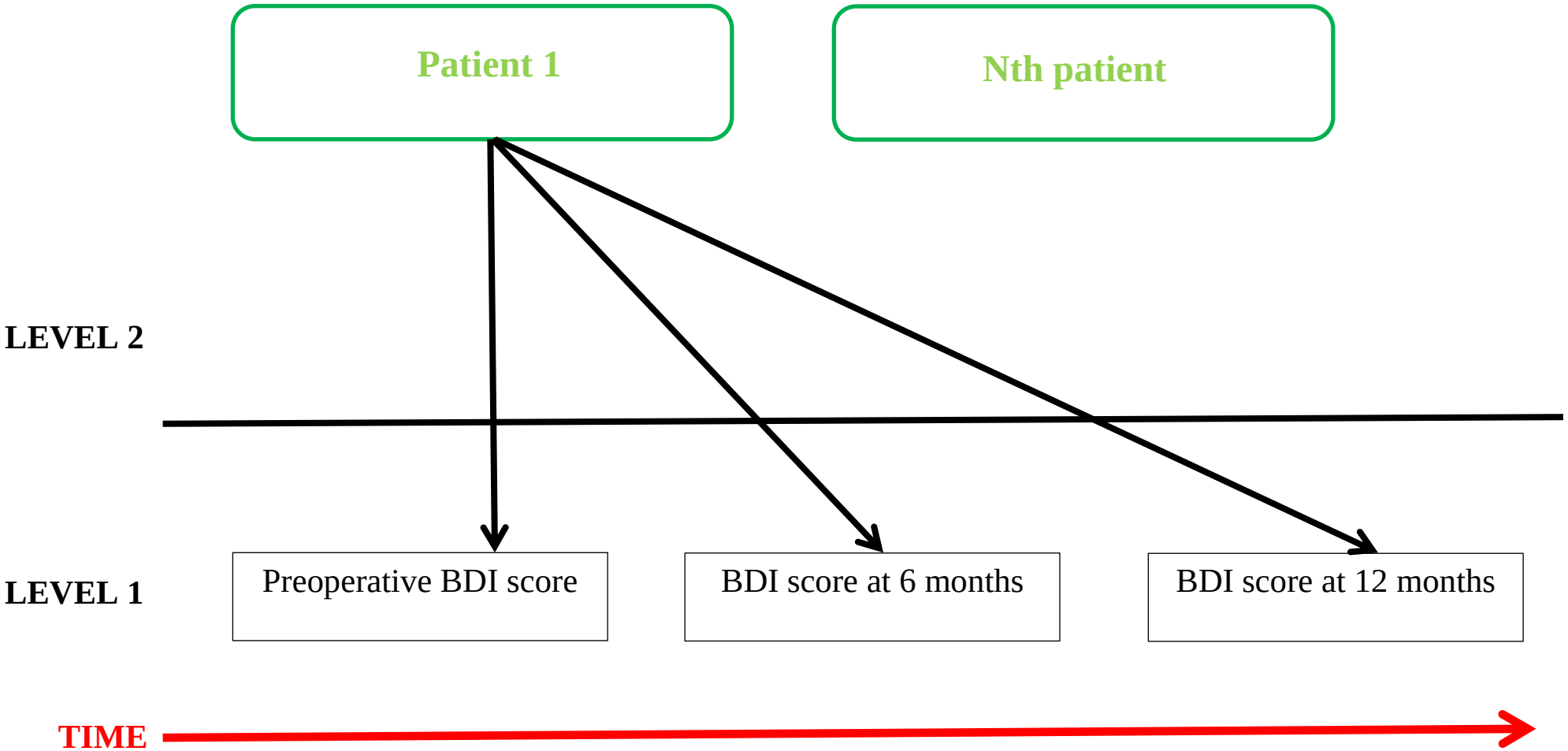

Figure 3. *An example of a 2-level hierarchical data structure, where level 1 is a repeated measure (Beck Depression Inventory, (BDI) score) nested within a patient at level 2.*

This inherent hierarchical structure therefore should be reflected in the statistical models that are used to analyse such data (Paterson & Goldstein, 1991). However, self-report data from longitudinal research is usually analysed using a conventional generalised linear model (GLM), such as repeated-measures analysis of variance (rANOVA) (see: Suchy et al., 2001; Spencer et al., 2003; Quigg et al., 2003; Reuber et al., 2004; Cankurtaran et al., 2005; Meldolesi et al., 2007; Witt et al., 2008; Metternich et al., 2009, for examples). However, rANOVA has a number of assumptions that when violated invalidate the model's accuracy, including:

1. Complete/balanced dataset – equal number of patients at *each* post-surgical follow-up

2. Sphericity – The variances in a characteristic of interest (e.g. Beck Depression Inventory; BDI) for *each* follow-up time are *equal*

3. Independence of observations – No correlation between residual scores in a characteristic of interest (e.g. BDI) between follow-up times

Due to sample attrition data sets may be unbalanced, violating assumption 1. To circumvent this problem, subjects with missing values may be removed from analysis reducing statistical power and introducing sample bias (e.g. listwise deletion; all subjects with missing value(s) for a characteristic of interest are deleted from the dataset) or imputation techniques employed (e.g. last observation carried forward), resulting in biased treatment estimates (see Gueorguieva & Krystal, 2004, for further discussion).

The assumption of sphericity is often violated in longitudinal research designs as consecutive observations on the *same* subject tend to be correlated more highly than observations on the

same subject taken further away in time (Gueorguieva et al., 2004). When this occurs, standard errors of the parameter estimates are reduced, inflating the type I error rate, leading to spuriously significant results.

Similarly, each subject's residual scores (assumption 3) in a characteristic of interest are likely to be auto-correlated as the *same* subject is measured on several occasions. Thus, any unexplained subject-specific time-invariant effect in the residuals will create a correlation across measurement occasions (Singer & Willet, 2003). This problem results in a downward bias in the estimation of standard errors, leading to an increased familywise error rate (Heck, Thomas & Tabata, 2010).

Only one prospective study reviewed (see, Hamid et al., 2011) has accounted for the hierarchical structure inherent in self-report longitudinal designs, by employing a multilevel model, specifically individual growth curve (IGC) modeling. This form of statistical modeling is necessary to describe the development/change of a variable of interest (e.g. BDI) over time. A multilevel model decomposes the variance in a characteristic of interest (e.g. BDI) and models whether the variability and rate of change varies across individuals in a *systematic* way, according between-subject predictors of interest (e.g. epilepsy lateralisation, history of psychopathology etc.). Therefore, it should be applied to longitudinal data where the primary interest is in modeling the structure and predictors of change over time (Luke, 2004).

Chapter 3. NEUROIMAGING CORRELATES OF PSYCHOPATHOLOGY IN TLE

3.1 Neuroimaging in TLE

Neuroimaging techniques have been exhaustively applied to the investigation of TLE, resulting in a wealth of scientific data and clinical applications (Duncan, 1997; Duncan, 2010). Structural MRI studies in mTLE show atrophy of the hippocampus, in addition to other mesial (enthorinal cortex, perirhinal cortex, amygdala, fusiform gyrus) and extra-temporal regions (striatum, cingulate gyrus, frontal/parietal neocortex and bilateral thalamus) (see Keller & Roberts, 2008; Li, Zhang & Shang, 2012, for reviews). Using diffusion tensor imaging (DTI), which captures the direction and integrity of white matter (WM) tracts, the connections between these regions have been found to be abnormal, particularly in the limbic and transcallosal WM (see Otte et al., 2012, for meta-analysis).

These structural abnormalities are paralleled in the functional neuroimaging literature. FDG-PET studies typically identify interictal regions of reduced glucose metabolism in the mesial temporal lobe and adjacent neocortex, insular cortex, putamen and thalamus in the interictal state. During seizures captured with ictal SPECT, increased perfusion has been reported in the ipsilateral mesial and lateral temporal lobe, striatum and bilateral thalamus. Decreased perfusion is seen in the frontal cortex and precuneus (Richardson, 2012, for review & Figure 4).

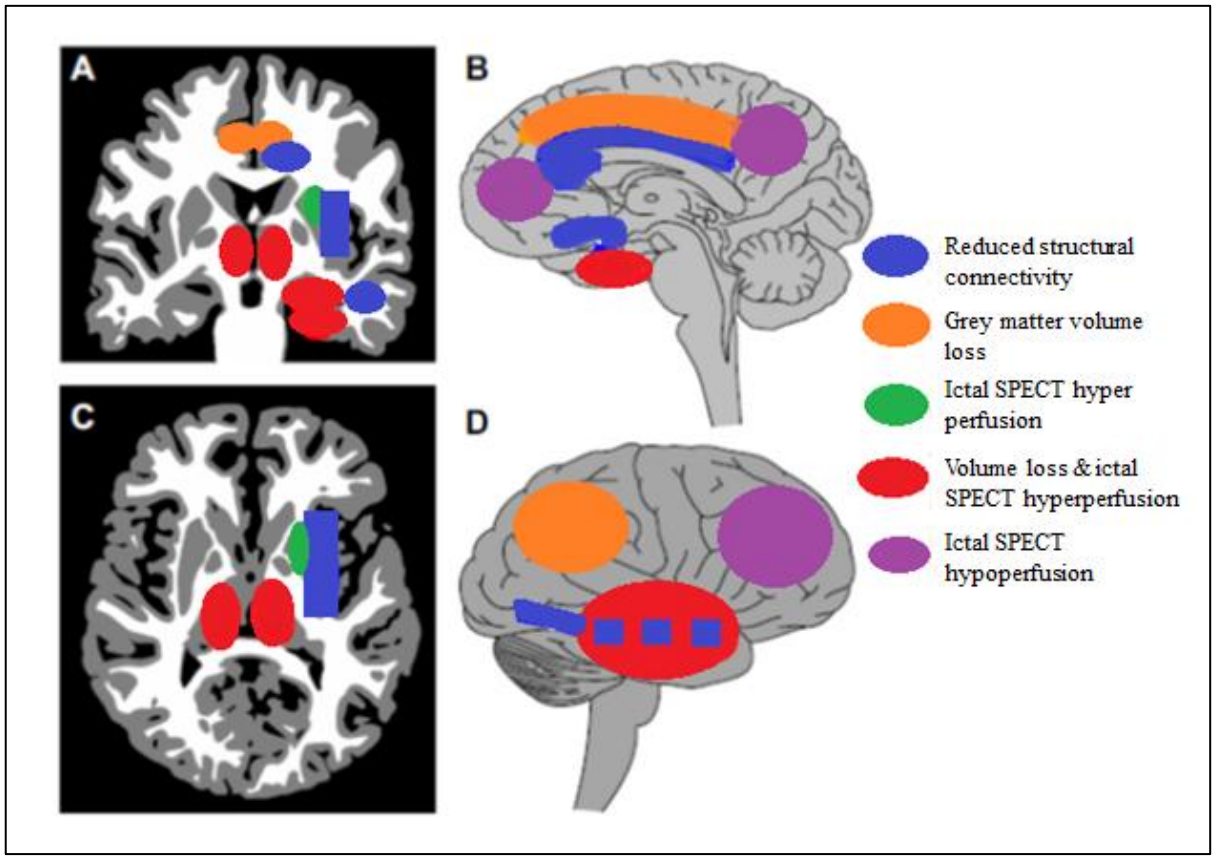

Figure 4. *A schematic summary of the widespread abnormalities reported in neuroimaging studies of mTLE patients. (A) coronal (B) medial view of ipsilateral right hemisphere (C) axial section (D) lateral view of ipsilateral right hemisphere. Adapted from Richardson, 2012*

As outlined in Chapter 1, imaging methods are used extensively for TLE surgical planning. Integration of structural and functional data into surgical image-guidance systems is currently underway, with the aim of improving seizure freedom rates and reducing postoperative neurological deficits (Duncan, 2010, for review).

Over the last two decades, a cumulative literature has linked structural and functional neuroimaging abnormalities with cognitive impairment in TLE. More recently, imaging studies have attempted to *predict* the impact of TLE surgery on neuropsychological (memory/language) outcome (see Bell et al., 2011, for review).

Less attention has been focussed on delineating the neuroimaging correlates of psychiatric comorbidities in TLE, or identifying preoperative cerebral markers that increase the risk of postoperative psychopathology. These studies are considered in this chapter.

3.2 Systematic literature review

A literature search was conducted using Medline, Embase and PsychINFO until June 2013 with the following search terms: temporal lobe epilepsy, neuroimaging (e.g., structural and functional), neurosurgical procedures and mental disorders (e.g., mood/anxiety disorders, and psychosis). Previous literature reviews were excluded (Kanner et al., 2002; Kanner, 2004; Theodore, 2004; Gilliam, 2005; Charyton, et al., 2010; Kanner et al., 2012a; Li, Zhang & Shang, 2012; Valente & Filho, 2013), although reference lists were checked to ensure no additional studies had been missed. The search yielded 2,547 articles relating to neuroimaging and TLE. Of these, 7% (n=179) investigated psychiatric comorbidity pre- and/or postoperatively. Studies on MEG, resting-state, palliative neurosurgical procedures,

stimulation studies, and studies not published in peer reviewed English language journals were excluded. Fifty one studies met these inclusion criteria and therefore were included, summarised in Appendix 1.

3.2.1 Depression

Structural imaging studies

Preoperative studies report increased depressive morbidity in TLE in association with enlarged amygdala volume (Tebartz van Elst, Woermann, Lemieux & Trimble, 1999; Richardson et al., 2007) or preserved contralateral amygdala T_2 relaxometry (Briellmann, Hopwood & Jackson, 2007). The syndrome mTLE has also been associated with depression (Quiske et al., 2000; Salgado, Yasuda & Cendes, 2010), but this is not a consistent finding (Adams et al., 2008; Wrench et al., 2009; Shamim et al., 2009). Left-sided mTLE has been suggested as a risk factor (Salgado et al., 2010), but this has not been confirmed by others (Quiske et al., 2000; Baxendale, Thompson & Duncan, 2005; Paparrigopoulos et al., 2008; Shamim et al., 2009; Finegersh et al., 2011; Butler et al., 2012).

Reduced hippocampal volume has been variably associated with greater depressive symptomatology. An early study by Quiske et al. (2000) reported that patients with hippocampal sclerosis (mTLE-HS) had higher BDI scores than neocortical TLE patients, independent of the lateralisation of the lesion. Notably, the mean BDI scores in the mTLE-HS group were in the 'mild' range. This finding has been replicated, although the atrophy was specific to the hippocampus *contralateral* to the seizure onset (Baxendale et al., 2005; Shamim et al., 2009). A subsequent study using 3D surface mapping, also found

significantly increased contralateral hippocampal atrophy in depressed (BDI ≥14) mTLE patients (Finegersh et al., 2011). Others however have not found an association between hippocampal volumetry and depression (Richardson et al., 2007; Briellmann et al., 2007; Wrench et al., 2009).

Alternative imaging modalities have offered insights into the relationship of epileptogenicity of the limbic structures and depression (Kanner et al., 2012a). A study of MR spectroscopy in 31 TLE patients found that the extent of voxels in the hippocampi with decreased NAA (creatine/*N*-acetylaspartate metabolite ratio; biomarker of hippocampal dysfunction) was linearly associated with the severity of depression symptoms (Gilliam et al., 2007). No other variable was associated with depression, including seizure rate, number of AEDs, or self-assessed social and vocational disability. The extent of hippocampal dysfunction (NAA) explained 57% of the variance in mood state. Decreased NAA has been associated with cerebral regions of interictal spiking and seizure onset (Garcia et al., 1997), suggesting that chronic hyper-excitability of the hippocampus may negatively influence the limbic network toward a depressed state (Gilliam et al., 2007).

Studies investigating extra-limbic structural correlates of depressive morbidity in TLE are limited in contrast with the primary depression literature (see Drevets & Price, 2012, for review). Butler and colleagues (2012) used a measure of cortical thickness (FreeSurfer) and demonstrated bilateral orbito-frontal cortex (OFC) *thickening* in mTLE patients with increasing depressive symptoms compared to healthy controls. However, the role and morphological changes of the OFC in TLE patients with depressive symptoms is unclear due to the lack of a TLE-only control group.

Only one structural neuroimaging study has investigated neuroanatomical markers of de novo depression following TLE surgery. In an a priori region-of-interest (ROI) analysis, Wrench and colleagues (2009) manually segmented the hippocampi and found that reduced preoperative *contralateral* hippocampal volume was a significant risk factor in the development of de novo depression within the first year of surgery in mTLE patients.

Functional imaging studies

Decreased serotonergic function has been identified as a pivotal pathogenic mechanism of depression, evidenced by the efficacy of serotonin reuptake inhibitors (SSRIs) in treating depression (Kanner et al., 2002). A number of studies using serotonin receptor ligands for PET have yielded important insights into the neurobiology of depression in TLE (Kanner et al., 2012a). Investigations in TLE patients have reported a significant inverse relation between BDI score and reduced ipsilateral hippocampal binding, after partial volume correction (Giovacchini et al., 2005; Theodore et al., 2007).

Serotonergic abnormalities have also been demonstrated in extra-temporal structures including the anterior cingulate cortex (ACC) (Savic et al., 2004; Hasler et al., 2007; Lothe et al., 2008), insular cortex (Lothe et al., 2008; Martinez et al., 2013) and ipsilateral (Salzberg et al., 2006) and bilateral (Bromfield et al., 1992; Lothe et al., 2008) frontal regions (Salzberg et al., 2006).

Schmitz and colleagues (1997) found a negative relationship between BDI score and contralateral temporal and bilateral frontal perfusion in left-sided focal patients using interictal SPECT. A similar study of TLE patients meeting the diagnostic criteria for a major

depressive episode failed to find any cerebral areas of hypo-perfusion compared to healthy controls (Ring et al., 1999).

The majority of studies have reported that epilepsy-related variables, for example seizure laterality (Victoroff et al., 1994; Theodore et al., 2007; Hasler et al., 2007), age of epilepsy onset/duration (Savic et al., 2004; Salzberg et al., 2006; Theodore et al., 2007) or pathology (Salzberg et al., 2006; Theodore et al., 2007; Hasler et al., 2007) are unrelated to preoperative depressive morbidity.

An FDG-PET study suggested that ipsilateral OFC metabolism may be a predisposing factor for developing depression in TLE and also following TLE surgery (Salzberg et al., 2006). However, it is unclear whether reduced metabolism in this region is a predisposing factor for *de novo* depression; particularly as hypo-metabolism was found in the same area in depressed patients preoperatively (Salzberg et al., 2006).

3.2.2 Anxiety

Structural imaging studies

In a cross-sectional study, relative preservation of the right amygdala was found in patients with refractory partial epilepsy and associated state anxiety (Satishchandra et al., 2003). Interestingly, patients with high anxiety scores had a significantly earlier onset and longer duration of epilepsy, suggesting neurobiological and/or psychological processes may explain and contribute to this association. However, in a longitudinal study of surgical epilepsy patients, no relationship between amygdalar volume and a preoperative history of anxiety was reported (Halley et al., 2010). This discrepancy may be due to methodological

differences between studies. Satishchandra et al. (2003) selected a homogenous sample of 16 patients with or without comorbid anxiety *symptoms*, defined using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Halley et al. (2010) included patients who met the *diagnostic criteria* for anxiety disorders (DSM-IV). Additionally, patients with comorbid anxiety symptoms assessed by Satishchandra et al. (2003) showed a significantly earlier onset and longer duration of epilepsy, potentially increasing the chance of structural plasticity effects. Patient groups in Halley et al.'s (2010) study did not differ statistically on these variables.

One preliminary study has investigated the relationship between amygdala volume and postoperative anxiety (Halley et al., 2010). Relative to healthy volunteers, resection of an ipsilateral amygdala of normal volume was significantly associated with postoperative anxiety in patients who underwent mesial temporal lobe resections, regardless of seizure outcome. There was no association between amygdala volume and anxiety in patients with non-mesial resections or between contralateral amgdala volumes and anxiety in patients with mesial temporal resections.

Functional imaging studies

Similar to depression, few studies of the functional neurobiological markers of de novo anxiety have been published. Bonelli et al. (2009) used fMRI to investigate the role of the amygdala in processing emotions in TLE-HS patients and whether this was a potential biomarker for emotional disturbance following surgery. They found that postoperatively right TLE patients demonstrated significant correlations between preoperative ipsilateral amygdala activation on viewing fearful faces and postoperative change in anxiety and depression levels; with greater preoperative activation being related with worsening severity

of anxiety (and depression) following ATLR. There was no association between postoperative mood disturbance and seizure outcome at 4 months follow-up.

3.2.3 Interictal Psychosis

Structural imaging studies

Early MRI studies concentrated on whether gross structural abnormalities in primary schizophrenia were also found in epilepsy patients with interictal psychosis (Conlon & Trimble, 1988), but these were limited in terms of imaging sensitivity and specificity.

More recently, advances in imaging techniques coupled with volumetric findings in idiopathic schizophrenia has led to investigation of hippocampal and amygdala abnormalities in patients with epilepsy and interictal psychosis, with variable results. Some have reported bilateral amygdala enlargement (Tebartz van Elst et al., 2002), left-sided (Marchetti et al., 2003) or bilateral (Maier et al., 2000; Sundram et al., 2010) volume loss in the temporal lobes of patients with interictal psychosis, but these are inconsistent findings (Marsh et al., 2001; Flugel et al., 2005; Flugel et al., 2006; Flugel et al., 2006a). A sub-group analysis however, revealed significant reductions in the magnetization transfer ratio (MTR; an index of signal loss/macromolecular structural integrity) in the left superior and middle temporal gyri in MRI-negative TLE psychotic patients, in the absence of any volumetric differences (Flugel et al., 2005). Furthermore, MTR imaging has been useful in investigating structural correlates of cognitive impairment (Flugel et al. 2006). For example, lower vocabulary test scores were correlated with MTR reductions in the fusiform gyrus of the left temporal lobe in TLE-interictal psychosis patients (Flugel et al. 2006).

Frontal cortical thinning (Gutierrez-Galve et al., 2012) and more widespread cortical and subcortical abnormalities have been reported in epilepsy patients with psychosis, suggesting pathogenic similarities with primary schizophrenia (Marsh et al., 2001; Sundram et al., 2010). However, others have failed to find diffuse cortical pathology and propose that interictal psychosis is a nosological entity distinct from schizophrenia (Rusch et al., 2004).

In contrast to the schizophrenia literature (Fitzsimmons, Kubicki & Shenton, 2013), limited research has examined WM abnormalities in patients with TLE and interictal psychosis. One study using diffusion tensor imaging (DTI; non-invasive information regarding the microstructure of WM) and a ROI approach has demonstrated subtle abnormalities in the fronto-temporal WM of patients with interictal psychosis (Flugel et al., 2006a). Specifically, fractional anisotropy (FA; directionality and coherence of axonal fibres) was significantly reduced in bilateral frontal and temporal regions, with significantly increased mean diffusivity (MD; quantitative measurement of the diffusion of water molecules) in frontal regions bilaterally, compared to non-psychotic TLE patients. Furthermore, these structural abnormalities were significantly related to clinical and neuropsychological impairments (Flugel et al., 2006a). A small whole brain VBM study has also found pronounced WM reductions in bilateral temporal and extra-temporal regions in patients with TLE and comorbid psychosis (Sundram et al., 2010).

Functional imaging studies

Few functional imaging studies have directly compared psychotic and non-psychotic epilepsy patients (Gallhofer et al., 1985; Marshall et al., 1993; Mellers et al., 1998). Mellers et al. (1998) reported reductions in cerebral blood flow as measured by SPECT in the left superior temporal gyrus associated with performance on a verbal fluency task. Marshall et al. (1993)

found hypo-metabolism in the left medial temporal region; while a third study highlighted lower regional oxygen extraction in the fronto-temporal regions using PET (Gallhofer et al., 1985). These studies involved small and heterogenous samples.

3.2.4 Postictal Psychosis (PIP)

Neuroimaging studies of post-ictal psychosis (PIP) are rare (Butler et al., 2012). Results from structural imaging studies have reported bilateral pathology, generalised cerebral atrophy (Morrow et al., 2006), preserved ipsilateral anterior hippocampal volume (Briellman et al., 2000) and cortical abnormalities in PIP patients (DuBois et al., 2011). In the largest MRI study to date, right rostral thickening and thinning of the right angular gyrus and left temporal gyrus distinguished PIP patients from epilepsy-only and healthy controls (DuBois et al., 2011).

Results from functional imaging studies have indicated that widespread or diffuse brain dysfunction may be key factors. Case reports using SPECT during an acute episode have found increased perfusion in contralateral basal ganglia (Fong et al,. 2000); bi-temporal and bi-frontal areas (Leutmezer et al., 2003); and widespread ipsilateral fronto-temporal networks (Nishida et al., 2006). Interictal bitemporal hypometabolism has also been documented in single case studies (Seeck et al., 1999; Kuba et al., 2012).

3.2.5 Conclusion

Depression was the most common psychiatric comorbidity explored in the brain imaging studies reviewed. The experimental findings described indicate that similar structures

involved in primary depression (amygdala, hippocampus, OFC) (Drevets et al., 2012) are also abnormal in patients with TLE and co-morbid depression. However, the heterogeneity of epilepsy syndromes, diagnostic methodologies (DSM/BDI), scanning techniques (ROI/VBM/partial volume correction), radioactive ligands, duration of psychopathology, possible drug confounds (psychiatric/AEDs), small sample sizes, cross-sectional designs and lack of adequate controls, impedes the establishment of firm and consistent conclusions and comparisons with the primary depression literature.

Only one structural ROI study has investigated neuroanatomical markers of de novo depression following TLE surgery. Wrench et al. (2009) reported preoperative *contralateral* hippocampal volume loss was a significant risk factor in the development of de novo depression within the first year of surgery in mTLE patients. Further research is warranted into the structural neuroanatomical markers of de novo depression following TLE surgery using a whole brain fully automated computerised volumetric method (e.g. VBM). The advantage of VBM is that is not restricted to the study of one brain region at a time (Keller & Roberts, 2008), and therefore can examine the possible role of extra-limbic structures, such as the OFC, in the development of de novo depression.

Anxiety disorders have been described as the *"forgotten psychiatric comorbidity in epilepsy"* (Kanner, 2011, p. 90). This view is supported by the lack of neuroimaging research into the condition (n=3/51; see Tables 7 & 10). Both structural studies (Satishchandra et al., 2003; Halley et al., 2010) used ROI analyses of the mesial temporal structures, but found contrasting results, which may be due to methodological differences.

One study investigated the relationship between amygdala volume and postoperative anxiety (Halley et al., 2010). Relative to healthy volunteers, resection of an ipsilateral amygdala of

normal volume was associated with postoperative anxiety in patients who underwent mesial temporal surgeries. However, the sample size was small (Fisher exact analyses were performed) and requires replication with larger cohorts.

The low prevalence of inter- and post-ictal psychosis prohibits well-powered imaging studies into the underlying pathophysiological mechanisms of the psychoses of epilepsy (Foong et al., 2007). Some suggest that interictal psychosis and primary schizophrenia share pathogenic correlates (Marsh et al., 2001; Sundram et al., 2010), but the literature is unconvincing (Rusch et al., 2004). Patients with inter-ictal psychosis rarely undergo surgical intervention and de novo cases are rare (Foong et al., 2007), therefore predictive neuroimaging studies have not been conducted.

The majority of PIP studies are dominated by single/multiple case studies following intracranial electrode implantation for different epilepsy syndromes (Morrow et al., 2006; Fong et al., 2000; Leutmezer et al. 2003; Seeck et al., 1999; Kuba et al. 2012). Collectively, intracranial and functional imaging research has implicated widespread brain dysfunction in PIP patients (Fong et al,. 2000; Leutmezer et al., 2003; Nishida et al., 2006; Seeck et al., 1999; Kuba et al., 2012). Despite diffuse cortical abnormalities, patients with a history of PIP are not excluded from surgical consideration and it has been argued that there may be an *indication* to consider resective surgery in order to prevent the evolution into chronic (interictal) psychosis (Kanner, 2009). To date, no study has investigated whether the preoperative neuroimaging correlates of PIP are predictive of poor surgical (psychiatric/seizure) outcome.

Overall, evidence from structural and functional imaging studies to date indicates that abnormalities extending beyond the epileptogenic temporal lobe may have a role in the development and maintenance of psychiatric symptoms.

Chapter 4. PSYCHOPATHOLOGY & RELATIONSHIP TO COGNITIVE FUNCTION

4.1 Memory Function in TLE

There has been extensive research regarding memory functioning in TLE (Hamberger & Drake, 2006; Hoppe, Elger & Helmstaedter, 2007; Hermann et al., 2009; Bell et al., 2011). Helmstaedter and Kockelmann (2006) reported approximately 70% of TLE patients have declarative memory dysfunction, and memory impairment has been viewed as the 'signature' cognitive deficit in TLE (Bell et al., 2011). However, it is increasingly recognised that TLE patients may exhibit cognitive difficulties indicating more widespread cerebral disruption, extending beyond the epileptogenic temporal lobe.

4.2 Cognitive Function in TLE

Hermann and colleagues (1997) examined a broad range of cognitive abilities and found that neuro-pathologically confirmed TLE+HS (n=66) patients demonstrated a pattern of generalised cognitive disruption compared to TLE patients without HS (n=41). Weaker performance was noteworthy for intelligence, language, and visuo-spatial functions. Academic under-achievement was a feature of the TLE+HS group. More recently, a study by the same group reported diffuse cognitive morbidity in TLE patients (n=96) compared with healthy controls (n=82) (Oyegbile et al., 2004). TLE patients exhibited not only poorer memory function, but poor performance across measures of intelligence, language, executive function and motor speed (see Figure 5). Some cognitive abilities, namely confrontation

naming and speeded motor dexterity were affected at least as severely as memory function. This pattern was confirmed in patients with unilateral left and right TLE. The degree of cognitive morbidity was positively associated with the chronicity of epilepsy and this relationship remained significant after controlling for AEDs, history of status epilepticus, initial precipitation injury and number of lifetime SGTCS, but was more evident in patients with less than 12 years formal education (Oyegbile et al., 2004).

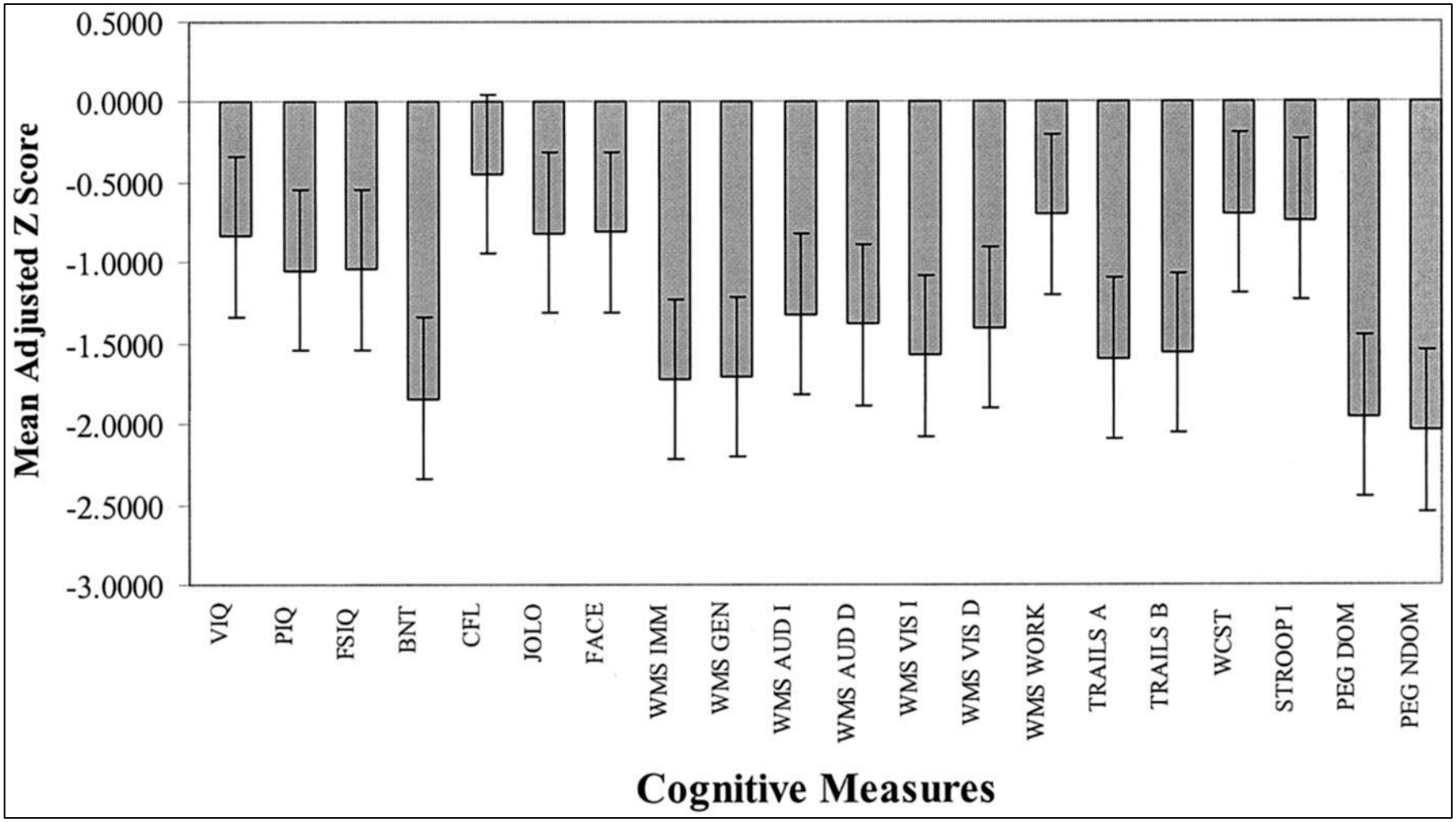

Figure 5. *Mean adjusted (age, gender, education)* z *scores for patients with TLE compared with healthy control subjects.*
BNT = Boston Naming Test; CFL = Letter Fluency; JOLO = Judgment of Line orientation; FACE = Facial Recognition; WMS IMM = Wechsler Memory Scale–III Immediate Memory; WMS GEN = Wechsler Memory Scale–III General Memory; WMS AUDI = Wechsler Memory Scale–III Auditory Immediate; WMS AUDD = Wechsler Memory Scale–III Auditory Delay; WMS VISI = Wechsler Memory Scale–III Visual Immediate; WMS VISD = Wechsler Memory Scale–III Visual Delay; WMS WORK = Wechsler Memory Scale–III Working Memory; TRAILS A = Trail Making Test A; TRAILS B = Trail Making Test B; WCST = WCST-64 Wisconsin Card Sorting Test–Preservative Responses; STROOP-I = Stroop Color–Word Interference; PEG DOM = Grooved Pegboard–Dominant Hand; PEG NDOM = Grooved Pegboard–Nondominant Hand. Adapted from Oyegbile et al., 2004.

Similarly, a cross-sectional study of TLE patients reported a large proportion (86%) had cognitive impairment compared to normative test data (Wang et al., 2011). Of these, 78% demonstrated neuropsychological morbidity in at least one domain, in order of magnitude: semantic memory (87%), language (78%), psycho-motor speed (69%), verbal episodic memory (64%) and executive function (55%).

4.3 Executive function in TLE

The frontal lobes play a crucial role in higher-level cognitive processes and are a key substrate for executive function (Gilbert & Burgess, 2008). Executive function refers to the ability to maintain an appropriate problem solving set for the attainment of future goals, and encompasses: decision making, response inhibition, concept formation, cognitive flexibility, planning, sustained attention (Zamarian et al., 2011). Lesion and neuroimaging evidence has consistently reinforced the role of the pre-frontal cortex (PFC) in executive function (Alvarez & Emory, 2006). More recently, however, studies have shown that executive function is sustained by a distributed neural circuit composed of multiple sectors of the PFC interacting with other cortical and subcortical regions that are themselves richly interconnected (Clark, Chamberlain & Sahakian, 2009). For example, patients with focal lesions in the basal ganglia exhibit cognitive switching difficulties (Cools, Ivry & D'Esposito, 2006), and lesions in the caudate nucleus have been shown to be associated with impaired executive function (Nys et al., 2006).

There are numerous direct reciprocal connections between the PFC and the medial temporal lobe (Simmons & Spier, 2003), and neuropsychological studies indicate that executive dysfunction in TLE is not uncommon (Stretton et al., 2012). In a seminal study, Hermann et

al. (1988) used the Wisconsin Card Sorting Task (WCST) in 35 TLE patients. The WCST is a well-established executive function measure that taps planning, organisation and the use of environmental feedback to shift cognitive set. Fifty-seven per cent of the TLE group (n=20) performed in a manner suggestive of frontal-lobe pathology (increased preservative responses), compared to 17% of a primary generalised epilepsy control group. Consistent with these findings, Corcoran and Upton (1993) used the modified WCST in TLE+HS, TLE-only and FLE patients. TLE+HS patients took significantly longer to complete the task and made more perseverative errors than the TLE-only and FLE groups. Based on the number of perseveration errors, 75% of TLE+HS patients were categorised as having 'frontal lobe damage' compared to 28% of the FLE group. Similarly, Strauss, Hunter and Wada (1993) assessed 77 pathologically heterogeneous unilateral TLE patients with the WCST. Perseveration errors were significantly greater in left TLE patients, but only if TLE onset occurred before the age of one year. Set-shifting ability in right TLE patients was less severe, but occurred independently of age of onset. Subsequent studies have also reported executive impairment (increased perseveration errors on the WCST) in TLE patients (Horner et al., 1996; Oddo et al., 2003; Oyegbile et al., 2004; Kim et al., 2007; Zamarian et al., 2011), particularly those with HS (Giovagnoli et al., 2001).

There is limited research using other measures of executive function in TLE (Stretton et al., 2012). Labudda et al. (2009) assessed decision-making in 20 unilateral mesial TLE patients using a computerised version of the Iowa Gambling Task (IGT). This test is designed to examine how feedback moderates the decision-making process. Compared to healthy controls, mTLE patients were significantly impaired in their decision making, with a preference for increased disadvantageous decisions. Sub-group analysis revealed that those

patients with the poorest decision-making performed less well on other tests of executive function.

Zamarian et al. (2011) used a battery of neuropsychological tests to assess different aspects of executive function in mTLE. Relative to healthy controls (n=20), unilateral TLE patients (n=28) performed poorly on tests of working memory (Digit Span Backwards), cognitive flexibility (Trail Making Test), categorical verbal fluency, set-shifting (WCST; perseveration errors), categorisation (WCST; completed categories) and planning.

One possible explanation for the observed executive skills weakness in association with TLE is that structural/functional abnormalities may extend beyond the temporal lobe, and these extra-temporal abnormalities may have additional cognitive consequences (Bell et al., 2011). Few neuroimaging studies have examined the relationship between executive function and TLE (Stretton et al., 2012). An FDG-PET study demonstrated that hypometabolism in prefrontal structures were related to executive impairment in patients with TLE (Jokeit et al., 1997). A neuropsychological test battery tapping executive function was administered to 96 TLE patients within 3 months of scanning. Prefrontal hypometabolism was reported in 28% of patients. Patients with prefrontal hypometabolism (versus those without) performed significantly more poorly on measures of frontal lobe function; the degree of hypometabolism was positively related to poorer performance.

Keller and colleagues (2009) investigated executive function in TLE using quantitative MRI (VBM) in 43 unilateral TLE patients and 30 health controls. Relative to healthy controls, patients with TLE had atrophy in the ipsilateral hippocampus and bilateral PFC. Executive function as measured by phonemic fluency was positively correlated with the left dorsal PFC and left hippocampal volumes.

The range of cognitive impairments observed in TLE has led to attempts to identify cognitive phenotypes (Hermann et al., 2007; Dabbs et al., 2009). Hermann et al. (2007) applied a cluster analysis to the test scores 96 chronic TLE patients and 82 healthy controls. Three cognitive profile types were identified: (1) minimally impaired (47%); (2) memory impaired (24%); and (3) memory, executive and speed impaired (29%). The latter subset presented with reduced cortical thickness in temporal and extra-temporal structures, compared to healthy controls and the less cognitively compromised TLE patients (Hermann et al., 2007; Dabbs et al., 2009). The clinical and demographic features between the cluster groups were not strikingly different given the divergent nature of the cognitive and imaging results (Dabbs et al., 2009). Notably, the authors did not consider possible psychopathological differences between the groups.

The mechanism responsible for frontal lobe dysfunction in TLE remains unclear (Devinsky et al., 2005). Suggestions include more widespread brain pathology as discussed above, the secondary spread of epileptic activity to frontal brain circuitry, and the propagation of temporal lobe hypo-metabolism to the thalamus, secondarily affecting the frontal lobes (Hermann et al., 1988; Bell et al., 2011). More research is needed to understand the widespread cognitive sequelae of TLE, including whether psychopathology and cognition are associated, and what could be the potential mechanisms underlying such an association (Gilliam, Albertson & Driscoll, 2011; Wilson, 2011).

4.4 Relationship between Psychopathology and Cognitive Function in TLE

Evidence from both neuropsychological and neuroimaging studies suggest that temporal and extra-temporal cognitive function may be compromised in TLE (Stretton et al., 2012). It is also recognised that neurocognitive impairment, including compromised executive function, attention and concentration, memory and processing speed occur in primary major depressive disorder (MDD) (see Austin, Mitchell & Goodwin 2001; Clark et al., 2009; McClintock et al., 2010).

Gorwood et al. (2008) assessed memory function in a large primary care cohort (n=8,229) who fulfilled the DSM-IV criteria for MDD. Using structural equation modelling, they found that prose recall was negatively associated with the number of past depressive episodes. Memory performance was cumulatively impaired by 2-3% for each depressive episode up to four episodes. The authors suggest that depression is directly involved in hippocampal atrophy, a hypothesis supported by consistent neuroimaging evidence of hippocampal atrophy in MDD (Cambell et al., 2004); the most common histo-pathological substrate of TLE (Kim et al., 2001).

In parallel to neuropsychological evidence in TLE, executive dysfunction in MDD is evident across a range of paradigms (Rogers et al., 2004). Martin et al. (1991) found that MDD patients performed significantly less well on the Digit Span subtest of the WAIS-R compared to dysthymic and healthy subjects. Additionally, depressive symptom severity as measured by BDI score was found to be an independent predictor of total errors, perseverative responses and failure to maintain set on the WCST. In a larger study, Grant et al. (2001) administered the WCST to 123 non-medicated depressed outpatients. Relative to healthy

controls, depressed patients completed fewer categories and exhibited increased perseverative errors. Stordal et al. (2004) compared the performance of 45 recurrent MDD patients to healthy controls on a neuropsychological test battery tapping sub-components of executive function. MDD patients performed significantly less well on 80% of the tasks, including measures of verbal fluency, inhibition, working memory and set-shifting.

Despite the prevalence of depression and widespread neuropsychological morbidity in TLE, and the historical association of depression and diffuse cognitive dysfunction (Clark et al., 2009; McClintock et al., 2010), few studies have directly investigated the possible *relationship* between depressed mood and cognition in TLE. It is clear that to fully understand the cognitive *and* psychiatric comorbidities in TLE, they should not be studied in isolation (Gilliam et al., 2011).

In an early investigation, Hermann and co-workers (1991) examined the relationship between WCST performance and depressive symptoms in 64 unilateral TLE patients. Overall, 45% of TLE patients obtained in excess of 19 perseveration responses, indicating clinically significant frontal lobe dysfunction. As predicted, there was a positive relationship between frontal lobe function (perseverative responses) and dysphoric mood state, particularly for left-sided patients.

Corcoran and colleagues (1993) explored the determining factors of memory complaints in epilepsy patients and included indicators of mood. Those reporting significant memory difficulties were significantly more depressed and anxious compared to non-complainers. A relationship between depressive morbidity and diminished verbal and visual memory performance was also observed. This latter finding possibly suggests that bi-temporal cognitive functions may be compromised in epilepsy patients with comorbid

psychopathology. Consistent with this hypothesis, Wishart et al. (1993) reported that depressive symptoms were related to performance deficits in attention/concentration, verbal and visual memory in a heterogeneous epilepsy cohort.

In the only study to specifically investigate the relationship between cognition and mood state in newly diagnosed epilepsy patients (n=51), Pulliainen et al. (2000) found no association between emotional state and cognitive function. However, the variability of depressive symptoms was within the normal range, and none of the patients had major depression. Thus, this negative finding only relates to epilepsy patients with sub-clinical depressive symptoms. It may also indicate that a longer duration of epilepsy with poorer controlled seizures may be a pertinent variable.

Paradiso et al. (2001) found that after controlling for seizure frequency, clinically depressed psychotropic-naive TLE+HS patients (n=24) exhibited poorer performance on measures of IQ, language, visuo-spatial skills, memory and executive function, compared to TLE-only controls (n=46). Sub-group analyses revealed that the deleterious impact of depression was accentuated in patients with left (n=15) compared to right TLE (n=9).

In a retrospective analysis of 84 medically refractory TLE patients, Dulay et al. (2004) examined the relationship between the severity of depression and performance on measures of auditory memory and learning. They found that the severity of depressive symptoms was inversely associated with auditory memory test performance, particularly for left-sided TLE patients. Although suggestive of an interaction, the authors warrant caution due to limited statistical power. In a well-powered prospective study, Helmstaedter et al. (2004) examined the interaction of depressive mood (BDI >12) and memory, as a function of seizure lateralisation and localisation (mesial/lateral, left/right). They found a main effect of

laterality with left-sided TLE patients demonstrating verbal learning deficits and right-sided patients exhibiting visual learning deficits. Furthermore, compared to lateral TLE patients, mesial patients performed more poorly. Correlational analyses revealed interactions between memory and mood only for the left lateral TLE group, and this was present for both measures of verbal and nonverbal memory. The authors propose that epileptic activity from the left temporo-lateral lobe may establish a pathological circuit that includes the frontal brain regions, resulting in both memory and mood dysfunction.

Tracy et al. (2007) investigated whether depressed TLE patients exhibited increased cognitive deficits relative to non-depressed epilepsy controls. Contradicting previous reports (Corcoran et al., 1993; Wishart et al., 1993; Parasido et al., 2001; Dulay et al., 2004; Helmstaedter et al., 2004), they found depression (BDI $\geq$ 10) was not related to memory performance, nor did it mediate the cognitive presentation of left or right TLE. However, the overall level of depressive morbidity in this study was low for both the left (mean BDI=9, SD=7) and right (mean BDI=7, SD=7) TLE groups. Furthermore, weak statistical power may have precluded the determination of interaction effects. These factors may have mitigated any possible effect of depressive morbidity on cognition to be detected.

4.5 Relationship between Preoperative Psychiatric Status and Cognitive Outcome Following TLE Surgery

Since the case of H.M, who underwent a bilateral temporal lobe resection for the relief of epilepsy and subsequently developed a dense amnesia (Corkin, 2013), a voluminous literature has focussed on memory outcome following temporal lobe surgery (see, Helmstaedter, 2004; Téllez-Zenteno et al., 2007; Baxendale, 2008; Baxendale, Thompson & Sander, 2013).

Sherman and colleagues (2011) conducted a systematic review of 23 neuropsychological studies using single pooled estimates of gains and losses for each cognitive domain (memory, language, executive function and attention) using a random effects model. Weighted estimates indicated the risk to verbal memory with left-sided TLE surgery (44%) was twice as high as the rate for right-sided surgery (20%). Naming was reduced in 34% of left-sided TLE patients, with few patients showing gains (4%). Pooled data on IQ, executive function and attention indicated few patients show declines postoperatively, but a substantial rate of improvement in verbal fluency with left-sided TLE surgery was found (27%). The authors however, did not subgroup their analyses according to preoperative psychiatric status.

To date, the relationship between pre-surgical psychopathology and cognitive change has received little attention. One retrospective study reported that patients with a poor pre-surgical mood status (BDI ≥16) who underwent a left ATLR had a greater decline in memory test performance (auditory delayed recall) compared to non-depressed patients at the 7 month follow-up (Busch et al., 2011). Differences in seizure outcome (Engel 1A: seizure freedom or 1B: continued auras) and post-surgical mood change could not account for the observed memory decline. The authors hypothesised that the greater decline in auditory memory capacity observed in depressed patients following surgery may be related to limited functional cognitive reserve.

Cognitive reserve refers to the proposal that individuals with neurological impairment utilise the cognitive capacity of undamaged brain regions to compensate for existing cognitive deficits. The higher the cognitive reserve capacity, as evinced by good cognitive test performance on tests subserved by intact brain regions, the better the cognitive outcomes. Previous neuroimaging evidence, as outlined in Chapter 3, indicated that patients with TLE and comorbid psychopathology show additional widespread functional brain abnormalities. Busch et al. (2011) accordingly suggested that depressed mood may be a biomarker of

reduced cognitive reserve. This study however, was limited by the relatively short follow-up, the failure to account for the diagnosis of depression on postoperative memory decline, and the inclusion of auras (Engel 1B), indicative of epileptic activity and limbic dysfunction, which may have confounded the primary finding.

4.6 Conclusion

Until recently, episodic memory impairment was viewed as the 'signature' cognitive deficit in TLE (Bell et al., 2011). The studies reviewed here suggest that the cognitive complications of TLE can be heterogeneous, deleteriously affecting diverse abilities such as language, attention and frontal lobe (executive) function.

The mechanism(s) responsible for executive dysfunction in TLE remains unclear. Our understanding of this association may be increased by research investigating the possible *relationship* between psychopathology and cognition in TLE, particularly as widespread neuropsychological morbidity is evident in primary depressive disorder (see Figure 6). It is clear that to fully understand the cognitive and psychiatric comorbidities in TLE, they should not be considered in isolation. Further research is warranted into the relationship between pre-surgical psychopathology and cognitive change.

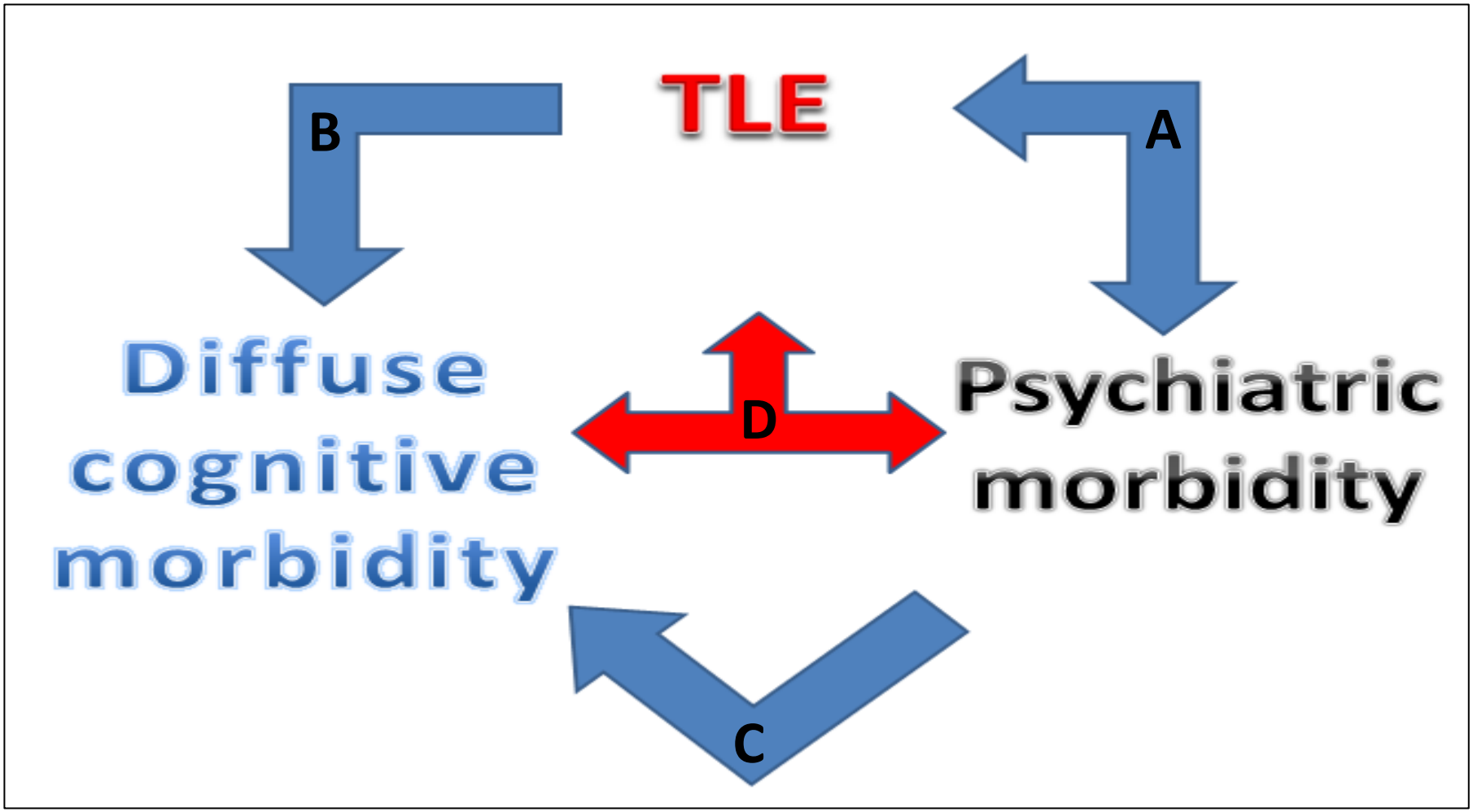

Figure 6. *A schematic summary of work reviewed. A) Epidemiological evidence suggests a bidirectional relationship between TLE and psychopathology (Forsgen et al., 1990; Hesdorffer et al., 2000; 2006; 2012; Adelöw et al., 2012). B) TLE is associated with temporal and extra-temporal (executive) cognitive dysfunction (Hermann et al., 1988; Corcoran et al., 1993; Strauss et al., 1993; Horner et al., 1996; Hermann et al., 1997; Drake et al., 2000; Giovagnoli et al., 2001; Oddo et al., 2003; Oyegbile et al., 2004; Kim et al., 2007; Wang et al., 2011; Zamarian et al., 2011); with limited evidence that cognitive morbidity is more pronounced in TLE patients with co-morbid depression (Hermann et al., 1991; Corcoran et al., 1993; Wishart et al., 1993; Parasido et al., 2001; Dulay et al., 2004; Helmstaedter et al., 2004). C) Similarly, MDD has been associated with diffuse neurocognitive impairment (Martin et al., 1991; Austin et al., 2001; Rogers et al., 2004; Stordal et al., 2004; Clark et al., 2009; McClintock et al., 2010). D) Few Studies have directly investigated the possible relation between cognitive and psychiatric morbidity in TLE. While memory decline is an established risk of TLE surgery, its association to pre-surgical psychiatric status remains unclear.*

Chapter 5. HYPOTHESES AND APPROACH

Epilepsy surgery is considered an effective treatment for refractory TLE, and carries a 60-70% chance of seizure freedom (Engel, 1996). For many surgical patients, the long-term psychosocial gains with respect to employment and independent living can be significantly more favourable than for patients who are medically treated (Mikati et al., 2006). Following TLE surgery however, psychiatric symptoms may develop for the first time (de novo) or pre-existing symptoms may be exacerbated. Understandably, this may tarnish an otherwise good surgical outcome, resulting in significant distress for patients and their families (Moss et al., 2009).

Evidence from the reviewed literature (see Chapter 2) indicates there is a high prevalence of psychiatric disturbance in medically refractory TLE. Despite this, less than 3% of TLE surgical outcome studies have investigated the psychiatric sequelae and morbidity associated with surgery. This is disproportionate to the extent of the problem. Variable rates have been reported for post-surgical depression, anxiety, interictal- and post-ictal psychoses. Until recently, very few studies distinguished de novo postoperative presentations from pre-existing conditions, making it difficult to accurately assess the impact of TLE surgery on psychiatric morbidity.

Whilst it is well documented that pre-surgical psychiatric conditions such as affective disorders (Devinsky et al., 2005; Wrench et al., 2011), increase the risk of post-surgical psychiatric morbidity, it is less clear whether there are risk factors for the development of postoperative de novo psychiatric disorders (Spencer et al., 2008). The pathogenic mechanisms and identification of surgical candidates at risk of de novo depression represents a current challenge in the practice of TLE surgery (Wrench et al., 2011a). Previous research has indicated that depression following TLE surgery is likely to be multi-factorial, including

psychosocial adjustment difficulties (Wilson et al., 2004), but few studies have investigated the neuroanatomical substrates of de novo depression (see Chapter 3). This is of interest given the current evidence of structural and functional abnormalities in primary depression, implicating orbital and medial prefrontal cortices and anatomically related structures within the limbic, striatal, thalamic and basal forebrain structures (see Price et al., 2012 for review).

As outlined in Chapter 4, the relationship between cognitive function and psychiatric outcome following TLE surgery has not been systematically studied to date. With the exception of IQ (Hermann et al., 1992; Ney et al., 1998; Blumer et al., 1998; Quigg et al., 2003), no study has examined whether pre-surgical memory deficits or the existence of more extensive cognitive disturbance is predictive of post-surgical psychopathology. This is of interest given the evidence of an interaction between depression and cognitive function (see Figure 6). Neuropsychological and neuroimaging studies in primary depression have reported executive and memory deficits (Austin et al., 2001), and frontal volumetric abnormalities (Bremner et al., 2002). A PET study has implicated extra-temporal or frontal dysfunction, including the inferior dorsolateral frontal cortex bilaterally, in TLE+HS patients with preoperative co-morbid depressive symptoms and no prior exposure to antidepressant treatment (Lothe et al., 2008). Salzberg et al. (2006) demonstrated that preoperative ipsilateral orbitofrontal hypometabolism in surgical TLE patients is a significant risk factor for the *development* of depression postoperatively. Preoperative bilateral independent spike discharges are significantly associated with poor post-surgical psychiatric outcome (Anhoury et al., 2000) and more recently, Wrench et al. (2009) found that patients with reduced preoperative contralateral hippocampal volume are at significantly greater risk for the *development* of postoperative depression. Collectively, these studies suggest that patients with more diffuse epileptogenicity and more widespread cognitive disturbance maybe at greater risk of developing de novo psychopathology.

The relationship between preoperative psychiatric status and postoperative seizure outcome warrants further investigation. It has been suggested by some that a lifetime psychiatric history may predict a poor seizure outcome following TLE surgery (Anhoury et al., 2000; Kanner et al., 2009; Guarnieri et al., 2009).

Further exploration of the aforementioned topics would contribute to the surgical decision-making process and enhance postoperative care.

5.1 Hypotheses

The main hypothesis formulated and explored here is that TLE patients with less localised cerebral dysfunction, as supported by electrophysiological, neuro-radiological and cognitive indicators, will be at risk for psychiatric disturbance preoperatively and have poorer outcomes following TLE surgery. Specifically:

Hypothesis 1: Patients with TLE under consideration for surgical treatment will have significant psychiatric comorbidity, with major depression as the most prevalent diagnostic category.

Hypothesis 2: Surgical candidates with psychopathology will have evidence of extra-temporal lobe dysfunction as measured by clinical and cognitive parameters.

Hypothesis 3: A lifetime psychiatric history will be associated with poorer surgical outcomes in terms of seizure control, cognitive and psychiatric status.

Hypothesis 4: Preoperative indicators of more widespread cerebral pathology will be risk factors for psychiatric morbidity following surgery.

5.2 Approach

These hypotheses were explored firstly using data derived from a retrospective survey with methods and findings presented in chapters 6-9; and secondly via prospective studies presented in chapters 11 and 12. The final chapter provides an overall summary of the findings, their implications, and discusses methodological limitations and directions for future research.

SECTION 2:

RETROSPECTIVE AND

PROSEPCTIVE STUDIES

Chapter 6. RETROSPECTIVE STUDY METHODOLOGY

This chapter describes common methods that were used for the studies detailed in Chapters 7-9. Methods used specifically for one study are described in the relevant chapters. All research studies were approved by the Research Ethics Committee of the UCL Institute of Neurology and UCL Hospitals.

6.1 Sample

Patients who had undergone epilepsy surgery at the National Hospital for Neurology and Neurosurgery between 1997 and 2007 were identified from a surgical database. Of the 384 patients identified, 104 were excluded from the study due to extra-temporal surgeries (n=31), palliative procedures (n=12), previous neurosurgery (n=16) or incomplete psychiatric data (n=45); the latter determined by the absence of a routine postoperative neuropsychiatric clinic letter (see Figure 7). A single coder (RAP) systematically collated information from case the notes of the remaining 280 temporal lobe surgical patients over a fourteen year period (1997-2011). However, due to sample attrition (see Figure 8) and therefore reduced statisical power, analyses were based on a 4-year follow-up.

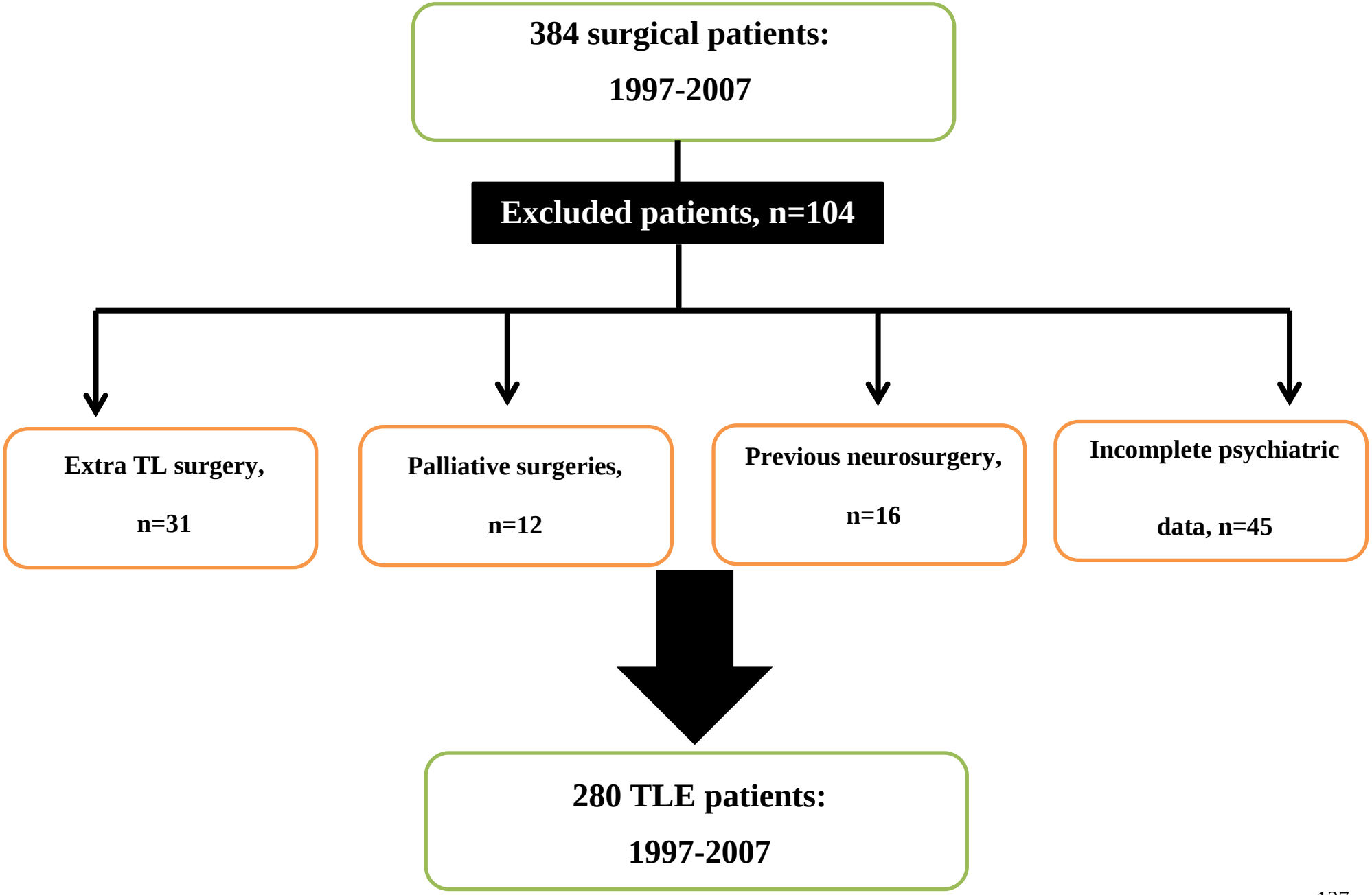

Figure 7. *Case selection process.*

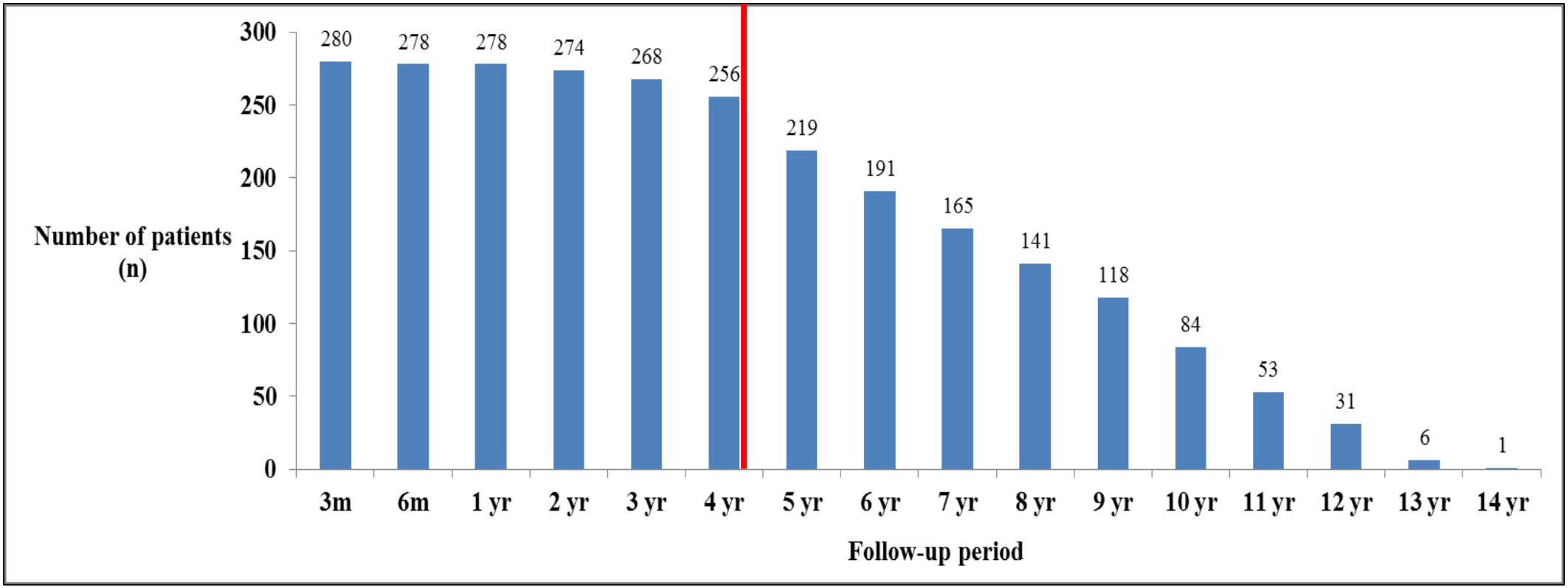

Figure 8. Sample attrition of the TLE patients (n=280) who underwent surgery between 1997 and 2007. Data analyses based on 4-year follow-up (red line).

6.2 Epilepsy

Seizure related variables were recorded from a standardised template completed during the pre-surgical evaluation. The following seizure related variables were recorded; a history of febrile convulsion(s), secondary generalised tonic-clonic seizures (SGTCS), status epilepticus, head trauma, CNS infection (meningitis/encephalitis) and family history of epilepsy. Postoperative seizure outcome was taken from a surgical follow-up database and classified according to the International League Against Epilepsy (ILAE) surgical classification scheme (Wieser et al., 2001; see Table 7).

Outcome Classification	Definition
1	Completely seizure free; no auras
2	Only auras; no other seizures
3	One to three seizures per year ± auras
4	Four seizure days per year to 50% reduction of baseline seizure days ± auras
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days ± auras
6	More than 100% increase of baseline seizure days ± auras

Table 7. ILAE surgical classification scheme. Adapted from Wieser et al., 2001

6.3 Neuropsychiatric classification

All patients were assessed by a neuropsychiatrist as part of their pre-surgical evaluation. Psychiatric diagnoses pre- and postoperatively were made by a neuropsychiatrist following a clinical interview as described previously (Anhoury et al., 2000), and written documentation of psychiatric treatment (CBT/psychotherapy/psychiatric medication) was recorded. There were a few cases (n=5) of psychiatric ambiguity, for example a psychiatric medication was mentioned in a neurological clinical letter without prior introduction in the neuropsychiatry notes. In such instances, clarification was sought from the treating neurologist.

The presence or absence of diagnosed family psychopathology (first-degree relative) was also documented. Psychiatric conditions were categorised according to the DSM-IV-R Axis I diagnoses, namely mood and anxiety disorders. The presence of postictal psychosis (PIP), interictal psychosis (IP) and non-epileptic seizures (NES) was also recorded. For comorbid psychopathology, a positive entry was made into each diagnostic category. Medication related psychiatric symptoms diagnosed by the neuropsychiatrist, defined as psychopathology temporally related to AED change(s) that resolved following AED titration/discontinuation, were excluded.

Psychiatric outcome was derived from neuropsychiatry clinic letters and documentation of psychiatric treatment. The emergence or continuation of postoperative psychopathology was recorded according to when a *formal* diagnosis was documented by the neuropsychiatrist, and classified according to the DSM-IV-R pre-surgically, but with the addition of adjustment disorders.

6.4 De novo neuropsychiatric cases

De novo psychopathology was only coded if a patient had *no* preoperative psychiatric history and could only be termed as such at *one* mutually exclusive post-surgical time-frame. All patients had a clinical neuropsychiatric evaluation at 3 and 6 months post-surgically. Psychiatric symptomatology emerging after this would be identified by the general practitioner or the treating neurologist resulting in a review by the epilepsy surgical team's neuropsychiatrist. Subsequently, documented psychiatric disorders were then coded as appropriate into the following postoperative time-frames: 12, 24, 36 and 48 months.

6.5 Neuropsychological tests

Cognitive data was derived from neuropsychological assessments routinely performed pre-operatively and between three and six and twelve months post-operatively.

General ability:

Intellectual level was measured using the Wechsler Adult Intelligence Scales (WAIS-R/WAIS-III). Patients also underwent the Nelson Adult Reading Test (NART; Nelson, 1982) preoperatively. This measures reading competence and has been validated as a measure of intellectual potential (Bright et al., 2002; McGurn et al., 2004). A discrepancy between NART predicted IQ and assessed IQ in favour of the former measure indicates intellectual decline, and serves as an indicator of extra-temporal cerebral disturbance.

Memory

Scores from the List and Design Learning subtests from the Adult Memory and Information Processing Battery (AMIPB; Coughlan & Hollows, 1985) were used. The learning paradigms in particular have been demonstrated as sensitive to mesial temporal lobe pathology and surgical treatment (Baxendale et al., 2008).

List Learning Task

The patient is read a list of 15 high-frequency words on five occasions. The patient has to recall as many words as possible after each trial. The total number of words recalled is recorded (List A1-5; max=75). A second list of 15 distractor words is then presented. The patient is required to recall as many as possible from the second list (List B; max=15) and then from the original list (A6; max=15).

Design Learning Task

The format parallels that of the List-learning task. The patient is presented with a 9 element abstract design (Design A) and asked to reproduce it from memory on a 4 x 4 dot grid over 5 trials. A distractor design (Design B) is then presented. The patient is then asked to reproduce the original design without further exposure. The total number of elements recalled over the 5 trials is recorded (Design A1-5; max=45). The delayed recall of Design A (Design A6; max=9), is also recorded.

Performance levels for List- and Design Learning were translated into Z-scores and used as measures of hippocampal integrity.

Executive Functions

Sufficient data was available for only one measure considered sensitive to frontal lobe pathology, namely phonemic fluency (Robinson et al., 2012). The performance indicator employed was the total number of words beginning with "S" produced in 60 seconds; names of people, places and repetitions are not permitted.

6.6 Aetiology

The aetiology for each case (n=280) was identified as either (1) hippocampal sclerosis, (2) developmental pathology (encompassing dysembryoplastic neuroepithelial tumours [DNETs], microdysgenesis, cortical dysplasias and angiomas), (3) vascular pathology (encompassing cavernous malformation and arteriovenous malformation), and (4) "other" pathology (encompassing gliosis, gliomas, hamartoma and nonspecific pathology). For instances of more than one pathology, most usually hippocampal sclerosis and microdysgenesis, a positive entry was made in both diagnostic categories.

6.7 MRI & video-EEG data

Temporal lobe laterality was determined using preoperative MRI scans and VEEG reports. Preoperative telemetry reports were used to classify cases regarding the presence or absence of discordant interictal EEG abnormalities. Discordant interictal EEG was based on any epileptiform discharges that conflicted with neuro-radiological findings (e.g. independent bi-temporal or contralateral spikes/multifocal spikes/fronto-temporal discharges in the presence of unilateral HS) as defined by VEEG reports.

6.8 Statistical Analyses: Retrospective and Prospective Studies

For Chapters 7-11, all statistical analyses were conducted with SPSS for Windows (Inc, Chicago, IL, U.S.A.), and a criterion level of $p \leq 0.05$ was set for statistical significance.

6.8.1 Kolmogorov-Smirnov test

For parametric testing a key assumption is that the sampling distribution is normally distributed (Field, 2009). For continuous variables, the Kolmogorov-Smirnov test (K-S test) was used to assess the assumption of normality. The K-S test compares the scores in the sample to a normally distributed set of scores with the same mean and standard deviation. When the K-S test was non-significant ($p > 0.05$), indicating that the sample is not significantly different from a normal distribution, parametric tests were employed. However, if this test was significant (≤ 0.05), non-parametric analyses were conducted.

6.8.2 Mann-Whitney U test

If the assumption of normality was not met and there were two samples, the Mann-Whitney U test was employed. This test ranks the data (lowest to highest) for each sample, and then calculates whether the difference in ranks between the samples is greater than expected if the null hypothesis were correct (Field, 2009).

6.8.3 Chi-squared test (X^2)

For categorical variables the X^2 test was used. This test examines whether the frequencies *observed* in certain categories would be *expected* by chance. For small samples, Fisher Exact Test (FET) was employed (Field, 2009).

6.8.4 Logistic Regression

As discussed in Chapter 2.10, logistic regression is a preferable uni- and multivariable technique compared to X^2, as predictor variables can be continuous and/or categorical, and the association between predictor(s) and the categorical outcome variable can be quantified. Although there are many similarities between linear and logistic regression, the former assumes that there is a *linear* relationship between the variables (i.e. the mean values of the outcome variable for each increment of the predictor(s) lie along a straight line). However, when the outcome is dichotomous this assumption is violated (Miles & Shevlin, 2011). Therefore, in logistic regression the raw data is transformed using the logarithmic transformation and thereby expresses a non-linear relationship in a linear way.

For any mathematical modelling approach, equation 1 applies, where Y denotes the dependent variable as a function (*f*) of independent/predictor variables(s), X.

(Equation 1)

$$\mathbf{Y = \mathit{f}\,(X)}$$

In logistic regression, Y will be equal to the logarithm/logit (ln) of the odds (the probability of an event occurring (p) divided by the event not occurring (1-p)), as described below:

(Equation 2)

$$\mathbf{Ln(p/1\text{-}p) = \mathit{f}\,(X)}$$

Crucial to the interpretation of logistic regression is the odds ratio (OR), which is an indicator of the change (Δ) in *odds* (the probability of an event occurring divided by the event not occurring), resulting from one unit change in the predictor.

(Equation 3)

Δ odds = odds after a unit change in the predictor/original odds

If the value is greater than 1, it indicates that as the predictor increases, the odds of the outcome occurring increase. Conversely, a value less than 1 indicates that as the predictor increases, the odds of the outcome decrease.

For the studies outlined in chapters 7 and 9, the logit transformation was inverted by exponentiating (exp) (taking the anti-logarithm of both sides of equation 2) of the odds of the event (Field, 2009):

(Equation 4)

$$\mathbf{p/1\text{-}p = exp\,(\mathit{f}\,(X))}$$

$$p = (1-p) \exp (f(X))$$

$$p(1+\exp (f(X)) = \exp (f(X))$$

$$p = \exp (f(X)) / [1+\exp (f(X)]$$

This permitted the probability/*chance* of the event to be calculated. In addition, the contribution of each predictor and their combined effect on the chance (rather than odds) of an outcome could be assessed.

6.8.5 Spearman's Correlation Coefficient

The Spearman's correlation coefficient, r_s, was used to investigate the correlation between non-normally distributed data (Field, 2009). For significant correlations, r_s was squared (coefficient of determination, R_s^2) giving a measure of the proportion of shared variance between the two ranked variables.

Chapter 7.

Study 1. Predictors of Psychiatric and Seizure Outcome following Temporal Lobe Epilepsy Surgery

7.1 Study Aims

The aims of this study were (1) to investigate psychiatric morbidity in pre-surgical TLE patients, and to assess whether depression was the most prevalent diagnostic category. (2) Examine whether TLE patients with lifetime psychopathology had evidence of extra-temporal lobe dysfunction. (3) To assess whether lifetime psychopathology was associated with poorer surgical outcomes in terms of seizure control, cognitive and psychiatric status. (4) To explore whether preoperative indicators of diffuse cerebral pathology were risk factors for psychiatric (de novo) morbidity following surgery.

7.2 Methods

The study sample consisted of 280 patients who had undergone TLE surgery at the National Hospital for Neurology and Neurosurgery between 1997 and 2007 (see Figure 7). Demographic and clinical characteristics according to seizure laterality are summarised in Table 8; and these were comparable to those reported in previous surgical series (Anhoury et al., 2000; Wrench et al., 2009).

Neuropsychological tests

Poor test performance on *both* the List- and Design learning tests was taken as one indicator of more widespread brain dysfunction. It was anticipated that lifetime psychopathology would be associated with verbal and visual (bi-temporal) memory deficits and this cognitive

profile would place patients at greater risk of de novo psychopathology. For the purposes of X^2 and logistic regression analyses, patients were dichotomised into those who demonstrated preoperative bi-temporal memory deficits (globally weak memory) and those who did not. Globally weak memory was based on a preoperative score of at least 1.5 standard deviations below the mean for *both* verbal and non-verbal memory (see Figure 9a & b for distribution statistics and justification).

Post-operative memory decline was defined as a performance decline of at least one standard deviation on the List and Design Learning tests.

Executive skills deficits were also hypothesised to be associated with preoperative psychopathology, and considered a pertinent risk factor of developing a de novo psychiatric disorder postoperatively. Phonemic fluency performance was used as the indicator of executive function.

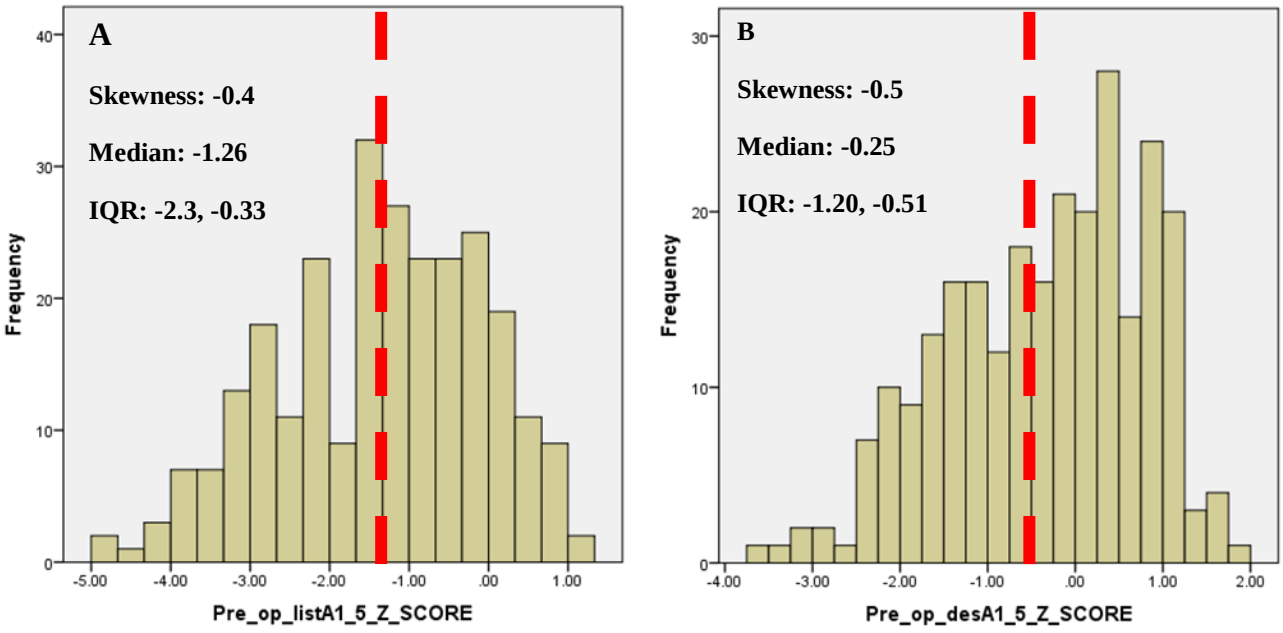

Figure 9. *Given the negative skew for both (A) verbal (List learning) and (B) non-verbal (Design learning) memory measures, 'globally (bi-temporal) weak memory' was based on a preoperative score of at least 1.5 standard deviations (dashed red line) below the mean, ensuring that the most clinically impaired TLE memory patients were correctly identified. IQR, interquartile range*

Variable	Right (*n* = 136)	Left (*n* = 144)	All (*n* = 280)
Age of seizure onset, y,[1]	11.8 (9.6)	10.1 (9.2)	10.9 (9.4)
Epilepsy duration, y,[2]	24 (16, 32)	25 (18, 33)	24 (17, 32)
Predisoposing Factors†			
History of febrile convulsions	62 (46%)	74 (51%)	136 (49%)
Family history of epilepsy	34 (25%)	30 (21%)	64 (23%)
History of status epilepticus	20 (15%)	17 (12%)	37 (13%)
History of head trauma	19 (14%)	21 (15%)	40 (14%)
History of CNS infection	8 (6%)	9 (6%)	17 (6%)
Presurgical Seizure Type†*			
Simple partial	95 (70%)	109 (76%)	204 (73%)
Complex partial	131 (96%)	144 (100%)	275 (98%)
Secondary generalised	95 (70%)	102 (71%)	197 (70%)
Medication			
Total number of AEDs trialled preoperatively[1]	4 (2)	5 (2)	4.5 (2)
Monotherapy at the time of surgery†	22 (16%)	12 (8%)	34 (12%)
Polytherapy at the time of surgery†	114 (84%)	132 (92%)	246 (88%)
Age at surgery, y,[1]	35.4 (9.4)	34.7 (9.5)	35 (9.4)
Histopathological Findings†			
Hippocampal sclerosis	101 (74%)	125 (87%)	226 (81%)
Developmental pathology	29 (21%)	21 (15%)	50 (18%)
Vascular pathology	9 (7%)	4 (3%)	13 (5%)
Other	7 (5%)	9 (6%)	16 (6%)
Dual pathology	10 (7%)	15 (10%)	25 (9%)
Cognitive variables[1,3]			
Verbal IQ	94.7 (14.6)	90.6 (12.2)	92.6 (13.6)
Performance IQ	95.4 (18.2)	95.5 (14)	95.4 (16.2)
Preoperative verbal learning	45.2 (10.1)	41.7 (10.1)	43.4 (10.2)
Preoperative visual learning	29.7 (8.3)	32.1 (8.3)	30.9 (8.4)
Postoperative verbal learning (at 12-month follow-up)	45.5 (8.4)	37.9 (10)	41.4 (10)
Postoperative visual learning (at 12-month follow-up)	29.6 (7.7)	31.3 (8)	30.5 (7.9)

† Values are number of patients (%)

* May have >1 seizure type

[1] Mean (SD)

[2] Median (IQR)

AED=anti-epileptic drugs

[3] For avaliable data

Table 8. *Demographic and clinical characteristics of 280 patients who underwent TLE surgery.*

7.3 Statistical Analyses

Chi-square (X^2) analysis was used to examine whether 1) lifetime psychopathology was associated with widespread cerebral dysfunction, as measured by clinical and cognitive parameters and 2) whether de novo psychiatric disorders were related to postoperative cognitive decline or the presence of seizure freedom within either 12 or 48 month follow-up.

Logistic Regression

The variables entered into the logistic regression analyses were selected on the basis of previous literature and those which had not previously been explored.

In univariable and multivariable logistic regression analyses, the independent pre-surgical variables to predict the odds of a de novo psychiatric diagnosis within four years follow-up were: globally weak memory (i.e. bi-temporal memory deficits); phonemic fluency score; discordant interictal EEG abnormalities; history of generalised seizures (SGTCS); history of status epilepticus; epilepsy duration; side of resection; family history of psychopathology.

The same independent variables were used to predict the odds of seizure freedom at one and four years with the exception that pre-surgical psychiatric diagnosis replaced family history of psychopathology.

7.4 Results

Psychiatric History

Preoperatively, 29% of TLE patients were diagnosed as having a current or past history of a psychiatric disorder (n=81), with some individuals meeting the criteria for more than one disorder (n=14/280; 5%). The most prevalent preoperative psychiatric diagnosis was mood disorders (51/280; 18%), particularly depression (n=43/280; 15%), with lower rates for postictal psychosis (n=20/280; 7%), anxiety disorders (n=13/208; 5%), NES (n=9/280; 3%) and interictal psychosis (n=2/280; 0.7%).

A positive family psychiatric history (25% vs 11%; $X^2(1)=8.4$, p=0.005) and history of head trauma (21% vs 11%; $X^2(1)=4.7$, p=0.03) were associated with lifetime psychopathology in TLE patients. Multivariable analysis revealed that the presence of both factors were independently associated with increased odds of lifetime psychopathology (head trauma: OR: 2.2, 95%CI: 1.1-4.4, p=0.03; family psychiatric history: OR: 2.7, 95%CI: 1.4-5.2, p=0.004). There were no other statistical associations between lifetime psychopathology and clinical or cognitive factors (see Tables 9 & 10, respectively).

Postoperative Psychopathology

One hundred and five patients (38%; n=280) had clinically significant mental health difficulties within four years following temporal lobe surgery. Sixty-seven per cent of patients (n=54/81) with a preoperative psychiatric history continued to experience significant psychiatric symptoms of diagnostic severity within four years following TLE surgery. Of these patients, 61% (n=49/81) continued to receive psychiatric treatment (pharmacological and/or psychological); 12% (n=10/81) required psychiatric hospitalisation and one patient

committed suicide within 3 months postoperatively. Patients with a preoperative psychiatric history had over six times the odds of developing a postoperative psychiatric disorder (OR: 6.12, 95%CI: 3.49-10.76, p<0.001).

For patients with pre- and postoperative psychopathology (n=54), the most frequent psychiatric condition was mood disorder (depression, n=38; bipolar II disorder, n=1; dysthymia, n=1), followed by anxiety disorders (not otherwise specified, n=6; generalised anxiety disorder, n=4; social phobia, n=1) and interictal psychosis (n=4). A few patients developed postoperative NES (n=2), postictal psychosis and adjustment disorder (n=1, respectively). Five patients (n=5/54; 9%) had comorbid psychopathologies.

De Novo Psychopathology

Fifty-one patients (18%; n=51/280) developed a de novo psychiatric condition within 48 months postoperatively (see Table 11 & Figure 9c). Of these, nine patients (n=9/51; 18%) developed two diagnosed psychiatric disorders during follow-up. Table 11 presents the point prevalence of de novo psychopathologies at specific time-intervals following TLE surgery. Forty-nine per cent of cases (n=25/51) presented within 6 months and 90% (n=46/51) had de novo psychopathology that persisted for at least 6 months (IQR: 12-30 months).

Overall, the most prevalent postoperative de novo psychiatric conditions were mood disorder (all depression, n=33), followed by anxiety disorders (not otherwise specified, n=6; panic disorder without agoraphobia, n=3; generalised anxiety disorder, n=2; posttraumatic stress disorder, n=1; obsessive-compulsive disorder, n=1), interictal psychosis, adjustment disorder (n=4, respectively), NES (n=3) and adjustment disorders (n=3). Forty patients (78%, n=40/51) required psychiatric treatment (pharmacological and/or psychological) within four year follow-up.

Predictors of De Novo Psychopathology

In univariable analyses, a history of SGTCS was a significant predictor of de novo psychopathology within 4 years (OR: 2.53, 95%CI: 1.03–4.82, p=0.04). In the multivariable analysis, a history SGTCS remained a significant predictor of de novo psychopathology after adjusting for preoperative cognitive status, discordant interictal EEG abnormalities, side of resection, epilepsy duration, and a history of status and familial psychopathology (OR: 2.73, 95%CI: 1.14–6.57, p=0.02) (see Tables 12 & 13).

Variable	Lifetime psychiatric history (*n* = 81)	No psychiatric history (*n* = 199)
Age of seizure onset, y,[1]	9 (3, 15.5)	9 (3, 16)
Epilepsy duration, y,[1]	24 (17, 34)	24 (16.5, 30)
Predisoposing Factors†		
History of febrile convulsions	36 (44%)	100 (50%)
Family history of epilepsy	19 (24%)	45 (22%)
History of status epilepticus	15 (19%)	22 (11%)
History of head trauma	**17 (21%)**	**22 (11%)**
History of CNS infection	3 (4%)	14 (7%)
Side of seizure focus (L/R)	42/39 (52%/48%)	102/97 (51%/49%)
Family history of psychopathology	**20 (25%)**	**22 (11%)**
Presurgical Seizure Type†*		
Simple partial	61 (75%)	143 (72%)
Complex partial	81 (100%)	195 (98%)
Secondary generalised	57 (70%)	140 (70%)
Medication		
Total number of AEDs trialled preoperatively[1]	5 (3, 6)	4 (3, 6)
Monotherapy at the time of surgery†	10 (12%)	24 (12%)
Polytherapy at the time of surgery†	71 (88%)	175 (88%)
Age at surgery, y,[1]	33 (28, 41)	33 (28, 40)
EEG Findings†		
Discordant interictal EEG	41 (50%)	84 (44%)
Histopathological Findings†		
Hippocampal sclerosis	66 (81%)	160 (80%)
Developmental pathology	14 (17%)	36 (18%)
Vascular pathology	4 (5%)	9 (5%)
Other	6 (7%)	10 (5%)
Dual pathology	9 (11%)	16 (8%)

† Values are number of patients (%)

* May have >1 seizure type

[1] Median (IQR)

[2] Mean (SD)

AED=anti-epileptic drugs

[3] For avaliable data

Table 9. *Demographic and clinical characteristics of patients with (n=81) and without (n=199) a lifetime psychiatric diagnosis who underwent TLE surgery.*

Cognitive measure[1]	Lifetime psychiatric history (*n* = 81)	No psychiatric history (*n* = 199)
General ability		
VIQ[2]	92 (83, 104)	91 (82, 99)
PIQ[3]	94 (15)	96 (17)
NART[3]	99 (13)	99 (13)
NART and VIQ discrepancy[2]	-5 (-14, 2.25)	-5 (-13, -1)
Memory		
Verbal learning: trials[2]	-1.4 (-2.4, -0.3)	-1.2 (-2.3, -0.3)
delay[2]	-1.5 (-2.4, -0.3)	-1.1 (-2.3, -0.3)
Visual learning: trials[2]	-0.41 (-1.4, 0.4)	-0.1 (-1.2, 0.6)
delay[2]	0.4 (-1.2, 0.6)	0.1 (-1.0, 0.6)
Bi-temporal (global) memory weakness[4]	17 (22%)	27 (15%)
Executive functions		
Phonemic fluency ("S" only)[2]	14 (11, 16)	13 (11, 16)

[1] For available data

[2] Median (IQR)

[3] Mean (SD)

[4] Yes cases, n (%)

Table 10. *Cognitive characteristics of patients with (n=81) and without (n=199) a lifetime psychiatric diagnosis who underwent TLE surgery.*

De novo **psychopathologies (%)**	**3 months**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**Overall Total**
Mood disorder	3.6 (10)	1.8 (5)	2.9 (8)	2.2 (6)	0 (0)	1.6 (4)	12 (33)
Anxiety disorder	0.7 (2)	0.7 (2)	2.2 (6)	0.7 (2)	0.4 (1)	0 (0)	4.6 (13)
Adjustment disorder	1.1 (3)	0 (0)	0.4 (1)	0 (0)	0 (0)	0 (0)	1.4 (4)
Interictal psychosis	0 (0)	0.4 (1)	0.7 (2)	0 (0)	0.4 (1)	0 (0)	1.4 (4)
Postictal psychosis	0.4 (1)	0.4 (1)	0 (0)	0.4 (1)	0 (0)	0 (0)	1.1 (3)
NES	0.4 (1)	0 (0)	0 (0)	0.7 (2)	0 (0)	0 (0)	1.1 (3)

Table 11. *Point prevalence of diagnosed de novo psychopathology following TLE surgery (frequency of de novo diagnostic categories given in parentheses).*

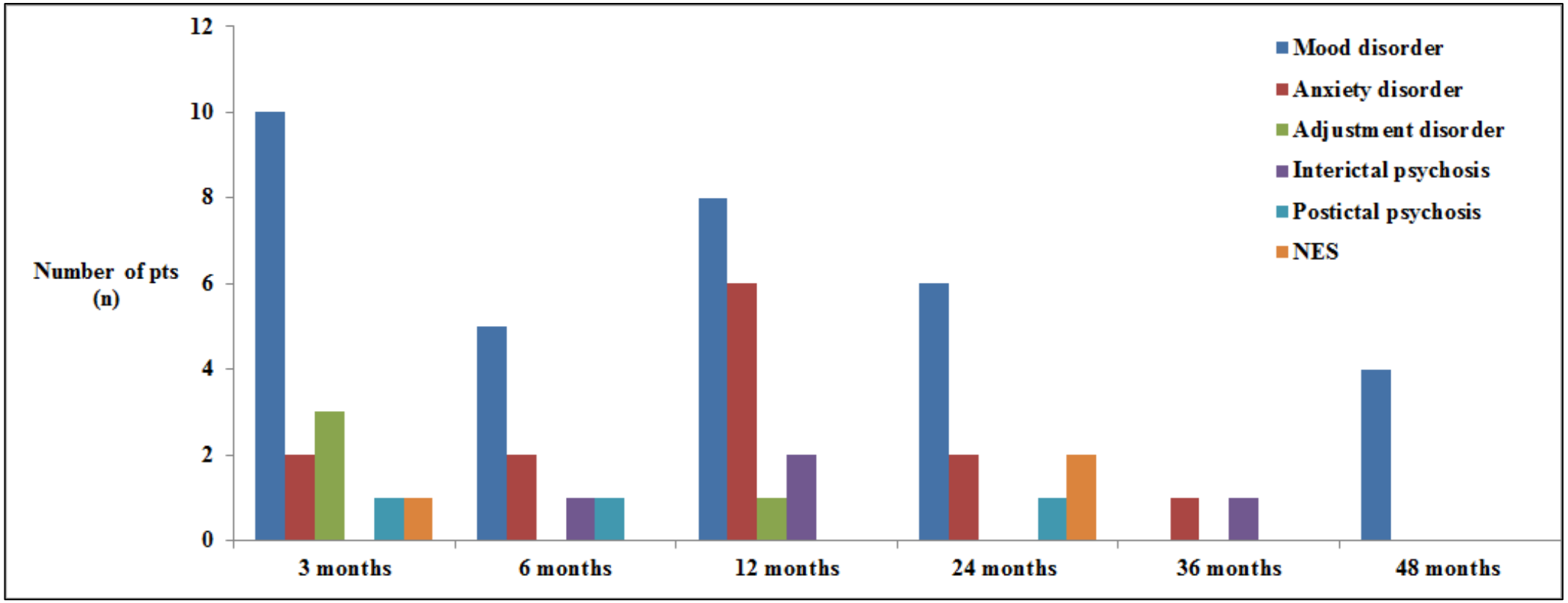

Figure 9c. *Histogram of point prevalence of patients (pts) diagnosed de novo psychopathologies following TLE surgery.*

	Pts without a *de novo* psychiatric diagnosis within 4yrs after surgery (n=229)	Pts with a *de novo* psychiatric diagnosis 4yrs within after surgery (n=51)	Overall (n=280)
Pre-op cognitive deficits:			
Globally impaired memory (n=259)*	37 (17.6%)	7 (14.3%)	44 (17%)
Verbal fluency (n=247)[2]	14 (10, 17)	12 (10, 18)	14 (10, 17)
EEG abnormalities:			
Discordant interictal EEG (n=274)*	97 (43.3)	27 (54.0)	124 (45.3)
Chronicity & severity of epilepsy:			
History of SGTCS (n=280)*	**155 (67.7%)**	**42 (82.4%)**	197 (70.4%)
History of status (n=280)*	30 (13.1%)	7 (13.7%)	37 (13.2%)
Epilepsy duration (n=280)[1,2]	24 (16.75, 33)	24 (17, 29)	24 (17, 32)
Other:			
Right TL resection (n=136)	110 (48.0%)	26 (51.0%)	136 (48.6%)
Left TL resection (n=144)	119 (52.0%)	25 (49%)	144 (51.4%)
Family history of diagnosed psychopathology (n=280)*	32 (14.0%)	10 (19.6%)	42 (15.0%)

* = yes cases

[1] = yrs

[2] = median (IQR)

Table 12. *Characteristics of TLE patients (pts) who developed a de novo psychiatric diagnosis within four postoperative years (n=51), versus those who did not (n=229).*

	Univariable analysis		Multivariable analysis	
	Odds Ratio (95% CI)	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Pre-op cognitive deficits:				
Globally impaired memory (Yes vs No)	0.78 (0.33-1.87)	0.60	0.78 (0.31-2.0)	0.60
Verbal fluency[1]	0.99 (0.93-1.10)	0.70	0.93 (0.66-1.30)	0.70
EEG abnormalities:				
Discordant interictal EEG (Yes vs No)	1.54 (0.83-2.85)	0.17	1.31 (0.66-2.60)	0.44
Chronicity & severity of epilepsy:				
History of SGTCS (Yes vs No)	2.53 (1.03-4.82)	**0.04**	2.73 (1.14-6.57)	**0.02**
History of status (Yes vs No)	1.01 (0.44-2.56)	0.91	0.84 (0.31-2.28)	0.84
Epilepsy duration[2]	0.93 (0.80-1.07)	0.29	0.90 (0.77-1.06)	0.23
Other:				
Side of resection (L vs R)	0.89 (0.48-1.63)	0.70	0.87 (0.44-1.41)	0.67
Family Hx of diagnosed psychopathology (Yes vs No)	1.50 (0.68-3.30)	0.31	1.38 (0.59-3.22)	0.46

[1] = for each 5 word increase

[2] = for each 5 year increase

Table 13. *Uni- and multivariable logistic regression analyses examining whether preoperative factors are predictive of patients who develop de novo psychopathology (n=51) versus those who do not (n=229) within 4 years following TLE surgery.*

Cognitive Outcome

A decline in memory test performance of at least one standard deviation was recorded for 67 patients for verbal memory, 54 patients for visual memory with 24 declining on both measures. We found no relationship between postoperative memory decline (at 12 month follow-up) and a lifetime psychiatric history, or the development of de novo psychopathology or within 12 or 48 month follow-up ($p \geq 0.05$).

Seizure Outcome

From patients with available seizure outcome data, 170 (61%; n=170/278) were seizure free (ILAE 1) 12 months following surgery and 127 (49%; n=127/258) remained seizure free during four years follow-up. There was no relationship between seizure outcome (ILAE 1 vs 2-6) and de novo psychiatric disorders within 12 or 48 months postoperatively ($X^2(1) = 0.29$, $p=0.61$; $X^2(1) = 0.36$, $p=0.63$, respectively, see Table 14 for further breakdown).

Predictors of Seizure Freedom

The odds ratio (OR) of being seizure free at 12 months, and during four years following TLE surgery, was significantly lower for patients with a history SGTCS (OR: 0.52, 95%CI: 0.28–0.98, p=0.04; OR: 0.47, 95%CI: 0.25–0.90, p=0.02, respectively) and also those with a preoperative psychiatric diagnosis (OR: 0.46, 95%CI: 0.26–0.82, p=0.009; OR: 0.53, 95%CI: 0.28–0.98, p=0.04, respectively). Both SGTCS and a preoperative psychiatric diagnosis were independent predictors of seizure outcome. Thus, compared with patients without a history of SGTCS, those with preoperative SGTCS had less than half the odds (OR: 0.47) of remaining seizure free the four year follow-up period (see Tables 15-18). The presence of a lifetime psychiatric disorder remained a strong predictor of a poor surgical outcome:

compared to patients without a prior history of psychopathology, those with a psychiatric history had nearly half (OR 0.53) the odds of attaining seizure freedom during the four year follow-up interval (see Figure 10). For clinical translation, we assessed the contribution of each predictor and their combined effect on the *chance* (rather than odds) of seizure freedom at 12 months, and remaining seizure free during 48 month follow-up (see Figure 11).

		ILAE outcome					
	(%)	**1**	**2**	**3**	**4**	**5**	**6**
12 months	***de novo***	61	13	10	14	2	0
	no psych	61	13	12	13	1	0
24 months	***de novo***	56	10	14	16	4	0
	no psych	68	9	10	11	2	0
36 months	***de novo***	65	6	8	17	4	0
	no psych	67	6	10	11	6	0
48 months	***de novo***	66	6	9	15	4	0
	no psych	69	8	7	10	6	0

Table 14. *ILAE seizure outcome for patients who developed de novo psychopathology versus those who did not (no psych) at 4 yearly intervals following TLE surgery.*

	Pts did not remain seizure free 12m after surgery (n=108)	Pts who remained seizure free 12m after surgery (n=170)	Overall (n=278)
Pre-op cognitive deficits:			
Globally impaired memory (n=257)*	16 (16.0%)	28 (17.8%)	44 (17.1%)
Verbal fluency (n=247)[2]	14 (10, 17)	13 (10, 17)	14 (10, 17)
EEG abnormalities:			
Discordant interictal EEG (n=272)*	50 (47. 2%)	73 (44.0%)	124 (45.3%)
Chronicity & severity of epilepsy:			
History of SGTCS (n=278)*	**83 (76.9%)**	**113 (66.5%)**	197 (70.5%)
History of status (n=278)*	14 (13.0%)	22 (12.9%)	36 (12.9%)
Epilepsy duration (n=280)[1,2]	23 (17, 32)	24 (16.4, 31)	24 (17, 31.4)
Other:			
Right TL resection (n=136)	48 (44.4%)	88 (51.8%)	136 (48.9%)
Left TL resection (n=144)	60 (55.6%)	82 (48.2%)	142 (51.1%)
Preoperative psychiatric diagnosis (n=278)*	**40 (37.0%)**	**40 (23.5%)**	80 (28.8%)

* = yes cases

[1] = yrs

[2] = median (IQR)

Table 15. *Characteristics of TLE patients (pts) who remained seizure free (ILAE=1) (n=170) versus those who did not (n=108) after TLE surgery at 12 month follow-up.*

	Univariable analysis		Multivariable analysis	
	Odds Ratio (95% CI)	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Pre-op cognitive deficits:				
Globally impaired memory (Yes vs No)	1.14 (0.58, 2.23)	0.70	1.16 (0.55, 2.43)	0.69
Verbal fluency[1]	0.94 (0.73, 1.19)	0.62	0.91 (0.68, 1.19)	0.50
EEG abnormalities:				
Discordant interictal EEG (Yes vs No)	0.87 (0.53, 1.43)	0.60	0.89 (0.51, 1.55)	0.68
Chronicity & severity of epilepsy:				
History of SGTCS (Yes vs No)	0.59 (0.34, 1.03)	**0.06**	0.52 (0.28, 0.98)	**0.04**
History of status (Yes vs No)	0.99 (0.48, 2.04)	0.99	1.15 (0.50, 2.61)	0.73
Epilepsy duration[2]	0.98 (0.88, 1.09)	0.77	1.00 (0.88, 1.13)	0.99
Other:				
Side of resection (L vs R)	0.74 (0.45, 1.21)	0.23	0.82 (0.47-1.43)	0.49
Preoperative psychiatric diagnosis (Yes vs No)	0.52 (0.30 - 0.88)	**0.01**	0.46 (0.26-0.82)	**0.009**

[1] = for each 5 word increase

[2] = for each 5 year increase

Table 16. *Uni- and multivariable logistic regression analyses examining whether preoperative factors are predictive of seizure freedom (ILAE=1) after TLE surgery at 12 month follow-up.*

	Pts did not remain seizure free within 4yrs after surgery (n=131)	Pts who remained seizure free within 4yrs after surgery (n=127)	Overall (n=258)
Pre-op cognitive deficits:			
Globally impaired memory (n=237)*	18 (15.1%)	22 (18.6%)	40 (16.9%)
Verbal fluency (n=226)[2]	14 (10, 18.5)	14 (10, 17)	14 (10, 17.3)
EEG abnormalities:			
Discordant interictal EEG (n=253)*	58 (44.6%)	55 (44.7%)	113 (44.7%)
Chronicity & severity of epilepsy:			
History of SGTCS (n=258)*	**101 (77.0%)**	**82 (64.6%)**	183 (70.9%)
History of status (n=258)*	20 (15.3%)	15 (11.8%)	35 (13.6%)
Epilepsy duration (n=258)[1,2]	24 (17, 32)	23.3 (15, 30)	24 (17, 31.1)
Other:			
Right TL resection (n=136)	57 (43.5%)	66 (52%)	123 (47.7%)
Left TL resection (n=144)	74 (56.5%)	61 (48%)	135 (52.3%)
Preoperative psychiatric diagnosis (n=258)*	**44 (33.6%)**	**27 (21.3%)**	72 (27.5%)

* = yes cases

[1] = yrs

[2] = median (IQR)

Table 17. *Characteristics of TLE patients (pts) who remained seizure free (ILAE=1) (n=127) versus those who did not (n=131) after TLE surgery during four years follow-up.*

	Univariable analysis		Multivariable analysis	
	Odds Ratio (95% CI)	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Pre-op cognitive deficits:				
Globally impaired memory (Yes vs No)	1.28 (0.65 - 2.54)	0.47	1.14 (0.53 - 2.43)	0.72
Verbal fluency[1]	0.90 (0.70 - 1.15)	0.42	0.83 (0.62-1.10)	0.20
EEG abnormalities:				
Discordant interictal EEG (Yes vs No)	1.00 (0.61 - 1.64)	0.98	1.00 (0.56 - 1.77)	0.99
Chronicity & severity of epilepsy:				
History of SGTCS (Yes vs No)	0.54 (0.31 - 0.93)	**0.03**	0.47 (0.25 - 0.90)	**0.02**
History of status (Yes vs No)	0.74 (0.36 - 1.52)	0.41	1.02 (0.45 - 2.31)	0.96
Epilepsy duration[2]	0.98 (0.96 - 1.00)	0.14	0.90 (0.79 - 1.03)	0.14
Other:				
Side of resection (L vs R)	0.71 (0.43 - 1.16)	0.17	0.82 (0.46 - 1.47)	0.51
Preoperative psychiatric diagnosis (Yes vs No)	0.53 (0.30 - 0.93)	**0.03**	0.53 (0.28 - 0.98)	**0.04**

[1] = for each 5 word increase

[2] = for each 5 year increase

Table 18. *Uni- and multivariable logistic regression analyses examining whether preoperative factors are predictive of seizure freedom (ILAE=1) during four years after TLE surgery.*

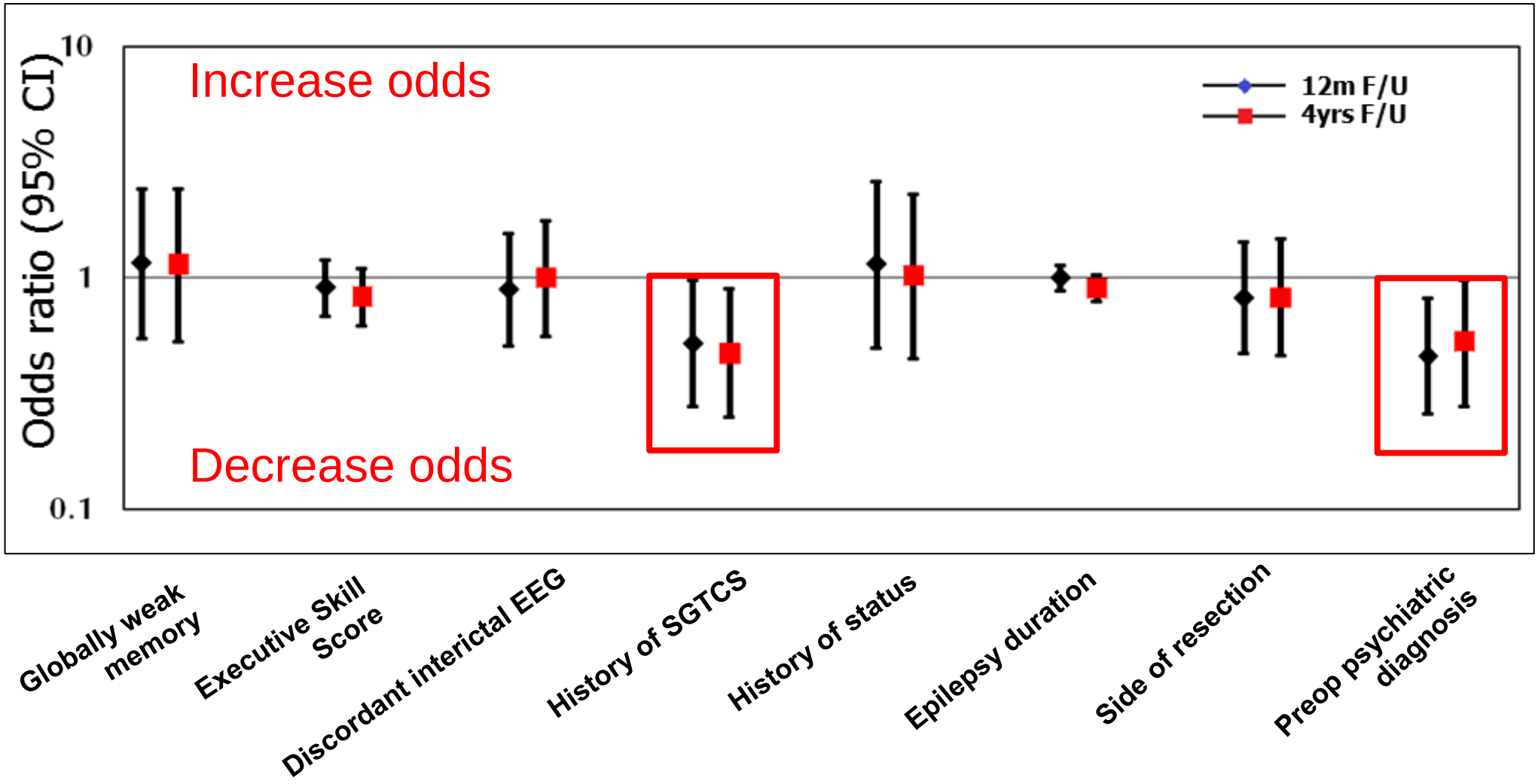

Figure 10. *Clustered boxplot depicting the odds seizure freedom (ILAE=1) at 12 and during 48 month after TLE surgery, as a function of preoperative clinical characteristics. Red boxes indicate that a history of SGTCS and/or a preoperative psychiatric diagnosis significantly reduced the odds of seizure freedom at 12 and during 48 month follow-up for TLE patients.*

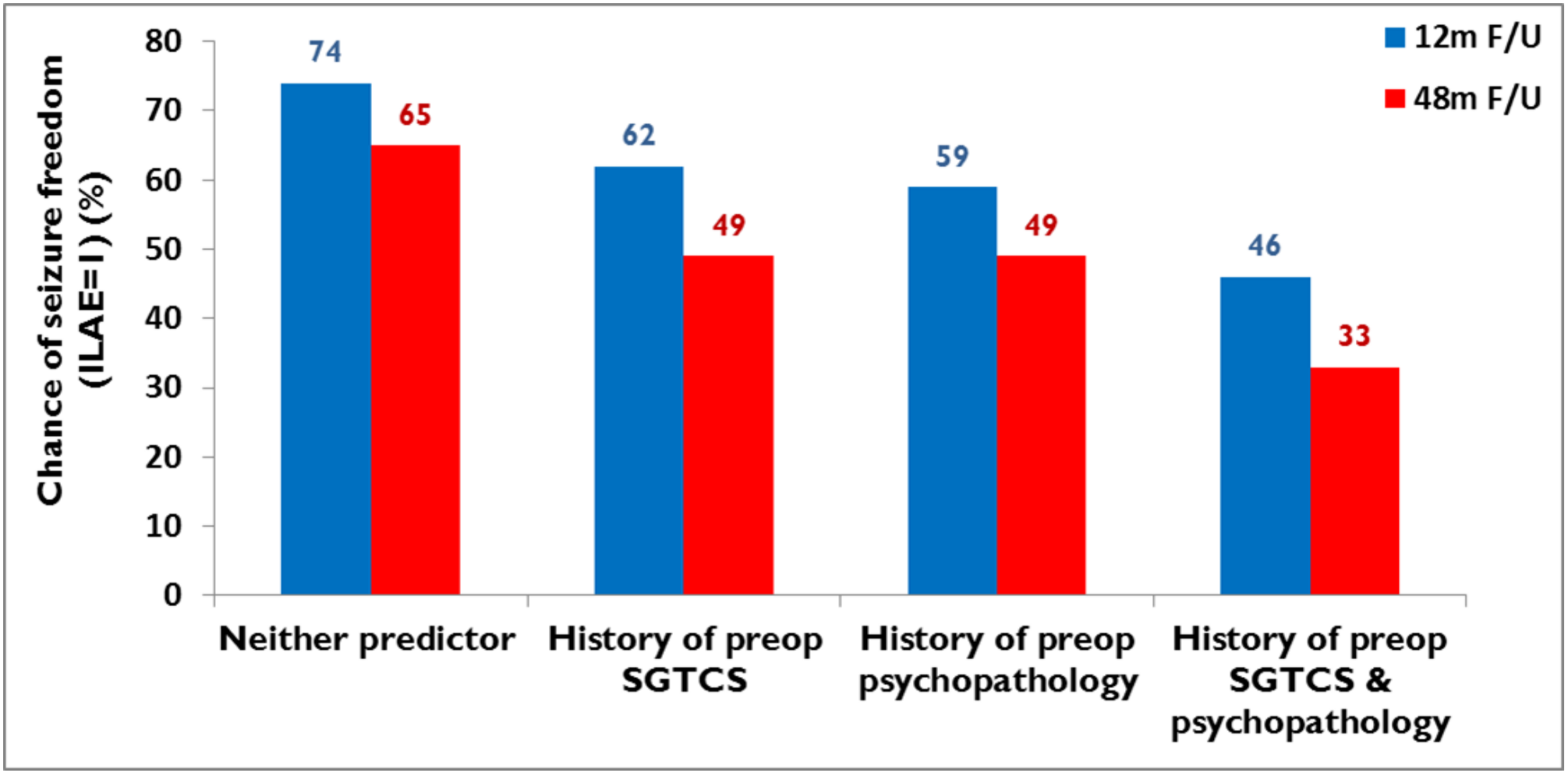

Figure 11. *The modifying effect of preoperative clinical factors on a patient's chance (%) of being seizure free at 12 months and remaining seizure free during 48 months after TLE surgery.*

7.5 Discussion

The results are in keeping with previous reports that TLE patients are affected by psychiatric problems (Gaitatzis, et al., 2004; Swinkels et al., 2005). As predicted and consistent with earlier reports, depression was the most prevalent preoperative psychiatric comorbidity in TLE patients (Ring et al., 1998; Anhoury et al., 2000; Kohler et al., 2001; Wrench et al., 2004; Devinsky et al., 2005; Kanner et al., 2009; Guarnieri et al., 2009; Adams et al., 2012; Filho et al., 2012; da Conceição et al., 2013). This study also found that psychopathology was prevalent following TLE surgery. Almost 50% (n=51/105) of patients with postoperative psychopathology presented with de novo presentations, particularly in the first two post-surgical years. De novo psychiatric morbidity persisted for at least 6 months and the majority of patients (78%; n=40/51) required psychiatric treatment. Contrary to expectations, preoperative cognitive variables indicative of diffuse cerebral pathology were not associated with pre- or postoperative (de novo) psychopathology.

TLE patients are considered at high risk of psychopathology, particularly depression due to limbic and/or frontal lobe dysfunction (Swinkels et al., 2005). The significant relationship between a history of head trauma and preoperative psychopathology lends some support to the role of extra-temporal pathology. Traumatic brain injury (TBI) predominantly causes damage to the fronto-temporal regions (Stuss et al., 2011), and is associated with executive function impairments (Manly & Murphy, 2012, for review). Although the current study failed to identify executive dysfunction in TLE patients with comorbid psychopathology, this may be due to methodological weaknesses. Earlier investigators reporting this association used attention and/or set-shifting tasks namely, the Trail Making Test (Paradiso et al., 2001) or Wisconsin Card Sorting Test (Hermann et al., 1991; Paradiso et al., 2001). However, owing to the retrospective nature of this study, data available with respect to executive skills

was limited, with reliance on only one measure (phonemic fluency). Conceivably, TBI may result in widespread disruption of fronto-limbic pathways, resulting in less focal cognitive pathology, which in turn may increase the likelihood of psychiatric morbidity in TLE patients.

The study found preoperative psychiatric history was predictive of postoperative psychopathology consistent with previous studies (Anhoury et al., 2000; Wrench et al., 2011). Those with a psychiatric history in our series had over six times the odds of a post-surgical psychiatric condition. Similar to previous reports (Anhoury et al., 2000; Kanner et al., 2009), the most common postoperative psychiatric disorders were mood disorders, namely depression (25%; n=71/280) followed by anxiety disorders (9%; n=24/280).

Replicating the primary psychiatric literature (Dean et al., 2010), a positive psychiatric family history independently increased the odds of a lifetime psychiatric diagnosis in TLE patients. Closer examination of the data revealed that nearly half of patients (n=9/20; 45%) had *different* psychopathologies compared to their first-degree relative(s). This is a novel finding in TLE and is consistent with a recent meta-analysis that reported familial psychiatric risk can extend across diagnostic boundaries and can be heterotypic (different from parental diagnosis) (Rasic et al., 2013). The mechanistic link of heterotypic familial transmission may be explained by findings from molecular genetic studies, indicating that many psychiatric disorders share a substantial proportion of their genetic susceptibility (Smoller et al., 2013; Serretti et al., 2013). Whether genetic pleiotropy is responsible for the observed divergent relation between familial-offspring psychopathology remains speculative.

Regarding whether preoperative indicators of cerebral pathology were risk factors for psychiatric (de novo) morbidity, a history of SGTCS was the only independent preoperative predictor. Additionally, the study confirmed previous findings that seizure remission

following resective TLE surgery is significantly reduced for patients with a pre-surgical history of SGTCS (Jansky et al., 2005). More widespread interictal cerebral hypometabolism on PET has been demonstrated in TLE patients with a history of SGTCS compared to those with focal-only seizures (Savic et al., 1997). Similarly, patients who develop de novo psychopathology have widespread frontal (Salzberg et al., 2006) and bi-temporal abnormalities (Anhoury et al., 2000). Taken together, our findings suggest that a history of SGTCS may reflect more widespread epileptogenicity, and thereby is a negative predictor for seizure and psychiatric outcome of TLE surgery.

None of the other seizure related factors selected predicted de novo post-surgical psychiatric morbidity. Previous studies examining risk factors for poor psychiatric outcome have reported conflicting findings (Foong et al., 2007; Spencer et al., 2008). Some have suggested that the risk factors for poor psychiatric outcome include localisation of surgery (temporal vs extra-temporal) (Wrench et al., 2000), laterality of resection (Ring et al., 1998), bilateral EEG abnormalities (Anhoury et al., 2000), or seizure outcome (Blumer et al, 1998; Devinsky et al., 2005; Hamid et al., 2011).

Regarding laterality of resection, some studies have delineated the *type* of postoperative psychiatric diagnosis in their analyses suggesting that left-sided temporal lobe surgery was associated with the development of anxiety (Ring et al., 1998) or that right-sided surgery was associated with postoperative depression (Quigg et al., 2003). However, for the regression analyses in this study, *all* types of de novo post-surgical psychiatric conditions were pooled, which may have decreased the ability to detect an effect of lateralisation (i.e. increase the chance of a type II error).

In this study, postoperative de novo psychopathology was not associated with seizure outcome. It could be argued that the use of a chi-squared analysis which did not allow for

subtyping postoperative de novo psychiatric morbidity, may account for this result. However, a number of studies that have subtyped post-surgical psychiatric disorders have also failed to find an association with seizure outcome (Wrench et al., 2011; Anhoury et al., 2000).

Paradoxically, the majority of de novo psychopathologies (66%) occurred in the context of seizure freedom (ILAE 1, see Table 20). A possible explanation is that this may due to the well described "burden of normality" (Wilson, Bladin & Saling, 2001). According to this model, post-surgical seizure freedom may provoke life-changing and profound psychosocial adjustment; a lack of preparedness and skills to cope with these new challenges may render the patient at greater risk to significant postoperative psychopathology (Wilson, Bladin, Saling, 2004). Evidence relating to this concept, and its link to de novo psychopathology, is still limited and requires further research.

This investigation did not replicate the finding that bilateral EEG abnormalities were related to poor psychiatric outcome (Anhoury et al., 2000). However, a caveat of this research was that epileptic spike counts were not performed in a uniform manner over time precluding quantification of interictal spike ratios. Prospective studies exploring this would be beneficial.

The pre-surgical cognitive variables used in this study, namely preoperative memory and executive skills weakness, did not predict those individuals at increased risk of developing a de novo psychiatric diagnosis. However as previously stated, data available with respect to executive skills was limited, with reliance on only one measure (phonemic fluency). Hence, the *degree* of widespread cerebral dysfunction in this surgical cohort could not be exhaustively examined. It would be valuable for prospective studies to explore the relationship of executive skills deficits, termed the 'extra-temporal neuropsychological

profile' (Keller et al, 2009), to psychiatric outcome using a more thorough assessment of this important cognitive domain.

An important finding was that a lifetime psychiatric diagnosis significantly lowered the odds of attaining seizure freedom in the 4 years following TLE surgery. This lends further support to the findings of three previous studies with smaller cohorts (Anhoury et al., 2000; Kanner et al., 2009; Guarnieri et al., 2009) that have reported a strong association between a lifetime psychiatric history and the failure to achieve seizure freedom. In the earliest study, the case-notes of 109 patients TLE surgical patients were reviewed one year following surgery (Anhoury et al., 2000), and another series of 100 consecutive temporal lobectomy patients were reviewed 2 years postoperatively (Kanner et al., 2009). In a larger series of 186 TLE cases, it was reported that those diagnosed with a preoperative anxiety or personality disorder were significantly less likely to attain seizure freedom (Guarnieri et al., 2009). This study employed a *clinical diagnosis* of pre- and postoperative psychopathology rather than self-report measures. No single method is ideal to assess psychiatric functioning pre- or post-surgery (Guangming et al., 2009), but the merit of a psychiatric evaluation is that it not only consider transient mood states reflected by self-reported indices, but the full context of the presenting symptoms including the history, other behavioural characteristics, and corroborative information from the family or carer(s). This is supported by evidence that TLE+HS patients with high depressive *symptoms* did not have poor seizure outcome within three post-surgical years (Lackmayer et al., 2013).

Although explanations for poor seizure outcome associated with pre-surgical psychiatric history could include poor AED compliance, pro-convulsant psychotropic medication and/or that persisting seizures are non-epileptic, these explanations are unlikely. Patients were under regular postoperative neurological review whereby AED compliance was monitored by inquiry of patients and relatives, supplemented with anticonvulsant drug levels. Pro-

convulsant psychiatric medications were purposively avoided. Based on discordant pre- and post-operative seizure semiology, three de novo NES cases were diagnosed clinically. Where there was doubt concerning the nature of postoperative seizures (n=15), patients were referred for VEEG monitoring; 93% (n=14) of cases were confirmed as epileptic events.

The findings do not imply that TLE patients with a preoperative co-morbid psychiatric diagnosis should be excluded from surgical consideration, rather they suggest that a psychiatric history is a pertinent risk factor for seizure freedom. In agreement with Kanner et al. (2009), it is possible that a psychiatric history may be a biomarker of a more severe seizure disorder or indicative of more diffuse cerebral pathology. Support for this hypothesis comes from a retrospective study of 780 patients with new-onset epilepsy, which found patients with psychiatric comorbidity, particularly depression, had more than twice the odds of developing pharmacoresistance (Hitiris et al., 2007). Similarly, a prospective study of 138 patients with newly diagnosed epilepsy syndromes prior to AED treatment reported that greater neuropsychiatric symptomatology was independently predictive of AED non-responsiveness (Petrovski et al., 2010). Whereas Adams et al. (2008) found that patients with refractory non-lesional (versus lesional) epilepsy are more than twice as likely to have a psychiatric diagnosis, particularly depression. Thus, a possible explanation for our findings is that these putative diffuse epileptogenic zones may become "unmasked" once the dominant temporal ictal focus is resected, resulting in seizure recurrence postoperatively.

As reviewed in Chapter 3, it has also been suggested that TLE and depression may share common widespread neuro-anatomical substrates. Extra-temporal or frontal abnormalities have been implicated in neuroimaging studies in patients with primary depression (Sheline, 2003; Price et al., 2012) and those with TLE and co-morbid depression (Salzberg et al., 2006; Lothe et al., 2008). One study found that a smaller contralateral hippocampal volume was related to de novo depression following mesial TLE surgery (Wrench et al., 2009). Clearly,

prospective studies utilising in vivo imaging techniques with neuropsychological and psychiatric measures to further elucidate the neural correlates of de novo postoperative psychopathology is warranted.

There were several limitations to this study due to its retrospective nature. Missing and incomplete preoperative data may have introduced sample bias. It was not possible to statistically investigate longer-term follow-up due to steep sample attrition after 4 years. This was due to patients being referred back to local services and that 4 years was the maximum follow-up time available given the end point of our study in 2007. However, pre- (OR: 1.64, 95%CI: 0.89–3.04, p=0.12) or postoperative psychiatric morbidity (OR: 1.32, 95%CI: 0.69–2.55, p=0.40) did not predict sample attrition. The limited neuropsychological data did not allow us to explore the relationship between pre-surgical executive deficits and pre- or postoperative (de novo) psychiatric morbidity in greater detail. Although all patients in this study had clinical pre- and post-surgical neuropsychiatric evaluations at 3 and 6 months, it is possible that psychiatric symptoms may have emerged *after* routine post-surgical neuropsychiatric screening. Research indicates that psychiatric morbidity in TLE patients is often unrecognised or overlooked in routine neurological consultations (Kanner, Kozak & Frey, 2000; Kanner, 2003). Therefore, the reported postoperative psychopathology prevalence rates may represent an underestimation. In addition, a lack of statistical power precluded the subtyping of preoperative psychopathology. Finally, due to a lack of systematic recording of psychopathology onset, it was not possible to delineate whether on-going (versus a history) of psychopathology at the time of surgery modifies the relationship with seizure outcome.

In summary, this study provides support for the hypotheses outlined. The data suggests that a lifetime history of psychopathology is related to diffuse cerebral pathology and genetic factors. The finding that post-surgical de novo psychiatric disorders are a significant and

persisting complication, particularly in the first 2 years, following TLE surgery has clinical implications. Hence it is imperative that patients, especially those with a history of SGTCS, and their families are counselled about the possible development or exacerbation of psychiatric symptoms following surgery. However, a recent survey found that only 16% of adult epileptologists and 13% of adult neurosurgeons discussed the possible psychiatric complications of TLE surgery during their pre-operative consultation (Demase et al., 2009). The data suggests that the identification and treatment of preoperative psychopathology may lead to substantial gains in postoperative seizure outcome; although the mechanisms mediating poorer postoperative seizure outcome in patients with presurgical psychopathology are unknown at this time, studies in animal models of epilepsy and humans with TLE (with and without depression) have suggested the existence of common serotinergic pathogenic mechanisms operant in psychopathology and epilepsy (see Kanner et al., 2005, for review). Thus, it is speculated that serotinergic agents (e.g. SSRIs) for *presurgical* mood/anxiety disorders may also improve *postoperative* seizure outcome. Finally, the finding that a preoperative psychiatric history, in surgical sample deemed comparable to other surgical cohorts (Anhoury et al., 2000; Wrench et al., 2009), significantly lowers the odds of seizure freedom 4 years following TLE surgery underscores the importance of a pre-surgical psychiatric evaluation. The inclusion of neuropsychiatric assessments in the pre-surgical evaluation may lead to an increase in the power of prognostic models used to predict the neurological outcome of TLE surgery.

Chapter 8.

Study 2. Neural Correlates of De novo Depression Following Left Temporal Lobe Epilepsy Surgery: A Voxel Based Morphometry Study of Pre-surgical Structural MRI

8.1 Study Aims

As outlined in Chapter 3, neuroimaging has revolutionised the investigation and treatment of TLE, and has enabled significant advances towards elucidating the pathophysiology of mood disorders. It also provides a means to further explore the hypothesis that more widespread cerebral pathology places TLE patients at increased risk of psychiatric (de novo) morbidity following surgery. To date, only a stereological region-of-interest (ROI) analysis has addressed this.

The aim of this study was to investigate whether pre-surgical abnormalities in cerebral volume are associated with de novo depression following mTLE surgery.

8.2 Methods

Study Sample

Eighty-seven TLE+HS (43 left, 44 right) patients had preoperative MRI imaging available to which voxel-based morphometry (VBM; Ashburner & Frston, 2000) had been applied.

In the right TLE group, 14 (32%; n=14/44) had a lifetime psychiatric history and only two (5%; n=2/44) patients developed de novo depression. The small number of de novo depression cases in the right TLE group precluded meaningful comparisons, and only left-sided TLE patients were examined in this study.

In the left TLE group, 12 patients (28%; n=12/43) had a lifetime psychiatric history (see Figure 12, for diagnostic categories) and 1 patient (2%; n=1/43) developed de novo PIP. These 13 (30%; n=13/43) patients were excluded from the analysis as the study focus was on de novo depression. Of the remaining 30 left TLE patients, 25 (83%; n=25/30) had neither pre- nor postoperative psychopathology (TLE-control group), and 5 (17%; n=5/30) developed de novo depression. Demographic and clinical characteristics are summarised in Table 19.

Neuropsychiatric evaluation (including de novo cases), epilepsy related variables, neuropsychological assessment, aetiological and MRI/video-EEG classification data have been described previously (see Chapter 6.3, 6.4, 6.2, 6.5 & 6.6, 6.7 respectively).

Magnetic Resonance Imaging

All subjects underwent an MRI scan on a 1.5-T GE Signa scanner (GE Medical Systems, Milwaukee, Wisconsin). A T1-weighted inversion recovery three-dimensional fast spoiled gradient echo (SPGR) (TE = 4.2 msec, TR = 15.5 msec, inversion time = 450 msec, flip angle = 20°, matrix = 256 × 192, FOV = 24 × 18 cm^2) were obtained for each subject. All images

were acquired in the coronal plane with 28 contiguous, 5-mm-thick slices. Images were processed and analysed using Statistical Parametric Mapping software (SPM8) (www.fil.ion.ucl.ac.uk).

Segmentation of the T1 images was performed using the "New Segmentation" algorithm of SPM8. The grey matter (GM), white matter (WM) and CSF tissue maps where normalized to MNI space using the diffeomorphic anatomical registration through exponentiated lie algebra (*DARTEL*) toolbox. GM segmentations were modulated by the Jacobian determinants derived from the registration step, in order to preserve each subject's tissue volume after warping. Finally, images were smoothed by an 8-mm full width at half maximum isotropic Gaussian kernel.

Voxel-wise grey matter volume (GMV) differences between patients that developed de novo post-surgical depression and patients with no pre- or postoperative psychiatric diagnoses were investigated, using independent samples t-tests. To account for differences in brain sizes, images were globally normalized using each subject's whole brain volume. Age, and gender were used as regressors of no interest (Takahash et al., 2011), as well as SGTCS which has been reported as a confound (see Chapter 7). Differences at a threshold of $p<0.001$, uncorrected for multiple comparisons are reported with a cut off of 50 contiguous voxels of activation. This threshold was chosen in order to avoid type II errors (false negatives), while ensuring a desirable balance with Type I errors (false positives) (Liberman & Cunningham, 2009). This approach was justified given the small sample size.

Neuropsychological Measures

It was anticipated that de novo depression would be associated with extra-temporal cerebral dysfunction as indicated by a larger discrepancy between NART predicted and assessed IQ, and reduced phonemic fluency.

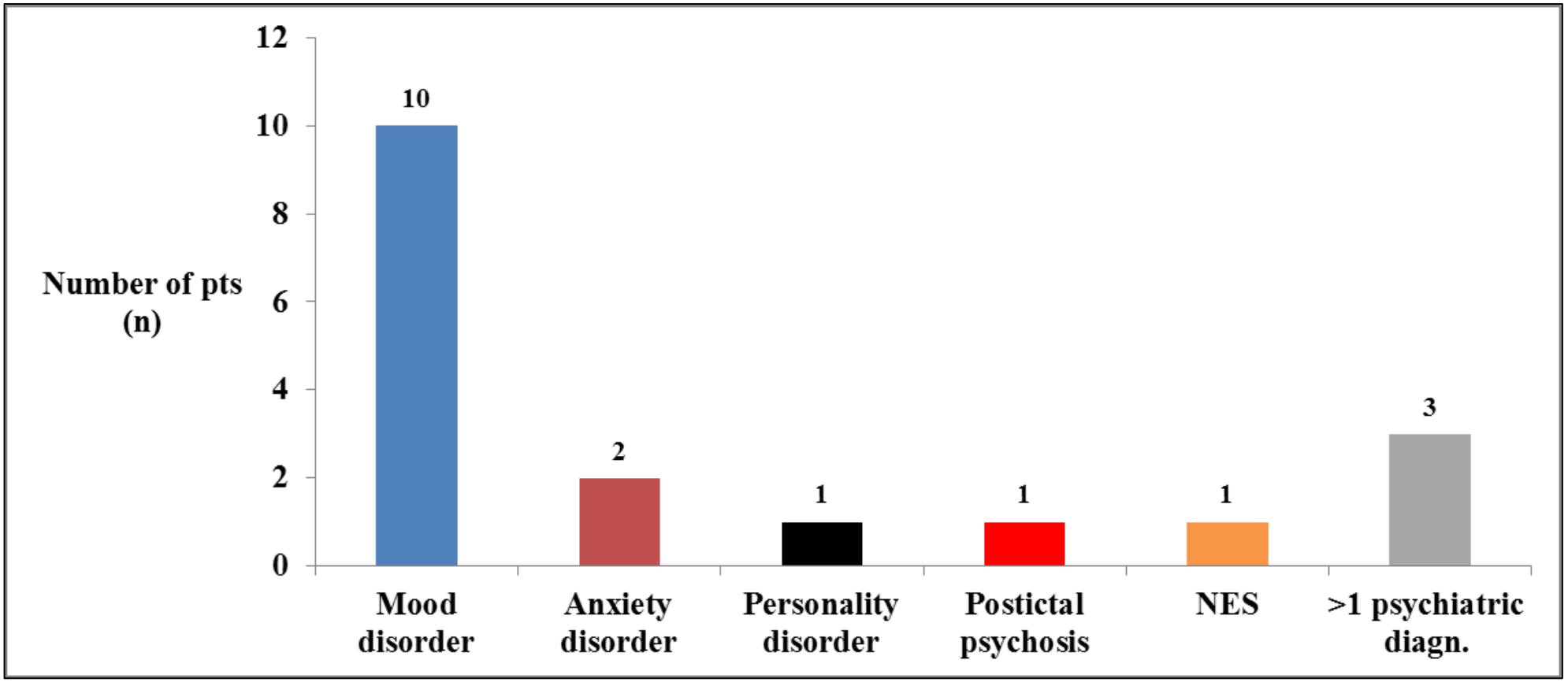

Figure 12. *Preoperative lifetime psychiatric history of the 12 (28%) left TLE patients (pts) excluded from the VBM analysis.*

Personality disorder = emotionally unstable.

	De novo Depression (n=5)	Left TLE controls (n=25)	P-value
Gender (female)[a]	2 (40%)	14 (56%)	0.64
Age of seizure onset, years[2]	2 (0.7-9.3)	5 (1.2-9.5)	0.40
TLE duration, years[2]	26 (20-33)	30 (19.5-35.1)	0.71
Predisposing Factors[a]			
History of FC	4 (80%)	13 (52%)	0.40
Family history of epilepsy	0 (0%)	6 (24%)	0.60
Family histoy of psychopathology	1 (20%)	3 (12%)	0.54
History of status epilepticus	0 (0%)	1 (4%)	1.00
History of CNS infection	0 (0%)	1 (4%)	1.00
History of head trauma	1 (20%)	2 (8%)	0.43
Presurgical seizure type†[a]			
Simple partial	3 (60%)	9 (64%)	1.00
Complex partial	5 (100%)	25 (100%)	n/a
SGTCS	5 (100%)	19 (76%)	0.60
Medication			
Lifetime number of AEDs trialled preoperatively[1]	6 (2)	5 (2)	0.38
Monotherapy at the time of surgery[a]	0 (0%)	5 (20%)	0.60
Polytherapy at the time of surgery[a]	5 (100%)	20 (80%)	0.60
Age at surgery, years[1]	29 (5.4)	35.1 (9)	0.15
EEG Findings[a]			
Discordant interictal EEG	5 (100%)	16 (70%)	0.29
Histopathological findings[a]			
Hippocampal sclerosis	5 (100%)	25 (100%)	n/a
Developmental pathology	2 (40%)	3 (12%)	0.18
Vascular pathology	0 (0%)	1 (4%)	n/a
Other	0 (0%)	0 (0%)	n/a
Dual pathology	2 (40%)	4 (16%)	0.25
Preoperative cognitive variables[b]			
VIQ[1]	86 (17)	92 (12)	0.33
NART[2]	89 (73-100)	100 (89-107)	0.17
NART/VIQ discrepancy[2]	-13 (-5, -3)	-5 (-9, -2)	0.58
Verbal learning: trials[1]	-2.08 (0.97)	-1.21 (1.07)	0.11
Visual learning: trials[1]	-1.07 (2.09)	-0.39 (1.32)	0.34
Phonemic fluency[2]	-0.21 (-2.31, 1.17)	-0.21 (-1.48, 0.85)	0.73

[a]Values are number of patients (%)
[b]For available data
[1]Mean (SD)
[2]Median (range)
†May have >1 seizure type
AEDs, anti-epileptic drugs
CNS, central nervous system
FC, febrile convulsions
SGTCS, secondary generalised tonic-clonic seizures

Table 19. *Clinical and demographic characteristics of patients who developed de novo depression (n=5) compared to those who did not (n=25) following TLE surgery.*

Memory Decline

Postoperative memory decline, as described in Chapter 7, was defined as a performance drop of at least 1 SD on the List and Design learning tests.

8.3 Statistical Analyses

Chi-square (X^2; with Fisher Exact Test (FET) when warranted) was used to evaluate comparisons between patients who developed de novo depression compared to those who did not (TLE-controls), and to explore whether memory decline was associated with de novo depression. Differences between continuous variables were evaluated using the independent samples t-test, with the exception of variables that were non-normally distributed as defined by the Kolmogorov-Smirnov test (Field, 2009), for which Mann-Whitney U tests were employed.

8.4 Results

De Novo Depression

Five TLE patients (17%; n=5/30) developed de novo depression within four years following surgery. Sixty per cent (n=3/5) presented within 12 months, all cases (100%; n=5/5) persisted for at least 6 months (range: 6-60 months), and required psychiatric medication. One patient (20%; n=1/5) attempted suicide on two separate occasions, necessitating hospitalisation admissions within the 4-year follow-up. All patients were prescribed selective serotonin reuptake inhibiters (SSRIs: paroxetine, fluoxetine or citalopram) in isolation.

Clinical Characteristics

The two groups did not differ in terms of age of seizure onset, epilepsy duration, history of febrile convulsions, status epilepticus, head trauma or CNS infection, frequency of discordant interictal EEG abnormalities or family history of epilepsy or psychopathology. No differences in the frequency of simple partial, complex partial or history of SGTCS were determined (see Table 19).

VBM Findings

Pre-surgical MRI revealed significant areas of atrophy within bilateral OFC, and left cingulate gyrus and left thalamus in TLE patients that developed de novo depression following an ATLR (see Figure 13).

Seizure Outcome

Forty three per cent (n=13/30) remained seizure-free (ILAE=1) during four years follow-up. There was no relationship between seizure outcome (ILAE 1 vs 2-6) and de novo depression within 48 months postoperatively (FET; p=1.0).

Cognitive Outcome

From patients with available cognitive outcome data, a decline in memory test performance of at least 1 SD was recorded in 6 (n=6/26; 61%) patients for verbal memory and 5 (n=5/25; 58%) patients for visual memory. We found no relationship between postoperative memory decline and the development of de novo depression within the 12 month follow-up ($p > 0.05$).

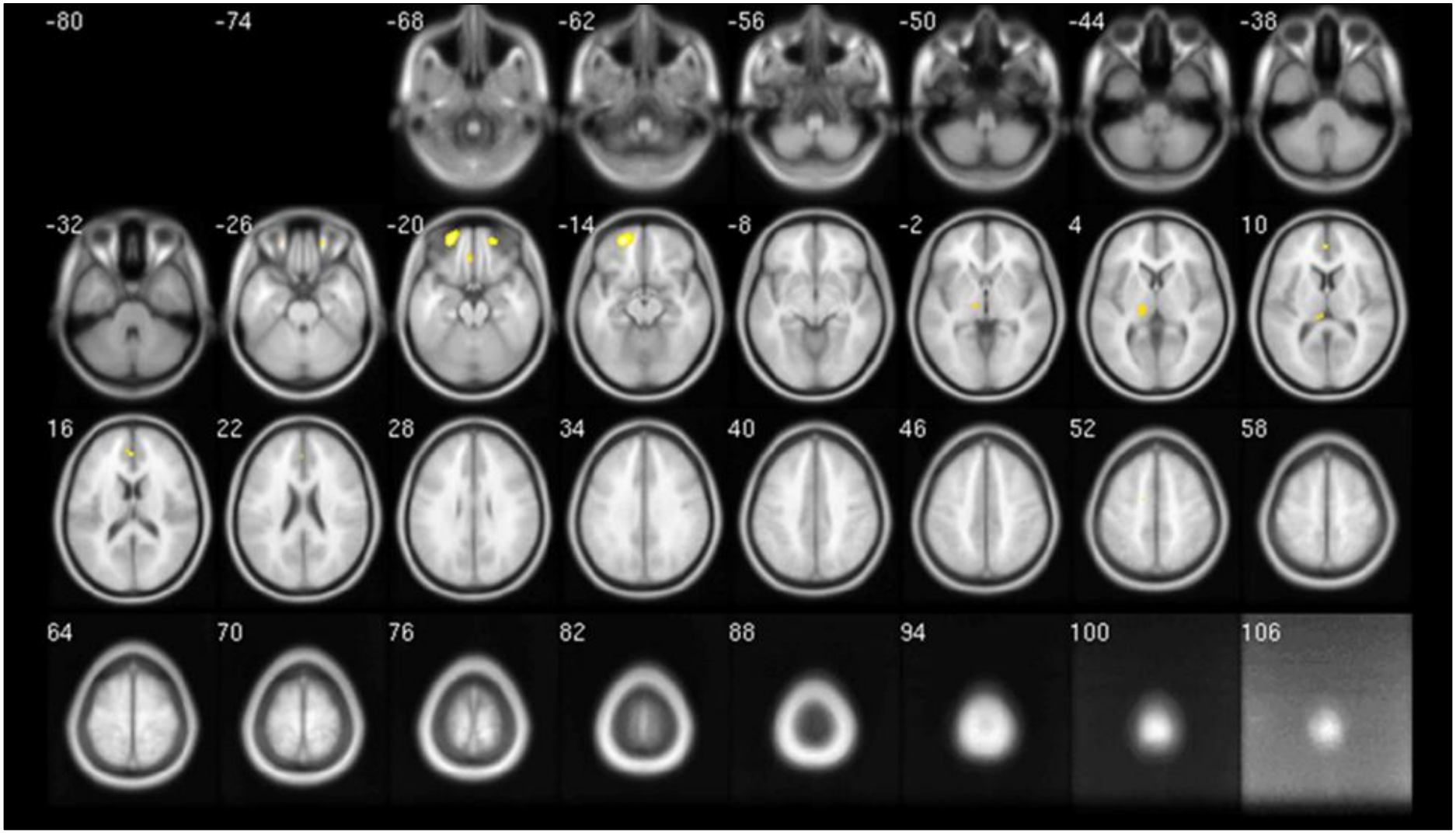

Figure 13. *Bilateral OFC (slice:-20) and ipsilateral cingulate gyrus (slice:10) and thalamic atrophy (slices: -2, 4 & 10) in left-sided TLE+HS patients who developed de novo depression (n=5) compared to patients with no pre- or postoperative psychopathology (n=25) (p<.001, unc); controlling for age, gender and SGTCS.*

8.5 Discussion

Preoperative bilateral OFC, ipsilateral cingulate and thalamic atrophy was identified in patients with left hippocampal sclerosis who developed de novo depression following TLE surgery, compared to patients without pre- or postoperative psychopathology. In keeping with previous literature (Chapter 7; Altshuler et al., 1999; Cankurtaran et al., 2005), the majority of cases developed within the first postoperative year. All de novo depression presentations persisted for at least 6 months and required psychiatric intervention, thus reinforcing the recommendation that it is neither sufficient nor accurate to measure the efficacy of surgery solely by examining seizure outcome (Wrench et al., 2011).

These findings are consistent with meta-analytic reports in the primary affective disorder literature of reduced GMV in the OFC, cingulate gyrus (Kempton et al., 2011; Arnone et al., 2012; Lai, 2013) and thalamus (Kempton et al., 2011) compared to healthy controls. It has been postulated that major depressive disorder (MDD) results from dysfunction within a neural network involving these structures (Drevets et al., 2012).

The finding of OFC atrophy also lends support to previous reports of OFC abnormalities, namely focal hypo-metabolism in the ipsilateral orbitofrontal cortex in TLE patients with postoperative depression (Salzberg et al., 2006). However, there are important methodological differences compared to earlier work. Firstly, to explore the development of *de novo* depression, patients with a preoperative psychiatric history (n=12), and those who developed de novo psychopathology *other than* depression (PIP; n=1), were excluded from the imaging analyses. This allows confidence that the de novo depression group was psychiatrically homogenous.

Secondly, as Salzberg and colleagues (2006) did not conduct a volumetric analysis of the OFC, it is uncertain whether the reported ipsilateral OFC hypo-metabolism in the de novo

depression group was related to *structural* (i.e. reduced GMV) abnormalities in the region. Therefore, further correlational studies investigating OFC atrophy and hypo-metabolism in de novo depression patients will be needed to clarify this.

This study did not replicate the finding that reduced preoperative contralateral hippocampal volume was a significant risk factor in the development of de novo depression in mTLE patients (Wrench et al., 2009). This divergent result may be due to methodological differences between studies. Wrench and co-workers (2009) manually segmented the hippocampi, which relies on investigator expertise and is associated with potential biases (Keller et al., 2008). A fully automated, whole brain VBM method (Ashburner et al., 2000) was employed which is a powerful and unbiased tool that overcomes the limitations of the ROI approach (Lai, 2013). Moreover, DARTEL was used in the image pre-processing step, which improves realignment of temporal lobe inner structures, particularly the hippocampus (Yassa & Stark, 2009).

Although this investigation did not replicate the previous finding that a history of SGTCS was an independent predictor of de novo psychopathology (see Study 1), this may be due to the small sample size. Notably, the areas of significant atrophy in patients who developed de novo depression were mainly *ipsilateral* to the epileptic focus. This suggests that the propagation of epileptic seizures that extend beyond the seizure onset zone (e.g. SGTCS) may also contribute to the pathogenesis of depression. More widespread interictal cerebral metabolism on PET has been reported in TLE patients with a history of SGTCS compared to those with focal–only seizures (Savic et al., 1997). Future studies with larger cohorts are needed to assess whether the history or frequency of SGTCS mediates the degree of GMV loss in patients who develop de novo depression.

No clinical or other pathological factors distinguished the patient groups. Previous studies examining risk factors for de novo depression have reported conflicting findings (Cleary et al., 2013). Some have suggested that temporal (versus extra-temporal) epilepsy surgery (Wrench et al., 2004) or poor seizure outcome (Blumer et al., 1998; Devinsky et al., 2005) increases the risk of de novo depressive morbidity.

Regarding localisation of resective surgery, as only patients with unilateral left-sided HS were included it is not possible to generalise the findings to right-sided TLE-HS patients, those with neocortical TLE or extra-temporal patients.

Similar to previous research, this study found no relationship between de novo depression and seizure freedom within four post-operative years (ILAE=1 vs 2-6) (Wrench et al., 2009). Conceivably, low mood may be temporally linked to seizure recurrence. However, three of the five patients were seizure free at the time of the de novo depression. This suggests that de novo depression following TLE surgery cannot be solely attributed to a failed procedure. Larger cohort studies are warranted to further examine the relationship between de novo depression and the *recurrence* of conscious-altering seizures (ILAE 1-2 vs ≥3). Furthermore, the genesis of de novo depression may be influenced by surgical morbidity other than seizure recurrence. No patient in this study developed a neurological deficit such as hemiparesis; a rare occurrence in temporal lobe resections (Hader et al., 2013), and there was no relationship between memory decline and the development of de novo depression.

The research literature suggests that de novo depression frequently occurs within 3-12 months after surgery (see Chapter 2). In this study 40% (n=2/5) of the cohort developed de novo depression at between 24 and 48 months. There are several possibilities for this divergent finding. First, psychiatric comorbidities TLE are often unrecognised or overlooked in routine neurological consultations and remain undertreated (Kanner et al., 2000; Rai et al.,

2012). Second, patients and families often under-report psychiatric symptomatology, viewing them as a "natural reaction" to difficult life circumstances (Kanner et al., 2002). This problem is complicated further as patient disclosure can be modified by context. For example, a cross-sectional study of 574 epilepsy patients found that 0% spontaneously reported depressive symptoms, whereas 31% reported depressive morbidity when administered a self-report questionnaire (Carreno et al., 2008). It is of course also possible that depression would have developed had surgery not been undertaken.

The pre-surgical cognitive variables used in this study, namely preoperative memory and executive skills weakness were not associated with the development of de novo depression. However, data available with respect to executive function was limited as discussed in Study 1, with reliance on one measure (phonemic fluency). Hence, the degree of widespread cerebral dysfunction in this surgical cohort could not be exhaustively examined.

There are several limitations of this study. Although the de novo depression group is similar in size to previous studies (Salzberg et al., 2006; n=5; Wrench et al., 2009; n=4), nonetheless the small sample size results in limited statistical power. However, as all patients had a clinical psychiatric evaluation pre-surgically, which considered the full context of psychopathology, including medication-related and peri-ictal symptoms, it is with confidence that the diagnosis of de novo depression can be made. Whilst no single method is optimal to assess psychiatric state in TLE (Guarnieri et al., 2009), an evaluation by an experienced neuropsychiatrist is considered the gold standard (Jones et al., 2005). Although the retrospective study does not allow comment on the qualitative nature of the de novo depressive episodes, the long duration of treatment (6-60 months) merits consideration. It is conceivable that these cases were refractory to SSRI therapy. However, the majority of patients (80%) remained on their initial anti-depressant for the entire course of their depression and there was little variance in drug titration over this period. Therefore, it is

likely that patients were not symptomatic during this period, but rather remained on psychiatric medication due to mood stabilising benefits. It was not possible to investigate follow-up longer than 4 years due to sample attrition. Despite all patients undergoing post-surgical postoperative neuropsychiatric evaluations at 3 and 6 months, it is possible that psychiatric symptoms may have emerged later or were missed, as research indicates that psychiatric morbidity in TLE is often unrecognised or overlooked in routine neurological consultations (Kanner et al., 2000). These scenarios however, would have been the same for both patient groups.

A possible confounding factor in this study was the impact of AEDs on mood. The psychotropic properties of AEDs are well recognised and a minority have been linked to depressive morbidity and suicide (FDA, 2008). Whereas other AEDs demonstrate mood stabilising-protective effects, such as valproate and carbamazepine (Britton & Shih, 2010). Therefore, it is conceivable that the findings are linked to changes in AED therapy following surgery, rather than pre-surgical structural abnormalities. This is an unlikely explanation as it is clinical practice that within the first 12 months, unless seizure frequency worsens, patients remain on the same preoperative AED regimen. There was no relationship between change of AED regimen and group membership (TLE-controls: n=3/25, 12% versus De novo Depression: n=1/5, 5%; p=0.60).

In conclusion, this study shows pre-surgical structural brain differences in those patients that *develop* depression after left ATLR and confirms de novo depression as a significant and persisting complication of TLE surgery in left-sided TLE+HS patients. The findings support the hypothesis that structural abnormalities *remote* from the epileptogenic focus are relevant to the development of post-surgical de novo depression.

Chapter 9.

Study 3. Postictal Psychosis in Temporal Lobe Epilepsy: Risk Factors & Post-surgical Outcome?

9.1 Study Aims

As highlighted in Chapter 3, the pathophysiological mechanisms of PIP are not fully understood and most evidence has been derived from single and multiple case studies. The aims of this study therefore were to examine further the risk factors associated with PIP in TLE patients, including EEG, cognitive and neuropathological factors, and to investigate whether a history or frequency of PIP predicted psychiatric, cognitive or seizure outcome following TLE surgery.

9.2 Method

Study Sample

Of the 280 TLE cases, 20 patients with a history of PIP (TLE+PIP) were identified and age-matched with 60 TLE controls with *no* history of psychopathology (TLE-only; n=60). The sample was selected blind for neurological history, family history of seizures and psychopathology, VEEG and MRI results. Demographic and clinical characteristics are summarised in Table 20.

Neuropsychiatric Classification

For the TLE+PIP group, the number of PIP was episodes documented. None of these PIP episodes were as a result of drug reduction/withdrawal during pre-surgical VEEG. Any family psychiatric history was also documented. For comorbid psychopathology (e.g. a history of PIP *and* depression), a positive entry was made into each diagnostic category.

For the TLE+PIP group, de novo psychopathology was only coded if a patient had *no* preoperative psychiatric history of *that* psychiatric disorder. For example, if a TLE+PIP patient had preoperative *and* postoperative depression, but *developed* and anxiety disorder post-surgically, only the latter condition would be considered de novo. For the TLE control group, *all* postoperative psychiatric conditions were coded as de novo as these patients had no previous psychiatric history. All de novo cases could only be termed as such at one mutually exclusive time frame. All patients had neuropsychiatric evaluation only at 3 and 6 months post-surgically and subsequently diagnosed psychiatric disorder(s) were then coded as appropriate into the following postoperative time-frames: 12, 24, 36 and 48 months.

Neuropathology

Neuropathological examination was undertaken by a Consultant Clinical Neuropathologist (Dr Maria Thom). All tissue from each surgical resection was routinely-processed and embedded in paraffin. Sections were cut at 5-14 microns and were examined with H&E and Luxol fast blue/cresyl violet (LFB/CV) stain. The immunohistochemistry selected for each case varied according to the underlying pathology, but more commonly used markers included GFAP (1:1500, polyclonal Dako, Glostrup, Denmark), CD68 (1:100, monoclonal Dako, heat pre-treatment) , Neurofilaments (Sternberger Mononclonals (SMI32&31), USA, both 1: 500) and Dynorphin (1:100 AbD Serotec, Kidlington, Oxford, UK).

The pathology findings in the cases were groups as follows (1) hippocampal sclerosis (HS) alone; (2) HS with additional focal cortical dysplasia (FDC type IIIa); (3) glioneuronal tumour (dysembryoplastic neuroepithelial tumour (DNT) or ganglioglioma); (4) cavernomas or other vascular formations; (5) Non-specific gliosis only, with no specific pathological lesion identified and (6) dual pathology comprising of cases with HS and another lesions (e.g. cavernoma, DNT, but HS+FCDIIIa was not regarding as dual pathology) (Blumcke et al., 2011).

Video-EEG Data

Pre-surgical VEEG reports were used to classify cases demonstrating ‘localised’ or ‘non-localised’ ictal or interictal epileptiform abnormalities. Specifically, non-localised ictal or interictal EEG was based on any epileptiform discharges that were discordant with neuro-radiological findings (e.g. independent bi-temporal spikes/multifocal spikes/fronto-temporal discharges in the presence of unilateral HS) as defined by VEEG reports.

Variable	TLE+PIP (*n* = 20)	TLE-only (*n* = 60)	All (*n* = 80)
Age of seizure onset, y[1]	6 (2.1-14)	9 (4-15)	8.5 (3-15)
Epilepsy duration, y[1]	29 (21-40.3)	24 (16-30)	25 (17-32)
Seizure laterality (R/L)	40/60%	55/45%	51/48%
Predisposing Factors			
History of febrile convulsions	55%	50%	51%
History of status epilepticus	30%	20%	23%
History of head trauma	20%	12%	14%
History of CNS infection	10%	7%	8%
Family history of epilepsy	25%	15%	18%
Pre-surgical Seizure Type*			
Simple partial	75%	78%	78%
Complex partial	100%	80%	99%
History of SGTCS	65%	80%	76%
Medication			
Total number of AEDs trialled preoperatively[1]	5 (3-7)	4 (3-6)	5 (3-6)
Monotherapy at the time of surgery	5%	10%	9%
Polytherapy at the time of surgery	95%	90%	91%
Presurgical Investigations			
SEEG	5%	7%	6%
Ictal SPECT	5%	0%	1%
PET	0%	0%	0%
Localised ictal EEG	**40%**	**65%**	58%
Localised interictal EEG	25%	41%	38%
Pre-surgical Psychiatric History			
Mood disorder	25%	0%	6%
Anxiety disorder	15%	0%	4%
Interictal psychosis	0%	0%	0%
Psychiatric treatment	60%	0%	15%
Suicidal ideation	15%	0%	4%
Suicidal attempts	0%	0%	0%
Psychiatric hospitalisation	55%	0%	14%
Family history of psychopathology	**25%**	**7%**	11%
Histopathological Findings[3]			
Hippocampal sclerosis	71%	67%	68%
HS + FCDIIIa	12%	9%	10%
Glioneuronal tumour	12%	15%	14%
Cavernomas/vasucular malformations	0%	4%	3%
Non-specific gliosis only	0%	0%	0%
Dual pathology	6%	4%	5%

* May have >1 seizure type

[1] Median (IQR)

[2] Mean (SD)

[3] For available data

AED=anti-epileptic drugs

Table 20. *Demographic and clinical characteristics of TLE+PIP and TLE-only patients who underwent TLE surgery.*

Neuropsychological Measures

Measures of general ability and memory have been detailed previously (see Chapter 6.5)

Contralateral memory weakness:

As previous research has suggested that contralateral memory dysfunction is a risk factor for PIP (So et al., 1990; Savard et al., 1991; Mathern et al., 1995; Christodoulou et al., 2002; Falip et al., 2009), the contralateral memory score for each case was derived (i.e. Z-score on verbal memory (List Learning) in *right* TLE patients and visual memory (Design Learning) Z-score in *left* TLE patients). This composite measure of contralateral memory function (i.e. overall group mean contralateral Z-score) was compared between the groups.

Semantic Processing:

Semantic memory has previously been shown to be impaired in interictal psychotic TLE patients compared to TLE controls (Flugel et al., 2006). Therefore performance on semantic processing tasks was included in the current investigation. Data from four tests were available that measured semantic processing and that have been shown to involve neural networks involving more lateral temporal regions. Two were taken from the WAIS, namely the Vocabulary and Similarities subtests. In addition, data from the Graded Naming Test (GNT) (McKenna, 1980), which requires the patient to name 30 black and white drawings that are arranged in a hierarchy of difficulty, and a category ('animal') fluency test were used. Neuropsychological and neuroimaging evidence suggest that performance on category fluency depends upon the left (anterior) temporal cortex (Jefferies, 2013).

Executive Functions:

For two measures working memory was considered a major component, namely the Digit Span Test from the WAIS and the phonemic fluency test. Working memory is an early and key stage in most cognitive processing, but is fundamental to executive functioning and evidence supports a fronto-parietal cerebral network (Schlosser et al., 2006).

Memory Decline

The difference in pre- and postoperative List- and Design Leaning performance was calculated by a change in Z-scores at 3 and 12 months following TLE surgery. Patients' ipsilateral and contralateral Z-scores, according to resection laterality, were then entered into linear regression analyses.

9.3 Statistical Analyses

Chi-square (X^2; with Fisher Exact Test (FET) when warranted) was used to evaluate comparisons between TLE+PIP and control patients (TLE-only) on categorical variables. Differences between continuous variables were evaluated using independent samples t-test, or Mann-Whitney U, as appropriate.

Uni- and multivariable logistic regression was used to examine whether the frequency of PIP predicted postsurgical (de novo) psychiatric outcome. Specifically, dummy variables with four levels (Field, 2009) were computed to control for the possible confounding influence of a history of SGTCS and co-morbid psychopathology other than PIP (e.g. PIP and depression), as both have been demonstrated as independent predictors of postoperative psychopathology (see Study 1). This dummy (predictor) variable was entered into multivariable logistic regression analysis.

Univariable logistic regression was also used to explore whether a history (yes vs no) or frequency (0 vs 1 vs ≥2) of PIP predicted seizure freedom (ILAE=1) at 12 or 48 months. Whereas, linear regression explored whether a history (yes vs no) or frequency (0 vs 1 vs ≥2 episodes) of PIP predicted ipsilateral or contralateral memory decline at 3-6 and 12-18 months postoperatively.

9.4 Results

Clinical Characteristics

The two groups did not differ in terms of age of seizure onset, epilepsy duration, history of febrile convulsions, status epilepticus, head trauma, CNS infection or family history of epilepsy.

There were no differences in the frequency of simple partial, complex partial or history of SGTCS or lateralisation of seizure onset.

TLE+PIP patients had significantly less localised ictal EEG recordings (see Chapter 6.7 for definition) than controls (40% vs 65%; $X^2(1)=3.8$, p=0.05). The interictal EEG indicated a similar but non-significant trend (TLE+PIP: 25% vs controls: 41%, p=0.20).

A family psychiatric history was significantly more common in the TLE+PIP patients (25%) compared to the controls (7%) (p=0.04, FET). Univariable logistic regression analysis indicated that TLE+PIP patients had over four and a half times the odds of a positive family psychiatric history compared to controls (n=4/20 vs 4/60; OR: 4.67, 95%CI: 1.11-19.55, p=0.04).

Neuropsychology

Table 21 indicates both groups demonstrated similar neuropsychological profiles with weak naming and memory. There were no significant differences in cognitive findings between the groups (p values >.05).

De Novo Psychopathology

Table 22 presents the point prevalence of de novo psychopathologies for each group at specific time-intervals following TLE surgery.

TLE+PIP Group

Nine of 20 (45%) patients with a history of PIP developed de novo psychopathology during the four year follow-up. De novo psychopathologies were most apparent within the first post-surgical year (IQR: 3-33 months) and the majority (78%; n=7/9) persisted for at least 6 months (IQR: 5-33 months).

The most common de novo psychiatric condition was mood disorders (depression, n=3; mixed affective state, n=1; bipolar disorder, n=1) followed by interictal psychosis (n=3) and anxiety disorders (not otherwise specified, n=1). Six patients (67%; n/9) required psychiatric treatment (pharmacological and/or psychological) within four year follow-up.

Predictors of De Novo Psychopathology: Group Analysis

In univariable analyses, only a history of PIP was a significant predictor of de novo psychopathology within 4 years (OR: 3.0, 95%CI: 1.01-8.65, p=0.05). In the multivariable analysis, a history of PIP remained a significant predictor of de novo psychopathology after

controlling for preoperative psychiatric status and a history of SGTCS (OR: 5.06, 95%CI: 1.23-20.82, p=0.03).

Recurrent Episodes of PIP and De Novo Psychopathology

Patients with *only* one episodes of PIP did *not* have significantly increased odds of de novo psychiatric morbidity within 4 years after surgery (OR: 1.36, 95% CI: 0.31-5.85, p=0.68). However, patients with *two or more* PIP episodes had significantly increased risk of de novo psychiatric morbidity within 4 postoperative years, even after controlling for SGTCS and co-morbid psychopathology (OR: 9.11, 95%CI: 1.53-54.10, p=0.02). For clinical translation, the increased *chance* (rather than odds) of de novo psychopathology was assessed as a function of PIP episodes (0 vs 1 vs ≥2), after adjusting for SGTCS and co-morbid psychiatric conditions (see Figure 14).

Histopathology

There were no significant differences in histopathological findings between TLE+PIP and control patients (see Table 20).

Cognitive Outcome

Linear regression analyses indicated that neither a history of PIP or the number of episodes (0 vs 1 vs ≥2) predicted ipsilateral or contralateral memory decline at 3- or 12 month follow-up (p values >.05).

	TLE+PIP (*n* = 20)		TLE-only (*n* = 60)	
Cognitive measure[1]	**Mean (SD)**	**centile**[*]	**Mean (SD)**	**centile**[*]
VIQ	93 (10)	32nd	94 (15)	34th
PIQ	95 (14)	37th	96 (19)	39th
NART	97 (12)	37th	100 (14)	50th
NART and VIQ discrepancy	-2.8 (8.8)	-	-5.2 (9.8)	-
Memory				
Verbal learning: trials	43 (10)	5-10th	46 (10)	10-25th
delay	8 (3)	10th	8 (3)	10th
Visual learning: trials	30 (8)	10th	31 (9)	10-25th
delay	6 (3)	5-10th	6 (3)	5-10th
Contralateral memory weakness	-0.5 (1.4)	-	-0.5 (1.1)	-
Semantic knowledge				
Vocabulary (scaled score)	8 (2)	21st	8 (3)	21st
Similarities (scaled score)	9 (2)	32nd	9 (3)	32nd
Graded Naming Test score	15 (6)	10th	16 (5)	10-25th
Category fluency score	17 (6)	50-55th	18 (5)	55-63rd
Executive functions				
Working memory (Digit Span)	10 (2)	50th	10 (3)	50th
Phonemic fluency	15 (3)	37th-45th	16 (6)	45th-50th

[1] For available data

[*] Based on group mean age, y

Table 21. *Preoperative cognitive performance of TLE+PIP and TLE-only patients.*

De novo Psychopathologies		3 months	6 months	12 months	24 months	36 months	48 months	Overall total
Mood disorder	TLE+PIP	3	0	1	1	0	0	5
	TLE-only	4	0	1	2	1	1	9
Anxiety disorder	TLE+PIP	0	0	0	0	0	1	1
	TLE-only	0	1	0	0	0	0	1
Adjustment disorder	TLE+PIP	0	0	0	0	0	0	0
	TLE-only	1	0	0	0	0	0	1
Interictal psychosis	TLE+PIP	1	1	1	0	0	0	3
	TLE-only	0	0	0	0	1	0	1
Postictal psychosis	TLE+PIP	0	0	0	0	0	0	0
	TLE-only	0	0	0	1	0	0	1
NES	TLE+PIP	0	0	0	0	0	0	0
	TLE-only	0	0	0	0	0	0	0

Table 22. *New cases of de novo psychopathologies for each group at specific time-intervals following TLE surgery.*

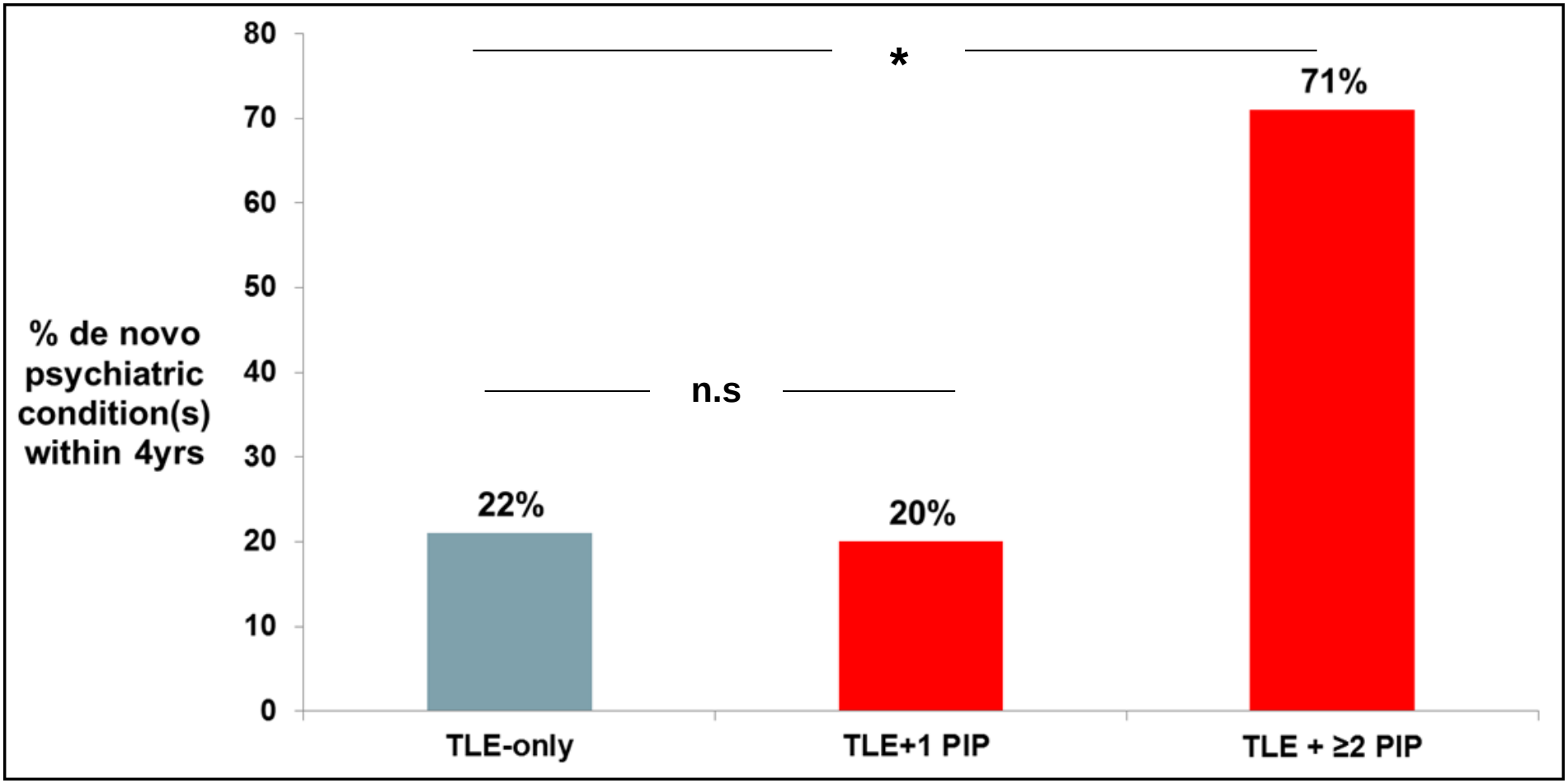

Figure 14. *The modifying effect of preoperative PIP episodes (0 vs 1 vs ≥2) on a patient's chance (%) of developing de novo psychopathology within 4 years following TLE surgery.*p=0.02.*

Seizure Outcome

There were no significant differences in the number of patients who were seizure free (ILAE=1) at 12 months (TLE-only: 62% vs TLE+PIP: 50%, p=0.44) or remained seizure free over 4 years (TLE-only: 45% vs TLE+PIP: 35%, p=0.6). In addition, there were no significant associations in seizure freedom and the number of PIP episodes (p values >.05).

9.5 Discussion

In keeping with previous findings, this study found a greater prevalence of non-localised ictal epileptiform activity in TLE+PIP patients (So et al., 1990; Kanner et al., 2008; Falip et al., 2009) compared to those without PIP. This suggests that more widely distributed epileptogenic networks may contribute to the development of PIP. This finding also supports the emerging evidence from functional neuroimaging studies that more diffuse brain abnormalities can be detected in PIP patients' interictally (Seeck et al., 1999; Takeda et al., 2001). There have also been some reports of diffuse structural brain abnormalities in patients with PIP (Morrow et al., 2006; DuBois et al., 2011). However, these changes may be subtle and warrant more advanced or sensitive imaging techniques.

There were no histopathological differences between the TLE+PIP and TLE-only groups. In contrast, a small study (n=6) found PIP to be associated with temporal lobe dysplasia (Briellman et al., 2000). The sample employed here was larger and applied a refined clinico-pathological classification system (Blumcke et al., 2011).

There were no significant differences in the other epilepsy variables between the groups. This is consistent with previous retrospective (Devinsky et al., 1995; Falip et al., 2009) and prospective (Alper et al., 2008) studies. However, investigators have indicated that SGTCS (Devinsky et al., 1995; Alper et al., 2008), status epilepticus (Falip et al., 2009) and

encephalitis (Devinsky et al., 1995; Alper et al., 2008) are risk factors for PIP. However, this current study lacked reliable information to subtype CNS infections (e.g. meningitis/encephalitis) or quantify the frequency of SGTCS and status epilepticus, which may explain the lack of association.

The finding that a positive family psychiatric history was significantly associated with PIP, and the most common diagnosis was mood disorders, is consistent with previous research (Alper et al., 2008). Notably, no first- or second degree relative included in the analysis had a diagnosis of psychosis/schizophrenia. The genetic mechanism(s) underlying this association is unclear.

Preoperative cognitive measures did not differentiate between our TLE+PIP and the TLE-only controls. While most previous studies do not report the neuropsychological status of PIP patients, a few have documented bi-temporal neuropsychological dysfunction (So et al., 1990; Savard et al., 1991; Mathern et al., 1995; Christodoulou et al., 2002; Falip et al., 2009). However, it may be difficult to compare the current findings given the smaller sample sizes of previous studies, and the unspecified nature of the cognitive measures used.

Postsurgical Outcome

Consistent with previous reports (Kanemoto et al., 1998; Kanemoto et al., 2001), a history of PIP was associated with postsurgical de novo psychopathology. However, this study extends previous findings in several ways. This study had a much larger sample size, identified patients with co-morbid pre-surgical psychiatric diagnoses and/or SGTCS and controlled for these possible confounds in the analyses. Furthermore, the study determined that patients with a history of two or more PIP episodes had a significantly increased risk of developing de novo psychopathology within four postoperative years (see Figure 14). Notably, the 3 patients in the TLE+PIP group who developed a postoperative chronic interictal psychosis

had a history of more than 2 PIP episodes (range: 2-6). This is concordant with Tarulli et al.'s (2001) findings that 5 out of 6 of their patients with interictal psychosis had a previous history of at least 2 or more PIP episodes. The findings of this investigation may suggest that resective TLE surgery should not be delayed in patients with a history of PIP (Kanner et al., 2009).

Few studies have examined the postsurgical seizure outcome of PIP patients (Kanner et al., 2008). To date, this is the first study to investigate surgical outcome (ILAE=1) in TLE+PIP patients compared to controls over a four year period (at yearly intervals). It was found that postsurgical seizure outcome (ILAE 1 vs 2-6) did not significantly differ between the groups at 12 or during 48 months, nor did the number of PIP episodes predict seizure freedom. Alper et al. (2008) also found no difference between seizure freedom rates in PIP versus non-PIP epilepsy patients. In Kanemoto et al.'s (1998) study, whilst the majority (81%) of the 52 TLE patients in their study achieved an Engel class I, the surgical outcomes of 5 PIP patients were not specifically reported. In contrast, a retrospective controlled study found patients without a history of PIP (n=17/20; 85%) were significantly more likely to become seizure free compared to a small sample of PIP patients (n=2/3; 67%) (Kanner et al., 2008). The lack of consensus with regards to seizure freedom in patients with PIP may reflect methodological differences (e.g. sample size and/or seizure classification systems).

Neither a history nor frequency of PIP episodes significantly predicted ipsi- or contralateral memory decline at 3- and 12 months. Future research to investigate whether extra-temporal (executive function) decline is evident in PIP following TLE surgery is warranted.

There are several limitations of this study due to its retrospective design, including limited follow-up (four years), the possibility that after 3 and 6 months psychiatric symptoms may have emerged or were missed (Kanner et al., 2000). Furthermore, this study was unable to

determine whether the development of de novo psychopathology was modified by the temporal relationship between the onset of PIP and surgical intervention. A lack of statistical power precluded an investigation into the possible linear relationship between PIP episodes and de novo psychopathology or seizure outcome. Exploration of subtypes of de novo psychiatric morbidity was precluded with owing to a small sample size, but this could be addressed by larger cohort studies.

In conclusion, this study demonstrates that preoperative PIP is associated with poorly localised ictal EEG indicating that surgical candidates may require the recording of several seizures during VEEG to determine the extent of the epileptogenic zone (Kanner et al., 2008). The data also suggests that genetic predisposing factors may increase the risk of PIP. Lastly, patients with *recurrent* episodes of PIP are at greater risk of developing de novo psychopathology following surgery. TLE patients with recurrent episodes of PIP should be counselled about the increased psychiatric risks following TLE surgery, and closely monitored for postsurgical psychiatric morbidity.

Chapter 10. PROSPECTIVE STUDIES

10.1 Introduction

The previous studies failed to find an association between psychopathology and cognitive variables in TLE and this may be due to a number of factors. Firstly, the pooling of *all* pre-surgical psychiatric diagnoses (depression, anxiety, psychoses, NES) in statistical analyses (see Study 1), may have resulted in a type II error. Second, the retrospective nature of the data used limited a thorough investigation of the 'extra-temporal neuropsychological profile' (Keller et al, 2009), and the relation to pre- and/or postoperative (de novo) depressive morbidity (see Studies 1 and 2). Third, epilepsy-related factors indicative of more widespread cerebral dysfunction were not systematically quantified in patients' notes and thus, were categorised binomially (yes versus no) (see Studies 1-3), potentially reducing sensitivity and statistical power. Fourth, the date of psychiatric onset and severity were not consistently available in previous data-sets. In the prospective studies described here an attempt was made to address the above deficiencies. In particular, the postoperative course of Axis I psychopathology and the relationship to cognitive measures was more closely investigated.

10.2 Sample

Patients under consideration for epilepsy surgery from September 2009 to December 2012 at the NHNN, who fulfilled the following inclusion criteria, and were able to provide informed consent, were invited to participate in the study (see Appendix 2 for the patient information sheet and consent form).

10.3 Inclusion Criteria

1. Age ≥ 18 years
2. IQ > 70
3. Probable TLE
4. Fluent English speakers
5. No history of previous neurosurgery

One hundred and six patients with epilepsy were recruited, of whom 87 (82%) subjects remained in the study and participated in the full assessment protocol. Of these, 49 (56%) patients had TLE surgery (see Figure 15).

10.4 Procedure

All patients were seen preoperatively (n=106) and those who underwent TLE surgery (n=49), were seen at 6 months (n=41), 12 months (n=29) and 24 months (n=9) postoperatively.

10.5 Pre-surgical Clinical Measures

The following data was collected.

10.5.1 Clinical History

All patients underwent a detailed medical assessment as part of their pre-surgical evaluation. Records of birth history (history of febrile convulsions; CNS infection), seizure related variables (head trauma, age of epilepsy onset, epilepsy duration, seizure types and frequency, seizure semiology, history of status epilepticus); family history and social status were recorded.

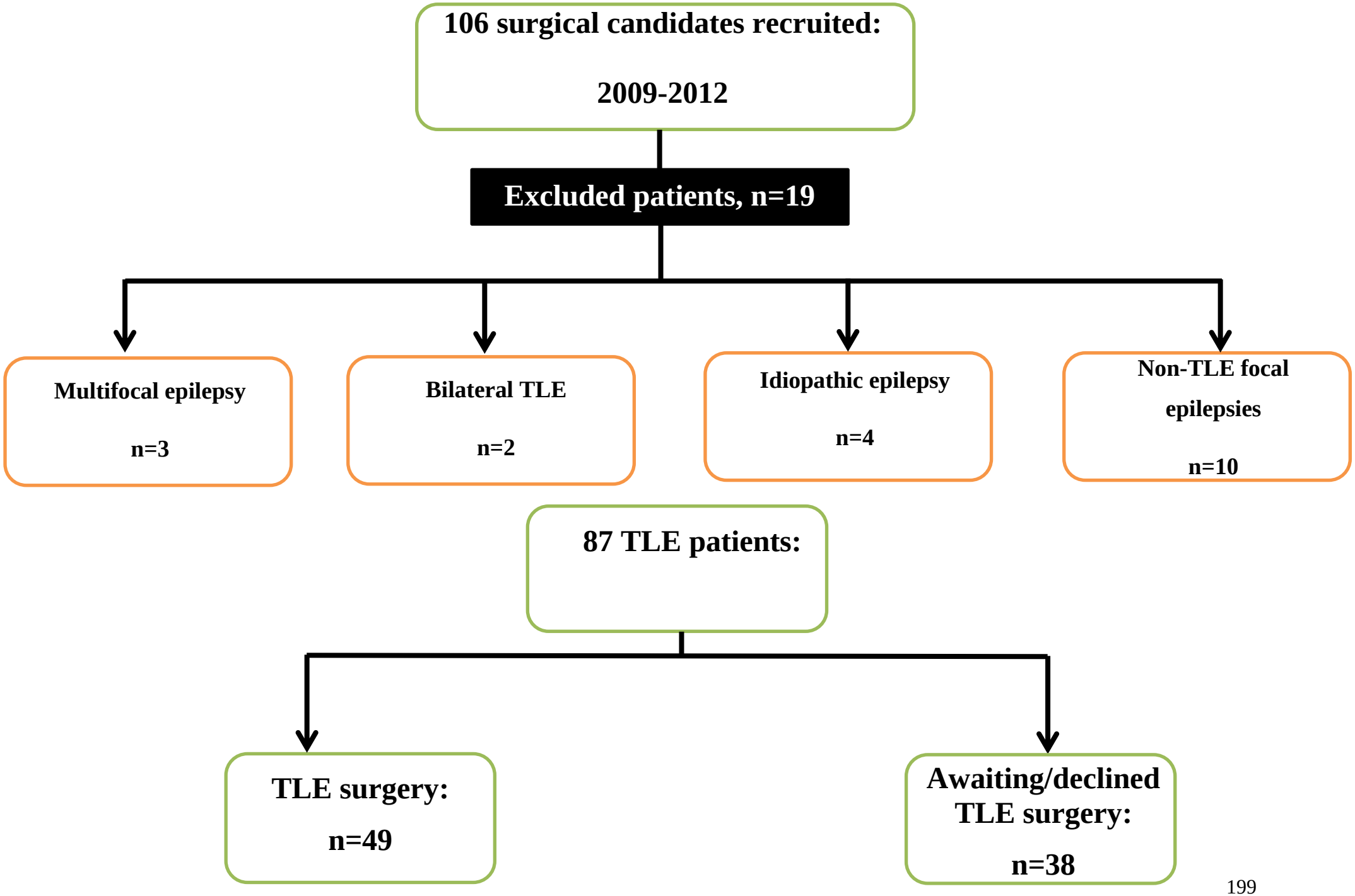

Figure 15. *Case selection process.*

10.5.2 MRI Scan

All patients underwent MRI scanning with hippocampal volumetry. MRI studies were performed on a 3T General Electric Excite HDx scanner (General Electric, Milwaukee, Wisconsin, U.S.A.), using a body coil for transmission, and eight channel phased array coil for reception. Standard imaging gradients with a maximum strength of 40 mTm^{-1} and slew rate 150 $Tm^{-1}s^{-1}$ were used. Standard clinical sequences were performed and included a coronal T1-weighted volumetric acquisition with 170 contiguous 1.1 mm thick slices (matrix 256 x 256, in-plane resolution 0.9375 x 0.9375mm).

Manual segmentation of the hippocampi was performed using MRreg software by trained neuro-radiographers (Lemieux, Liu, Duncan, 2000). This involves manual segmentation of the entire hippocampi using a mouse-driven cursor according to the anatomical boundaries specified by Watson et al. (1992). Following the tracing, MRreg automatically calculates the hippocampal volume by summing the trace area of each slice and multiplying by the slice thickness. The hippocampal volumes were corrected for total brain size by dividing by the cerebral volume.

10.5.3 Prolonged Scalp Video-EEG

The diagnosis of TLE was established by prolonged scalp video-EEG monitoring with electrode placement according to the extended International 10-20 system (Klem et al., 1999), including bilateral anterior temporal and bilaterally placed sphenoidal electrodes. For the majority of patients, provocative seizure-inducing procedures (i.e. drug reduction, sleep deprivation, exercise) were performed.

Pre-surgical video-EEG reports were classified by a clinical electro-physiologist into cases demonstrating ‘localised’ or ‘non-localised’ ictal or interictal epileptiform abnormalities

dependent on the neuro-radiological findings (e.g. bilateral temporal, extra-temporal, multifocal, bi-frontal and unilateral temporal, widespread fronto-temporal discharges in the presence of unilateral HS).

10.5.4 Neuropsychological Assessment

Preoperative neuropsychological data was collected in the following domains preoperatively and 6- and 12 months postoperatively:

5. **Intellectual functioning**

   (i) Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997).

   (ii) The National Adult Reading Test (NART) (Nelson & Willison, The Revised National Adult Reading Test - Test Manual, 1991).

6. **Semantic knowledge**

   (i) Category fluency: Patients were required to name as many exemplars from the category "animals" as they could in 60 seconds.

   (ii) Graded Naming Test (GNT) (McKenna, 1980).

7. **Memory**

   The List- and Design- learning tasks from the BIRT Memory and Information Processing Battery (BMIPB; Coughlan, Oddy, & Crawford, 2007) were used as measures of verbal and non-verbal memory, respectively. This is the successor to the AMIPB used in the retrospective studies (see Chapters 6 and Studies 1-3). Performance on List- and Design learning were translated to Z-scores and used as measures of hippocampal integrity.

Contralateral memory weakness:

As described in Chapter 9, the contralateral memory weakness for each patient was calculated.

8. Executive functions

Rationale

Chapter 4 highlighted the limited understanding of more widespread cognitive sequelae in TLE, particularly frontal lobe dysfunction, and the relationship to psychopathology (see Figure 6). The retrospective studies only provided a single indicator of executive function, namely phonemic fluency. To address this, additional neuropsychological measures assessing different aspects of executive function were employed (planning, set-shifting, categorisation, verbal working memory, inhibition).

(i) The Spatial Working Memory (SWM) subtest from the Cambridge Automated Test Battery (CANTAB) (Sahakian & Owen, 1992). The CANTAB is a computersied neuropsychological assessment that was orginally developed to diagnose dementia in geriatric cohorts (Fray et al., 1996). The task stimuli are nonverbal and language proficiency is necessary only to understand the instructions. The validity of the CANTAB for assessing brain-behaviour relations in adults has been supported by numerous studies of patients with brain lesions, degenerative disorders and psychiatric illness (see http://www.camcog.com/bibliography.asp).

The SWM sub-test was chosen as it reliably differentiates between patients with frontal versus temporal lobe pathology (Owen et al., 1996), and it has an acceptable test/retest coefficient (R=0.68) (Lowe & Rabbitt, 1998). This self-

ordered computerised test measures executive function (search strategy) and the updating and monitoring of spatial information in working memory (WM). The screen displays a number of coloured boxes (see Figure 16a).

Patients were required to 'search' through the boxes on the screen in order to locate blue tokens hidden inside and once located, to place the token in an empty column on the right hand side of the screen (see Figure 16b & c).

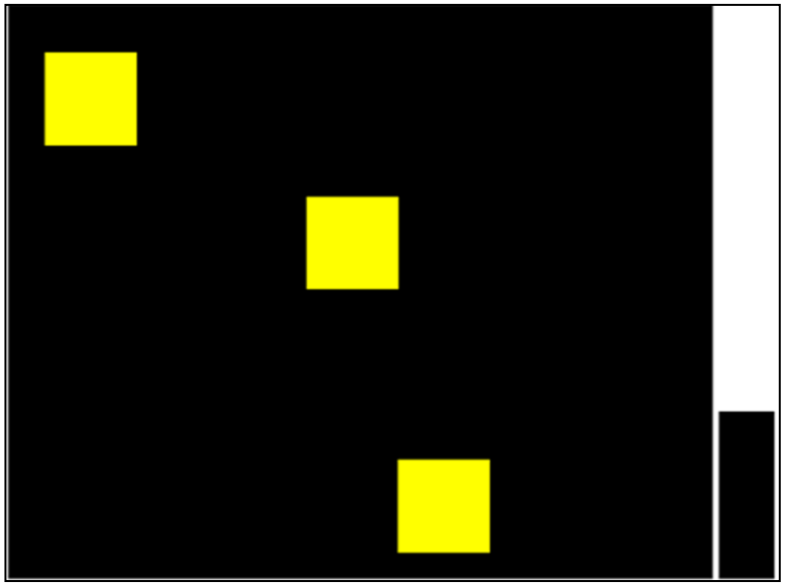

Figure 16a. *CANTAB's SWM display for the 3-box trial.*

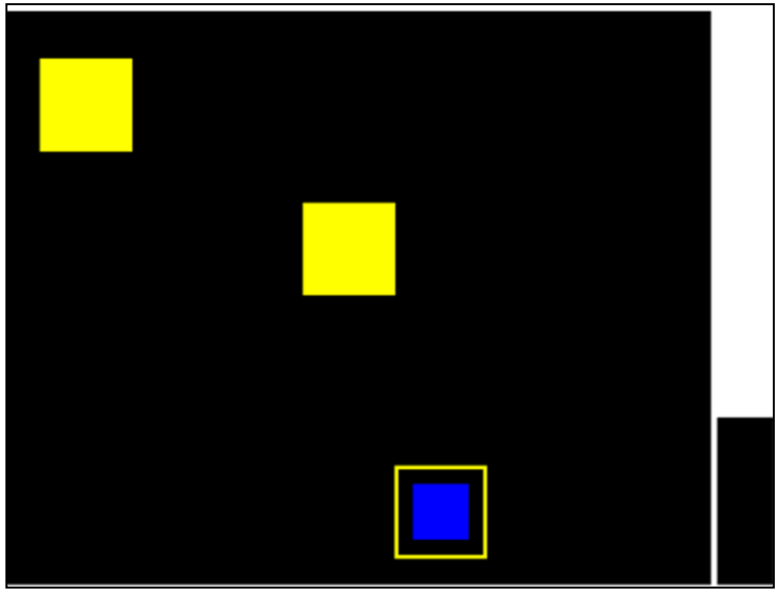

Figure 16b. *Blue token 'found' in the 3-box trial of CANTAB's SWM task.*

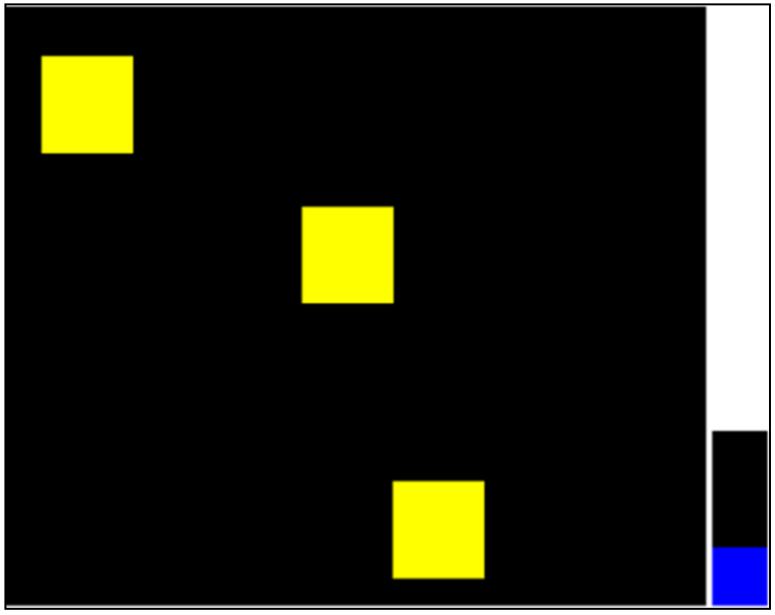

Figure 16c. *The blue token has been placed in the column on the right hand side of the screen for the 3-box problem of CANTAB's SWM task.*

The patients were instructed that once a token had been found within a particular box, then that box would *not* be used again to hide any of the remaining tokens for that particular trial. There are four example trial stages with 3-boxes, followed by three levels of difficulty: 4-, 6- and 8-box problems, all of which contain four trials; allowing for a graded approach that avoids ceiling or floor effects (Lezak et al., 2012). Two types of performance indices were recorded at each level of difficulty (4-, 6- and 8-box problems). The 'between errors' score indicates when a patient has returned to a box in which a blue token had *already* been located during a previous searching sequence. This is a stringent measure of short-term WM failure and perseveration (Flugel et al., 2006). A 'strategy score', was also recorded for performance at the more difficult levels (i.e. 6- and 8-box levels), and demonstrates the adoption of a systematic searching approach (beginning with the *same* box once a token has been found). The total score provides a composite measure of strategy with a high score (many sequences beginning with a different box) representing low strategy use and a low score (many sequences starting with the same box) representing efficient strategy use and executive functions (Flugel et al., 2006). Previous research indicates that these performance indices are sensitive to neurocognitive dysfunction in patients with primary depressive disorder (Porter et al., 2003).

Based on normative data provided by CANTAB from over 2000 control subjects (aged 4-90) who participated in various research studies (see, http://www.camcog.com/faqs.asp), the 'between errors' and 'search strategy' scores were converted to Z-scores for subsequent statistical analyses.

(ii) Wisconsin Card Sorting Task (WCST) (Berg, 1948) is a widely utilised neuropsychological measure which was originally developed to assess "human

abstraction" and "shift of set". It has been shown to examine executive functions mediated by the frontal lobes, such as problem-solving, strategic planning, use of environmental feedback to shift-set, and inhibition of impulsive responding (Demakis, 2003). A meta-analysis of neuroimaging studies in a highly selected cohort of frontal-lobe damaged patients, reported that the WCST is associated fronto-parietal activation patterns, particularly in the lateral and ventral pre-frontal cortices bilaterally (Buchsbaum et al., 2005).

A shortened version has been developed (WCST-64: Kongs et al., 2000), with psychometric properties commensurate with the full version. Generalizability coefficients ranging from 0.60 to 0.85 are documented, and scores have been shown to discriminate between control groups and individuals with various neurological disorders (Paolo et al., 1996; Kongs et al., 2000).

Patients were shown four specific stimulus cards, composed of geometric elements, laid out in a row. Ordinarily, participants are given 64 cards and asked to sort them one at a time by placing each response card on top of one of the four stimulus cards, according to a given criterion (colour, shape or number). However, pilot data indicated that this was too difficult for TLE patients. Therefore, to minimise patient distress and a premature floor effect, patients were given 36 cards and asked to sort them one at a time by placing each response card on top of one of the four stimulus cards, according to a given criterion (colour, shape or number). No instructions regarding card sorting was given by the tester. After each card was sorted, the tester informed the patient if they correctly or incorrectly sorted the card (according to the sorting rule only known by the experimenter). After six cards, the tester told the patient that the sorting rule had changed. The test continued until all cards were sorted. Two scores were

calculated: the number of categories completed (maximum 6) and the number of perseveration errors (i.e. the number of cards classified on the basis of a previous sorting criterion). The latter was used in statistical analyses as an indicator of executive dysfunction; with higher preservation scores indicating poor set-shifting ability.

(iii) Trail Making Test (TMT; Halstead, 1947) is comprised of two parts. In part A the subject uses a pencil to connect a series of 25 encircled numbers in numerical order. In part B, the subject connects 25 encircled numbers and letters in numerical and alphabetical order, alternating between numbers and letters. For example, the first number "1" is followed by the first letter "A", followed by the second number "2" and the second letter "B" and so on. The numbers and letters are placed in a semi-random fixed order, as to avoid overlapping lines being drawn by the subject (Bowie & Harvey, 2006). The primary variables of interest are the total time to completion for parts A and B. Part A is a test of visual search and motor speed skills, whereas part B is also considered to test higher level cognitive skills such as mental flexibility, and the ability to modify a plan of action or to maintain two trains of thought simultaneously (Crowe, 1998; Arbuthnott & Frank, 2000). The TMT has excellent inter-rater reliability and psychometric properties (Strauss, Sherman & Spreen, 2006).

(iv) Digit Span (WAIS-III; Wechsler, 1997): Requires repetition of orally presented digit strings (digit forward, e.g., 1, 6, 8) and then recall of digits in reverse order (digit backwards e.g., 8, 6, 1). Digit sequences range from 2 to 8 with two trials per sequence. A well-powered neuroimaging study, using voxel-based lesion-symptom mapping of patients with focal brain damage (n=241), reported a significant relationship between digit span performance and activations in the left

frontal and parietal cortices (Glascher et al., 2009). Digit span score was used to assess verbal working memory (Flugel et al., 2006) and executive function.

(v) Dysexecutive Questionnaire (DEX; Burgess et al., 1996; see Appendix 3): The DEX is a 20-item questionnaire constructed to sample a range of 'everyday' symptoms of dysexecutive (or 'frontal lobe') syndrome, and forms part of the Behavioural Assessment of the Dysexecutive Syndrome test battery (BADS; Wilson et al., 1996). The questions sampled include changes in (1) emotional responsivity or personality (2) motivation, (3) behaviour and (4) cognition. The DEX assesses a number of characteristics, including abstract thinking problems, impulsivity, confabulation, planning problems, euphoria, lack of insight, apathy disinhibition, distractabiity, knowledge-response dissociation, lack of concern, and disregard for social rules (Lezak et al., 2012). Each item was scored on a 5-point Likert scale, ranging from 'never' to 'very often', with a high score indicating higher frequency of dysexecutive behaviour in everyday life. One version of the questionnaire was completed by someone who knew the patient well (usually either a relative or carer; DEX-I), and the other version was completed by the patient (DEX-S). Internal consistency is reported to be high (>0.90), and investigators have reported a significant positive relation between the DEX and measures of executive dysfunction (Bennett, Ong & Ponsford, 2005).

(vi) Phonemic fluency: This measure used in the retrospective studies was also employed again, with patients required to name as many words beginning with "S" in a 60 second epoch. Research has demonstrated this task is highly sensitive and specific to frontal lobe damage (Robinson et al., 2012); with structural and functional imaging showing that frontal lobe pathology disproportionately impairs *phonemic* fluency, while temporal lobe damage has a greater effect on semantic

fluency (Bird et al., 2010).

10.5.5 Neuropsychiatric Assessment

As part of standard clinical care, all patients were assessed by neuropsychiatrist as part of their pre-surgical evaluation. A single psychiatrist conducted clinical interviews and diagnoses were determined using the DSM-IV-TR axis I (American Psychiatric Association, 2000) and ILAE criteria (Krishnamoorthy, Trimble & Blume, 2007). For comorbid psychopathology, a positive entry was made into each diagnostic category. Medication related psychiatric symptoms, defined as psychopathology temporally related to AED change(s) that resolved following AED titration/discontinuation, were excluded. Information regarding whether any first-degree relation had a history and/or current psychiatric diagnosis was documented. Data concerning lifetime history of psychiatric treatment, defined as any past treatment with psychiatric drugs, past psychiatric hospitalisation, and deliberate self-harm/suicide attempts were also documented on first clinical interview.

All patients were seen by the same psychiatrist six months following surgery. The continuance (or remission) of lifetime psychopathology was recorded and classified according to the DSM-IV-TR (American Psychiatric Association, 2000) as for the pre-surgical ones, but with the addition of adjustment disorders. Post-surgical psychiatric hospitalisation and deliberate self-harm/suicidal ideation or attempts were documented in detail. De novo psychopathology was only coded if a patient had *no* preoperative psychiatric history and could only be termed as such at *one* mutually exclusive post-surgical time-frame. Psychiatric symptomatology emerging after 6 months was identified by the general practitioner or the treating neurologist resulting in a review by the epilepsy surgical team's neuropsychiatrist. Subsequently documented psychiatric disorders were then coded as appropriate into the following postoperative time-frames: 12 or 24 months.

10.5.6 Psychiatric Rating Scales

All patients completed the The Beck Depression Inventory-Fast Screen (BDI-FS) (Beck, Steer, & Brown, BDI-Fast Screen for medical patients: manual, 2000; see Appendix 4) and the Beck Anxiety Inventory (BAI) (Beck & Steer, Beck Anxiety Inventory Manual, 1990; see Appendix 5). These measures were completed preoperatively (within 6 months of TLE surgery), and 6, 12 and 24 months postoperatively.

Becks Depression Inventory

This measure is comprised of seven items from the 21-item Beck Depression Inventory-II (Beck, Steer, & Brown, Manual for the Beck Depression Inventory-II, 1996) pertaining to (1) feelings of sadness, (2) discouragement about the future (pessimism), (3) personal failures, (4) perceived decreases in self confidence, (5) a sense of being overly self-critical, (6) the ability to derive pleasure from activities (anhedonism) and (7) suicidal ideation. Somatic items are excluded to increase specificity for medical patients. Items are rated for the past two weeks on a four-point likert scale (0-3), yielding scores ranging from 0-21. The suggested cut-off scores are 0-3 (minimal symptoms); 4-6 (mild symptoms); 7-9 (moderate symptoms); 10-21 (severe symptoms). The BDI-FS has been reported as a psychometrically rigorous depression screening tool in a variety of medical populations (Nezu et al., 2010).

Becks Anxiety Inventory

This scale measures 21 symptoms associated with anxiety. Patients are asked to rate on a four-point likert scale ranging from 0 (“not at all”) to 3 (“severely, I could barely stand it”) how much these symptoms have bothered them over the past week. Scores range from 0-63. Recommended cut-offs were employed: 0-7 (minimal anxiety); 8-15 (mild anxiety); 16-25

(moderate anxiety); 26-63 (severe anxiety). The BAI has a high internal consistency (Cronbachs α =.92) and a test-retest reliability of .75 (Beck, Epstein, Brown, & Steer, 1988).

Chapter 11.

Study 4. Temporal Lobe Epilepsy & Depressed Mood: Correlations with Cognitive and Clinical Factors

11.1 Study Aims

Chapter 4 highlighted the neuropsychological evidence suggesting that temporal and extra-temporal cognitive function may be compromised in the presence of TLE and primary depressive disorder. Few studies, however, have directly investigated the *relation* between depressed mood and cognition in TLE.

The aims of this prospective study were two-fold: (1) determine whether depression is the most prevalent psychiatric diagnostic category in TLE patients under consideration for surgical treatment and (2) further examine the hypothesis that TLE surgical candidates with a *current* diagnosis of depression have evidence of extra-temporal dysfunction as measured by cognitive and clinical factors.

11.2 Methods

Study Sample

Eight-seven TLE patients were assessed for epilepsy surgery between 2009 and 2012 (see Figure 15). Given that an aim of this study was to determine whether patients with a *current* diagnosis of depression had evidence of extra-temporal dysfunction, twenty-four patients (28%; n=24/87) were excluded due to a *past* history of psychopathology. Of the remaining 63 patients, 12 (19%; n=12/63) had a current diagnosis of depression and 51 (81% n=51/63) patients had no psychiatric history (TLE-control group).

Procedure

As described in Chapter 10, pre-surgical evaluations consisted of 1) a detailed medical assessment, 2) high-resolution MRI of the brain with volumetric hippocampal measurements, 3) prolonged VEEG recording, 4) neuropsychological testing and 5) a neuropsychiatric clinical interview, conducted by the same psychiatrist in all patients.

11.3 Statistical Analyses

For comparing frequencies in demographic and clinical variables between patients with a current diagnosis of depression versus those with no formal psychiatric diagnosis, Chi-square (X^2; with Fisher Exact Test (FET) when warranted) was used. Univariable logistic regression was conducted to quantify the odds of group membership ('depressed' versus 'TLE-controls') for any significant association identified using X^2.

Differences between continuous variables were evaluated as appropriate using independent samples t-test, or Mann-Whitney U test.

11.4 Results

Lifetime and Current Psychopathology

The lifetime and current psychopathologies of the sample as a whole (n=87) are presented in Figure 17. A mood disorder was the most prevalent lifetime (n=27/87; 31%) or current (n=12/17; 71%) psychiatric diagnosis (all depression). Nine patients (n=9/87; 10%) had a lifetime diagnosis other than depression (n=6 anxiety; n=5, PIP; n=1, interictal psychosis; n=2 NES); five (n=5/9; 56%) of which had lifetime comorbid psychopathologies (n=3, depression and anxiety disorder; n=1, depression and NES; n=1, anxiety and PIP).

Demographic and clinical variables for each group are presented in Table 23. No significant differences were found between the depressed and non-depressed groups in terms of demographic variables, predisposing factors, seizure frequency or type, MRI findings or hippocampal volumes.

Depressed TLE patients had significantly *less* localised ictal EEG recordings than controls (40% vs 74%; $X^2(1)=4.3$, p=0.05). Univariable logistic regression analysis indicated that TLE patients with non-localised ictal EEG patterns had over four times the odds of being in the 'depressed' group compared to patients with localised ictal EEG recordings (OR: 4.25, 95%CI: 1.02, 17.70, P=0.05). A similar trend was observed for localised interictal EEG, but this did not reach statistical significance (64% vs 83%; OR: 2.71, 95%CI: 0.64-11.52, p=0.18).

Patients with diagnosed depression exhibited significantly greater self-reported depressive and anxiety symptoms compared to TLE-controls (p values >.05; see Table 23). All depressed patients were receiving psychiatric treatment (p<0.001).

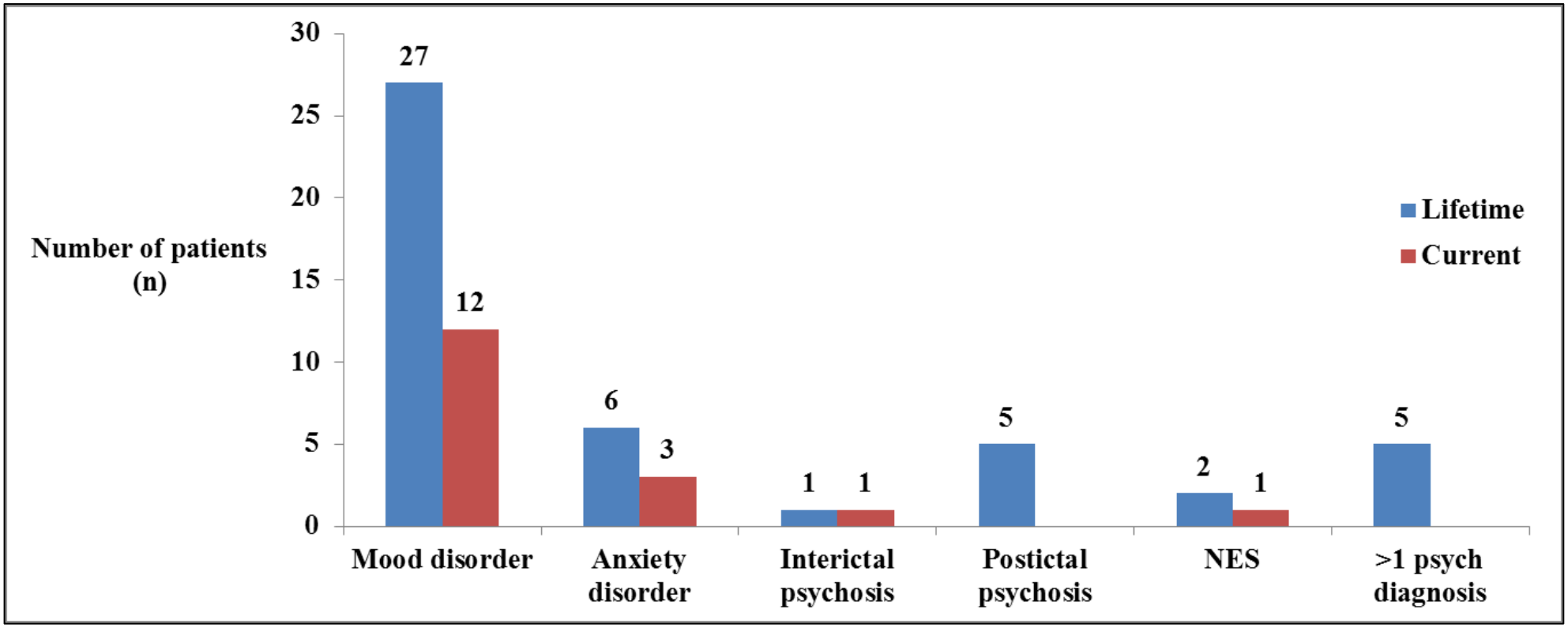

Figure 17. *Lifetime (blue bars) and current (maroon bars) psychiatric diagnoses of TLE patients (n=87).*

Variable	Depression (n=12)	TLE-controls (n=51)	p-value
Female†	10 (83%)	29 (57%)	0.11
Chronological age[1]	40 (25-42)	37 (28-47)	0.71
Age of TLE onset, years[2]	12 (10)	16 (11)	0.31
TLE duration[2]	23 (11)	22 (13)	0.77
TLE laterality (R/L)	67/33%	45/55%	0.21
Predisposing Factors†			
History of febrile convulsions	1 (8%)	18 (35%)	0.09
History of status epilepticus	1 (8%)	5 (10%)	1.00
History of head trauma	1 (8%)	10 (20%)	0.67
History of CNS infection	1 (8%)	3 (6%)	1.00
Family history of epilepsy	5 (42%)	14 (28%)	0.49
Seizure Type[3]			
Simple partial†	10 (83%)	43 (84%)	1.00
Complex partial†	12 (100%)	50 (98%)	1.00
SGTCS†	6 (50%)	19 (37%)	0.52
Seizure frequency SGTCS/month[1]	1 (0-2)	0 (0-1)	0.38
Seizure frequency/month[1]	7 (2-19)	6 (6-10)	0.60
Medication			
Total number of AEDs trialled preoperatively[1]	3 (2-3)	2 (2-3)	0.08
Monotherapy†	0 (0%)	6 (12%)	0.60
Polytherapy†	12 (100%)	44 (88%)	0.60
MRI†			
Normal	3 (25%)	7 (14%)	0.39
HS	5 (42%)	30 (59%)	0.28
FCD	2 (17%)	4 (8%)	0.32
Cavernoma	1 (8%)	4 (8%)	1.00
DNT	0 (0%)	9 (18%)	0.19
Other (abn. gyral folding/epidermoid)	2 (17%)	3 (6%)	0.24
Dual pathology	1 (8%)	6 (12%)	1.00
Hippocampal Volumes[2,4]			
Ipsilateral HC volume	2.4 (0.4)	2.3 (0.7)	0.28
Contralateral HC volume	2.7 (0.3)	2.8 (0.4)	0.45
Video-EEG Findings†[,5]			
Localised ictal EEG	**4 (40%)**	**34 (74%)**	**0.05**
Localised interictal EEG	7 (64%)	38 (83%)	0.21
Psychiatric variables			
Family history of psychopathology†	5 (42%)	13 (26%)	0.30
BDI-FS[1]	**9 (4-14)**	**1 (0-2)**	**<0.001**
BAI[1]	**15 (9-22)**	**6 (3-10)**	**<0.001**
Psychiatric treatment†	**12 (100%)**	**0 (0%)**	**<0.001**

CNS, central nervous system
DNT, dysembryoplastic neuroepithelial tumour
FCD, focal cortical dysplasia
HC, hippocampal
HS, hippocampal sclerosis
† Values are number of patients (%)
[1]Median (IQR)
[2]Mean (SD)
[3]May have >1 seizure type
[4]Corrected for intracranial volume
[5]For available data

Table 23. *Demographic and clinical characteristics of TLE patients with a current diagnosis of depression (n=12) versus those with no psychiatric history (n=51).*

Cognitive Performance

The performances of the groups on neuropsychological tests are shown in Table 24.

The Mann-Whitney U test revealed that the discrepancy between premorbid and assessed IQ was significantly greater in the depressed group compared to controls, (U=161, z = -2.1, p=0.04).

Reported dysexecutive symptoms by both patients (t(60) = -4.33, p<0.001) and their informants (t(51) = -2.00, p=0.05) were significantly increased for depressed patients. The difference between patient and informant DEX ratings did not significantly differ according to group (t(51) = 10.4, p=0.18).

Exploratory correlational analyses revealed there was a significant positive association between preoperative depressive symptomatology (BDI-FS) and patient and informant dysexecutive symptoms (r_s = 0.61, p = <0.001; R_s^2 = 37%; see Figure 18; r_s = 0.30, p = 0.04; R_s^2 = 8%; see Figure 19, respectively). There were no significant associations between the premorbid and assessed IQ discrepancy, BDI-FS or reported DEX measures (Table 25a); and accordingly partial correlations were not performed.

Patient and informant DEX ratings were correlated with the five neuropsychological measures of executive functioning to determine the extent to which they were assessing a common construct. The DEX measures were significantly related (r_s = 0.39, p = <0.01; R_s^2 = 15%); however only weak non-significant inter-correlations were found with neuropsychological measures of executive function (see Table 25b).

There were no other significant differences in cognitive findings between the groups (p values >.05; see Table 26).

Interaction: Depression and Seizure Focus

Due to small sample sizes and incomplete data, statistical analyses examining cognitive performance as a function of laterality and depression were not performed. Descriptive statistics for each subgroup, however, are presented in Table 27. Depressed patients performed less well on 13 out of 18 tasks (72%), particularly for left-sided depressed patients (poorer performance: 9/13 tasks).

Variable[1]	Depression (n=12)	TLE-controls (n=51)	p-value
NART[2]	100 (87, 111)	97 (83, 108)	0.70
VIQ[2]	87 (79, 99)	91 (82, 102)	0.40
NART/VIQ discrepancy[2]	**-7 (-12, -5)**	**-2 (-10, 6)**	**0.04**
Verbal learning: trials[3]	-1.2 (1.1)	-1.0 (1.2)	0.70
delay[2]	-0.4 (-1.9, 0)	-1.0 (-1.6, 0)	0.83
Visual learning: trials[3]	-0.8 (1.2)	-0.7 (1.4)	0.83
delay[2]	-1.3 (-2.1, 0.4)	-0.4 (-2.1, 0.4)	0.64
Contralateral memory weakness[2]	-0.9 (1.3)	-0.8 (1.2)	0.83
Semantic knowledge			
Graded Naming Test[3]	18 (6)	17 (5)	0.57
Category fluency[3]	18 (5)	18 (5)	1.00
Executive functions			
Wisconsin Card Sorting Test (Perseveration error)[2]	2 (0-2)	1 (0-4)	0.96
Trail making B (secs)[2]	73.5 (65.5, 101)	64 (54, 89)	0.20
Phonemic fluency ("S" only)[3]	13 (9)	13 (5)	0.93
Working memory (Digit Span)[2]	8 (6-9)	8 (7-10)	0.60
Spatial WM (between errors)[2]	-0.7 (-1.5, 0.1)	0 (-0.7, 0.5)	0.12
Spatial WM (strategy)[3]	0.1 (1.0)	0.08 (1.2)	0.95
DEX-informant[3]	**24 (12)**	**16 (10)**	**0.05**
DEX-subject[3]	**32 (14)**	**17 (10)**	**<0.001**

[1]For available data

[2]Median (IQR)

[3]Mean (SD)

† Values are number of patients (%)

Table 24. *Preoperative cognitive performance of TLE patients with a current diagnosis of depression (n=12) versus those with no psychiatric history (n=51).*

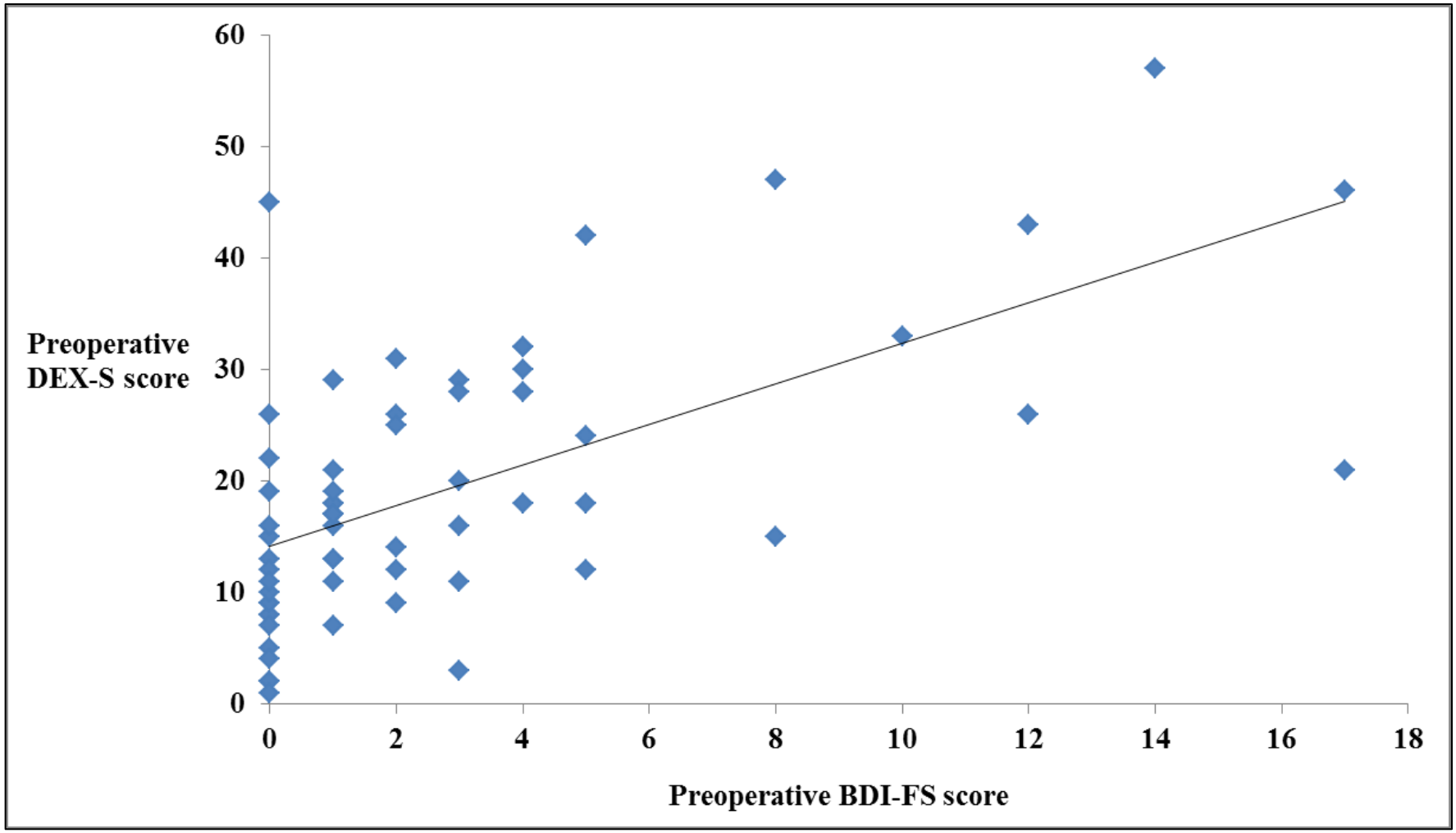

Figure 18. *Positive correlation between preoperative depressive symptoms (BDI-FS) and patient reported dysexecutive symptoms.*

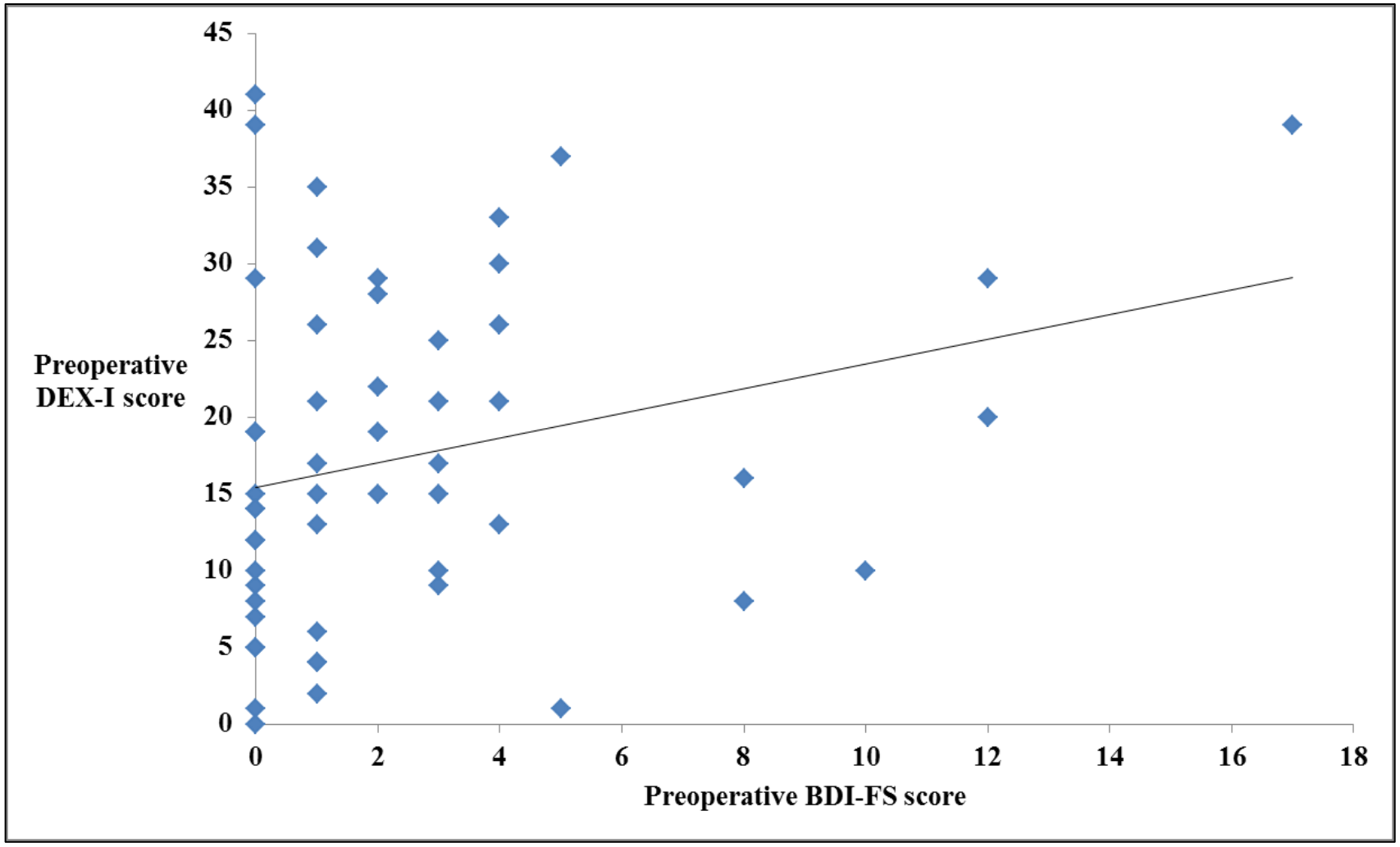

Figure 19. *Positive correlation between preoperative depressive symptoms (BDI-FS) and informant reported dysexecutive symptoms.*

Spearman's Rho		Preoperative			
		BDI-FS	DEX-S	DEX-I	NART-VIQ discrepancy
Preoperative	BDI-FS	1.00			
	DEX-S	**0.61*** **	1.00		
	DEX-I	**0.30***	**0.39****	1.00	
	NART-VIQ discrepancy	-0.18	-0.24	-0.17	1.00

Table 25a. *Spearman's Rho correlations between preoperative depressive symptoms (BDI-FS), premorbid and assessed IQ discrepancy, and patient (DEX-S) and informant (DEX-I) reported dysexecutive symptoms.*

**p<0.05; **p<0.01; ***p<0.001*

Spearman's Rho		Preoperative	
		DEX-S	DEX-I
Preoperative	DEX-S	1.00	**0.39***
	DEX-I	**0.39***	1.00
	WCST (perseveration errors)	0.09	0.02
	TMT (B)	0.28	0.28
	Digit Span	-0.02	-0.22
	CANTAB:		
	Between errors	-0.27	-0.18
	Strategy score	-0.22	-0.06
	Phonemic fluency	0.10	-0.05

Table 25b. *Spearman's Rho correlations between patient and informant DEX ratings, and preoperative neuropsychological measures of executive functioning.*

**p<0.01*

Variable[1,2]	Left-TLE Depression (n=4)	Right-TLE Depression (n=8)	Left-TLE Controls (n=27)	Right-TLE Controls (n=24)
NART	98 (74, 115)	100 (84, 107)	**95 (87, 103)**	98 (82, 109)
VIQ	92 (65, 109)	**84 (83, 93)**	96 (82, 101)	91 (82, 104)
NART and VIQ discrepancy	-6.5 (-8.5, -5.0)	**-10 (-18, -4)**	-2 (-6, 7)	-4 (-12, 5)
Verbal learning: trials	**-2.3 (-2.3, -1.4)**	-0.9 (-2.3, 0.23)	-1.0 (-2.1, 0.23)	-0.9 (-1.6, 0.5)
delay	**-1.7 (-2.9, -0.7)**	-0.1 (-2.4, 0.76)	-1.1 (-1.5, 0.0)	-0.8 (-1.7, 0.0)
Visual learning: trials	**-1.0 (-2.7, 0.3)**	-1.0 (-1.7, 0.6)	-0.2 (-1.4, 0.6)	-0.5 (-1.9, 0.6)
delay	**-1.7 (-2.8, 0.1)**	-0.1 (-5.4, 0.4)	0.1 (-1.2, 0.5)	-0.9 (-2.7, 0.4)
Contralateral memory weakness	-1.0 (-2.8, 0.1)	**-1.0 (-5.4, 0.4)**	0.1 (-1.2, 0.5)	-0.9 (-2.7, 0.4)
Semantic knowledge				
Graded Naming Test	22 (11, 22)	**15 (14, 17)**	16 (13, 21)	16 (14, 20)
Category fluency	**16 (13, 16)**	18 (14, 23)	18 (16, 21)	18 (13, 22)
Executive functions				
Wisconsin Card Sorting Test (Perseveration error)	**2 (2, 2)**	1 (0, 3)	1 (0, 3)	1 (1, 4)
Trail making B (secs)	68 (64, 68)	71 (58, 75)	61 (54, 72)	**80 (80, 128)**
Phonemic fluency ("S" only)	**7 (1, 7)**	13 (4, 22)	13 (9, 17)	14 (9, 17)
Working memory (Digit Span)	8 (3, 13)	8 (6, 8)	8 (7, 10)	**7 (6, 10)**
Spatial WM (between errors)	n/a	**-0.7 (-1.1, -0.1)**	0.2 (-0.5, 0.9)	-0.5 (-1.3, 0.2)
Spatial WM (strategy)	n/a	0.1 (-0.6, 1.2)	0.5 (-0.8, 1.7)	**-0.5 (-1.0, 0.2)**
DEX-informant	**29 (16, 29)**	23 (9, 29)	12 (6, 28)	15 (13, 22)
DEX-subject	**35 (25, 46)**	24 (15, 32)	16 (10, 22)	16 (10, 27)

[1]For available data

[2]Median (IQR)

n/a, not applicable

Table 26. *Preoperative cognitive performance of TLE patients with a current diagnosis of depression versus those with no psychiatric history, as a function of seizure focus. Bold text indicates poorest performance.*

11.5 Discussion

The present findings corroborate earlier investigations demonstrating increased psychiatric morbidity in TLE patients (Gaitatzis, et al., 2004; Swinkels et al., 2005; Grabowska-Grzyb et al., 2006), with depression the most prevalent pre-surgical psychiatric comorbidity (Ring et al., 1998; Anhoury et al., 2000; Kohler et al., 2001; Wrench et al., 2004; Devinsky et al., 2005; Kanner et al., 2009; Guarnieri et al., 2009; Adams et al., 2012; Filho et al., 2012; da Conceição et al., 2013). The data lends some support to the hypothesis that TLE patients with a current diagnosis of depression have evidence of extra-temporal dysfunction.

TLE patients are considered at high risk of depression due to limbic and/or frontal lobe dysfunction (Swinkels et al., 2005). The hypothesis that brain areas outside the epileptic focus may play a pathogenic role is supported by the relationship found between depression and less 'localised' ictal epileptiform activity. Video-EEG reports for these patients noted widespread, ipsilateral *fronto*-temporal ictal patterns. The role of extra-temporal regions is further strengthened by structural (Baxendale et al., 2005; Shamim et al., 2009; Wrench et al., 2009; Finegersh et al., 2011) and functional (Schmitz et al., 1997; Savic, et al., 2004; Hasler et al., 2007; Lothe et al., 2008; Martinez et al., 2013) neuroimaging studies indicating that more diffuse cerebral pathology/dysfunction is found in TLE patients with depressive morbidity. Butler and co-workers (2012) have shown that the orbitofrontal cortex (OFC), one of the first propagation sites of mesial temporal epileptic discharges (Lieb et al., 1991), is bilaterally thickened in depressed mesial TLE patients. Furthermore, the severity of the depression was positively correlated with the cortical thickness of these regions. The presence of a more extensively damaged cerebrum, as indicated by non-localised ictal epileptiform abnormalities, may also explain the association between a history of depression and a poorer response to anti-epileptic medication (Hitiris et al., 2007), and epilepsy surgery

(Study 1; Anhoury et al., 2000; Kanner et al., 2009). The correlational nature of this current study, and the evidence of a bidirectional relationship between depression and epilepsy (Forsgren et al., 1990; Hesdorffer et al., 2000; Hesdorffer et al., 2006; Hesdorffer et al., 2012), indicates longitudinal research is required to conclusively demonstrate that depression is causally associated with non-localised ictal EEG patterns.

None of the other demographic or epilepsy-related factors distinguished group membership. Previous studies examining risk factors for depression in TLE have reported conflicting findings (Foong et al., 2007). The role of gender is uncertain with higher rates reported in both males (Altshuler et al., 1999; Strauss et al., 1992) and females (Paradiso et al., 2001), with others finding no effect (Grabowska-Grzyb et al., 2006). The age of TLE onset, duration and seizure laterality do not appear to influence depression (Foong et al., 2007); suggesting other biological (e.g. concomitant frontal lobe dysfunction) and/or psychosocial determinants may be of importance.

Parasido and co-workers (2001) found that seizure frequency was increased in the presence of depression, particularly for right-sided patients (Paradiso et al., 2001). However, due to limited statistical power such interactional effects were unable to be investigated in this current examination, and require replication with larger cohorts.

This study provides some support for previous research indicating that depressed mood is significantly associated with neuropsychological dysfunction remote from the epileptogenic focus (Hermann et al., 1991; Corcoran et al., 1993; Paradiso et al., 2001; Helmstaedter et al., 2004). Depressed TLE patients demonstrated a significantly larger discrepancy between premorbid and assessed IQ, an indicator of more global cognitive decline and, an increased incidence of dysexecutive behaviours in daily life. The failure to find greater performance

deficits in association with depression conflicts with previous work (Paradiso et al., 2001), including a more global 'blunting' of cognitive performance reported in the neuropsychiatric literature (Austin et al., 2001; Castaneda et al., 2008; Clark et al., 2009; McClintock et al., 2010).

Antidepressant treatment likely complicates the cognitive presentation. The relation between cognition and depression appears *modified* by antidepressant treatment. Animal and human studies indicate that selective serotonin reuptake inhibitors (SSRIs) have neuro-protective and pro-cognitive effects (Gualtieri et al., 2006; Taler et al., 2013). Taler et al. (2013) reported that following SSRI (sertraline) treatment, mice exhibited significant improvements in spatial memory, using the Morris Water Maze task. This effect was positively associated with the up-regulation of brain derived neurotrophic factor (BDNF) in the hippocampus; a protein involved in neurogenesis and differentiation. Furthermore, widespread cognitive impairments have been shown to normalise following successful SSRI therapy in unipolar MDD patients (Gualtieri et al., 2006). Notably, all depressed patients in the current study were receiving SSRI monotherapy. Thus, the finding of a specific cognitive impairment may not be in direct conflict with previous reports (Paradiso et al., 2001); but rather supports the view that the relationship between global cognitive dysfunction and depression is modulated by psychotropic (SSRI) medication.

Contrary to previous reports, we did not replicate the finding that executive function test performance was poorer in relation to depressed mood. Hermann et al. (1991) reported that 45% of TLE patients had clinically significant frontal lobe dysfunction as assessed by perseveration errors on the WCST. Hermann and colleagues (1991) also reported a positive relationship between frontal lobe function (perseverative errors) and dysphoric mood state, particularly for left-sided patients. This divergent finding may be due to methodological differences between studies. Hermann et al.'s (1991) cohort was non-lesional; 88% requiring

bi-temporal and bi-frontal intracranial recordings. Most patients in the current study were lesional cases (n=54; 84%), and only 8 (13%) patients required invasive EEG recordings as part of their pre-surgical evaluation.

Depressed TLE patients in this study showed awareness of executive function deficits in daily life as measured by the DEX and experienced more difficulties than TLE-only patients, as demonstrated by the good agreement between patient and informant DEX ratings. The lack of an association however, between cognitive test performance and reported dysexecutive behaviours in depressed TLE patients requires consideration.

Burgess et al. (1998) proposed that neuropsychological tests may not always reflect the executive problems that patients encounter in real-life situations (i.e. low ecological validity). This may be due to the structured nature of cognitive tests (i.e. rules and goals are set, and behavioural initiation is prompted; van Beilen et al., 2006). In contrast, activities of daily living are usually unstructured, often without a clearly defined goal or solution, and with an unspecified behavioural trajectory. Thus, as reported previously (Burgess et al., 1998; Koerts et al., 2012), the lack of an association between reported dysexecutive behaviours and executive test performance may reflect the low ecological validity of the cognitive measures. In addition, other cognitive tasks such as the Iowa Gambling Task (Bechara et al., 1994), which have been modelled on real-life decision-making, may be better related to everyday executive function than the tests used in the current study. Labudda et al. (2009) found that TLE patients (with no information regarding depressive morbidity) were significantly impaired in their decision-making compared to healthy controls. Notably, those with a preference for disadvantageous decisions also performed less well on other tests of executive function.

An alternative explanation is that the DEX may not be directly assessing difficulties with executive functions in daily life, but rather indicating the associated negative affect (Gerstorf et al., 2008). This could therefore explain the current finding that depressed TLE patients reported significantly more problems with real-life executive tasks than TLE-only patients, even though there were no differences with regard to neuropsychological test performance. However, the positive relation between *informant* DEX ratings and patient BDI-FS symptoms argues against a subjective bias in the reporting of executive difficulties by depressed patients.

This study extends previous findings in several ways. First, temporal and extra-temporal cognitive function was examined. Previous studies have either limited investigation to memory function (Corcoran et al., 1993; Wishart et al., 1993; Dulay et al., 2004; Helmstaedter et al., 2004) or used a narrow neuropsychological test battery to assess depressed TLE samples (Hermann et al., 1991; Paradiso et al., 2001).

Although no single method is optimal to assess psychiatric state in TLE (Guarnieri et al., 2009), this study employed clinical rating scale (BDI-FS) in addition to a clinical assessment. The use of a *clinical* diagnosis of depression is important, as patients had elevated depressive symptoms (median BDI-FS = 9); prior work with minimal or mildly depressed TLE cohorts failed to relate depression and cognitive function (Pulliainen et al., 1999; Tracy et al., 2007). Furthermore, both approaches allow confidence that the depressed and control groups were psychiatrically homogenous. The removal of TLE patients with a past history depression also ensured that the findings were not complicated by cognitive deficits (sustained attention/executive function) that may persist following remission/recovery (Porter et al., 2003).

A limitation of this study is the relatively small number of TLE patients with current depression. This precluded statistical investigation into whether depression and seizure laterality interact and adversely impact cognitive performance. However, the suggestion that depression deleteriously impacts the neuropsychological status of depressed left-sided TLE patients (Paradiso et al., 2001; Dulay et al., 2004; Helmstaedter et al., 2004), receives cautious support. Studies with larger sample sizes are needed, particularly as cognitive deficits on left-sided tasks are more easily discerned than right-sided measures (Helmstaedter, 2004). Another limitation is that no correction for multiple comparisons was performed. Given the limited research in this area, a Bonferroni correction was considered too conservative, and may have increased the chance that genuine differences between the groups would not have been detected (Type II error).

In conclusion, depression is common in TLE and is associated with clinical and cognitive markers of more widespread cerebral dysfunction. Depressed TLE patients and their informants are aware of problems with executive functions in daily life, and report considerably more difficulties than TLE-controls. This may explain why depression is a powerful predictor of quality of life in epilepsy, whereas seizure-related factors have little predictive value (Boylan et al., 2004). Reported dysexecutive behaviours however, did not correspond with the results of neuropsychological measures. This lack of an association suggests that standard cognitive measures of executive function do not reveal the extent of problems patients encounter in their everyday life, and highlight the need for ecologically valid assessment tools. The findings suggest that the DEX questionnaire, which is easy to administer and yields valuable informant information, may have clinical utility in the assessment of executive dysfunction in TLE. Finally, longitudinal investigation is required to conclusively demonstrate that depression is causally associated with additional neuropsychological morbidity in TLE.

Chapter 12.

Study 5. Profiling and Predicting Psychiatric Outcome Following TLE surgery

12.1 Study Aims

The literature reviewed in Chapter 2, did not yield consistent or reproducible insights into the possible predictors of poor psychiatric outcome following TLE surgery. This may be due to the investigation of heterogeneous samples, limited information regarding preoperative psychiatric status, short-term follow-up, the application of diverse diagnostic criteria and/or inappropriate selection of statistical analysis techniques (see Chapter 2.9).

Study 1 found 18% of TLE patients experienced deterioration in psychiatric status postoperatively. De novo psychiatric disorders were persistent (lasting longer than 6 months), and the majority of patients required psychiatric treatment. Neither seizure nor cognitive outcomes were related to de novo psychiatric morbidity, but this may have been due to methodological weaknesses.

As hypothesised, previous studies have demonstrated that preoperative indicators of less focal epileptogenicity were predictive of poor post-surgical psychiatric outcome, including a history of SGTCS (Study 1), recurrent PIP episodes (Study 3) and more diffuse structural abnormalities (Study 8).

The aim of this prospective study was to use multilevel modelling (MLM) to further explore predictor(s) of poor psychiatric outcome following TLE surgery. Specifically, (1) to examine whether TLE patients with evidence of pre-surgical extra-temporal lobe dysfunction are at increased psychiatric risk following surgery. (2) To determine whether preoperative

depressed mood is predictive of poor psychiatric, cognitive and seizure outcome.

12.2 Methods

Study Sample

Forty-nine patients who underwent TLE surgery from September 2009 to December 2012 at the NHNN, participated in the study (see Figure 15). Demographic and clinical characteristics are summarised in Tables 27 and 28.

Procedure

As described in Chapter 10, the following pre-surgical evaluations consisted of 1) a detailed medical assessment, 2) high-resolution MRI of the brain with volumetric hippocampal measurements, 3) prolonged VEEG recording, 4) neuropsychological testing and 5) a neuropsychiatric clinical interview, conducted by the same psychiatrist in all patients.

Measures of intellectual function, semantic knowledge, memory and executive function were completed preoperatively and at 6 (n=41), 12 (n=29) and 24 months (n=9) following surgery.

The BDI-FS and BAI were administered at the same time intervals as the cognitive tests and were used as the main measures of mood status (i.e. outcome variables).

Variable	TLE patients (n=49)
Female†	32 (65%)
Chronological age, yrs[1]	38 (12)
Age of TLE onset, yrs[1]	15 (11)
TLE duration, yrs[1]	23 (14)
Predisposing Factors†	
History of febrile convulsions	16 (33%)
History of status epilepticus	4 (8%)
History of head trauma	7 (14%)
History of CNS infection	3 (6%)
Family history of epilepsy	11 (22%)
Seizure Type[2]	
Simple partial†	42 (86%)
Complex partial†	49 (100%)
SGTCS†	18 (37%)
Seizure frequency SGTCS/month[1]	1 (3)
Seizure frequency/month[3]	8 (1-40)
Medication	
Total number of AEDs trialled preoperatively[1]	3 (1)
Monotherapy†	2 (4%)
Polytherapy†	47 (96%)
MRI†	
Normal	6 (12%)
HS	29 (59%)
FCD	2 (4%)
Cavernoma	3 (6%)
DNT	9 (18%)
Other (abn. gyral folding/epidermoid)	7 (14%)
Dual pathology	7 (14%)
Hippocampal Volumes[4,5]	
Ipsilateral HC volume[1]	2.23 (0.61)
Contralateral HC volume[1]	2.71 (0.44)
Video-EEG Findings†,[5]	
Localised ictal EEG	29 (59%)
Localised interictal EEG	36 (74%)
Psychiatric variables	
Family history of psychopathology†	16 (33%)
Lifetime psychopathology†	18 (37%)
Lifetime mood/anxiety disorder†	15 (31%)
Current mood/anxiety disorder†	9 (18%)
Psychiatric treatment†	10 (18%)
BDI-FS[3,6]	3 (0-17)
BAI[3]	9 (0-38)
Surgical procedures†	
Right ATLR	24 (49%)
Left ATLR	22 (45%)
Right Lesionectomy	1 (2%)
Left lesionectomy	2 (4%)

ATLR, anterior temporal lobe resection CNS, central nervous system
DNT, dysembryoplastic neuroepithelial tumour;
FCD, focal cortical dysplasia; HC, hippocampal;
HS, hippocampal sclerosis; † Values are number of patients (%);
[1]Mean (SD); [2]May have >1 seizure type;
[3]Mean (range); [4]Corrected for intracranial volume;
[5]For available data; [6]Rounded to nearest whole number

Table 27. *Demographic and clinical characteristics of 49 patients who underwent TLE surgery.*

Variable[1-3]	TLE patients (n=49)	Performance level:
NART	95 (14)	average
VIQ	92 (14)	average
NART and VIQ discrepancy	-2.7 (11)	-
Verbal learning: trials	-0.9 (1.2)	low average
delay	-0.8 (1.2)	low average
Visual learning: trials	-0.6 (1.1)	low average
delay	-1.1 (1.7)	low average
Semantic knowledge		
Graded Naming Test	16 (5)	low average
Category fluency	18 (5)	average
Executive functions		
Wisconsin Card Sorting Test (Perseveration error)[3]	2 (0-11)	-
Trail making B (secs)	78 (38)	-
Phonemic fluency	14 (6)	average
Working memory (Digit Span)	8 (3)	low average
Spatial WM (between errors)	-0.5 (1.2)	-
Spatial WM (strategy)	0.1 (1.7)	-
DEX-informant	20 (0-59)	-
DEX-subject	20 (2-47)	-

-, not applicable; [1]For available data
[2]Mean (SD); [3]Mean (range)

Table 28. *Cognitive characteristics of 49 patients who underwent TLE surgery.*

12.3 Statistical Analyses

Multilevel Modeling (MLM)

A mixed-model repeated measures analysis was implemented using Stata 10 (StataCorp, 2007). This statistical program was chosen as it contains specific commands (i.e. **xtmixed**) for fitting multilevel models and saves syntax, data organisation and output formats, as a "do-file". This allows the *same* model or set of commands to be applied to different outcomes of interest (e.g. BDI-FS and BAI) in *one* step (by re-running the do-file). Thus, do-files facilitate an efficient and reproducible workflow reducing data management time, and Stata's computational speed afford significant advantages over other statistical packages (Long, 2009).

The advantages of multilevel modeling (MLM) have been described elsewhere (see Chapter 2.10). MLM is the preferred technique to longitudinal data where the primary interest is in modeling the structure and predictors of *change over time* in an outcome of interest (Luke, 2004), for example mood rating scores following TLE surgery.

A multilevel model decomposes the variance in a characteristic of interest (e.g. BDI) and models whether the variability and rate of change over time varies across individuals in a *systematic* way, according between-subject predictors of interest (e.g. epilepsy lateralisation, history of psychopathology etc.). Although MLM computations are dealt with by statistical programs (Stata 10), the following theory is outlined to aid interpretation of the following results.

Fixed and Random Coefficients

In normal general linear regression models (e.g. ANOVA), it is assumed that the regression parameters (intercept, B_0; slope, B_1) are *fixed* as described below (Field, 2009):

$$\mathbf{Y_i = B_0 + B_1X_{1i} + \varepsilon_i}$$

Note the outcome (Y; e.g. BDI), the predictor X and the error (ε) all vary as a function of i, which represents the time points in the dataset (e.g. preoperative, 6 and 12 months etc.) – the level 1 variable (see Chapter 2.10, Figure 3). Therefore, if we wanted to know a patient's BDI at 6 months, we could replace the i's with the level 1 variable of interest:

$$\mathbf{BDI_{(6m)} = B_0 + B_1X_{1(6m)} + \varepsilon_{(6m)}}$$

The inherent assumption here is that the model holds true across the *entire sample*. Thus, for *every* patient in the sample we can predict the outcome (BDI at 6 months) using the *same* values for the intercept (B_0) and slope/gradient (B_1) (Field, 2009), as described by the single (red) regression line in Figure A below:

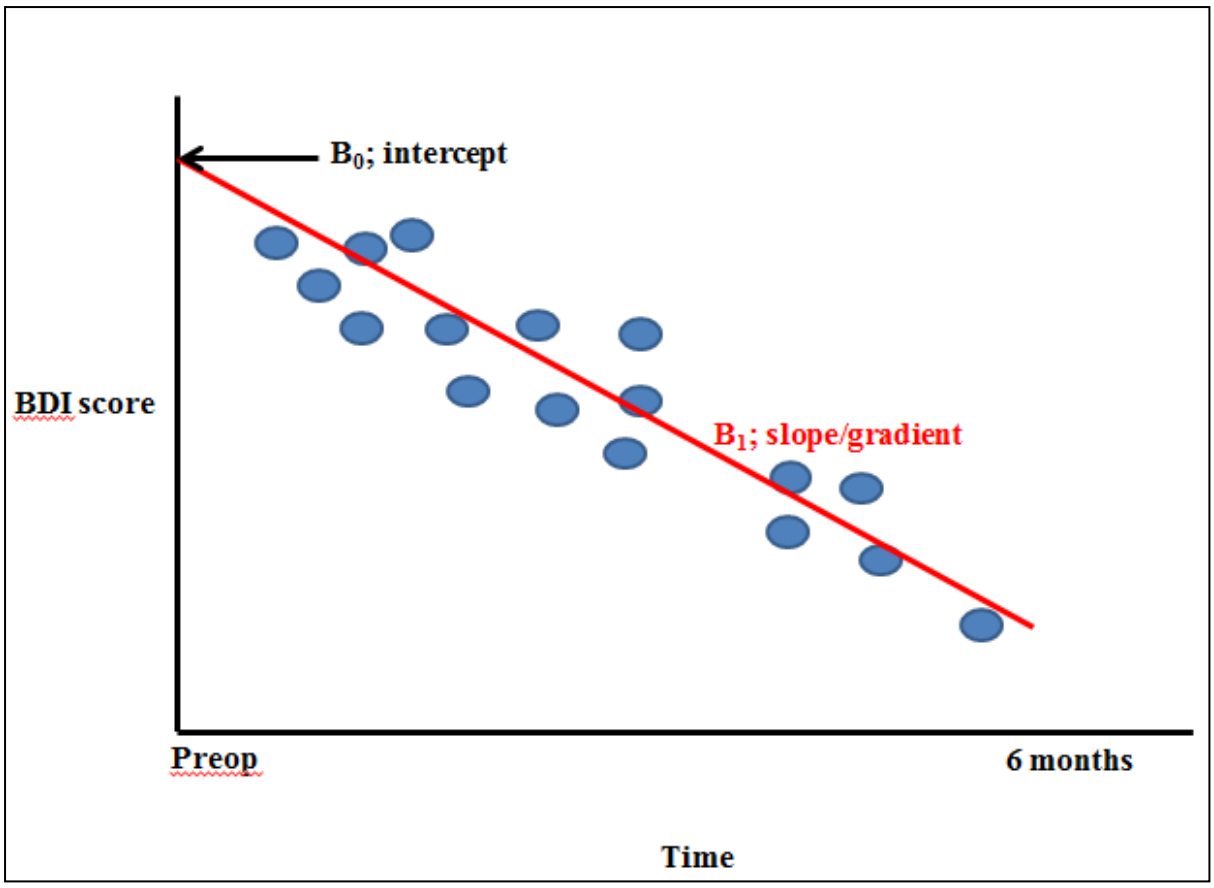

Figure A. *Schematic of a fixed effect simple linear regression model; blue dots = patient data points*

The cornerstone of multilevel modeling is that each individual has their *own* regression/growth parameters (B_0; intercept and B1; slope), and therefore growth parameters can *vary across patients* – at level 2 (see Chapter 2.10, Figure 3).

Random Intercept Only Model

To include a random intercept for BDI, a component is added to the intercept that measures the variability in intercepts, u_{0j}. Therefore, the intercept term changes from B_0 to become $B_0 + u_{0j.}$ This term estimates the intercept of the overall model fitted to the data, B_0, and the variability of intercepts around that overall model, u_{0j}:

$$Y_{ij} = (B_0 + u_{0j}) + B_1X_{1ij} + \varepsilon_{ij}$$

The j's in the equation denote the levels of the variable over which the intercept *varies* (i.e. across patients) – the level 2 variable (see Chapter 2.10, Figure 3). Therefore, to estimate patient 1's BDI at 6 months, the equation becomes *idiosyncratic to patient 1* (see Figure B):

$$BDI_{(6m\ patient1)} = (B_0 + u_{0patient1}) + B_1X_{16m,\ patient\ 1} + \varepsilon_{6m,\ patient\ 1}$$

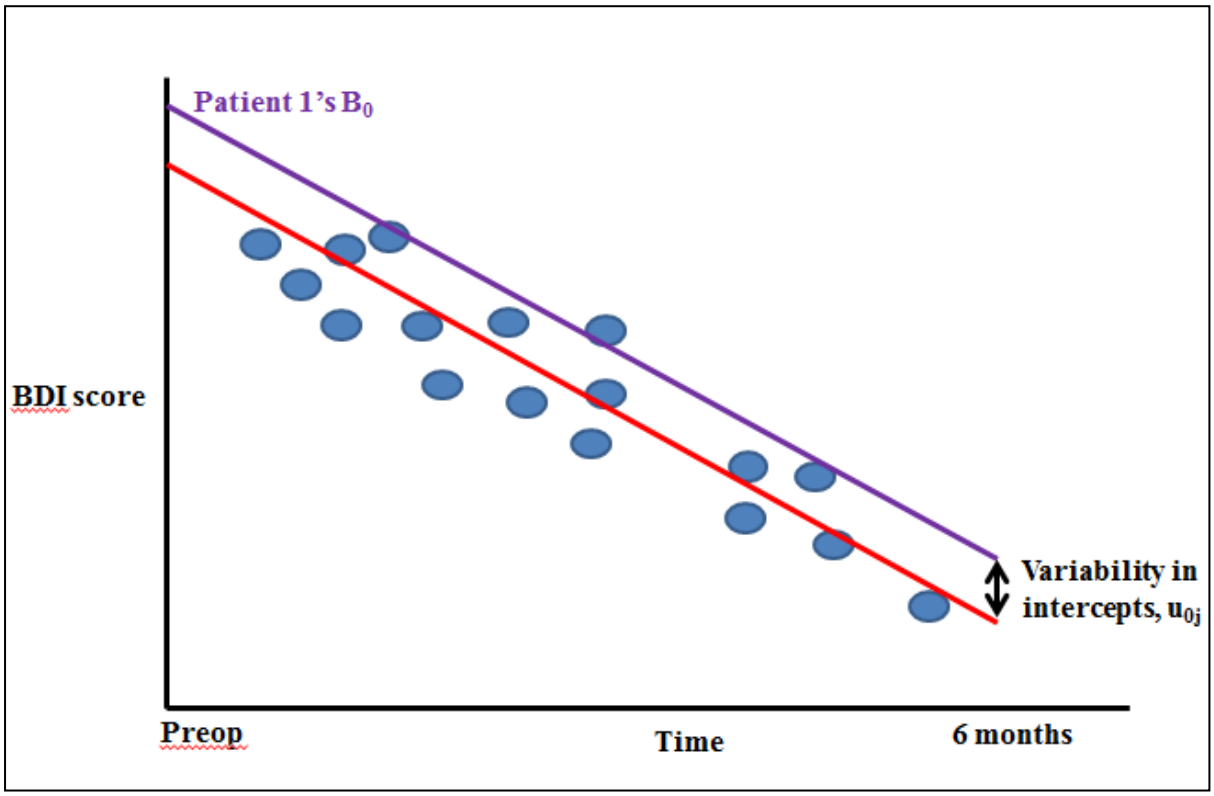

Figure B. *Schematic of a fixed effect simple linear regression model (red line) and the regression line for patient 1 (purple line). The difference between the model and patient's intercept* ($B_{0\ model}$ - $B_{0\ patient1}$) *is depicted by* u_{0j}*; blue dots = patient data points*

Random Intercept and Slope Model

As described above, the intercept and slope for the overall model (B_0 and B_1) is estimated, but the variability in the intercepts, u_{0j} *and* slopes, u_{1j} is included:

$$\mathbf{Y_{ij} = (B_0 + u_{0j}) + (B_1 + u_{1j})X_{1ij} + \varepsilon_{ij}}$$

Now patient 1's BDI at 6 months with a varying intercept *and* slope can be estimated (see Figure C):

$$\mathbf{BDI(_{6m\ patient1}) = (B_0 + u_{0patient1}) + (B1+u_{1patient\ 1})X1_{6m,\ patient\ 1} + \varepsilon_{6m,\ patient\ 1}}$$

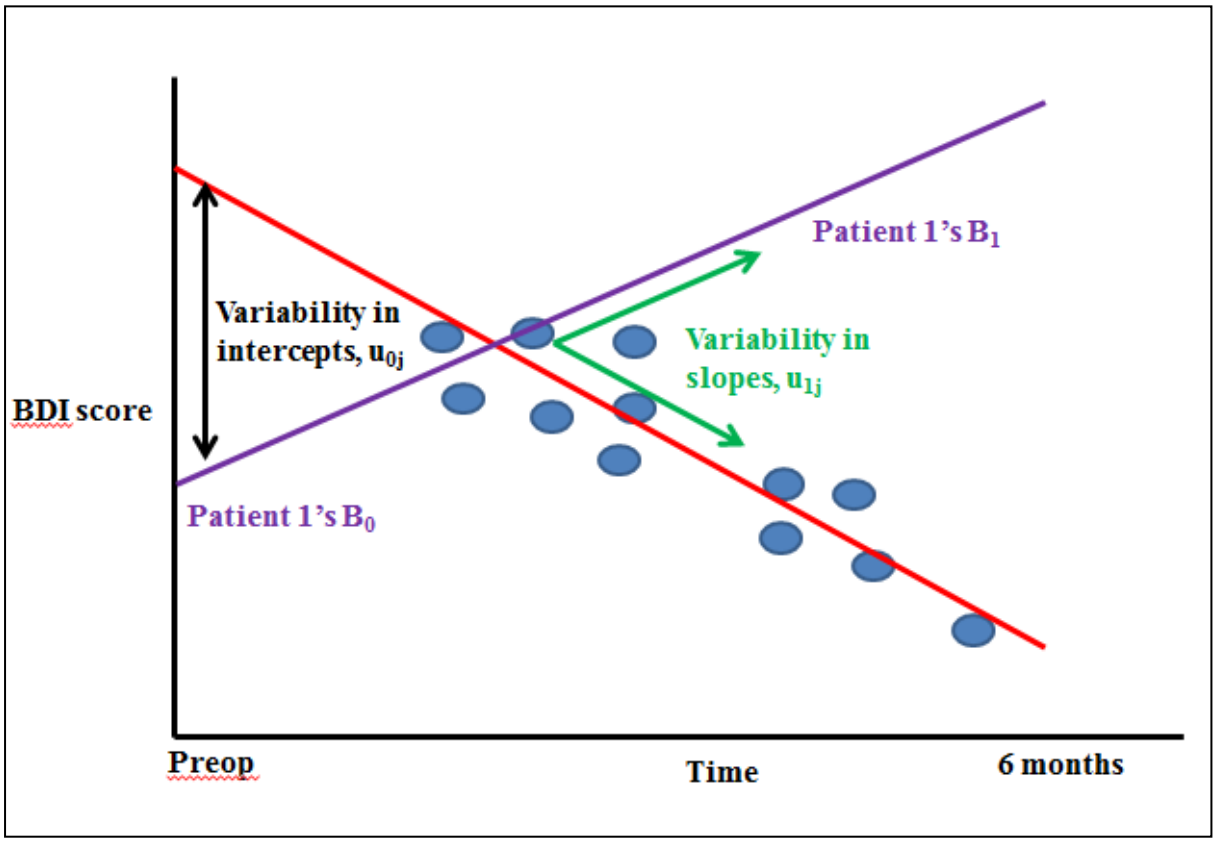

Figure C. *Schematic of a fixed effect simple linear regression model (red line) and the regression line for patient 1 (purple line). The difference between the model and patient's intercept* ($B_{0\ model} - B_{0\ patient1} = u_{0j}$) *and slope* ($B_{1\ model} - B_{1\ patient1} = u_{1j}$) *is depicted; blue dots = patient data points*

Hypothesis Testing

Although MLM is a flexible technique, hypothesis testing is still required to evaluate whether a **random intercept only, or random intercept *and* random slope model** is the best fit to the observed data. This decision is guided by the likelihood-ratio test. This test compares the overall fit of the two candidate models (random intercept only versus random intercept *and* random slope), and whether the null hypothesis that the addition of a random slope makes no significant difference to the overall fit of the model (compared to the random intercept only model), can be rejected (Heck et al., 2010). For this form of hypothesis testing full maximum-likelihood estimation (MLE) must be used (Field, 2009).

Maximum Likelihood Estimation

The method of MLE is the most popular approach to statistical estimation (Singer et al., 2003). Conceptually, the aim of MLE is to determine the unknown population parameters that maximise the probability of observing a particular sample of data.

The derivation of a MLM estimate for a population parameter is accomplished by the construction of the *likelihood function* – an expression that describes the probability of observing the sample data as a function of the model's unknown parameters. The statistical program (Stata) then numerically examines the relative performance of potentially competing estimates until those that maximise the likelihood function are found (see Singer et al., 2003, for further discussion).

Covariance Structure

Fitting a multilevel model requires the specification of a covariance structure to the dataset (Field, 2009). This part of the model represents the *variation/error* in measuring each

individual over time (i.e. level 1 residual errors). By definition, these errors are *unobserved* and require assumptions about the distribution of the level 1 residuals to be invoked, from occasion to occasion (preoperative – 6m; preoperative – 12m), and from patient to patient (Singer et al., 2003).

The covariance structure specifies the form of the variance-covariance matrix (a matrix in which the diagonal elements are variances and off diagonal elements are the covariance) and is the starting point to estimate model parameters. Therefore, different results are yielded depending on which covariance structure is chosen. Specifying a structure that is too simple will increase the chance of a Type I error (erroneously concluding a parameter is significant). Whereas, specifying one that is too complex may result in a Type II error (erroneously concluding parameters are non-significant) (Field, 2009). There are four common structures: (1) unstructured, (2) identity, (3) diagonal and (4) auto-regressive.

For longitudinal data, an auto-regressive structure is preferred as it assumes that correlations between repeated measurements is *highest* at adjacent time-points and *decreases* over time (e.g. preoperative and 6 months BDI-FS score is more related than preoperative and 12 month BDI-FS score). An auto-regressive structure was adopted for all the models in this thesis.

Assumptions of Multilevel Models:

1. **Variable types:** All predictor variables must be quantitative or categorical (with only two categories). The outcome variable must be quantitative, continuous and unbounded (i.e. no constraints on the variability of the outcome).

2. **Non-zero variance:** The predictors should have variation in value (i.e. they do not have variances of zero).

3. **No perfect multicollinearity:** No perfect linear relationship between two or more of the predictors ($r \geq 0.9$).

4. **Normally distributed standardised residuals:** The residuals in the model are random and normally distributed (i.e. no more than 5% of the data will have $\geq \pm 2$ standard deviations from the mean).

Taxonomy of Statistical Models:

1. **Unconditional Means Model:** Instead of describing the *change* in outcome (BDI-FS/BAI) over time, this model simply describes and partitions the outcome *variation*. The primary reason for fitting this model is to estimate the (between- (σ^2_B) and within-subject (σ^2_w) variance). For each outcome variable (BDI-FS/BAI), the model produces the interclass correlation (ICC) that describes the amount of variance in the outcome attributed to differences *between* people (at level 2):

   $ICC = (\sigma^2_B / \sigma^2_{B+} \sigma^2_w)*100$

   Thus, the ICC evaluates the necessity of modeling the nested data structure (i.e. any significant variation in individual initial status of the outcome variable). If the ICC is low (i.e. <25%), incorporating random coefficients (intercepts and/or slopes) are not required and a multilevel model strategy has no significant gains than traditional methods (repeated measures ANOVA) (Shek et al., 2011).

2. **Does the slope vary randomly across patients?**

   This model focusses on defining the *shape* of patients' growth trajectories (i.e. how BDI-FS/BAI changes over time) and determines whether the initial intercept and/or

slope varies across patients (Heck et al., 2010). In this step, two models are generated – the **random intercept only** and **random intercept and slope models**.

At this point, checking the model's assumptions (described above, assumptions 1-4) is crucial for determining the tenability of the model and subsequent conclusions. For multilevel modeling, Singer et al. (2003) suggest that the visual inspection of standardised residuals (using probability plots) is the most efficient way to ensure the distribution is normal (see assumption 4). For both self-report indices (BDI-FS/BAI), there were marked deviations from the predicted line (more than 5% of the data had ≥ ± 2 standard deviations from the mean) (Field, 2009); indicating that the assumption of normality of residuals has been violated (see Appendix 6a & c). Therefore, for both outcomes (BDI-FS/BAI) the data was transformed using the logarithmic function (Weiss, 2005). For a logarithmic transformation, no observation in the data set can be 0 (see Weiss, 2005, for discussion). Therefore, all values were increased by one unit so that 0 values had been increased sufficiently to permit a logarithmic transformation.

Following the power transformation, the log standardised residuals probability plots were visually inspected to evaluate whether the assumption of normality has been met (i.e. the data points lie along the predicted line). For BDI-FS and BAI, the residuals were normally distributed (i.e less than 5% of the data deviated ≥ ± 2 standard deviations from the prediction line; see Appendix 6b & d).

The likelihood-ratio test was then computed to assess which model captured more variability in the outcome (**random intercept only** versus **random intercept and slope**). For both outcome measures (BDI-FS/BAI), the random intercept only model

was sufficient (all p-values for the likelihood-ratio test >.05) and was used in the subsequent uni- and multi-variable analyses (steps 3 & 4).

3. Adding Predictors: Univariable analyses

For each logarithmic (log) random intercept only model (BDI-FS/BAI) the following between-subject predictors (n=30) were added singly (see Table A); affording the assessment of whether a level 2 variable (e.g. gender) effects the outcome (e.g. BDI-FS/BAI), adjusting for the main effect of time.

Two cross-level interaction terms were also included in each model to examine whether a level 2 variable (e.g. gender) had a significant effect on the outcome variable (BDI-FS/BAI) over *different levels* of the level 1 variable (i.e. time at 6 *or* 12 months, relative to preoperative score).

Variable*
Gender
Age of TLE onset, yrs
TLE duration, yrs
TLE laterality
Hippocampal volumes[1]
Ipsilateral HC volume
Contralateral HC volume
Pathology
Hippocampal sclerosis vs other
Video-EEG Findings[2]
Localised ictal EEG
Localised interictal EEG
Cognitive variables[2]
Preoperative VIQ
NART/VIQ discrepancy
Verbal learning: trials
delay
Visual learning: trials
delay
Contralateral memory weakness
Semantic knowledge
Graded Naming Test score
Category fluency score
Executive functions
Phonemic fluency score
Trail making B (secs)
Wisconsin Card Sorting Test (Perseveration error)
Working memory (Digit Span)
Spatial WM (between errors)
Spatial WM (strategy)
DEX-informant
DEX-subject
Psychiatric variables
Family history of psychopathology
Lifetime psychopathology
Lifetime mood/anxiety disorder
Current mood/anxiety disorder

Table A. *Preoperative predictors of change in mood rating scales following TLE surgery used in univariable analyses.*

For predictor selection into a multivariable model, variables from step 3 were retained if the p-value was ≤ 0.20. This less conservative p-value was adopted as a Type I error rate of 5% is too conservative for predictors that may have borderline significance in a univariable model, but may be significant when controlling for *covariates* in a multivariable model (Field, 2009). Only significant ($p \leq 0.05$) interaction terms are reported as these coefficients are not included in a multivariable model and describe how a between-subject factor differentially affect the outcome over different time points.

As described previously, for each of the univariable log-random intercept only model per outcome (BDI-FS/BAI), standardised residuals probability plots were computed and all were normally distributed.

4. Adding Predictors: Multivariable analyses

For each outcome variable (BDI-FS/BAI) a "final" model assessed whether predictors retained from step 3 (univariable analyses) remained significant after controlling for other possible covariates (i.e. the degree to which a predictor affects the outcome, if the effects of all the other predictors are held *constant*). Employing a multivariable model also controls for the inflated family-wise error rate that occurs after running multiple univariable analyses (i.e. 1/20 or 5% of the uni-variable models will be significant purely by chance).

As suggested by Singer et al. (2003), a taxonomic modelling structure was employed to identify preoperative predictors of change in mood rating scales (BDI-FS/BAI) at 6- and 12 months compared to baseline (i.e. preoperative scores). Twenty-four month follow-up was not included in the model due to steep sample attrition (see Figure 20).

Logistic Regression

Logistic regression analyses were used to examine whether postoperative mood rating scores (BDI-FS and BAI) or change (i.e. postoperative minus preoperative) in mood rating scales at 12 months, were related to seizure outcome (ILAE=1).

Univariable logistic regression analyses were also used to investigate whether de novo psychopathology was related to preoperative factors; specifically, seizure laterality, TLE duration, presence of SGTCs during the pre-surgical evaluation or a family history of psychopathology.

Limited statistical power precluded analyses regarding the relation between depressive symptoms (BDI-FS) and cognitive outcome at 12 month follow-up (see Appendix 9A-F).

12.4 Results

Preoperative Psychopathology: Lifetime and Current

Eighteen patients (n=18/49; 37%) had a lifetime psychiatric history (depression, n=13/18; panic disorder without agoraphobia, n=2; generalised anxiety disorder, n=3; PIP, n=3; non-epileptic seizures (NES), n=1). Of which, four patients (n=4/18; 22%) had more than one lifetime psychiatric diagnosis (depression and panic disorder without agoraphobia, n=1; depression and NES, n=1; depression and generalised anxiety disorder, n=2).

Fifty per cent (n=9/18) of patients with a lifetime psychiatric history had a psychiatric diagnosis at the time of TLE surgery (depression, n=6/9; 67%; anxiety disorders, n=3/9; 33%: panic disorder without agoraphobia, n=1; not otherwise specified, n=2). Eight patients (n=8/9; 89%) were receiving psychotropic medication (see Figure 21).

Of the nine patients with a clinically significant mental health problem at the time of surgery, seven (n=7/9; 78%) were seen six months postoperatively and five (n=5/9; 56%) at the twelve month follow-up. During this time period, no patient had remission of their pre-surgical psychiatric disorder and all patients continued on psychotropic medication.

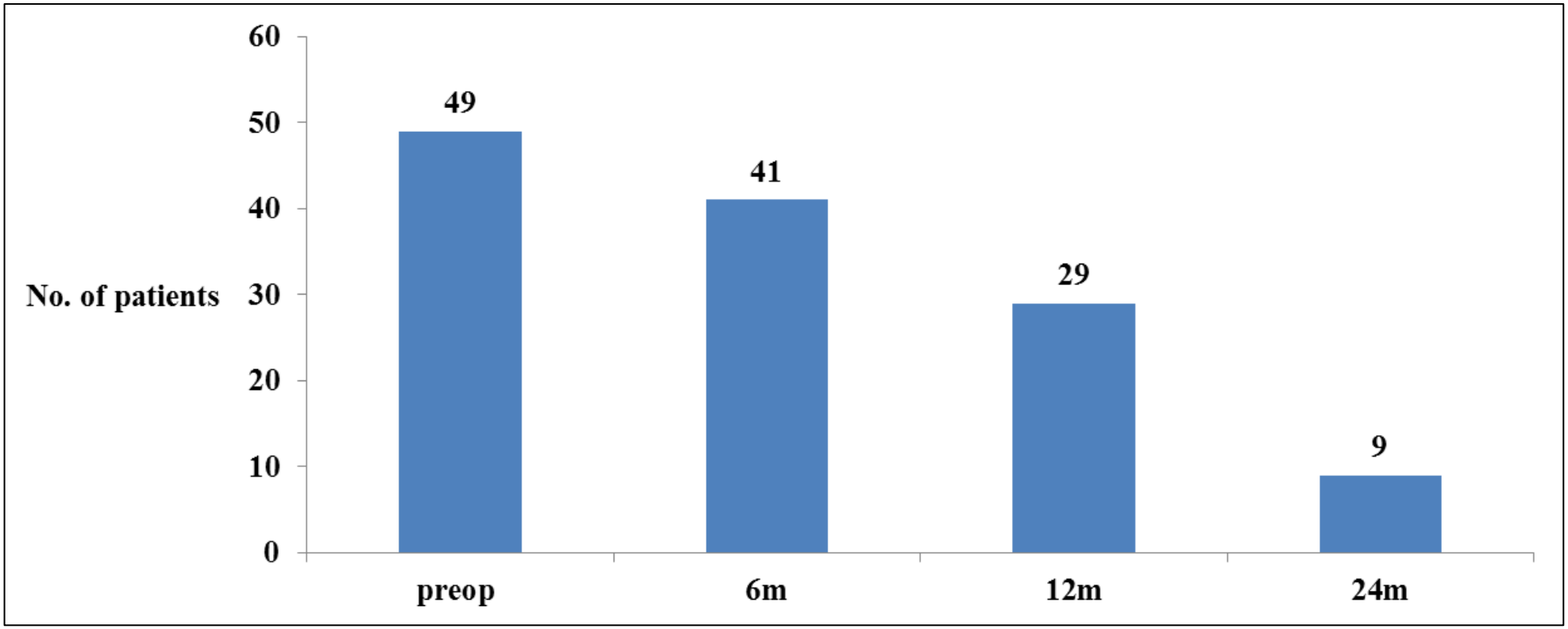

Figure 20. *Sample attrition of the TLE patients (n=49) who underwent TLE surgery.*

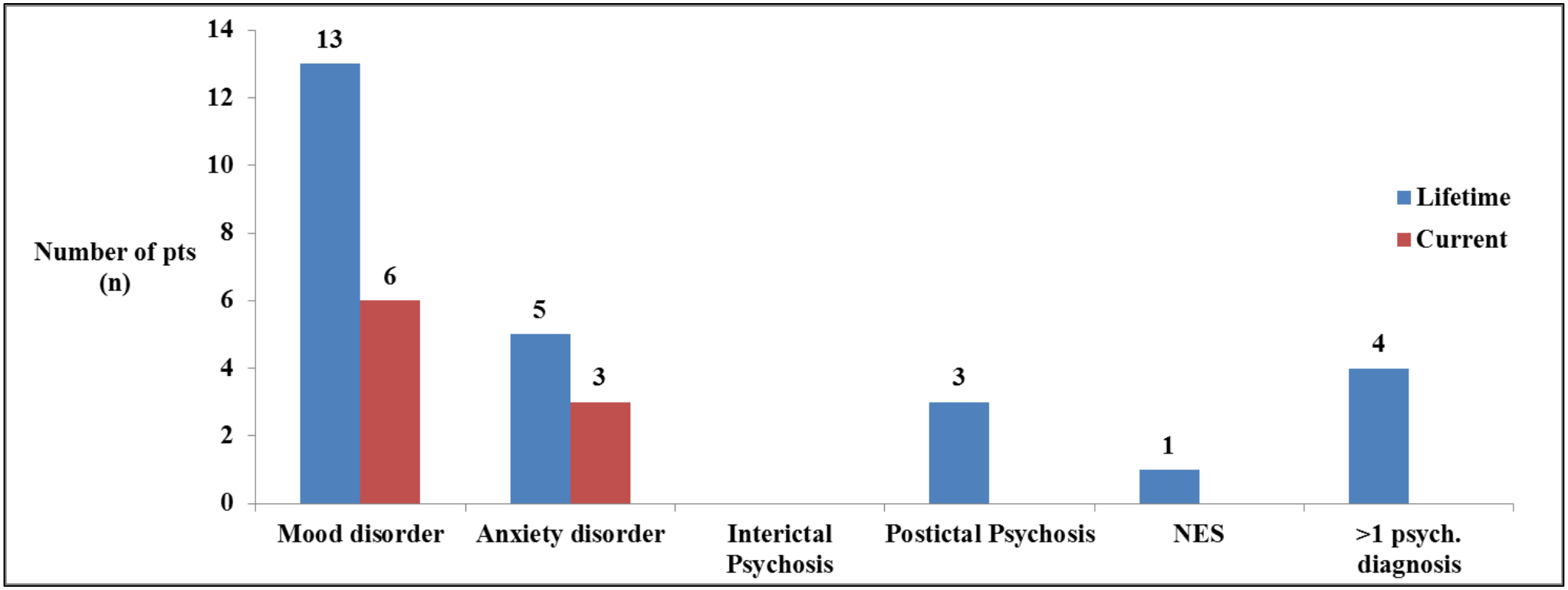

Figure 21. *Lifetime (blue bars) and current (maroon bars) psychiatric diagnoses of patients (n=49) who underwent TLE surgery.*

De Novo Psychopathology

Of the 31 patients with no history of psychopathology, five (16%) developed de novo psychopathology within 12 postoperative months (depression, n=2; generalised anxiety disorder, n=3; adjustment disorder, n=1; NES, n=1; see Figure 22); of which two patients (n=2/5) had de novo comorbid psychopathologies (depression and generalised disorder, n=1; depression and adjustment disorder, n=1), within 6 months follow-up. All patients (n=5; 100%) required psychotropic medication (SSRI: citalopram; anxiolytic; diazepam) and one de novo case (depression and generalised disorder) reported prominent suicidal ideation in the early (< 3 months) postoperative period in the context of seizure freedom.

De novo psychopathology (n=5 cases) was unrelated to seizure laterality (or: 0.67, 95%CI: 0.10-4.39, p=0.67), TLE duration (OR: 0.98, 0.91-1.05, p=0.50) or a family history of psychopathology (OR: 3.67, 95%CI: 0.53-23.98, p=0.19). The odds of a de novo psychiatric disorder within 12 postoperative months were increased for patients with pre-surgical SGTCs, compared to those without (80% vs 32%; OR: 8.5, 95%CI: 0.87-83.9, p=0.06), although the results were borderline significant.

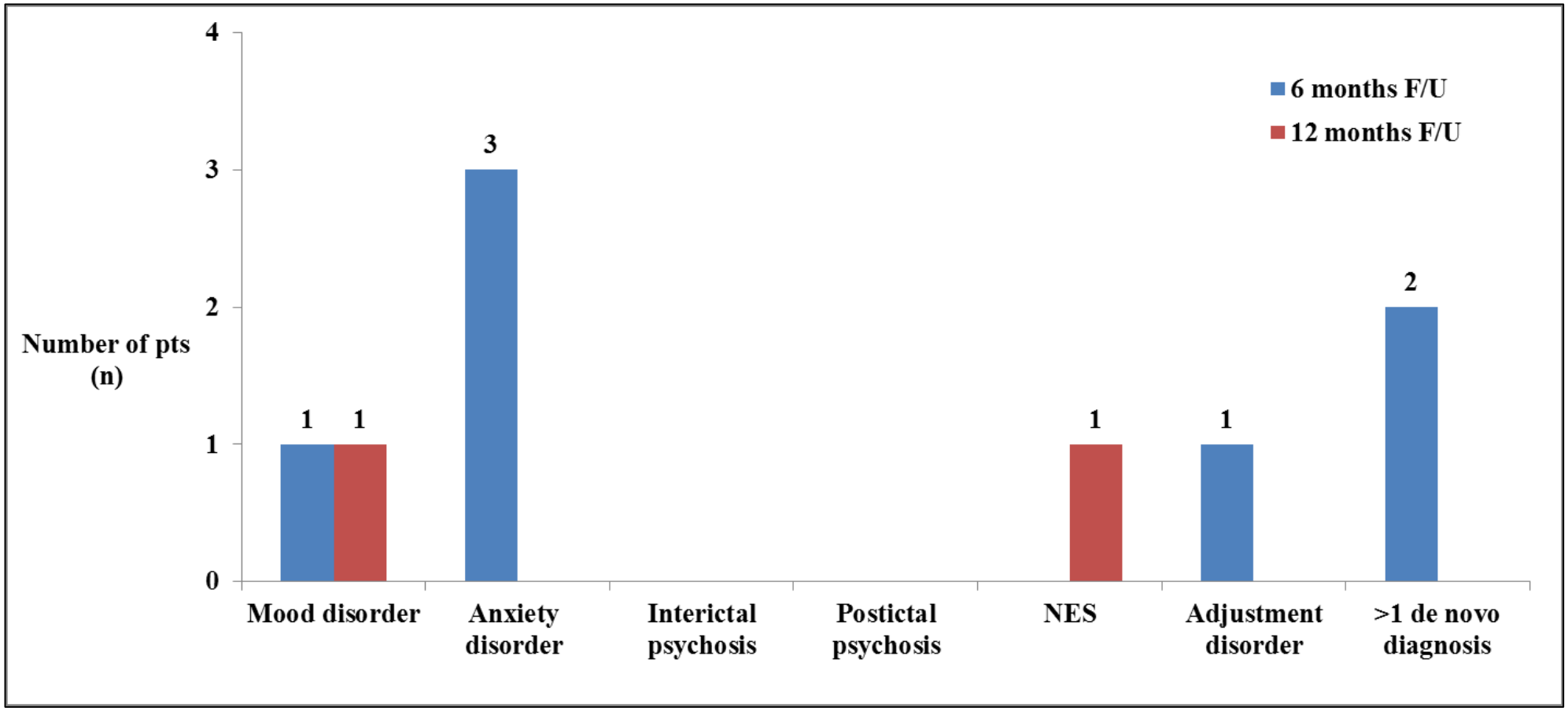

Figure 22. *Point prevalence of diagnosed de novo psychopathologies at 6- (blue bars) and 12 (red bars) month follow-up following TLE surgery.*

Preoperative Mood Rating Scores

Of the pre-surgical TLE cohort (n=49), 33 (67%) patients had minimal depressive symptoms, 8 (16%) were mildly depressed, 2 (4%) were moderately depressed, and 6 (12%) reported severe depressive morbidity. Twenty-three (47%) patients reported minimal anxiety, 18 (37%) were mildly anxious, 6 (12%) were moderately anxious and 2 (4%) patients reported severe anxiety symptoms, (see Figure 23).

Temporal Profile of Psychiatric Rating Scales

At a group level, there was a non-significant decrease in mean log-BDI-FS scores following TLE surgery compared to the mean preoperative (baseline) score (log-random intercept only BDI-FS model at 6 months: B = -0.04, 95%CI: -0.31 – 0.22, p=0.74; log-random intercept only BDI-FS model at 12 months: B = -0.14, 95%CI: -0.44 – 0.16, p=0.35) (see Figure 24A).

Postoperative anxiety ratings (log-BAI) significantly decreased following TLE surgery relative to the mean preoperative (baseline) level, particularly at 6 month follow-up (log-random intercept only BAI model at 6 months: B = -0.40, 95%CI: -0.69 – -0.11, p=0.005; log-random intercept only BAI model at 12 months: B = -0.42, 95%CI: -0.74 – -0.01, p=0.01) (see Figure 24B).

However, inspection of empirical growth plots of patient mood ratings over time (Singer et al., 2003) indicates a large degree of inter-subject variation (see Figures 25 and 26). For example, patient 1 had minimal preoperative depressive symptoms (BDI-FS=0) that did not change over time, whereas patient 38's pre-surgical depression rating was severe (BDI-FS= 12), decreasing to minimal rates postoperatively. This variability was also evident in BAI ratings. For example, patient 63 had mild (BAI=8) anxiety before surgery, which linearly increased (6 month BAI=24, moderate; 12 month BAI=36, severe) during follow-up, whereas

patient 101 had severe preoperative anxiety (BAI=38) that sharply decreased following surgery (6 month BAI=4, minimal; 12 month BAI=8, mild). This variance in preoperative mood ratings was quantified by the unconditional means models for BDI-FS (ICC=0.48; 48%) and BAI (ICC=0.51; 51%). These ICC values indicate that a large degree of variation in pre-surgical mood rating scores are attributable to preoperative between-subject (level 2) factors; necessitating a prediction model that permits the incorporation of random coefficients (intercepts and/or slopes), namely multilevel modeling (Shek & Ma, 2011).

Predicting Change in Mood Rating Scales Following TLE Surgery

Univariable log-random intercept only models for BDI-FS and BAI are described to aid adjusting for the main effect of time, are presented in Tables 29 and 30.

There were no significant cross-level interactions for any of the univariable log-random intercept only models (data not shown; all p-values > 0.05); demonstrating that none of the preoperative between-subject (level 2) factors significantly affected mood ratings (log-BDI-FS/log-BAI) over *different levels* of the level 1 variable (i.e. time at 6 *or* 12 months, relative to preoperative score).

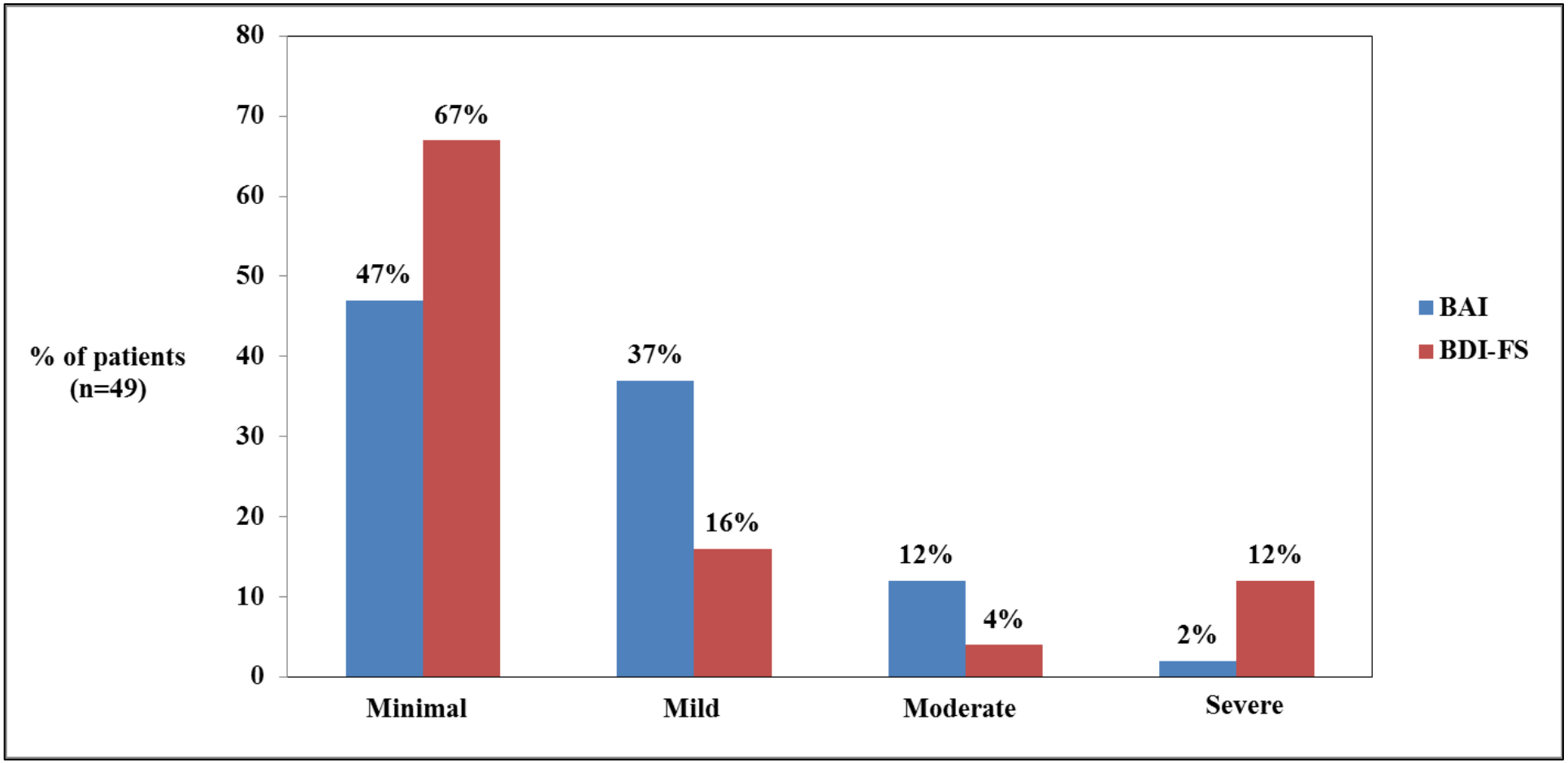

Figure 23. *Preoperative mood rating scores (BDI-FS & BAI) for the TLE surgical cohort (n=49).*

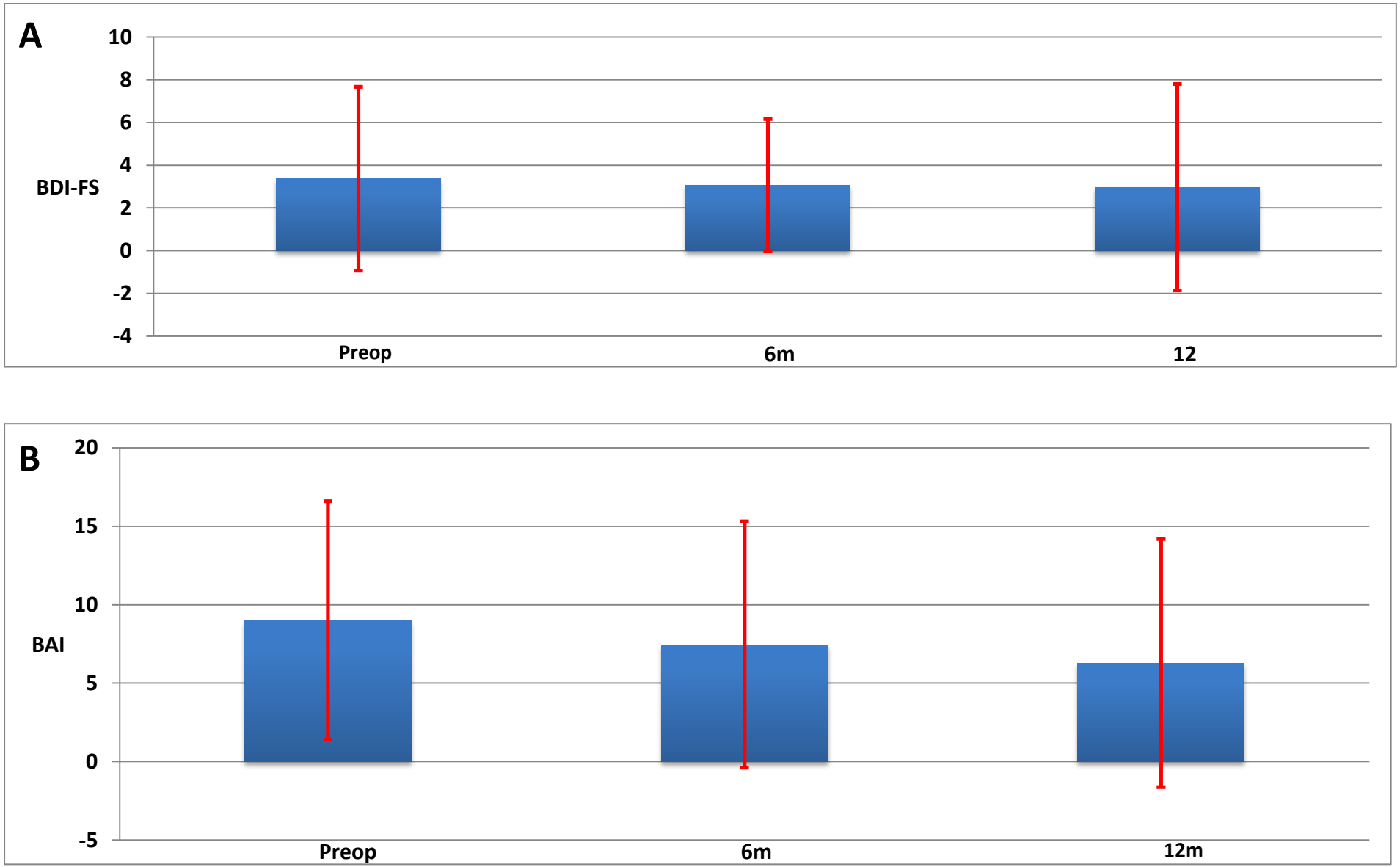

Figure 24. *Change in mean BDI-FS (A) and BAI (B) ratings following TLE surgery.*

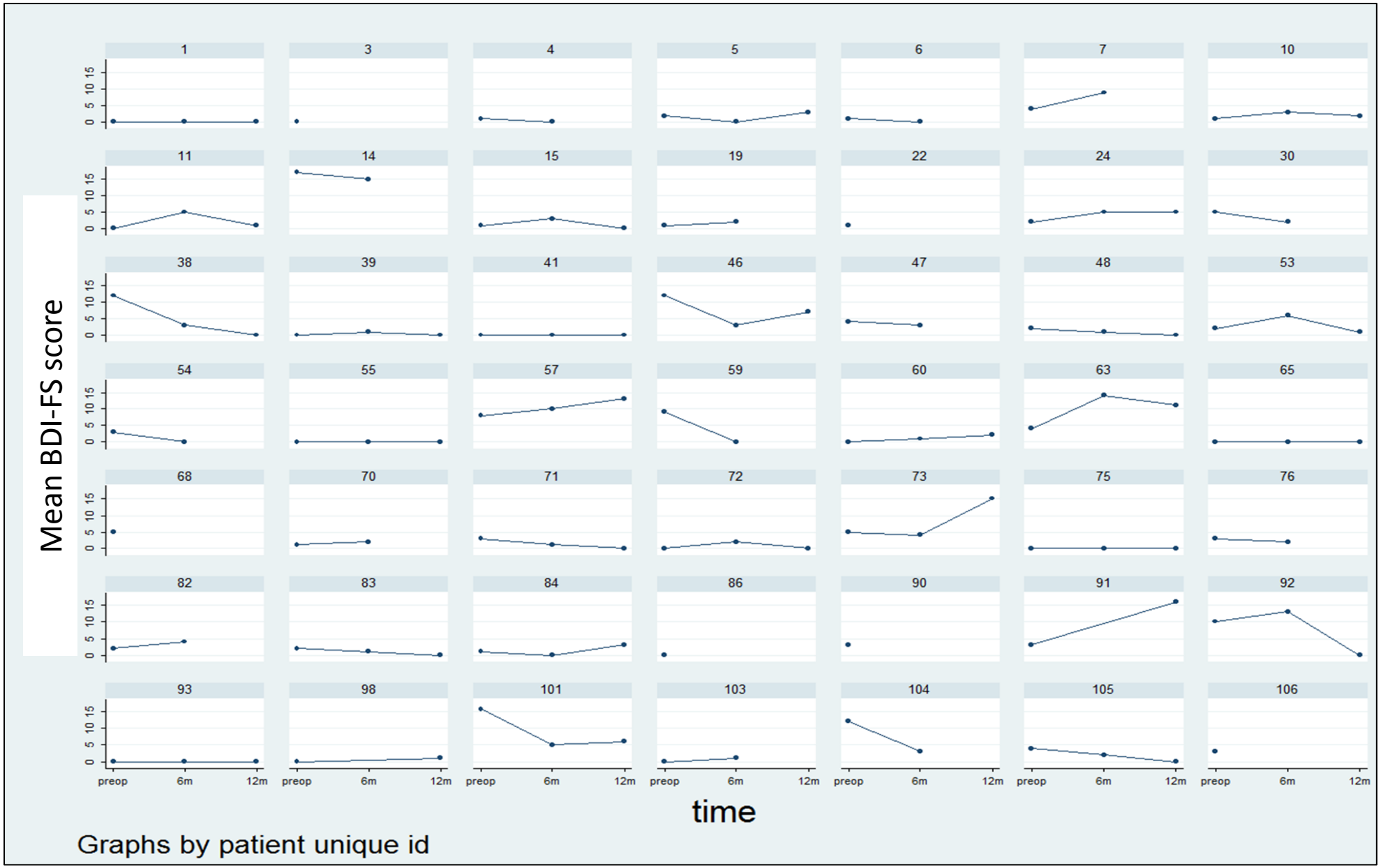

Figure 25. *Empirical growth plots of mean BDI-FS rating for each patient (n=49) following TLE surgery. The single dots indicate patients that were only seen preoperatively (n=6).*

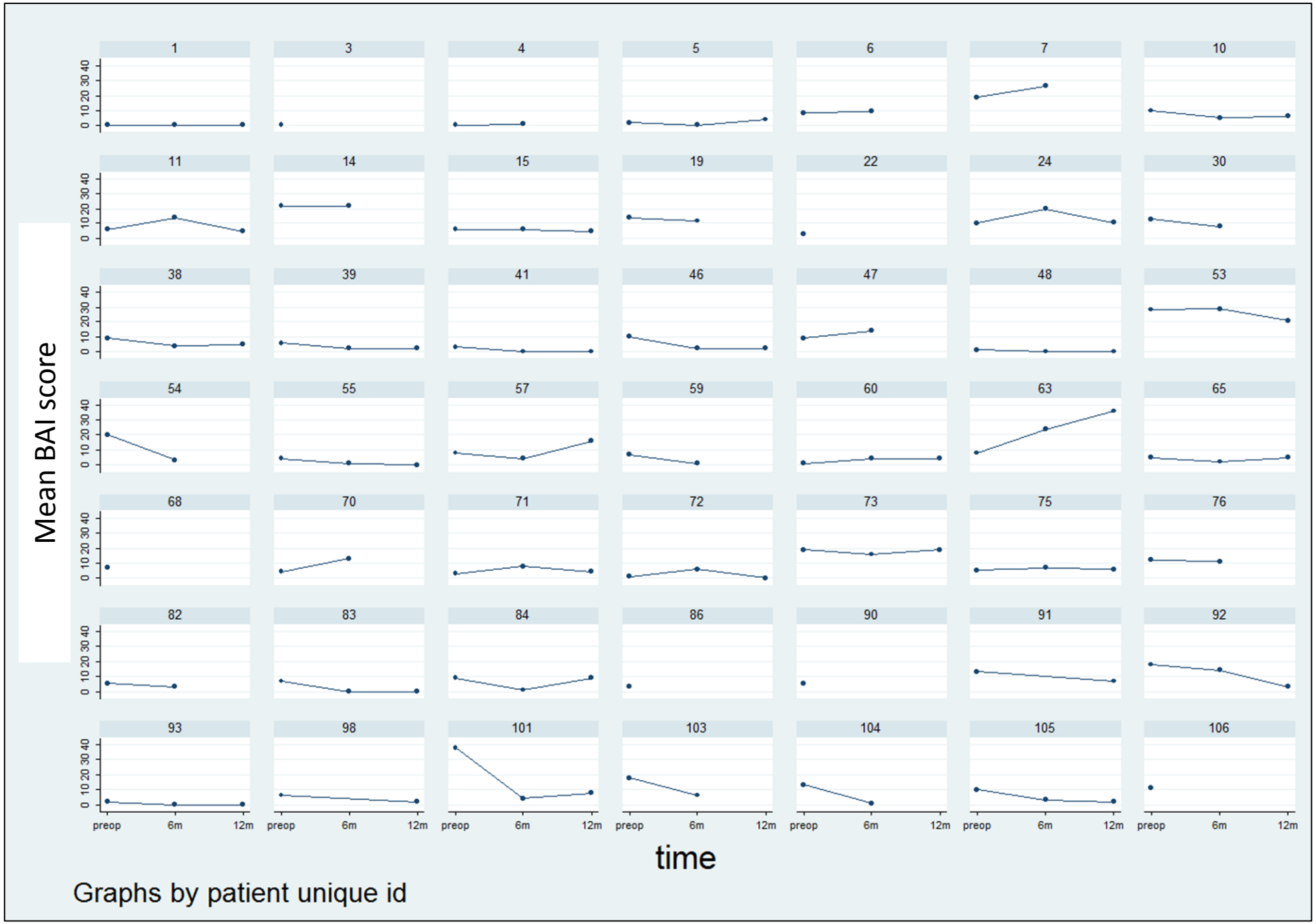

Figure 26. *Empirical growth plots of mean BAI rating for each patient (n=49) following TLE surgery. The single dots indicate patients that were only seen preoperatively (n=6).*

Variable*	Beta Coefficient (B)	Standard Error B	p-value	95% CI
Gender	-0.14	0.27	0.60	-0.67,0.38
Age of TLE onset, yrs	0.00	0.01	1.00	-0.02, 0.02
TLE duration, yrs	0.01	0.01	0.48	-0.01, 0.02
TLE laterality	-0.27	0.25	0.29	-0.77, 0.23
Hippocampal volumes[1]				
Ipsilateral HC volume	-0.23	0.21	0.28	-0.64, 0.18
Contralateral HC volume	-0.17	0.30	0.57	-0.74, 0.40
Pathology				
Hippocampal sclerosis vs other	0.03	0.26	0.90	-0.47, 0.54
Video-EEG Findings[2]				
Localised ictal EEG	-0.16	0.29	0.58	-0.73, 0.41
Localised interictal EEG	-0.52	0.32	**0.10**	-1.17, 0.11
Cognitive variables[2]				
Preoperative VIQ	-0.01	0.01	**0.10**	-0.03, 0.01
NART/VIQ discrepancy	-0.02	0.01	**0.06**	-0.04, 0.01
Verbal learning: trials	-0.10	0.11	0.35	-0.32, 0.11
delay	-0.06	0.10	0.53	
Visual learning: trials	-0.02	0.12	0.84	-0.26, 0.21
delay	-0.06	0.77	0.38	-0.21, 0.08
Contralateral memory weakness	0.04	0.13	0.73	-0.20, 0.29
Semantic knowledge				
Graded Naming Test score	-0.02	0.03	0.46	-0.07, 0.03
Category fluency score	-0.05	0.02	**0.05**	-0.10, 0.01
Executive functions				
Phonemic fluency score	0.01	0.02	0.67	-0.04, 0.06
Trail making B (secs)	0.01	0.01	**0.12**	-0.001, 0.01
Wisconsin Card Sorting Test (Perseveration error)	0.16	0.05	**0.001**	0.06, 0.26
Working memory (Digit Span)	-0.05	0.05	0.27	-0.16, 0.04
Spatial WM (between errors)	-0.03	0.12	0.81	-0.30, 0.20
Spatial WM (strategy)	-0.01	0.12	0.96	-0.24, 0.23
DEX-informant	0.02	0.01	**0.004**	0.01, 0.05
DEX-subject	0.04	0.01	**<0.001**	0.03, 0.07
Psychiatric variables				
Family history of psychopathology	0.45	0.27	**0.09**	-0.07, 1.00
Lifetime psychopathology	1.20	0.23	**<0.001**	0.75, 1.67
Lifetime mood/anxiety disorder	1.20	0.25	**<0.001**	0.71, 1.68
Current mood/anxiety disorder	1.16	0.32	**<0.001**	0.54, 1.80

*Univariable log-random intercept only models; therefore all values in the table (apart from p-values) are log transformed

[1]Corrected for intracranial volume

[2]For available data

Table 29. *Univariable logarithmic random intercept only models for BDI-FS, adjusting for the main effect of time.*

Variable*	Beta Coefficient (B)	Standard Error B	p-value	95% CI
Gender	-0.35	0.27	0.21	-0.89, 0.19
Age of TLE onset, yr	0.01	0.01	0.58	-0.01, 0.03
TLE duration, yr	0.003	0.009	0.68	-0.01, 0.02
TLE laterality	-0.10	0.27	0.70	-0.63, 0.43
Hippocampal volumes[1]				
Ipsilateral HC volume	0.06	0.22	0.76	-0.37, 0.51
Contralateral HC volume	-0.08	0.31	0.78	-0.70, 0.53
Pathology				
Hippocampal sclerosis vs other	-0.03	0.28	0.90	-0.57, 0.51
Video-EEG Findings[2]				
Localised ictal EEG	-0.14	0.33	0.66	-0.79, 0.50
Localised interictal EEG	-0.58	0.36	**0.10**	-1.28, 0.12
Cognitive variables[2]				
Preoperative VIQ	-0.02	0.01	**0.01**	-0.04, 0.00
NART/VIQ discrepancy	-0.03	0.01	**0.01**	-0.05, -0.01
Verbal learning: trials	-0.04	0.12	0.68	-0.28, 0.18
delay	-0.01	0.11	0.91	-0.23, 0.21
Visual learning: trials	-0.13	0.12	0.28	-0.38, 0.11
delay	-0.10	0.08	**0.20**	-0.26, 0.05
Contralateral memory weakness	-0.03	0.13	0.78	-0.29, 0.22
Semantic knowledge				
Graded Naming Test	-0.02	0.02	0.31	-0.08, 0.02
Category fluency	-0.05	0.03	**0.07**	-0.10, 0.01
Executive functions				
Phonemic fluency	0.01	0.02	0.90	-0.05, 0.05
Trail making B (secs)	0.01	0.00	**0.03**	0.00, 0.01
Wisconsin Card Sorting Test (Perseveration error)	0.05	0.05	0.33	-0.05, 0.16
Working memory (Digit Span)	-0.13	0.05	**0.01**	-0.23, -0.02
Spatial WM (between errors)	-0.12	0.11	0.28	-0.36, 0.10
Spatial WM (strategy)	-0.09	0.12	0.47	-0.32, 0.15
DEX-informant	0.01	0.01	0.37	-0.01, 0.03
DEX-subject	0.05	0.01	**<0.001**	0.03, 0.07
Psychiatric variables				
Family history of psychopathology	0.40	0.30	**0.18**	-0.18, 0.96
Lifetime psychopathology	0.72	0.27	**0.009**	0.18, 1.25
Lifetime mood/anxiety disorder	0.59	0.29	**0.04**	0.03, 1.15
Current mood/anxiety disorder	0.57	0.36	**0.12**	-0.14, 1.30

*Univariable log-random intercept only models; therefore all values in the table (apart from p-values) are log transformed

[1]Corrected for intracranial volume

[2]For available data

Table 30. *Univariable logarithmic random intercept only models for BAI, adjusting for the main effect of time.*

From the univariable step (Table 29), the following variables were entered (as single block) into the multivariable BDI-FS log-random intercept only model, based on the criteria p-value ≤ 0.20. This less conservative p-value was adopted as a Type I error rate of 5% is too conservative for predictors that may have borderline significance in a univariable model, but may be significant when controlling for *covariates* in a multivariable model (Field, 2009).

1. Localised interictal EEG
2. Preoperative VIQ
3. NART/VIQ discrepancy
4. Category fluency
5. Trail Making B
6. Wisconsin Card Sorting Test (Perseveration errors)
7. DEX-informant
8. DEX-subject
9. Family history of psychopathology
10. Lifetime psychopathology
11. Lifetime mood/anxiety disorder
12. Current mood/anxiety disorder

With the addition of the main effects of time (at 6 and 12 month BDI-FS score, relative to the preoperative score) and the intercept (B_0), 15 parameters required estimation. However, due to steep sample attrition and missing BDI-FS data postoperatively (see Figure 20), the model lacked statistical power permitting the inclusion of only 8 predictors (including the two main

effects of time and the intercept (B_0)). To avoid over-fitting/saturating the model, which increases the chance of a type I error (Field, 2009); quantitative predictors were entered into a correlation matrix (see Table 31).

There was a large degree of multicollinearity between preoperative VIQ and (1) category fluency (r_s = -0.51, p = <0.01; R_s^2 = 26%), (2) Trail making B (r_s = -0.60, p = <0.01; R_s^2 = 36%), (3) DEX-subject (r_s = -0.43, p = <0.01; R_s^2 = 18%) and (4) NART-VIQ discrepancy (r_s = 0.36, p = <0.05; R_s^2 = 23%), so preoperative VIQ was removed. DEX-S and DEX-I were positively correlated (r_s = 0.34, p = <0.05; R_s^2 = 12%), so the latter was removed from the model as more data was collected for DEX-S (n=48/49; 98%) compared to DEX-I (46/49; 94%), and there was good agreement between patient (Mean: 20, SD: 12) and informant (Mean: 20, SD:13) ratings (t(92) = 0.25, p=0.81).

Given the study aims and limited statistical power, the following predictors were selected and entered into the BDI-FS log-random intercept only multivariable model:

1. Category fluency
2. Wisconsin Card Sorting Test (perseveration error)
3. DEX-subject
4. Current mood/anxiety disorder
5. Lifetime mood/anxiety disorder

The model's residuals were checked and the assumption of normality had not been violated (see Appendix 7). Therefore, the (non-log) BDI-FS random intercept only model was selected. Predictors were considered significant at p = 0.05 (two-tailed) and results are presented in Table 32.

Spearman's Rho		Preoperative						
		VIQ	NART and VIQ discrepancy	Category fluency	TMT (B)	WCST (Perseveration errors)	DEX-I	DEX-S
Preoperative	VIQ	1.00						
	NART/VIQ discrepancy	**0.36***	1.00					
	Category fluency	**0.51****	0.22	1.00				
	TMT (B)	**-0.60****	**-0.49****	**-0.45****	1.00			
	WCST (Perseveration errors)	-0.29	0.32	-0.23	-0.60	1.00		
	DEX-I	-0.23	-0.12	-0.17	0.32	0.15	1.00	
	DEX-S	**-0.43****	**-0.29***	-0.24	0.25	0.22	**0.34***	1.00

Table 31. *Correlation matrix of quantitative variables considered for multivariable BDI-FS analysis.*

**p<0.05; **p<0.01*

Variable*	Beta Coefficient (B)	Standard Error B	p-value	95% CI
Time 1 (6 months)†	-0.18	0.76	0.81	-1.67, 1.30
Time 2 (12 months)†	-0.47	0.84	0.57	-2.14, 1.18
Cognitive variables[1]				
Category fluency	-0.08	0.07	0.23	-0.22, 0.05
WCST (Perseveration error)	0.41	0.13	**0.002**	0.15, 0.67
DEX-S	0.11	0.03	**0.001**	0.04, 0.17
Psychiatric variables				
Current mood/anxiety disorder	3.70	1.56	**0.02**	0.60, 6.73
Lifetime mood/anxiety disorder	1.61	0.95	0.09	-0.24, 3.48

*Multivariable variable random intercept only model

†Compared to preoperative BDI score

[1]For available data

Table 32. *Multivariable random intercept only model for BDI-FS, adjusting for the main effect of time.*

Multivariable Model: Predicting Change in Depressive Symptoms Following TLE Surgery

Similar to the group level results, there was a non-significant decrease in mean BDI-FS rating scores following TLE surgery compared to preoperative (baseline) levels, controlling for preoperative cognitive and psychiatric variables (random intercept only BDI-FS model at 6 months: -0.81, 95%CI: -1.67 – 1.3, p=0.81; random intercept only BDI-FS model at 12 months: -0.47, 95%CI: -2.47, 1.18, p=0.57).

The multivariable analysis indicated that two cognitive variables, WCST perseveration errors and DEX-subject ratings, were independent predictors of postoperative BDI-FS score, adjusting for time, category fluency and a current or lifetime affective (mood/anxiety) disorder. The significant beta coefficient (B: 0.41) specifies that for every preoperative WCST perseveration error, postoperative BDI-FS increases by a factor of 0.41, adjusting for time and other included covariates. Similarly, after the effects of all the other predictors are held constant, postoperative depressive morbidity increases by a factor of 0.11 per unit increase in pre-surgical patient-reported dysexecutive behaviours.

The presence of a *current* affective (depression/anxiety) diagnosis remained a strong predictor of postoperative BDI-FS, after adjusting for time and other pre-surgical factors: compared to patients without a current affective diagnosis, patients with a diagnosis had a substantial increase in post-surgical depressive symptoms (B = 3.70, 95%CI: 0.60-6.73, p=0.02). There was a similar trend for a lifetime diagnosis, but this failed to reach significance (B = 1.61, 95%CI: -0.24, 3.48, p=0.09).

Seizure Outcome: Relation to Depressive Symptoms

Twenty three patients (79%; n=23/29) were seizure free (ILAE 1) at 12 month follow-up. There was no relationship between preoperative depressive symptoms (BDI-FS) and seizure outcome (ILAE 1 vs 2-6) at 12 months (OR: 1.15, 95%CI: 0.84-1.56, p=0.38, see Figure 27 for further breakdown), or change in depressive symptoms at 12 months compared to preoperative levels (OR: 0.92, 95%CI: 0.76-1.10, p=0.34).

Cognitive Outcome: Relation to Depressive Symptoms

Small samples and limited variation precluded statistical investigation into the relation between preoperative depressive symptoms (BDI-FS) and neuropsychological outcomes at 12 month follow-up (see Appendix 9A-F). For descriptive purposes however, cognitive outcomes (memory/executive function) for those with a preoperative current diagnosis of depression (n=6) were compared to patients with no psychiatric history (n=31) are presented in Table 33.

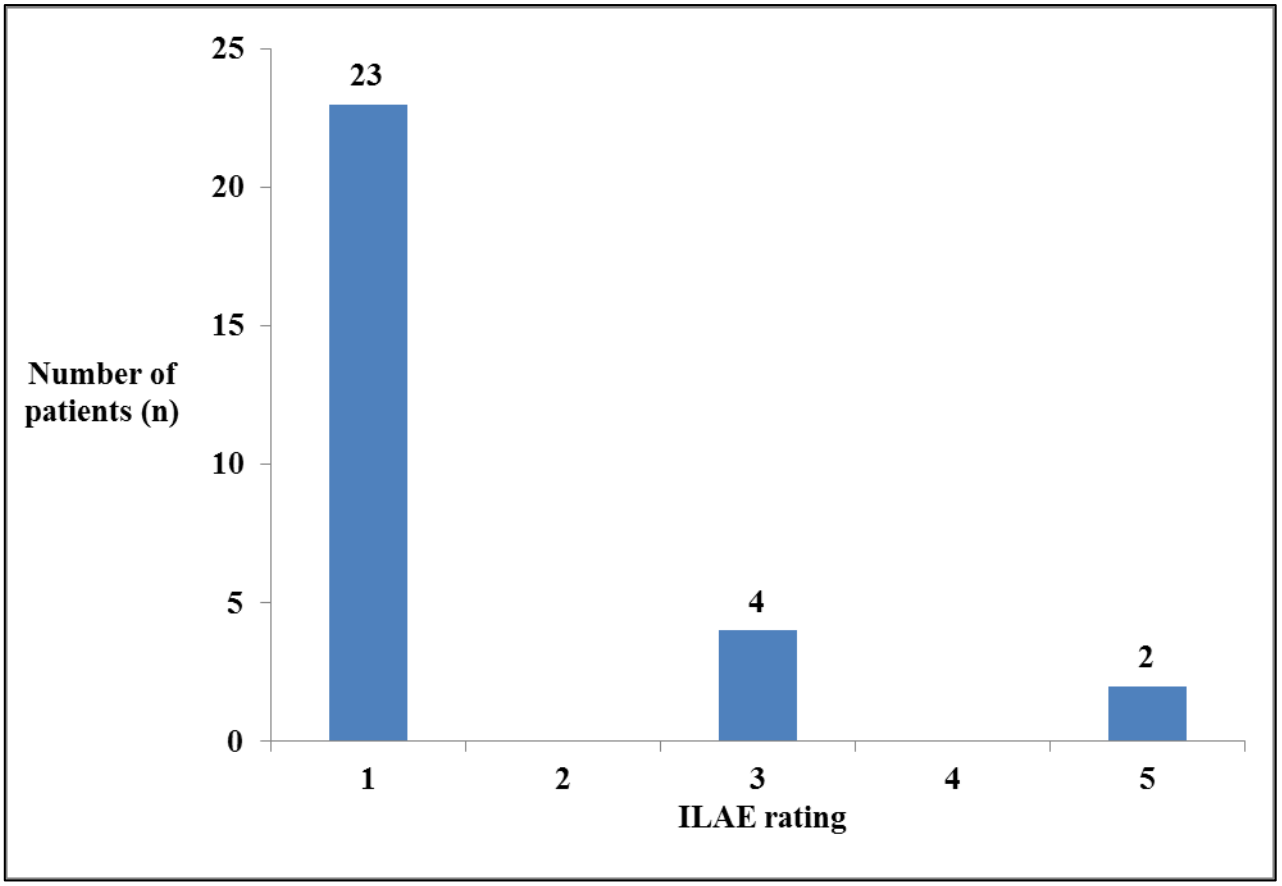

Figure 27. *ILAE rating for TLE patients (n=29) following surgery.*

Variable[1]	Preoperative current depression (n=6)	TLE-controls (n=31)
Verbal Learning	-0.14 (-1.11, 0.00)	0.12 (-0.64, n/a)
Visual Learning	-1.18 (-2.10, -1.19)	-0.25 (-1.48, 0.98)
Spatial WM (between errors)	-0.18 (-0.93, n/a)	0.05 (-0.45, 0.45)
Spatial WM (strategy score)	-0.39 (-2.20, n/a)	-0.44 (-1.32, 0.44)

[1]Median (IQR)
n/a; not applicable as sample size <3

Table 33. *Change in neuropsychological status (preop- minus postoperative) for patients with a current pre-surgical depressive diagnosis (n=6) compared to TLE patients with no psychiatric history (n=31).*

Multivariable Analyses: BAI

From the univariable step (see Table 30), the following variables were entered (as single block) into the multivariable BAI log-random intercept only model, based on the criteria p-value ≤ 0.20.

1. Localised interictal EEG
2. Preoperative VIQ
3. NART/VIQ discrepancy
4. Design learning (delay)
5. Category Fluency
6. Trails Making B
7. Digit Span
8. DEX-subject
9. Family history of psychopathology
10. Lifetime psychopathology
11. Lifetime mood/anxiety disorder
12. Current mood/anxiety disorder

Similar to the BDI multivariable analysis, with the addition of the main effects of time (at 6 and 12 months, relative to baseline) and the constant (B_0), 15 parameters required estimation. However, due to sample attrition and missing BAI data postoperatively (see Figure 20), the model lacked statistical power permitting the inclusion of only 8 predictors (including the

two main effects of time and the constant (B_0)). To avoid over-fitting/saturating the model, which increases the chance of a type I error (Field, 2009); quantitative predictors were entered into a correlation matrix (see Table 34).

There was a large degree of multicollinearity between preoperative VIQ and all other variables considered, so the former was removed (see Table 34). Given the aims of the study and limited statistical power, the following predictors from the correlation matrix were selected and entered into a multivariable model:

1. Trails making B
2. Digit Span
3. DEX-subject
4. Lifetime mood/anxiety disorder
5. Current mood/anxiety disorder

The model's residuals were checked and the assumption of normality had not been violated (see Appendix 8). Therefore, the (non-log) BAI random intercept only model was selected. Predictors were considered significant at $p = 0.05$ (two-tailed) and results are presented in Table 35.

Spearman's Rho		Preoperative						
		VIQ	NART & VIQ discrepancy	Design learning (delay)	Category fluency	TMT (B)	Digit span	DEX-S
Preoperative	VIQ	1.00						
	NART/VIQ discrepancy	**0.36***	1.00					
	Design learning (delay)	**0.41****	0.26	1.00				
	Category fluency	**0.51****	0.22	0.26	1.00			
	TMT (B)	**-0.60****	**-0.49****	-0.21	**-0.45****	1.00		
	Digit span	**0.68****	**0.34***	**-0.38****	**-0.49****	**-0.63****	1.00	
	DEX-S	**-0.43****	**-0.29***	-0.17	-0.24	0.25	-0.16	1.00

Table 34. *Correlation matrix of quantitative variables considered for multivariable BAI analysis.*

**p<0.05; **p<0.01*

Variable*	Beta Coefficient (B)	Standard Error B	p-value	95% CI
Time 1 (6 months)†	-3.73	1.19	**<0.001**	-6.06, -1.39
Time 2 (12 months)†	-3.91	1.40	**<0.001**	-6.64, -1.18
Cognitive variables[1]				
TMT B	0.07	0.03	0.18	0.10, 0.13
Digit span	0.26	0.46	0.94	-0.64, 1.15
DEX-S	0.23	0.06	**0.01**	0.10, 0.36
Psychiatric variables				
Lifetime mood/anxiety disorder	-1.32	3.14	0.47	-7.50, 4.83
Current mood/anxiety disorder	-1.16	2.41	0.39	-5.90, 3.56

*Multivariable variable random intercept only model

†Compared to preoperative BAI score

[1]For available data

Table 35. *Multivariable random intercept only model for BAI, adjusting for the main effect of time.*

Multivariable Model: Predicting Change in Anxiety Symptoms Following TLE Surgery

Replicating the group level results, there was a significant decrease in mean BAI rating scores following TLE surgery compared to preoperative (baseline) levels, controlling for preoperative cognitive and psychiatric variables (random intercept only BAI model at 6 months: -3.73, 95%CI: -6.06 – -1.39, $p<0.001$; random intercept only BAI model at 12 months: -3.91, 95%CI: -6.64 – -1.18, $p<0.001$). The small degree of change (-0.18) in the beta coefficients between six (B: -3.73) and twelve (B: -3.91) months suggests that there is a significant reduction in mean BAI rating at 6 months, but no *additional* reduction from 6- to 12 month follow-up. To investigate this further, the reference (baseline) category in the multivariable BAI model was changed from the preoperative mean BAI score to the mean BAI score at 6 months, and the model was re-run. As suspected, the mean preoperative BAI level was significantly higher (+3.73 points) relative to the 6 month BAI score (B: 3.73, 95%CI: 1.39 - 6.06, $p=0.002$); but this was not the case for the mean BAI score at 12 months (B: -0.18, 95%CI: -3.00, 2.62, $p=0.90$).

The multivariable analysis also indicated that the rate of change (decrease) in mean BAI score over time is significantly reduced in the context of preoperative dysexecutive behaviours, after adjusting for other cognitive (digit span, trail making B) and psychiatric variables (B: 0.23, 95%CI: 0.10, 0.36, $p=0.01$). None of the other variables included significantly predicted self-reported anxiety symptoms following TLE surgery.

Seizure Outcome: Relation to Anxiety Symptoms

There was no relationship between preoperative anxiety symptoms (BAI) and seizure outcome (ILAE 1 vs 2-6) at 12 months (OR: 1.04, 95%CI: 0.91-1.20, p=0.57, see Figure 27 for further breakdown), or change in BAI at 12 months compared to preoperative levels (OR: 0.84, 95%CI: 0.66-1.60, p=0.14).

12.5 Discussion

The findings are consistent with previous reports that patients with TLE are affected by psychiatric problems pre- and postoperatively, particularly affective disturbance (Gaitatzis, et al., 2004; Swinkels et al., 2005; Wrench et al., 2011). Although anxiety, and to a lesser extent depressive symptoms, improved following TLE surgery; the *magnitude* of this improvement was significantly moderated by preoperative extra-temporal lobe dysfunction, as predicted (i.e. patients with increasing preoperative dysexecutive dysfunction had worsening depressive and anxiety symptoms following surgery). Support for the hypothesis that an affective disorder at the time of surgery is predictive of postoperative depressive morbidity was confirmed (Malmgren et al., 2002; Quigg et al., 2003; Devinsky et al., 2005; Pintor et al., 2007; Wrench et al., 2011). Demographic and epilepsy-related factors had little predictive value. Contrary to expectation, preoperative psychiatric status was unrelated to seizure freedom (ILAE=1).

The current results confirm that psychopathology is a common comorbidity in TLE (Study 1; Wrench et al., 2011). Over a third of patients (n=18/49; 37%) had a psychiatric diagnosis before surgery, particularly depression (Glosser et al., 2000; Devinsky et al., 2005; Filho et

al., 2012; da Conceição et al., 2013). This finding coupled with the detrimental impact of depression on patients' quality of life (Boylan et al., 2004), and it's deleterious interaction with seizure freedom following TLE surgery (Study 1; Anhoury et al., 2000; Kanner et al., 2009; Guarnieri et al., 2009), underscore the need for a thorough pre-surgical psychiatric assessment in patients with TLE. It is also noteworthy that the prevalence rate of presurgical psychopathology in this study (37%) is higher than the general population (25%; http://www.hscic.gov.uk/pubs/psychiatricmorbidity07).

The reported rate of de novo psychopathology (n=5/31; 16%) is not dissimilar to earlier work using a psychiatric diagnostic interview pre- and postoperatively (Hellwig et al., 2012). Anxiety and depression were the most common de novo diagnoses, with all cases emerging within 6 postoperative months, and necessitating psychotropic medication (Study 1; Blumer et al., 1998; Altshuler et al., 1999; Wrench et al., 2011). Neither seizure laterality, epilepsy duration nor a family history of psychopathology predicted de novo psychiatric disturbance.

Regarding seizure lateralisation, previous studies have reported an increased risk of de novo psychopathology following right (Glosser et al., 2000) and left-sided TLE surgery (Ring et al., 1998); with others finding no laterality effect (Devinsky et al., 2005). These conflicting results suggest that other biological (e.g. concomitant frontal lobe dysfunction/extent of resection, with a less conservative approach for the non-dominant temporal lobe) and/or psychosocial factors may be important determinants of psychiatric health following TLE surgery. This hypothesis is supported by Wrench et al. (2011) who found that the 'burden of normality' symptoms (Wilson et al., 2001) and poor postoperative family dynamics were related to the development of depression following mesial TLE surgery. The significance of biological factors influencing postoperative psychiatric status is evinced by the current finding that a history of secondary generalised seizures (SGTCS), a biomarker of more

widespread cerebral pathology (Savic et al., 1997), increased the likelihood de novo psychopathology (see Study 1).

Contradicting previous findings, there was no *significant* improvement in depressive symptoms following TLE surgery (Devinsky et al., 2005; Pintor et al., 2007; Hamid et al., 2011). This may be due to methodological differences between studies. First, this study measured change in depressive symptomatology using the BDI-FS; a rating scale purposely developed to be used with patients whose medical symptoms/medication side effects may confound the interpretation of depressive disorder symptoms (Benedict et al., 2003). It is conceivable that previous studies, using the standard BDI, may have detected alterations in seizure or medication status following TLE surgery, rather than changes in depressive symptoms *per se* (Devinsky et al., 2005; Pintor et al., 2007; Hamid et al., 2011). This may explain the improvement in mood following surgery in seizure-free cohorts (Devinsky et al., 2005; Hamid et al., 2011). Second, the application of multilevel modeling afforded investigation of postoperative BDI-FS change, adjusting for patient variability in baseline (preoperative) depression levels (BDI-FS range: 0-17; see Figure 27). Furthermore, this statistical technique reduced the chance of a Type I error (i.e. erroneously concluding BDI-FS score reduces postoperatively), by accounting for the auto-correlation in residual scores produced from measuring the same subject on several occasions (Heck et al., 2010).

There was an overall improvement in anxiety symptoms following surgery, confirming previous reports (Devinsky et al., 2005; Pintor et al., 2007). Mean preoperative anxiety declined from 'mild' to 'minimal' levels after TLE surgery, with a steeper decline in the immediate postoperative period (≤ 6 months). Although unrelated to seizure control, this temporal pattern suggests that neurobiological and/or psychological factors that improve emotional well-being are active within in the early postoperative epoch (Devinsky et al.,

2005). Candidate neurobiological anxiety-protective factors include an enlarged ipsilateral amygdala volume (Halley et al., 2010) and/or the absence of pre-surgical fear auras (Kohler et al., 2001); whereas a reduced fear of seizures, improved sense of self-control and/or a positive change in family dynamics may be important psychosocial factors. Alternatively, this initial drop may be due to a placebo response (transient effect of surgery) and/or social desirability effects. These latter explanations seem unlikely however, as depressive symptoms did not follow the same postoperative trajectory, despite being collected on the same day.

A current challenge in the practice of TLE surgery is the prediction of individual psychiatric outcome (Wrench et al., 2011a). Research into possible predictors of poor post-surgical psychopathology has provided mixed results (Foong et al., 2007; Macrodimitris et al., 2011; Wrench et al., 2011a). Neuroimaging studies have linked key components of the limbic system to postoperative mood disturbance, including the OFC (Study 2; Salzberg et al., 2006), the hippocampus (Wrench et al., 2009) and the amygdala (Halley et al., 2010). To date, little research has examined whether TLE patients with evidence of widespread pre-surgical *functional* deficits are at increased psychiatric risk following surgery.

This study found that pre-surgical cognitive indices of widespread cerebral disturbance were significant predictors of poor mood outcome following TLE surgery. Increased WCST perseveration errors and self-reported dysexecutive behaviours were independently predictive of increased depressive morbidity following surgery. Multivariable analyses indicated that these factors remained significant after controlling for the effects of other confounding variables (time, category fluency and lifetime affective history). Correlational studies have demonstrated that depressed TLE patients exhibit frontal lobe dysfunction (see Study 4; Hermann et al., 1991; Paradiso et al., 2001) consistent with the unipolar depression literature

(Rogers et al., 2004). The current finding extends correlational approaches, as executive dysfunction was predictive of the *development* of depressive morbidity. This suggests that executive impairment directionally associated with mood disturbance in TLE and is not a reactive functional change. It is acknowledged however that a confounding factor not included in this study may also mediate this relationship. The mechanism responsible for frontal lobe dysfunction in TLE remains unclear (Devinsky et al., 2005). Suggestions include more widespread brain pathology, the secondary spread of epileptic activity from the epileptogenic zone impacting on frontal brain circuitry and the propagation of temporal lobe hypo-metabolism to the thalamus, secondarily affecting the frontal lobes (Hermann et al., 1988; Hermann et al., 1991; Bell et al., 2011). Indeed evidence from the developmental literature suggests that executive dysfunction is evident *before* the clinical manifestation of a seizure disorder. For example, Hesdorffer et al. (2004) found that attention deficit hyperactivity disorder (a neurobehavioural disorder characterised by marked executive dysfunction) was a risk factor for epilepsy in a paediatric population. Despite pathogenic ambiguity, this study indicates that pre-surgical executive compromise in TLE serves as a valuable predictor of post-surgical depressive morbidity.

This study also contributes to the clinical question of whether TLE patients with varying degrees of pre-surgical affective morbidity have the same risk of postoperative mood disturbance following surgery. Psychiatric assessment, in addition to patients' rating scale scores, allowed investigation into whether affective disorder refractoriness influenced psychiatric outcome. Patients with an affective disorder at the point of surgery had a greater risk of post-surgical depression than recovered affective disorder TLE patients. The mechanism by which the severity of affective disorder influences postoperative mood is uncertain. Multiple factors are likely to contribute including, duration/type of psychiatric

treatment, locus of control and self-esteem, the development of strategies to cope with challenging or adverse life events and/or degree of social support.

The lack of an association between pre-surgical depression and seizure outcome warrants consideration. Using a structured psychiatric interview, Anhoury et al. (2000) found that TLE patients with a past psychiatric history were less likely to gain seizure freedom or 90% reduction following surgery. This interaction has also been replicated by a number of others (Study 1; Kanner et al., 2009; Guarnieri et al., 2009). However, investigators using a self-report measure of depression have yielded conflicting results (Metternich et al., 2009; Lackmayer et al., 2013). An elevated BDI-FS score indicates an increased probability of having an actual depressive disorder, but is not a diagnostic measure (Jones et al., 2005). Thus, the severity of depressive morbidity (trait versus state) may play a modulatory role in the relation between depression and seizure outcome, accounting for divergent findings.

Postoperative anxiety symptoms also worsened in the context of pre-surgical executive dysfunction. Multivariable analysis confirmed that preoperative patient-reported dysexecutive behaviours significantly predicted increased post-surgical anxiety, after the effects of other predictors were held constant (time, trail making, digit span and lifetime affective history). Animal and human studies have pointed to an association between anxiety and the amygdala (Phelps et al., 2005; Damsa et al., 2008). Resection of an amygdala of normal volume as part of the resection (compared to healthy controls), has been associated with postoperative anxiety in mesial TLE patients, regardless of seizure outcome (Halley et al., 2010). Bonelli et al. (2009) reported a positive relationship in right TLE patients between preoperative ipsilateral amygdala activation on viewing fearful faces and postoperative change in anxiety levels; with greater preoperative activation being related with worsening severity of anxiety following ATLR. However, converging structural and functional

neuroimaging also indicate that the prefrontal cortex (particularly the OFC) is implicated in the pathophysiology of anxiety disorders (Milad & Rauch, 2007; Jackowski et al., 2012). These findings are supported by neuropsychological evidence of executive dysfunction in anxiety disorders (Ferreri, Lapp & Peretti, 2011). The OFC is involved in a variety of higher-order executive tasks, including: control and inhibition of inappropriate behavioural/emotional responses, decision making and maintaining behavioural flexibility. Therefore, preoperative dysexecutive behaviour may indicate prefrontal lobe dysfunction, which may predispose TLE patients to post-surgical anxiety.

There are several aspects of the study that limit interpretation and generalisability of the findings. Despite using a linear mixed-effects model that is unaffected by missing data (Gueorguieva et al., 2004), the sample size at 24 month follow-up was too small to yield meaningful clinical interpretations. Statistical power also limited the number of predictors that were included in the multivariable models, the ability to predict de novo psychiatric presentations, and the investigation of cognitive decline. It was also not feasible, given the prospective nature and limited time frame of the study, to collect data beyond a 24 month follow-up period. However, postoperative mood disturbance is usually apparent within the first year of surgery (Foong et al., 2007; Macrodimitris et al., 2011), and individual empirical growth plots indicated a linear decrease in postoperative mood ratings. Given the scarcity of neuroimaging studies investigating postoperative mood disturbance in TLE (Wrench et al., 2009); it would be interesting to examine whether preoperative executive dysfunction is associated with pre-surgical volumetric abnormalities in the prefrontal lobe.

In conclusion, this is the first longitudinal study to provide evidence that pre-surgical cognitive indices of widespread cerebral dysfunction are predictive of poor psychiatric outcome following TLE surgery. The high rate of psychopathology pre- and postoperatively

suggest that patients undergoing resective surgery, particularly those with a current affective diagnosis and/or evidence of executive dysfunction, should be counselled about this potential risk.

Chapter 13. Conclusions, limitations and future work

13.1 General Discussion

The central hypothesis formulated and examined here was that TLE patients with less localised cerebral dysfunction, as supported by electrophysiological, neuro-radiological and cognitive indicators, would be at risk for psychiatric disturbance preoperatively and have poorer outcomes following TLE surgery. The ultimate aim was to provide findings with clinical utility, particularly with respect to improving surgical decision making and prediction of potential positive and negative outcomes.

In the subsequent discussion, I present the main findings of this thesis, outline the methodological limitations (clinical and statistical), and propose future research directions.

Summary of the Main Findings

Preoperative Psychopathology

TLE patients undergoing pre-surgical evaluation had a high prevalence of psychopathology, particularly affective morbidity (Studies 1, 4 and 5; Hypothesis 1 supported). Extending previous work, it was found that preoperative psychiatric conditions were associated with a positive family psychiatric history and less focal cerebral pathology (Studies 1, 2 and 4; Hypothesis 2 supported). Evidence of less focal epileptogenicity (SGTCS) and lifetime psychopathology were independent predictors of poor post-surgical seizure outcome (Study 1; Hypothesis 3 supported). This latter finding suggests that the inclusion of neuropsychiatric

assessments in the pre-surgical evaluation may lead to an increase in the power of prognostic models to predict the neurologic outcome of TLE surgery.

Consistent with previous reports (Kanemoto et al., 1998; Kanemoto et al., 2001), a history of PIP was associated with postsurgical de novo psychopathology (Hypothesis 4 supported). However, Study 3 forms a distinct contribution to the field. Firstly, this was the first study to systematically investigate the clinical *and* cognitive risk factors associated with PIP in TLE patients, demonstrating that PIP is related to diffuse brain abnormalities. The novel finding was that the frequency of PIP *modulates* the risk of de novo psychopathology. This study may therefore, (1) aid clinical decision-making regarding early surgical intervention and (2) increase psychiatric monitoring for postoperative de novo psychiatric morbidity.

De novo Psychopathology

Following TLE surgery psychiatric symptoms developed for the first time (de novo) and pre-existing symptoms worsened (Study 1 and 5; Hypothesis 3, supported). De novo psychiatric conditions emerged early during recovery and were persistent, necessitating psychotropic medication and notably, were unrelated to seizure freedom (Study 1; Hypothesis 3, relating to seizure outcome, not supported). Predictors of de novo depression included diffuse epileptogenic networks (Study 1; Hypothesis 4, supported) and widespread pre-surgical cerebral grey matter volumetric abnormalities (Study 2; Hypothesis 4, supported).

Using a novel statistical technique, predictors of post-surgical mood change in TLE were determined (Study 5). These included evidence of pre-surgical extra-temporal lobe dysfunction, particularly frontal lobe compromise (Hypothesis 4, supported). This study also

demonstrates that the time-course of affective morbidity is asynchronous; depressive morbidity persists at 12 month follow-up, whereas anxiety abates early in the postoperative period.

Collectively, this work reinforces the recommendation that it is neither sufficient nor accurate to measure the efficacy of TLE surgery by solely examining seizure outcome (Wrench et al., 2011a).

Psychopathology and Relationship to Cognitive Function

Confirming previous reports, Study 4 found that depressed mood is significantly associated with neuropsychological dysfunction remote from the epileptogenic focus (Hermann et al., 1991; Corcoran et al., 1993; Paradiso et al., 2001; Helmstaedter et al., 2004; Hypothesis 2, supported). However, this study extends previous findings in several ways. First, temporal *and* extra-temporal cognitive function was examined. Previous studies have either limited investigation to memory function (Corcoran et al., 1993; Wishart et al., 1993; Dulay et al., 2004; Helmstaedter et al., 2004) or used a narrow neuropsychological test battery to assess depressed TLE samples (Hermann et al., 1991; Paradiso et al., 2001). The use of a large number of frontal lobe measures suggests that behavioural reports (DEX subject and informant) may be more sensitive than standard executive tests. Another novel finding was that depressed TLE patients and their informants were aware of problems with executive functions in daily life (Study 4; Hypothesis 2, supported).

This thesis is the first to examine the relationship between executive dysfunction and the *development* of affective disturbance following TLE surgery (Hypothesis 4, supported).

Study 5 provides evidence that frontal lobe compromise (DEX-S score) is a valuable predictor in the prognosis of mood deterioration following TLE surgery. This finding is also consistent with Study 2 that found a relationship between bilateral OFC atrophy and the development of de novo depression (Hypothesis 4, supported).

Collectively, these findings provide evidence for the hypothesis that executive dysfunction is a pertinent risk factor for the development of pre- and post-surgical affective morbidity (Hypothesis 4, supported). In addition, Studies 4 and 5 have provided a clinically useful questionnaire (DEX-S) that is short to administer and is sensitive to executive dysfunction in TLE. Thus, examination of this cognitive domain in the pre-surgical evaluation may lead to an increase in the power of prognostic models used to predict the psychiatric outcome of TLE surgery.

13.2 Methodological Limitations

13.2.1 Clinical

Sample

The sample used in this thesis consisted of adult patients with severe refractory TLE and were referred to a tertiary epilepsy centre for pre-surgical evaluation. This limits the generalisability of the findings to adult patients with medically refractory TLE.

Control Group

Although initial attempts were made to collect control data by assessing *pre-surgical* patients

twice (i.e. after the patient was placed on the surgical list and 6 months later, before surgery) this proved challenging. Firstly, the delay between first assessment and surgery was often too short for any possible change in psychiatric status to emerge. Secondly, those patients who remained on the 'waiting-for-surgery' list for at least 6 months were patients who had *less localised* epilepsy and required additional investigations, often in the form of intracranial electrode implantation. This would have been an inadequate control group and introduced sample bias.

The lack of a control group and the high psychiatric comorbidity in adult patients with pharmaco-resistant TLE, limits the assessment into whether TLE surgery per se is a psychiatric risk factor. Future studies comparing the psychiatric outcome of surgical TLE patients with those treated medically are warranted.

In addition, as I did not include patients with chronic neurological and/or non-neurological conditions. It is important to consider the psychiatric prevalence rates reported here within this wider context. For example, it is noteworthy that the prevalence rates of pre- (29%) and postoperative (de novo; 18%) psychopathology in the retrospective study (Chapter 7) are not hugely dissimilar to those in the general population (25%; http://www.hscic.gov.uk/pubs/psychiatricmorbidity07), or non-brain surgical cases such as organ transplant recipients (range: 25-63%; Dimartini et al., 2008). Rates however are inflated compared to chronic neurological (migrane; Rai et al., 2012) and non-neurological (Type I diabetes: 10%; Perini et al., 1996) cohorts.

Non-blinded

For the retrospective studies, the pre- and postoperative psychiatric status was known by the

investigator (RAP). This may have led to bias in categorising VEEG data. This seems unlikely however, as no significant association between 'discordant interictal EEG' and lifetime psychopathology was discerned (Studies 1 and 2). In an effort to minimise selection bias in Study 8, the sample was selected blind for neurological history, family history of seizures and psychopathology, VEEG and MRI results.

One prospective study found a significant relation between less 'localised' ictal EEG patterns and depressive morbidity (Study 4). Notably, VEEG analysis and categorisation for prospective chapters were conducted by an independent, Clinical Electro-physiologist (Dr Mary-Anne Wright) based at NHNN, blinded to pre- or postoperative psychiatric status. For future studies, the investigator should be unaware of patients' psychiatric morbidity. Where this is not possible (e.g. the patients are known to the examiner), VEEG data analysis should be repeated, preferably by a second examiner and inter-rater reliability coefficients reported.

Duration of TLE

The duration of TLE was determined from the date of diagnosis, as outlined in the medical notes, and used in statistical analyses. However, it is possible that patient's experienced seizures long before their diagnosis. In these cases, the duration of TLE recorded would have been shorter than the actual duration of seizures. To circumvent this issue, age of seizure onset was also included in uni- and multivariable analyses.

Clinical History

Clinical data obtained from medical notes often relies on historical accounts from the patient, family and/or carers, which may not always be accurate. To overcome this limitation in the

retrospective studies, strict criteria were applied for the inclusion of certain historical data. For example, a positive history of febrile convulsion was only included if there was a hospital record of the event, thereby minimising the risk of inaccurate data collection. This issue limited the inclusion of the frequency/severity of particular variables. For example, epilepsy-related factors indicative of more widespread cerebral dysfunction were not systematically quantified in patients' notes and thus, were categorised binomially (yes versus no) (Studies 1-3), potentially reducing sensitivity and statistical power

TLE Surgery Type

All patients in this thesis underwent either an en bloc anterior temporal lobe resection or a temporal lobe lesionectomy. Although this ensured a high degree of surgical homogeneity, more tailored surgical approaches for mesial TLE patients that preserve the temporal neocortex are undertaken (e.g., selective amygdalohippocampectomy, SAH). Systematic reviews concerning comparative seizure and cognitive outcomes between surgical approaches have been published (Schramm, 2008; Josephson et al., 2013). The psychiatric outcomes however, have received limited investigation (Bujarski et al., 2013). Given the aforementioned surgical approaches used in this thesis, this work cannot add or extend the literature regarding the psychiatric outcome of tailored and more selective TLE resections.

Axis II Psychopathology

As outlined in Chapter 2, personality disorders in TLE are under-researched. One patient (n=1/280; 0.4%) in the retrospective study and none of those included in the prospective study had an Axis II diagnosis. Previous research suggests that epilepsy patients with personality disorders, and organic personality traits, are at increased risk of poor psychiatric

and psychosocial outcomes (Inoue et al., 2001; Koch-Stoecker, 2002). To further explore the relation between preoperative personality traits and psychiatric outcome, studies including a personality inventory (e.g. Personality Assessment Schedule; Tyrer et al., 1979) would be needed.

Intellectual Disability

Patients with an intellectual disability (IQ < 70) were excluded from the current investigation. Behavioural/psychiatric disorders in patients with epilepsy and intellectual disability are not uncommon, but assessment can be problematic due to cognitive and/or communication deficits (Kerr et al., 2013). None of the included cognitive/psychiatric measures used in this work have been validated in this clinical population, and at present, few exist. It is acknowledged that this limits the generalisability of this work and represents an important area of on-going research (Kerr et al., 2013).

Psychosocial Variables

In Study 5, multilevel modeling was applied to investigate predictors of change in psychiatric mood ratings following surgery. The 2-level hierarchical data structure incorporated level 1 repeated-measure mood rating scores (BDI-FS/BAI) that were nested within patients at level 2. Patients however, are *themselves* nested within variant socio-economic, marital, ethnic and employment categories. Patients will vary in their subjective perception of cognitive morbidity, stigma, quality of life and expectations of surgery and perceived success. These higher-level factors may have an additional impact on postoperative mood change and may explain the current finding that change in mood ratings was not related to seizure outcome.

13.2.2 Statistical

Study design

A major limitation of the present work was the reliance on retrospective data (Studies 1-3). This served to restrict the number of extra-temporal cognitive parameters included in statistical analyses and reduced the specificity of the conclusions drawn. Although the prospective study (Study 1) attempted to address these methodological limitations; the extent to which widespread cerebral pathology predicts the development of de novo psychopathology of *diagnostic* severity (rather than change in rating scores) could not be assessed.

Furthermore, as continuous measures were not employed in the retrospective data collection statistical power to investigate the relationship between 'per unit change' of an independent variable on an outcome of interest was precluded.

Statistical Power

Although the studies included are among the largest to date investigating pre- and postoperative psychiatric morbidity in TLE (Studies 1-5), a recurrent theme throughout this work has been a lack of statistical power. For example, the suggestion that preoperative depression deleteriously impacts neuropsychological status, particularly in left-sided patients received some support (Study 4). However, only four patients were included in this group, and the study was underpowered to detect a significant effect. In addition, statistical power precluded the investigation into whether extra-temporal pre-surgical grey matter volumetric abnormalities in *right*-sided TLE patients are risk factors for de novo depression. Well-

powered prospective studies are also needed to further investigate the possible relation between pre- and postoperative psychiatric status and postsurgical cognitive change. Moreover, a small sample size inflates the range of the associated confidence interval of a statistical test. Large confidence intervals were particularly evident in Study 3 given the small numbers of PIP cases available (n=20 TLE+PIP). However, there is an inverse square root relationship between sample size and confidence interval range (Field, 2000; in order to halve a confidence interval requires a *quadruple* sample size e.g. n=80 TLE+PIP patients); this would not be feasible given a 7% incidence rate of PIP and the time restraints of the study (Kanner et al., 1996; Alper et al., 2001). A method of overcoming this restriction would be to combine data from different surgical epilepsy centres.

A linked issue regarding the small sample sizes available in this work (particularly in Studies 8, 9, 11) was the lack of power calculations or specification of an accepatble effect size.

Multiple Comparisons

The investigative nature of this work required multiple comparisons between groups to be performed, depending on the research question. In an effort to control for Type I error multivariable analyses were performed (Studies 1 and 4), a more conservative p-value employed (Study 2), or dummy variables were used (Study 3). It is acknowledged that these approaches may have reduced statistical power or increased the chance of a Type II error. Although data reduction techniques could have been employed (e.g. principle components analysis, Field, 2009), the weak inter-correlations between dysexecutive symptoms and cognitive measures of executive performance (see Table 31b) argued against this approach.

13.3 Future Research Directions

Neuroimaging:

There is a growing body of evidence that brain abnormalities in mesial TLE are not limited to the hippocampus and epileptogenic temporal lobe, but extend into several widespread areas in both hemispheres (Berg et al., 2010). This paradigm shift was prompted by neuropathological, electrocorticographic and neuroimaging evidence indicating that more extensive cerebral damage accompanies hippocampal sclerosis (Bell et al., 2011), including limbic (entorhinal/perirhinal cortices and the amygdala), subcortical (thalamus), and neocortical regions (PFC) (Cataldi, Avoli & de Villers-Sidani, 2013; Maccotta et al., 2013). Abnormalities in these brain structures/neural networks are also associated with the pathophysiology of primary mood disorders (Drevets, Price & Furey, 2008).

Recently developed brain-imaging techniques (fMRI analysis of resting state connectivity) have shown that the PFC is part of a larger "default system" of cortical areas that include the dorsal PFC, mid- and posterior cingulate cortex, anterior temporal pole, and entorhinal and parahippocampal cortex, which has been implicated in self-referential functions (Whitfield-Gabrieli & Ford, 2012). Available evidence suggests the default mode network (DMN; Raichle et al., 2001; Raichle & Snyder, 2007) is adversely affected in neuropsychiatric conditions (Buckner et al., 2008; Broyd et al., 2009; Anticevic et al., 2012) *and* TLE (Danielson et al., 2011; Cataldi et al., 2013, for reviews).

Preliminary evidence suggests that DMN dysfunction may provide a unifying biological model in explaining the genesis psychiatric comorbidity in TLE. For example, fMRI

connectivity analysis has shown that treatment-naive TLE patients with depressive symptoms had significantly *reduced* functional connectivity between the anterior PFC, the limbic system and the temporal cortex compared to non-depressed mTLE patients and healthy controls (Chen et al., 2012). This prefrontal-limbic system 'disconnection' may manifest in increased dysexecutive behaviours in pre- and postoperative depressed TLE patients, as found in this thesis (Studies 4 and 5). Thus, a dysfunctional distributed *network* (e.g. DMN) may provide a complimentary rather than contradictory account for the widespread, anatomically distinct regions (hippocampus, amygdala, OFC) implicated in the development and maintenance of psychopathology in TLE. This hypothesis, however, remains speculative and requires clinical studies designed to directly assess the correlation between the severity of psychopathology in TLE and resting state network impairment.

Data on the Psychological Therapies for Psychopathology in TLE:

Despite promising pilot work in children with epilepsy (Bocher et al., 2013), the efficacy, adaptability, and feasibility of psychological therapies (e.g. cognitive behavioural therapy, CBT) in adult TLE cohorts is lacking (Charyton et al., 2010). This is surprising given the large evidence base for non-pharmacological treatment in primary depressive and anxiety disorders (NICE, 2009 NICE, 2011, respectively). Of the few studies in this area, there is an emphasis on studying the influence of CBT interventions on reducing seizure severity or frequency (Spector et al., 1999; Reiter & Andrews 2000) rather than on reducing comorbid psychiatric symptoms. More recently, a pilot study (n=18) assessed change in depression and anxiety symptoms using group CBT for adult patients with epilepsy (Macrodimitris et al., 2011). There were significant improvements in depression and anxiety scores, and negative automatic thoughts. Despite the limitations of this study (e.g. small, heterogenoues sample size, psychiatric *diagnostic* interview was not performed, limited follow-up and no control

group, or inclusion of seizure frequency, which may have confounded the results), these results suggest further investigation of CBT tehniques for the amelioration of psychiatric morbidity is warranted. Thus, the recent funding of a randomised control trial assessing the benefits of antidepressant treatment or CBT on mood, function and QOL in patients with refractory epilepsy and MDD is welcomed (http://clinicaltrials.gov/show/NCT00026637?displayxml=true).

Randomised controlled trials/meta-analyses:

There is still a need for randomised controlled trials into the psychiatric outcome treatment options for refractory TLE patients. Although this may prove ethically unfeasible, given the possible increased risk of mortality and severe disability due to unremitting seizure activity in 'waiting-for-surgery' group, it remains a shortcoming in the literature.

Owing to the limited studies into the psychiatric outcome of TLE surgery (sees Chapter 2), meta-analytic studies have not been sufficiently powered to identify consistent predictors of patients at high risk of postoperative (including de novo) psychopathology following TLE surgery.

APPENDICES

Appendix 1. Structural studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Tebartz van Elst et al. (1999). Prospective; controlled	MRI GE Signa Horizon 1.5T; 1.5mm **ROI:** Y (amygdala were manually segemented) **Whole brain correction:** Y	48: **24 TLE+I.E.D** (6/24 also had dysthymia) Age: 30.1 [18-49] yrs **24 TLE-I.E.D** (5/24 also had dythymia) Age: 33.8 [19-56] yrs **Controls:** 20 HC Age: 36.5 [22-58] yrs	**Duration, yrs:** **TLE+I.E.D:** 22.4 [5-45] **TLE-I.E.D:** 24.5 [7-46] **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** DSM-IV BDI-13 STAI SDAS-21 **Syptom type:** - **Pharmacological intervention:** None	-	**TLE+I.E.D:** HS: 33% Other: 29% None: 67% Amyg. Atrophy: 21% **TLE-I.E.D:** HS: 79% Other: 0% None: Unclear Amyg. Atrophy: 4%
Quiske et al. (2000). Prospective; uncontrolled	MRI (no further details)	60 TLE (31 L:29 R): **43 MTS** Age: 37 ± 10 yrs; **17 NTL** Age: 36 ± 10 yrs **Controls:** -	**Duration, yrs:** **MTS:** 10.51 ± 10.44 **NTL:** 20.71 ± 6.26 **Onset, yrs:** **MTS:** 10.51 ± 10.44 **NTL:** 20.71 ± 6.26	**Onset:** - **Duration:** - **Assessment:** BDI **Syptom type:** - **Pharmacological intervention:** -	-	**MTS:** HS: 100% **NTL:** CAV: 41% Post-trauma: 18% Tumor: 23% Hamartia: 18%
Baxendale et al. (2005).* Retrospective; uncontrolled	MRI GE Signa 1.5T; 1.5mm	87 TLE: **31 RHS** Age: 37 ± 9.4 **56 LHS** Age: 33.9 ± 10 **Controls:** -	**Duration, yrs:** - **Onset, yrs:** **RHS:** 13.3 ± 11.6 **LHS:** 10.8 ± 8.9	**Onset:** - **Duration:** - **Assessment:** HADS **Syptom type:** - **Pharmacological intervention:** -	-	HS: 100%
Richardson et al. (2007).* Retrospective; uncontrolled	MRI & FDG-PET GE Signa 1.5T; 1.5mm **ROI:** (Hippocampi & amygd.) **Whole brain correction:** Y	18 TLE: Age: 34.5 ± 13.2 **Controls:** -	**Duration, yrs:** 20.9 ± 14.7 **Onset, yrs:** 13.7 ± 8.1	**Onset:** - **Duration:** - **Assessment:** BDI **Syptom type:** - **Pharmacological intervention:** -	-	-

Appendix 1. Structural studies: Mood disorders in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Tebartz van Elst et al. (1999). Prospective; controlled	-	-	Non-surgical study	1. No sig. differences in amyg. volumes between patient groups (TLE+I.E.D vs TLE-I.E.D) 2. Sig. bilateral amyg. enlargement in pts with dysthymia compared to patient & HC; controlling for I.E.D & gender did not change the results 3. No correlation between amgd. volumes & SDAS/STAI 4. Sig positive correlation between L & R amygd. volume & BDI
Quiske et al. (2000). Prospective; uncontrolled	-	**Verbal IQ:** MTS: 99.84 ± 12.99 NTL: 105.53 ± 13.01	Non-surgical study	1. Sig. ↑ BDI score for MTS compared to NTL pts 2. No sig. laterality effect 3. No sig. interaction between laterality & 'affected structure' (MTS vs NTL)
Baxendale et al. (2005).* Retrospective; uncontrolled	-	**VIQ:** RHS: 89.3 ± 11.6 LHS: 90.7 ± 12.8 **PIQ:** RHS: 90.6 ± 13.5 LHS: 92.6 ± 15.6	Non-surgical study	1. No sig. difference in HADS between the groups 2. RHS group: HADS was positively correlated with greater degree of hippocampal symmetry (i.e. *smaller* L hippocampal volume) 3. No sig. correlations between hippocampal symmetry & HADS in the LHS group
Richardson et al. (2007).* Retrospective; uncontrolled	-	-	Non-surgical study	1. R & L amyg. volumes were postiviely associated with BDI scores 2. No sig correlation between BDI score and hippocampal volumes 3. Non sig. correlation between resting PET states & BDI score for hippocampus/amyg.

Appendix 1. Structural studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Gilliam et al. (2007). Prospective; uncontrolled	MRI spectroscopy (^{1}H-MRSI) 4.1T **ROI:** Y (Hippocampi)	31 TLE: Age: 35.4 ± 10.8 yrs **Controls:** -	**Duration, yrs:** - **Onset, yrs:** 15 ± 12 yrs	**Onset:** 15 ± 12 yrs **Duration:** - **Assessment:** QOLIE-89; POMS **Syptom type:** - **Pharmacological intervention:** -	-	-
Briellman et al. (2007).* Retrospective; controlled	MRI GE LX Horizon 3T; 1.5mm **ROI:** (Hippocampi & amygd.) **Whole brain correction:** Y	34 TLE+HS: **15 TLE+MDD:** Age: 42 ± 10 yrs **19 TLE only:** Age: 35 ± 10 yrs **Controls:** 55	**Duration, yrs:** **TLE+MDD:** 31 ± 17 **TLE only:** 21 ± 12 **Onset, yrs:** **TLE+ MDD:** 10 ± 12 **TLE only:** 14 ± 12	**Onset:** - **Duration:** (authors specify that the majority of pts had ≥1 depressive episode) **Assessment:** Austin CEP Interview (DSM-IV validated) **Syptom type:** **TLE+ MDD:** 5 (33%) had a current diagn. of MDD **Pharmacological intervention:** **TLE+ MDD:** 9 (60%) were on antidepressants	-	**TLE+ MDD:** HS: 15 (100%) **TLE only:** HS: 19 (100%)

Appendix 1. Structural studies: Mood disorders in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Gilliam et al. (2007). Prospective; uncontrolled	-	-	Non-surgical study	1. Sig. positive correlation between extent of ^{1}H-MRSI abnormality & POMS depression scale score. Other clinical factors (TLE duration/ work, driving, social scale/ GTC or CPS sz rate/gender/No. of AEDs) were unrelated to depression score
Briellman et al. (2007).* Retrospective; controlled	-	-	Non-surgical study	1. TLE+MDD pts had a sig. longer TLE duration (on average, 10 yrs) 2. TLE+MDD pts had sig. fewer antecedent events compared to TLE only pts 3. No sig. difference in hippocampal/amgdalal volumes between MDD and non-MDD TLE pts 4. Preserved T_2 relaxometry in the contralateral amygdala in TLE+MDD compared to TLE-only pts

Appendix 1. Structural studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Adams et al. (2008). Retrospective; EP-controls	MRI 1.5T	312: **212 MTS** Age: 37 yrs **TLE (other lesions)** Age: 35.5 yrs **TLE (non-lesional)** Age: 36.8 yrs **ETLE (lesional)** Age: 37.7 yrs **ETLE (non-lesional)** Age: 34.5 yrs **Controls:** -	**Duration, yrs:** - **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** DSM-IV *(not all pts had neuropsychiatric assessment)* **Syptom type:** **Lifetime diagn.** **MTS** Depression: 26.4% Psychosis: 8.3% **TLE (other lesions)** Depression: 27.6% Psychosis: 8.6% **TLE (non-lesional)** Depression: 41.9% Psychosis: 5.4% **ETLE (lesional)** Depression: 35.7% Psychosis: 8.6% **ETLE (non-lesional)** Depression: 41.2% Psychosis: 4.8% **Pharmacological intervention:** -	-	-

Appendix 1. Structural studies: Mood disorders in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Adams et al. (2008). Retrospective; EP-controls	-	-	Non-surgical study	1. No sig. difference between the prevalence of any psychiatric disorder (depression/psychosis) & TLE vs ETLE 2. Pts with non-lesional EP (both TLE & ETLE) had sig. higher prevalence of psychiatric disorders (69.2%) than those with lesional EP (inc. TLE & ETLE pts) (52.9%) 3. No sig. differences in the prevalence of *any* psychiatric disorder & pts with TLE vs ETLE 4. In multivariable analyses, the odds of any psychiatric diagn. were 2.4 times *higher* for pts with *non-lesional* focal EP vs lesional EP (MTS & other lesions); although this was due to pts with a lifetime diag. of depression 5. The laterality of the seizure foci (R/L/bilateral) were not sig. predictors of psychopathology 6. No sig. difference between the lifetime prevalence of depression between TLE (31.2%) & ETLE (37.9%) pts 7. Pts with non-lesional EP exhibited higher prevalence of depression (41.6%) compared to those with lesional EP (28.5%) 8. Lifetime psychiatric diag. was not predicted by MTS or another lesion 9. Multivariable analyses indicated that a lifetime diag. of depression was only sig. predicted by *non-lesional* EP. The odds of a lifetime diagnosis of depression was almost double (OR: 1.96, 95%CI: 1.16-3.31, p=.01) for pts with non-lesional vs lesional EP 10. Lifetime diag. of depression was not predicted by MTS or another lesion 11. The laterality of the seizure foci (R/L/bilateral) were not sig. predictors of depression 12. There were no sig. relationships between any of the EP variables & a history of psychosis 13. Similarly, logistic regression did not find any sig. EP variables (laterality/TLE vs ETLE/lesional vs non-lesional/pathology type) predicted psychosis

Appendix 1. Structural studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Paparrigopoulos et al. (2008). Retrospective; uncontrolled	MRI GE Sigma 1.5T; 1.5mm **ROI:** Y (Hippocampi & amygd.) **Whole brain correction:** Y	35 TLE **Controls:** -	**Duration, yrs:** 21.1 ± 9.1 **Onset, yrs:** 10.8 ± 7.7	**Onset:** - **Duration:** - **Assessment:** BDI & BAI (only postop scores detailed) **Syptom type:** - **Pharmacological intervention:** -	-	Mixed (no further details)
Wrench et al. (2009).* Prospective; controlled	MRI Siemens Magnetom/ Signa Echospeed Superconducting Imaging System 1.5T; 0.5x1x0.5 **Whole brain correction:** Y	42 TLE: **26 MTR** (23 ATLR & 3 PHG LesX) Age: 36 ± 11.9 yrs **16 non-MTR** (6 NTLRx/8 FLRx/ 2 OLRx) Age: 33 ± 9.8 yrs **Controls:** 41 Age: 35 ± 12.9 yrs	**Duration, yrs:** - **Onset, yrs:** **MTR:** 15.31 ± 11.9 **non-MTR:** 15.5 ± 11.2	**Onset:** - **Duration:** - **Assessment:** Austin CEP Interview (DSM-IV validated); BDI-II **Syptom type:** **Depression *(diagnosed during surgical evaluation):*** MTR: 46% non-MTR: 38% **Pharmacological intervention:** -	-	**MTR:** MTS: 77% Other: 23% **non-MTR:** MTS: 0% Other: 100%

Appendix 1. Structural studies: Mood disorders in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Paparrigopoulos et al. (2008). Retrospective; uncontrolled	-	-	BDI: 6.1 ± 5.2 BAI: 5.2 ± 6.4 20 (57%) were sz free; mean F/U period unknown (range: 6m-14yrs postop)	1. BDI scores sig correlated with intact HV & absolute difference difference between the intact & remnant HV for L sided TLE pts (trend for R-sided) 2. BDI & BAI postop scores were not related to age, age at surgery, onset/duration of EP 3. Depressed pts (BDI >10) had smaller remnant AV 4. BAI was negatively associated with the HV remnant in left-sided resections 5. No sig laterality effect in BDI or BAI
Wrench et al. (2009).* Prospective; controlled	-	-	**Depression: pre/postop:** MTR: 46-42% non-MTR: 38-19% **De novo depression:** MTR: 15% non-MTR: 0%	1. History of febrile convulsions sig. more common in MTR group 2. Non-MTR group had sig. more frequent szs 3. Main effect of group & depression postop (MTR 42% vs non-MTR 19%) 4. No laterality effect for either group 5. No relationship between L/R hippocampal volumes and preop depression for either group **MTR group:** 1. No main effect of ipsilateral hippocampal volume/sz outcome; no interaction effects between depression & seizure outcome 2. Main effect of *contralateral* hippo-campus & postop depression 3. No main effect of contralateral hippocampal volume and seizure outcome 4. Trend (p=.06) between sz outcome, postop depression & contralateral hippocampal volume **De novo depression:** 1. MTR group (15%) had sig. *smaller* contralateral hippocampal volume than those MTR pts without de novo depression **non-MTR group:** 1. No sig. difference in contra- or ipsilateral hippocampal volumes and postop depression 2. No sig. relationship between sz outcome and hippocampal volume; no interaction effects

Appendix 1. Structural studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Shamim et al. (2009).* Prospective; uncontrolled	MRI GE Sigma 1.5mm **ROI:** Manual tracing of the hippocampi	55 TLE: Age: 35 [18-62] yrs (27 LTLE; 23 RTLE; 5 bitemporal EP) **Controls:** -	**Duration, yrs:** - **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** BDI: 51 pts SCID: 34 pts **Syptom type:** **Depression** **Lifetime diagn. of depression:** RTLE: 6 pts (43%) LTLE: 8 pts (40%) BDI & SCID: 31 pts **Pharmacological intervention:** At the time of study, no pts were on antidepressant therapy, although they may have been exposed previously	-	-
Salgado et al. (2010). Prospective; controlled	VBM Elscint Prestige 2T **Customised templates:** Y **Modulation:** Y **IGK:** 8mm **ROI:** N **Whole brain correction:** Y	48 MTLE: Age: 39.18 ± 8.4 **Controls:** 96 Age: 37.11 ± 8.9	**Duration, yrs:** 27.8 ± 10.4 **Onset, yrs:** 9.7 ± 7.6	**Onset:** - **Duration:** - **Assessment:** DSM-VI; SCID-I; BDI **Syptom type:** 24/48 (50%) MTLE pts had depression at the point of scanning **Pharmacological intervention:** 1/24 pt: anti-depressant therapy	-	-

Appendix 1. Structural studies: Mood disorders in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Shamim et al. (2009).* Prospective; uncontrolled	-	-	Non-surgical study	1. Across the patient sample, pts with depression in SCID/BDI did not differ in hippocampi volume from pts without a history of BDI score of depression 2. No laterality effect of seizure focus & BDI depression score/SCID 3. No relationship between L & R depression scores on BDI & hippocampi volumes 4. Severity of depression (BDI scores) did not show a relation to hippo-campi volumes 5. RTLE depressed pts on SCID had Sig. lower L hippocampus volumes compared to non-depressed RTLE pts 6. Pts with MTS on qualitative reading did not have higher BDI/ frequency of SCID diagnoses of depression
Salgado et al. (2010). Prospective; controlled	-	-	Non-surgical study	1. No sig. differences MTLE onset/ duration/frequency of szs between pts with & without depression 2. No laterality effect of pathology between groups 3. The L MTLE group had sig. more severe BDI depression scores compared to the R MTLE group 4. In MTLE + depression group, there was no corrrelation between BDI scores and GMV ***Compared to HC group only:*** MTLE pts with depression had **bilateral**↓GMV volumes: hippocampus, parahippocampal gyrus, uncus, inferior & superior temporal gyrus. **Unilateral** GMV reductions: L thalamus, L postcentral gyrus, L occipital gyrus & L fusiform gyrus & R caudate body.

Appendix 1. Structural studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Finegersh et al. (2011). Retrospective; uncontrolled	MRI (RAM) GE & Phillips Achieva 1.5T=n 38; 3T=n 2	40 TLE: Age: 34 [16-56] yrs (all unilateral cases; 23 L: 17 R) **Controls:** -	**Duration, yrs:** 20 ± 15.5 **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** BDI-II ≥ 14 = depression **Syptom type:** **BDI ≥ 14:** 11 (28%) pts **Pharmacological intervention:** No pts were on antidepressant therapy at the point of scanning; although some cases were previously exposed	-	**BDI ≥ 14:** MTS: 8/11 (72%) **BDI ≤ 14:** MTS: 13/29 (45%)

Appendix 1. Structural studies: Mood disorders in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Finegersh et al. (2011). Retrospective; uncontrolled	-	-	Non-surgical study	1. Pt age and EP duration were both negative associated with IHC, but not CHC volumes 2. No sig. correlations between BDI categories & IHC/CHC 3. Pts with a FC history were sig. older, had a longer EP duration, smaller IHC & more frequently had MTS (compared to pts with an afebrile history) 4. Pts with a history of FC had atrophy in regions CA1 & CA3 subfields in the CHC compared to pts without a history of FC (after controlling for EP duration, gender, seizure focus & BDI score). Notably, FC positive pts did not have IHC atrophy 5. Pts with a BDI $\geq$ 14 had atrophy in the superoanterior portion of the CHC, compared to pts with a BDI score of $\leq$ 14 (after controlling for FC, EP duration, gender & seizure focus) 6. No sig. relationship between BDI categories & seizure laterality

Appendix 1. Structural studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Sanchez-Gistau et al. (2012). Retrospective; non-MTS lesional & non-lesional pt controls	MRI	308: **115 Lesional MTS:** Age: 35.36 ± 11.95 yrs **106 Lesional non-MTS:** Age: 35.44 ± 11.96 yrs **87 Nonlesional:** Age: 35.24 ± 12.3 yrs **Controls:** -	**Duration, yrs:** - **Onset, yrs:** **Lesional MTS:** 23.6 ± 12.1 **Lesional non-MTS:** 22.09 ± 12.86 **Nonlesional:** 19.89 ± 12.09	**Onset:** - **Duration:** - **Assessment:** DSM-IV (SCID-I); HADS **Syptom type:** **HAD-A/HAD-D** ***(within the last 12 m):*** **Lesional MTS:** 7.65/11.71 **Lesional non-MTS:** 6.9/12.3 **Nonlesional:** 5.87/10.91 **Pharmacological intervention:** **Total group:** Any: 19% Antidepressants: 13% **Lesional MTS:** Any: 22% Antidepressants: 13% **Lesional non-MTS:** Any: 19% Antidepressants: 14% **Nonlesional:** Any: 17% Antidepressants: 12%	-	-
Butler et al. (2012). Prospective; controlled	MRI GE EXCITE 1.5T **IGK:** 15mm **Whole brain correction:** Y	36 MTLE: Mean age: 37 yrs (22 L: 12 R: 2 bilateral) **Controls:** 45 Mean age: 40 yrs	**Duration, yrs:** - **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** BDI-II **Syptom type:** - **Pharmacological intervention:** -	-	-

Appendix 1. Structural studies: Mood disorders in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Sanchez-Gistau et al. (2012). Retrospective; non-MTS lesional & non-lesional pt controls	-	-	Non-surgical study	1. 107 (35%) had a lifetime diagn. of MDD 2. 66 (21%) had a MDD in the previous yr prior to psychiatric evaluation 3. Multivariate analysis revealed that MTS (as well as female gender, primary education, anxiety comorbidity & antidepressant therapy) were independent predictors of lifetime MDD (MTS vs non-MTS: OR: 2.46, 95%CI 1.28-4.73, P=.006) after controlling for age/occupation/ duration of EP/sz freq/lateralisation). 4. The predictive value of the model (i.e. the degree of lifetime MDD variance explained by the predictors) = 83.1% 5. Multivariate analysis identified that being married (vs. single/widow/divorced) was a sig. protective factor against lifetime MDD 6. No sig. differences between lesional (=MTS & lesional non-MTS) & nonlesional groups in lifetime/current prevalence of mental health difficulties 7. No sig. differences in HADS scores across the groups 8. No effect of laterlity on lifetime prevalence of MDD
Butler et al. (2012). Prospective; controlled	-	-	Non-surgical study	1. TLE pts were sig. more depressed than HCs 2. There was no sig. effect of laterality of TLE & BDI score **Between group analysis:** BDI-thickness corelation diferred significantly between pts and HCs in the bilateral OFC: the correlation was positive in TLE pts & negative in HCs

Appendix 1. Functional studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Number of controls (n)	Epilepsy details	Epilepsy Onset, yrs	Psychiatric details	EEG
Bromfield et al. (1992). Prospective; controlled	PET (Neuropet); ^{18}F-2-deoxyglucose **Targets/ROI:** ILT; IMT; IF; MT; TH; HCaud; MF; ST; SF **Whole brain correction:** Y (ROI/CMR-glc)	23 CPS (10L:8R:5bilateral) Age: 30.5 ± 7.6 yrs **Controls:** 26 Age: 32.8 ± 7.6 yrs		**Duration, yrs:** **L-sided only:** BDI > 10: 25 yrs BDI < 10: 22.2 yrs **Onset, yrs:** -		**Onset:** 5 (22%) pts had a history of MDD **Duration:** 3/5 L-sided pts with BDI > 10, completed BDI within 1 day of scanning **Assessment:** SADS (present/ lifetime affective symptoms); BDI = 61% assessed on day of scan **Symptom type:** **L-sided only:** BDI > 10: 5 pts BDI < 10: 5 pts **Pharmacological intervention:** -	-
Victoroff et al. (1994). Prospective; uncontrolled	PET; ^{18}FDG (370 MBq) **ROI:** N; visual inspections of scans	53 CPS (Age: 30.1 yrs) **Controls:** -	-	**Duration, yrs:** - **Onset, yrs:** -	-	**Onset:** - **Duration:** - **Assessment:** DSM-III (SCID-P); Ham-D **Symptom type:** **Ham: D (whole group):** 6.1 ± 4.4 **Pharmacological intervention:** -	**Ictal:** L: 38% R: 40%

Appendix 1. Functional studies: Mood disorders in epilepsy, continued

Study	Pathology	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Ictal	Interictal	Findings
					Blood flow/glucose metabolism	Blood flow/glucose metabolism	
Bromfield et al. (1992). Prospective; controlled	-	-	-	Non-surgical study	-	1. Pts with BDI > 10 (all L-sided) had sig reduced IF glucose metabolism compared to nondepressed pts & controls 2. Nondepressed pts did not differ from controls	1. No sig. differences in age/gender between R-/ L-sided pts or controls 2. No R-sided pt scored in the depressed range (BDI > 10) (i.e. sig. laterality effect) 3. L-sided pts with depressive symtoms (BDI > 10) exhibited reduced cerebral glucose metabolism in the IF bilaterally
Victoroff et al. (1994). Prospective; uncontrolled	-	-	-	Non-surgical study	-	-	1. 33 (62%) had a lifetime history of ≥1 interictal depressive disorder 2. No sig association between depressive episodes and age/gender/age of sz onset 3. No sig association between Ham-D rating & laterality of ictal onset/ hypometabolism **Univariable analysis:** 1. Sig association between a history of MDDs & L TL hypometabolism **Multivariable analysis:** 1. After adjusting for sex/L TL ictal onset/ degree of hypometabolism, there was a non-sig trend between L TL hypometabolism & MDDs 3. The *combination* of L TL hypometabolism & 'high-degree' hypometabolism was sig associated with a history of MDD

Appendix 1. Functional studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Number of controls (n)	Epilepsy details	Epilepsy Onset, yrs	Psychiatric details	EEG
Schimitz et al. (1997). Prospective; uncontrolled	SPECT (GE neurocam); ^{99M}Tc-HMPAO (av. dose: 606 MBq). **Targets/ROI:** fronto-temporal; basal ganglia; TL 1.5T; 9mm **IGK:** Y (4 cm^2)	31 (18R:13L) focal EP: Age: 29.1 ± 9.2 yrs **Controls:** -		**Duration, yrs:** - **Onset, yrs:** 10.6 ± 6.9		**Onset:** Some pts = previous episodes of psychopathology; no further details **Duration:** - **Assessment: Conducted on the day of scanning:** BDI; LOI; BFQ; SSSI **Symptom type: BDI:** R-focal EP: 12.6 ± 19.7 L-focal EP: 8.3 ± 4.9 **LOI:** R-focal EP: 25.6 ± 13.4 L-focal EP: 18.5 ± 5.8 **SSSI:** R-focal EP: 1.5 ± 2.5 L-focal EP: 0.5 ± 0.3 **Pharmacological intervention:** Nil	-
Ring et al. (1999). Prospective; controlled	SPECT (GE neurocam); ^{99M}Tc-HMPAO (av. dose 500 MBq). **Targets/ROI:** FL; PL; TL; caudate; TH; cerebellum **Customised templates:** Y	19 TLE (6R: 13L) **9 TLE+DEP:** Age: 33 ± 7.1 yrs **10 TLE-only:** Age: 31 ± 6.8 yrs (n.b. 7/19 pts had previous TL resective surgery) **Controls:** 40 Age range: 21-59 yrs (used for semi-quantitative ROI analysis)		**Duration, yrs: TLE+DEP:** 20 ± 8.6 **TLE-only:** 22 ± 6.2 **Onset, yrs:** -		**Onset:** - **Duration:** ≥ 3 wks **Assessment:** DSM-IV; HADS **Symptom type: TLE+DEP:** HADS: 21 ± 2 **TLE-only:** HADS: 4 ± 2 **Pharmacological intervention: TLE+DEP:** 4 (44%) = anti-depressant meds	-

Appendix 1. Functional studies: Mood disorders in epilepsy, continued

Study	Pathology	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Ictal	Interictal	Findings
					Blood flow/glucose metabolism	Blood flow/glucose metabolism	
Schimitz et al. (1997) Prospective; uncontrolled	-	-	**All pts:** VIQ: 92.4 ± 13.8 PIQ: 93.3 ± 16.5 **VIQ:** R-focal EP: 93.1 ± 14.2 L-focal EP: 91.5 ± 13.9 **PIQ:** R-focal EP: 92.1 ± 17 L-focal EP: 94.8 ± 16.5	Non-surgical study	-	**L-focal EP:** 1.Negative association between BDI scores & contralateral TL perfusion & bilateral frontal perfusion 2. Positive association between BDI scores & occipital cortex perfusion **R-focal EP:** 1. Positive association between LOI & ipsi-lateral TL/thalamic & basal ganglia perfusion & bilateral frontal perfusion	1. No laterality effect with any psychiatric measure 2. There were no sig. associations between BFQ or SSSI & cRBF 3. The higher the BDI scores in L-focal EP pts, the *lower* the perfusion in frontal areas bilaterally & contralateral temporal regions 4. Sig positive associations in R-focal EP pts between LOI & cRBF (see interictal findings) (n.b. multiple analyses were performed without the use of Bonferroni corrections)
Ring et al. (1999). Prospective; controlled	-	-	-	Non-surgical study	-	***Hyperperfusion:*** **TLE-DEP vs TLE-only:** L FL, L PL L TH **TLE-DEP vs HCs:** No sig differences	1. Hyperperfusion in TLE+DEP pts were evident in L dorsolateral prefrontal cortex; L striatum; L TH; L temporo-parietal regions compared to TLE-only controls 2. However, these areas of hyperperfusion were within normal range compared to HCs 3. No areas of hypoperfusion were evident in TLE-DEP vs TLE-only pts

Appendix 1. Functional studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Number of controls (n)	Epilepsy details	Epilepsy Onset, yrs	Psychiatric details	EEG
Savic et al. (2004). Prospective; controlled	PET (Siemens ECAT); [^{11}C]WAY-100 635 (250 Mbq) & [^{18}F]FDG **Targets/ROI:** Hippocampi; amygdala; OFC; insula; ACC; lateral TL; DLPFC; PL; cerebellum; raphe nuclei 1.5T; 1.2mm **Customised templates:** Y **Whole brain correction:** Y (PVC)	14 MTLE (8R:6L) Age range: 25-56 yrs **Controls:** 14 Age range: 21-53 yrs		**Duration, yrs:** 24 ± 14 **Onset, yrs:** Range: 2-30		**Onset:** At the time of scanning 6 (43%) pts had IDD **Duration:** - **Assessment:** MADRS; supplementary anxiety score **Symptom type:** **MTLE:** MADRS: 13 ± 10 Anxiety: 7 ± 2 **HC:** MADRS: 5 ± 2 Anxiety: 2 ± 1 **Pharmacological intervention:** -	**Interictal:** Fronto-temporal 3 (21%) Bilateral: 1 (7%) **Ictal:** Mesial TL: 14 (100%)
Giovacchini et al. (2005). Prospective; controlled	PET (Advanced Tomograph) ^{18}F-FCWAY (>18.5TBq/mmol) & ^{18}F-FDG **Targets/ROI:** Amygdala; hippocampus; FFG; PHG; cerebellum; raphe 1.5T; 1.5mm **IGK:** Y **Whole brain correction:** Y (PVC)	22 TLE Age: 37 ± 11 yrs **Controls:** 10 Age: 35 ± 9 yrs		**Duration, yrs:** 23 ± 13 **Onset, yrs:** 10 ± 15		**Onset:** - **Duration:** - **Assessment:** BDI **Symptom type:** - **Pharmacological intervention:** -	

Appendix 1. Functional studies: Mood disorders in epilepsy, continued

Study	Pathology	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Ictal	Interictal	Findings
					Blood flow/glucose metabolism	Blood flow/glucose metabolism	
Savic et al. (2004). Prospective; controlled	**HS (± gliosis):** 8 (57%) **Normal:** 6 (43%)	-	-	**2 TLE surgeries:** Depression continues for 1pt (on SSRI); auras continue, although less frequent	-	**[^{18}F]FDG (n=11):** 5 (45.5%) = ipsilateral hypometabolism 6 (54.5) = normal **MTLE vs HC:** Pts had reduced BP in the ipsil- & contralateral hippocampi; ipsilateral cingulate; ipsilateral insula; ipsilateral amygdala; ispilateral temporal neocortex; raphe nuclei **MADRS:** Sig negative correlation between BP of the ipsilateral ACC and MADRS score	1. MTLE had sig higher depression and anxiety scores relative to HCs 2. MTLE pts with high MADRS scores had sig lower BP in the ipsilateral ACC 3. No sig association between anxiety scores & BP in the MTLE pts 4. The duration of MTLE/frequency of szs were not sig correlated with $5HT_{1A}$ BP/relative volume/relative metabolism in the epilepto-genic hippocampus
Giovacchini et al. (2005). Prospective; controlled	MTS: 16 (73%) Normal: 6 (27%)	-	-	14 (64%) had surgery; psychiatric outcome unspecified; 10 pts (71%) sz free at 1 yr F/U	-	**Pre- PVC: (^{18}F-FCWAY)** Pts had sig reduced BP in ipsilateral TL regions; contralateral hippo-campus & parahippo-campus & bilateral insula & raphe. No sig. differences in FL, PL or OL compared to HCs **Post- PVC: (^{18}F-FCWAY)** Sig reduced BP remained in ipsilateral TL regions; (n.b. *lateral* TL group differences in BP = no longer sig.) & bilateral insula regions. No differences in FL, PL or OL compared to HCs ***Correlational analyses:*** 1. No sig differences between BP/CMRglu between age/duration of EP. 2. Sig positive relationship between BDI & BP (but not CMRglu) in the ipsilateral hippocampus only, pre- & post PVC	1. Sig inverse correlation between BP & BDI scores in TLE pts, before and after PVC, in the ipsilateral hippocampus only

Appendix 1. Functional studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Number of controls (n)	Epilepsy details	Epilepsy Onset, yrs	Psychiatric details	EEG
Salzberg et al. (2006). Retrospective; uncontrolled	PET (PEN-PET) F-18 FDG	23 TLE **9 Preop TLE+DEP:** Age: 41 ± 4 **14 Preop TLE only:** Age: 41 ± 4 **13 Postop TLE+DEP:** Age: 45 ± 4 **10 Postop TLE only:** Age: 35 ± 3 **Controls:** -		**Duration, yrs:** **Preop TLE+DEP:** 21 ± 5 **Preop TLE only:** 29 ± 4 **Postop TLE+DEP:** 31 ± 5 **Postop TLE only:** 23 ± 2 **Onset, yrs:** -		**Onset:** - **Duration:** - **Assessment:** DSM-IV **Symptom type*:** **Preop TLE+DEP:** MDD: 9 (39%) **Postop TLE+DEP:** MDD: 13 (27%) **Pharmacological intervention:** **Preop TLE+DEP:** 2 (22%) **Postop TLE+DEP:** -	-
Theodore et al. (2007). Prospective; controlled	PET (Advanced Tomograph) [^{18}F]FCWAY (370MBq) **Targets/ROI:** Hippocampus; raphe nuclei **IGK:** Y **Whole brain correction:** Y (PVC)	45 TLE Age: 35.4 ± 11.4 yrs **Controls:** 10 Age: 32.2 ± 8.8 yrs		**Duration, yrs:** 19.9 ± 13.1 **Onset, yrs:** 15.6 ± 9.3		**Onset:** - **Duration:** - **Assessment:** BDI **Syptom type*:** **BDI:** MTS: 10.4 ± 8.7 Non-MTS: 8.8 ± 11.3 **Pharmacological intervention:** -	-
Hasler et al. (2007). Prospective; TLE-controls	PET (Advanced Tomograph) ^{18}F-FCWAY (18.5TBq/mmol) **Targets/ROI:** ACC; PCC; anterior insula; hippocampus; raphe nucleus 1.5T; 1.5mm **Whole brain correction:** Y (PVC)	37 TLE **16 TLE+MDD:** Age: 38.5 ± 12 yrs **21 TLE-only:** Age: 35.4 ± 11.8 yrs **Controls:** -		**Duration, yrs:** **TLE+MDD:** 23.5 ± 16.9 **TLE-only:** 19.4 ± 11.9 **Onset, yrs:** **TLE+MDD:** 15 ± 11 yrs **TLE-only:** -		**Onset:** - **Duration:** - **Assessment:** DSM-V (SCID); BDI **Symptom type:** **TLE+MDD:** 2.4 ± 1.6 MDD episodes **TLE+MDD:** BDI: 14.4 ± 13 **TLE-only:** BDI: 5.3 ± 5.2 **Pharmacological intervention:** -	-

Appendix 1. Functional studies: Mood disorders in epilepsy, continued

Study	Pathology	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Ictal	Interictal	Findings
					Blood flow/glucose metabolism	Blood flow/glucose metabolism	
Salzberg et al. (2006). Retrospective; uncontrolled	MTS: 16 (70%) FCD: 2 (9%) Unknown: 5 (21%)	-	-	**De novo depression:** 5 (22%) pts No sig difference in sz outcome between (1) pts with preop DEP vs those without or (2) pts with postop DEP compared to those without	-	1. Sig hypometabolism in the ipsilateral OFC in pts with a history of DEP compared to pts without a lifetime diagn of DEP 2. Sig hypometabolim in the ipsilateral OFC in pts in whom postop DEP developed (5 de novo + 8 pre-existing cases) compared to pts without postop DEP	1. No sig differences between preop depressed and non-depressed pts in age/ gender/handedness/TLE duration/number of AEDs/prevalence of MTS 2. Pts with a lifetime diagn of DEP had sig hypometabolism in the ipsilateral OFC compared to pts with no such history 3. Pts who developed (de novo) and/or had a continuance of DEP postop, had sig ipsilateral OFC hypometabolism 4. No sig difference between pts with/ without ipsilateral OFC regarding sz outcome 3 or 12 months (Engel Class I)
Theodore et al. (2007). Prospective; controlled	MTS: 29 (64%)	-	-	Non-surgical study	-	1. Pts with unilateral TLE focus (L or R) had sig reducted contralateral BP compared to controls 2. Sig inverse relationship between [I] hippocampal BP & BDI score (after controlling for side of TLE focus) 3. Pts with BDI > 20 (n=4) had sig reduced BP in the [I] hippocampus compared to pts with BDI < 20 (medium & low groups)	1. Pts with unilateral TLE focus demostrated sig reduced [C] hippocampal BP compared to controls 2. Sig negative correlation between [I] hippocampus & BDI scores; no effect of laterality 3. Laterality of TLE/pathology/age of TLE onset /TLE duration/age at scan/gender were not sig related to BDI 4. Pts with severe depressive symptoms (BDI > 20) had sig lower BP in the [I] hippocampus compared to pts with BDI scores of < 20
Hasler et al. (2007). Prospective; TLE-controls	**TLE+MDD:** MTS: 8 (50%) Other focal: 1 (6%) **TLE-only:** MTS: 10 (48% Other focal: 2 (10%)	-	-	Non-surgical study	-	**TLE-MDD (lifetime) vs TLE-only:** 1. TLE-MDD pts had sig BP reductions in the ACC/ anterior insula/R hippo- campus 2. No sig in GM between TLE groups **Current MDD vs TLE-only:** TLE pts with current MDD had sig reduced BP in the hippocampus	1. No sig differences between age/gender/ MTS prevalence/laterality between the TLE groups 2. TLE-MDD had increased BDI scores compared to TLE-only pts 3. After bonferroni correction, TLE-MDD pts had sig lower BP in the ACC, R hippocampus & R medial & R superior TL (irrespective of laterality of sz onset) 4. Gender/age/current MDD/comorbid anxiety disorders were not sig effect modifiers

Appendix 1. Functional studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Number of controls (n)	Epilepsy details	Epilepsy Onset, yrs	Psychiatric details	EEG
Lothe et al. (2008). Prospective; uncontrolled	PET (CTI-SIEMENS) [^{18}F]MPPF (181.4 ± 32.1MBq) **Targets/ROI:** Raphe nuclei; Insula; post-central gyrus; cingulate; IFG; MFG **Customised templates:** Y (for raphe nuclei) **IGK:** Y	24 MTS Age: 37.6 ± 11.2 yrs **Controls:** -		**Duration, yrs:** 30.5 Range: 10-55 **Onset, yrs:** -		**Onset:** No previous anti-depressant exposure. No pts had current/lifetime psychoapthology **Duration:** N/A **Assessment:** BDI-2 **Symptom type:** 9 (38%) = BDI >11, suggestive of MDD; 8/9 pts had RMTS **Pharmacological intervention:** N/A	-

Appendix 1. Functional studies: Mood disorders in epilepsy, continued

Study	Pathology	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Ictal	Interictal	Findings
					Blood flow/glucose metabolism	Blood flow/glucose metabolism	
Lothe et al. (2008). Prospective; uncontrolled	100% = MTS; 4 (17%) pts = MTS+ISWM	-	-	17 (71%) underwent surgery; 16 (94%) pts were sz free (Engel I); psychiatric outcome unspecified	-	**Global BP & total BDI score (flipped):** Non sig positive correlation between total BDI and BP in the [C] insula **Voxel-based analyses & BDI symptom classes (flipped):** 1. Negative cognition & psych-motor anhedonia positively correlated with BP in the [C] insula 2. Somatic symptoms were sig associated with BP in the [C] mid-cingulate gyrus; MFG & IFG bilaterally; [I] mTL (=PHG & atrophic hippocampus) **ROI analyses & total BDI score (flipped):** Sig positive correlation between [C] insula; [C] postcentral gyrus; & raphe nuclei & BP & BDI total **ROI analyses & BDI symptom classes (flipped):** 1. Sig positive correlation between negative cognition & psych-motor anhedonia & BP in the [C] insula 2. Somatic symptoms were positively correlated with [C] cingulate, [I] hippocampus & [I] PHG 3. Negative cognition was positively correlated with BP in the [C] post-central gyrus	1. No difference between pts > BDI greater/ lower than 11 and AEDs known to promote the release of serotonin 2. Positive correlation between total BDI score & BP in the [C] insula, [C] post-central gyrus & raphe nuclei 3. Different depressive symptoms correlated with BP in distinct brain regions

Appendix 1. Functional studies: Mood disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Number of controls (n)	Epilepsy details	Epilepsy Onset, yrs	Psychiatric details	EEG
Assem-Hilger et al. (2010). Prospective; controlled	PET (GE Advance) [^{11}C]WAY-100635 (377 MBq) **Targets/ROI:** Hippocampi; PHG; amygdala; temporal pole; insula; STG; MTG; ITG	13 TLE Age: 41 ± 10.4 yrs **Controls:** 13 Age: 29.5 ± 5.4 yrs		**Duration, yrs:** 23.2 ± 13.6 **Onset, yrs:** 17.8 ± 15.7		**Onset:** - **Duration:** - **Assessment:** Ham-D; BDI **Symptom type:** Ham-D: 11.7 ± 9.4 BDI: 8.2 ± 6.7 6 (46%) = clinically relevant depression (Ham-D ≥ 15; BDI ≥ 11) **Pharmacological intervention:** Y - numbers unspecified	-
Martinez et al. (2013). Prospective; controlled	PET [^{11}C]DASB & [^{18}F]FCWAY **Targets/ROI:** Insula; hippocam-pus; amygdala; PHG; FFG & cingulate cortex 1.5 or 3T; 1.5mm **Customised templates:** Y **IGK:** Y **Whole brain correction:** Y (PVC)	13 focal EP Age: 34.5 ± 8.4 yrs **Controls:** 29 Age: 33.7 ± 8.5		**Duration, yrs:** - **Onset, yrs:** -		**Onset:** - **Duration:** - **Assessment:** BDI & SCID **Symptom type:** 4 (31%) = lifetime MDD **Pharmacological intervention:** 1 (8%) pt had previously taken fluoxetine; no pts were currently prescribed anti-depressant medication	-

Appendix 1. Functional studies: Mood disorders in epilepsy, continued

Study	Pathology	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Ictal	Interictal	Findings
					Blood flow/glucose metabolism	Blood flow/glucose metabolism	
Assem-Hilger et al. (2010). Prospective; controlled	HS (± hippocampal atrophy): 5 (38%) Hippocampal atrophy: 3 (24%) Normal: 5 (38%)	-	-	Non-surgical study	-	*(n.b continuous EEG recordings not conducted)* 1. Pts had sig reduced BP in epileptogenic lobe compared to HC 2. Pts with hippocampal atrophy vs normal MRI pts did not sig differ in BP in any ROI 3. [I] BP was sig reduced in all hippocampal ROIs compared to [C] ROIs 4. Depression scores were *not* sig correlated with BP in any ROI 5. AI was *not* sig correlated with depression scores 6. Sig positive correlation between TLE duration & AI in the hippocampus	1. Pts had sig reduced BP in [I] mesiotemporal areas & lateral TL structures compared to the [C] hemisphere 2. Compared to HCs, pts had sig reduced BP in the mesiotemporal structures only 3. No sig relationship between BP/AI & depression rating scales 4. Sig positive correlation between hippo-campal AI & TLE duration
Martinez et al. (2013). Prospective; controlled	-	-	-	Non-surgical study	-	**Lifetime MDD diag:** pts with a history of MDD had sig. higher [11C]DASB asymmetry in insular cortex & a trend for FFG - adding side of focus did not alter the results	1. Mean regional [^{11}C]DASB binding & asymmetry did not differ between pts & HCs 2. Mean [^{18}F]FCWAY was sig decreased in [I] hippocampus & amygdala compared to contralateral regions 3. MDD diagn. had a sig. effect on [^{11}C]DASB asymmetry: pts with a history of MDD had sig. higher asymmetry in insular cortex & a trend for FFG - adding side of focus did not alter the results 4. There was a trend for higher BDI to be correlated with increased [^{11}C]DASB asymmetry 5. Age of EP onset/EP duration/side of focus/ presence of MTS/LTG/CBZ/OXC did not have sig. effects on [^{11}C]DASB binding in pts with TLE

Appendix 1. Structural studies: Anxiety disorders in epilepsy

Study	Study type	Imaging modality/ details	MRI scanner	Sample (n)	Number of controls (n)	Epilepsy details	Epilepsy Onset, yrs	Assessment type	EEG	Pathology
Satishchandra et al. (2003).* Prospective; controlled		MRI GE Electric 1.5T **ROI:** Y (amygd. & hippocampi) Whole brain correction: Y		**16 'partial EP':** 8 EP+ANX Mean age: 59.1 yrs 8 EP-only Mean age: 50.9 yrs **Controls:** 15	15	**Duration, yrs:** - **Onset, yrs:** -	-	**Onset:** - **Duration:** - **Assessment:** SCAN **Symptom type:** - **Pharmacological intervention:** -	-	-
Halley et al. (2010). Prospective; controlled	Prospective; controlled	MRI Siemens medical systems 63 & Signa echospeed superconducting imaging system **ROI:** Y (=manual sementation of the amygdalae)	Siemens medical systems 63 & Signa echospeed superconducting imaging system	42: **26 MTLRx** (26=ATLR & 3 para-hippocampal gyral lesionectomies) Age 36 ± 12 yrs **16 NMTRx** (6 lateral temporal corticectomies; 8 FLRx & 2 OLRx) Age: 33 ± 10 yrs **Controls:** 41 Age: 35 ± 13 yrs		**Duration, yrs:** **MTLRx:** 15 ± 12 **NMTRx:** 16 ± 11 **Onset, yrs:** -		**Onset:** - **Duration:** - **Assessment:** DSM IV; Austin CEP interview **Symptom type: Lifetime diagn. of anxiety: MTLRx:** 7 (27%) **NMTRx** 4 (165) **Pharmacological intervention:** -	-	-

Appendix 1. Structural studies: Anxiety disorders in epilepsy, continued

	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Satishchandra et al. (2003).* Prospective; controlled	-	-	Non-surgical study	1. Age of EP sig. earlier in the ANX group 2. EP duration sig. longer in the ANX group **EP-only vs HCs:** Amyg. & hippocampal vols were smaller on the right in the EP-only group **EP+ANX vs EP-only:** Mean amyg. & hippocampal vols were *greater* on the right side
Halley et al. (2010). Prospective; controlled	-	-	**MTLRx:** Continued anxiety: 5 (71%) De novo anxiety: 7 (37%) **NMTRx:** Continued anxiety: 3 (75%) De novo anxiety: 3 (25%)	1. There was no sig. differences between the groups in the frequency of anxiety postoperatively 2. Pts with a history of anxiety were sig. more likely to experience postop anxiety, than to experience anxiety relief 3. 32% of pts experienced de novo anxiety within 12 months of surgery; there was no sig. differences between the groups 4. No laterality effect between de novo anxiety for either group 5. Sig. relationship between ipsilateral amygdala volume (compared to HC) and postop anxiety following MTLRx; regardless of sz outcome. 6. There was no relationship between contralateral amygdalar volume & postop anxiety 7. No sig. relationships between ipsi-/ contralateral amygdalar volumes & postop anxiety, or seizure outcome in NMTRx group 8. No sig. relationships between preop anxiety & ipsi-/contralateral amygdalae volumes for either group

Appendix 1. Functional studies: Anxiety disorders in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Bonelli et al. (2008).* Prospective; controlled	fMRI GE Excite 3T; 1.5mm **IGK:** Y	54 TLE Age range: 18-62 yrs **Controls:** 21 Age range: 22-62 yrs	**Duration, yrs:** - **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** HADS **Symptom type:** **HADS (D/A):** LTLE: 5.5/7 RTLE:4.5/9 HC: 1.5/5.5 **Pharmacological intervention:** -	-	MTS: 100%

Appendix 1. Functional studies: Anxiety disorders in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Included contrasts (fMRI)		Findings
				Negative valence	Positive valence	
Bonelli et al. (2008).* Prospective; controlled	-	-	**Mean change in anxiety scores (pre-postop):** LTLE (n=10/26): -0.5 (-8 to +3) RTLE (n=11/28): +1 (-5 to +7) **Mean change in depression scores (pre-postop):** LTLE (n=10/26): -1.5 (-6 to +1) RTLE (n=11/28): +1 (-7 to +6)	***Correlational analysis with preop HADS & fMRI activation (fearful vs neutral faces):*** 1. Sig positive correlation in RTLE pts between preop anxiety scores & fMRI activation in L & R amygdala, compared to LTLE pts 2. Sig positive association in RTLE pts between preop depression scores & fMRI activation in L & R amygdala, compared to LTLE pts ***Correlational analysis with preop fMRI activation & change in HADS 4m postop (fearful vs neutral faces):*** 1. Sig positive correlation in RTLE pts between preop fMRI activation in the R amygdala & change (increase) in anxiety scores 2. Sig positive correlation in RTLE pts between preop fMRI activation in the R amygdala & change (increase) in depression scores	***Happy vs neutral faces:*** No sig activations within TL at the group levels; therefore no correlational analyses with HADS data performed	1. No sig correlations between pre- or post-operative change in HADS scores 2. No sig differences in T_2 amygdala values between the R/L TLE groups 3. In RTLE pts only, there was a sig positive correlation between preop fMRI activation in L & R amygdala & preop anxiety & depression scores, compared to L TLE pts, when viewing fearful vs neutral faces 4. In RTLE pts only, there was a significant positive correlation between preop fMRI activation in the R amygdala and change (increase) in postop anxiety & depression ratings at 4m 5. No sig correlation between sz outcome & changes in HADS scores at 4m F/U

Appendix 1. Structural studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Conlon et al. (1988). Prospective; controlled	MRI **ROI:** Y (corpus callosum)	**28 EP:** 12 TLE+NS 16 EP-only **Controls:** **15=HCs** Mean Age: 35.5 yrs	**Duration, yrs:** - **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** PSE **Symptom type:** - **Pharmacological intervention:** -	-	-
Maier et al. (2000). Prospective; controlled	MRI spectroscopy GE Signa 1.5T; 1.5mm **ROI:** Y (Hippocampi & amygd. complex = treated as a *single* structure) **Whole brain correction:** Y	24 TLE: **12 TLE+SLP:** Age: 39.25 ± 7.98 yrs **12 TLE-only:** Age: 39.5 ± 8.8 yrs **Controls:** **26=SCZ** Age: 36.38 ± 8.54 **38=HCs** Age: 27.87 ± 9.73	**Duration, yrs:** - **Onset, yrs:** **TLE+SLP:** 11.3 ± 5.8 **TLE-only:** 13.9 ± 12.6	**Onset:** **TLE+SLP:** 26.8 ± 6.4 yrs **Duration:** - **Assessment:** - **Symptom type:** - **Pharmacological intervention:** -	**Interictal:** **TLE+SLP:** 6 (50%)=bilateral 4 (33%)=bilateral (L>R) 1 (8%)=R-sided 1 (8%)=unspecified **TLE+only:** 5 (42%)=bilateral 4 (33%)=bilateral (L>R) 3 (25%)=R-sided	**TLE+SLP:** 4 (33%)=no focal abn
Marsh et al. (2001).* Prospective; controlled	MRI GE Signa 1.5T; 3mm **ROI:** Y (TL; STG; hippo-campi; temporal horn; lateral ventricle; 3rd ventricle; fronto-parietal region **Whole brain correction:** Y	**9 EP+SLP** (4=L TLE; 1=primary generalised; 1=symptomatic generalised; 3=partial EP) **Controls:** **46=SCZ** Age: 38.4 ± 7.6 **18=TLE-only** Age: 32.1 ± 9.4 **57=HCs** Age: 38.7 ± 10.1	**Duration, yrs:** **EP+SLP:** 14.8 ± 8.8 **TLE-only** 18.9 ± 11.1 **Onset, yrs:** **EP+SLP:** 20 ± 13.1 **TLE-only** 13.1 ± 8.7	**Onset:** **EP+SLP:** 26 ± 8 yrs **SCZ** 23.1 ± 5 yrs **Duration:** **EP+SLP:** 10.1 ± 10.4 yrs **SCZ** 15.2 ± 7.9 yrs **Assessment:** DSM-III-R/ DSM-IV (SCID); BPRS **Symptom type:** **EP+SLP:** 7 (78%)=chronic schizophrenia 1 (11%)=psychotic disorder NOS 1 (11%)=psychotic affective disorder **SCZ:** 46 (100%)=chronic SCZ **Pharmacological intervention:** -	-	-

Appendix 1. Structural studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Conlon et al. (1988). Prospective; controlled	-	-	Non-surgical study	1. EP-only pts showed sig. greater midcallosal thickness than the TLE+NC & HCs
Maier et al. (2000). Prospective; controlled	-	-	Non-surgical study	1. TLE-only & TLE+SLP groups = sig reduced NAA bilaterally compared to HCs 2. No sig differences in NAA between the TLE groups 3. *Total* hippocampus/amygdala showed no sig differences in any of the groups compared to HCs **Specific regions of focal volume reduction:** 1. Bilateral volume reductions in specific areas of the hippocampal-amgydala complex (anterior to the fornix) bilaterally in TLE+SLP pts compared to HCs. However, regional bilateral volume reduction in these regions were *not* detected in TLE-only pts when comapred to HCs
Marsh et al. (2001).* Prospective; controlled	-	**NART:** EP+SLP: 103.4 ± 11.6 SCZ: 106.4 ± 9.2 TLE-only: unknown HCs: 111.3 ± 7.1 **VIQ:** EP+SLP: 87.4 ± 16.3 SCZ: unknown TLE-only: 98.1 ± 14.4 HCs: unknown **PIQ:** E+SLP: 85.6 ± 16.6 SCZ: unknown TLE-only: 100.8 ± 16.4 HCs: unknown **FSIQ:** E+SLP: 86 ± 16.3 SCZ: unknown TLE-only: 99.6 ± 15.2 HCs: unknown	Non-surgical study	1. HCs had sig higher NART-IQ score relative to both psychotic groups **Relative to HCs:** 1. All pt groups had ventricular enlargement & smaller TL, fronto-parietal and STG GM volumes; the extent of these abnormalities was greatest in EP+SLP pts (but differences between TLE-only, SCZ & EP+SLP were n.s) 2. TLE-only pts had TL WMem deficits, hippocampal atrophy, which were [I] to the seizure focus

Appendix 1. Structural studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Tebartz van Elst et al. (2002).* Retrospective; controlled	MRI GE Signa 1.5T; 1.5mm **ROI:** Y (Hippocampi & amygd.) **Whole brain correction:** Y	**26 TLE+SLP/PIP** **Controls:** **20=HCs** **24=TLE-only** *All groups were age- & gender matched*	**Duration, yrs:** *Groups were matched* **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** ICD-10 **Symptom type:** - **Pharmacological intervention:** **TLE+SLP/PIP:** 11 (42%) = anti-psychotics	**TLE+SLP/PIP:** R-sided: 6 (23%) L-sided: 8 (31%) Bilateral: 10 (38%) **TLE-only:** R-sided: 9 (38%) L-sided: 9 (38%) Bilateral: 5 (21%)	**TLE+SLP/PIP:** None: 13 (50%) R HS: 2 (8%) L HS: 6 (23%) Bilateral HS: 0 (0%) Other: 5 (19%) **TLE-only:** None: 7 (29%) R HS: 6 (25%) L HS: 10 (42%) Bilateral HS: 1 (4%) Other: 0 (0%)
Marchetti et al. (2003).* Prospective; controlled	MRI Philips Gyroscan 1.5T; 1.2mm **ROI:** Y (Hippocampi & amygd.) **Whole brain correction:** Y	**36 EP** Age: 40 ± 12 yrs (30 (83%)=MTLE) **Controls:** **30 HCs** Age: 42 ± 14	**Duration, yrs:** - **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** DSM-IV **Symptom type:** - **Pharmacological intervention:** -	-	**EP:** MTS=22 (61%) Cryptogenic=11 (31%) Tumour=1 (3%) Fahr disease=1 (3%)
Rusch et al. (2004).* Retrospective; controlled	MRI (VBM) GE Signa 1.5T; 1.5mm **Customised templates:** Y **IGK:** 12mm **Whole brain correction:** Y	**26 TLE+SLP/PIP** **Controls:** **20=HCs** **24=TLE-only** *All groups were age- & gender matched*	**Duration, yrs:** *Groups were matched* **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** ICD-10 **Symptom type:** - **Pharmacological intervention:** **TLE+SLP/PIP:** 11 (42%) = anti-psychotics	**TLE+SLP/PIP:** R-sided: 6 (23%) L-sided: 8 (31%) Bilateral: 10 (38%) **TLE-only:** R-sided: 9 (38%) L-sided: 9 (38%) Bilateral: 5 (21%)	**TLE+SLP/PIP:** None: 13 (50%) R HS: 2 (8%) L HS: 6 (23%) Bilateral HS: 0 (0%) Other: 5 (19%) **TLE-only:** None: 7 (29%) R HS: 6 (25%) L HS: 10 (42%) Bilateral HS: 1 (4%) Other: 0 (0%)

Appendix 1. Structural studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Tebartz van Elst et al. (2002).* Retrospective; controlled	-	**VIQ:** TLE+SLP/PIP: 86.4 ± 2.3 TLE-only: 95.1 ± 3 **PIQ:** TLE+SLP/PIP: 89.7 ± 2.6 TLE-only: 93.6 ± 2.9	Non-surgical study	1. VIQ was sig lower in the psychotic compared to non-psychotic TLE pts 2. Psychotic pts had sig smaller total brain volumes compared to both non-psychotic pts & HCs 3. There was no sig difference in hippocampal between the groups 4. TLE+SLP/PIP had a 16-18% bilateral enlargement of the amygdala compared to pt and HC groups; this finding was unchanged after removing pts taking anti-psychotic medication
Marchetti et al. (2003).* Prospective; controlled	-	-	Non-surgical study	1. Mean left hippocampal volume was sig smaller in the EP group compared to HCs (in the presence of MTS)
Rusch et al. (2004).* Retrospective; controlled	-	**VIQ:** TLE+SLP/PIP: 86.4 ± 2.3 TLE-only: 95.1 ± 3 **PIQ:** TLE+SLP/PIP: 89.7 ± 2.6 TLE-only: 93.6 ± 2.9	Non-surgical study	1. VIQ was sig lower in the psychotic compared to non-psychotic TLE pts **GM differences:** 1. There were no sig differences in GM concentration between the psychotic (TLE+SLP/PIP) & non-psychotic (TLE-only) groups 2. There were no sig differences between TLE+SLP & TLE+PIP pts 3. The TLE-only group had a sig increase in GM in the R TL

Appendix 1. Structural studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Flugel et al. (2005).* Prospective; controlled	MRI (VBM - MTI analysis) GE Signa 1.5T; 1.5mm **Customised templates:** Y **IGK:** 12mm **ROI:** Y - only for post-hoc analysis	40 TLE: **20 TLE+IP** Age: 39.1 ± 9.9 yrs **20 TLE-IP** Age: 38.7 ± 12.6 yrs **Controls:** 23 HC Age: 37 ± 12 yrs	**Duration, yrs: TLE+IP:** 32.7 ± 9.2 **TLE-IP:** 25.9 ± 14.7 **Onset, yrs: Mean: TLE+IP:** 6.3 yrs **TLE-IP:** 12.8 yrs	**Onset: TLE+IP:** 26.4 [17-38] yrs; 20.1 yrs following TLE onset **Duration: TLE+IP:** Mean: 12.6 yrs **Assessment:** DSM-IV; PANSS **Symptom type: TLE+IP:** NSS: 23.2 PSS: 16 **Pharmacological intervention:** Neuroleptics: 80%	No sig. differences between the groups	**TLE+IP:** HS: 50% No lesion: 50% **TLE-IP:** HS: 50% No lesion: 50%

Appendix 1. Structural studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Flugel et al. (2005).* Prospective; controlled	-	**NART:** TLE+IP: 93.1 ± 13.6 TLE-IP: 97.7 ± 12.3	Non-surgical study	1. No sig. differences in premorbid IQ/age/sz freq 2. TLE+PIP pts had sig. earlier onset of TLE & history of SE 3. No EEG differences between the groups (± IP/± lesion) 4. No sig. differences in MTR between groups 5. No sig. differences in the hippocampal volumes between the groups 6. No sig differences in MTR findings and clinical factors (age/SE/TLE onset/psychosis duration/current neoleptic meds/ PANSS scores) *No focal lesion subgroup analysis:* 1. TLE+IP had sig. reduction of MTR L middle & STG compared to TLE-IP and HC 2. No sig. differences in MTR between TLE-IP & HC groups 3. Sample size (n=8) was too small to assess laterality effect

Appendix 1. Structural studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Duration of Epilepsy, yrs	Psychiatric details	EEG	Pathology
Flugel et al. (2006).* Prospective; controlled	MRI (VBM - MTI analysis) GE Signa 1.5T; 1.5mm **Customised templates:** Y **IGK:** 12mm	40 TLE: **20 TLE+IP** Age: 39.1 ± 9.9 yrs **20 TLE-IP** Age: 38.7 ± 12.6 yrs **Controls:** -	**Duration, yrs: TLE+IP:** 32.8 ± 9.3 **TLE-IP:** 25.9 ± 14.7 **Onset, yrs: TLE+IP:** 6.3 ± 5.7 **TLE-IP:** 12.8 ± 7	**Onset: TLE+IP:** 26.4 ± 6.5 yrs **Duration: TLE+IP:** 12.5 ± 9.2 yrs **Assessment:** DSM-IV; PANSS **Symptom type: TLE+IP:** NSS: 23.2 PSS: 16 **Pharmacological intervention:** Neuroleptics: 80%	No sig. differences between the groups	**TLE+IP:** HS: 50% No lesion: 50% **TLE-IP:** HS: 50% No lesion: 50%

Appendix 1. Structural studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Flugel et al. (2006).* Prospective; controlled	-	**NART:** TLE+IP: 93.1 ± 13.6 TLE-IP: 97.7 ± 12.3 **VIQ:** TLE+IP: 78.8 ± 10.9 TLE-IP: 87.7 ± 13.3 **Semantic memory:** TLE+IP: 5.9 ± 2.8 TLE-IP: 8.6 ± 2.9 **Semantic fluency:** TLE+IP: 11.9 ± 6.4 TLE-IP: 17.5 ± 5.5 **Executive tasks:** *Arthimetic* TLE+IP: 5.7 ± 2.5 TLE-IP: 8.7 ± 3.5 *Spatial span* TLE+IP: 4.25 ± 1.2 TLE-IP: 5.4 ± 1.3 *SWM (BE)* TLE+IP: 59.4 ± 25.7 TLE-IP: 40.7 ± 23.1	Non-surgical study	1. No sig. differences in age/gender/sz freq/TLE duration/types or number of AEDs/premorbid IQ 2. TLE+PIP pts had sig. earlier onset of TLE & history of SE 3. TLE+IP pts had sig lower score than TLE-only pts for measures of semantic memory & semantic fluency 4. TLE+IP patients scored sig lower on executive tasks (listed) compared to TLE-IP pts 5. No sig differences on any cognitive measure between pts on neuroleptics vs. those not (n=4) 5. No sig. differences in the hippocampal volumes between the groups **TLE+IP group, MTR & cognition:** There was a sig positive correlation between sematic memory scores and MTR; lower scores correlated with MTR reductions in the FFG of the L TL **TLE-IP group, MTR & cognition:** No sig correlations

Appendix 1. Structural studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Flugel et al. (2006a). Prospective; TLE-controls	MRI (DTI) GE Signa 1.5T; 1.5mm **ROI:** Y (MTG & MFG bilaterally)	38 TLE: **20 TLE+IP** Age: 39.1 ± 9.8 yrs **18 TLE-IP** Age: Unspecified **Controls:** 18 TLE-IP	**Duration, yrs:** - **Onset, yrs:** **TLE+IP:** 6.2 ± 5.6 **TLE-IP:** 12.8 ± 7	**Onset:** **TLE+IP:** 26.7 ± 6.8 yrs **Duration:** **TLE+IP:** 12.3 ± 9.4 yrs **Assessment:** DSM-IV; PANSS **Symptom type:** - **Pharmacological intervention:** **TLE+IP:** Neuroleptics: 75%	No sig. differences between the groups	**TLE+IP:** HS: 50% No lesion: 50% **TLE-IP:** HS: 50% No lesion: 50%

Appendix 1. Structural studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Flugel et al. (2006a). Prospective; TLE-controls	-	**NART:** TLE+IP: 92.2 ± 13.7 TLE-IP: 97.94 ± 12.3 **VIQ:** TLE+IP: 78.28 ± 12.4 TLE-IP: 87.68 ± 13.3 **Semantic Fluency:** TLE+IP: 11.94 ± 6.4 TLE-IP: 17.52 ± 5.5 **Spatial Span:** TLE+IP: 4.17 ± 1.1 TLE-IP: 5.4 ± 1.3 **Spatial WMem:** TLE+IP: 59.89 ± 27.2 TLE-IP: 40.7 ± 23.1	Non-surgical study	1. TLE+IP had sig. lower VIQ/ semantic fluency/spatial span/ spatial Wmem 2. TLE+IP: Earlier age of TLE onset & SE history 3. No sig. differences in the hippocampal volumes between the groups 4. FA sig.↓ in bilateral frontal regions in TLE+IP pts (R>L) & bilateral TL regions 5. MD was sig. ↑ in bilateral frontal regions in TLE+IP pts *TLE+IP only:* 1. Sig. positive correlation between bifrontal & L temporal FA with semantic fluency 2. L FL FA positively correlated with VIQ 3. Bilateral FL FA positively correlated with spatial span 4. Semantic fluency sig. predictor of ↓ FA in L frontal & bilateral temproal regions 5. Spatial span sig. predictor of ↓ FA in R FL 6. Sig. negative correlations were found between age & bilateral frontal & temporal reductions in both groups 7. Negative symptom score sig. predicted L FL FA reductions

Appendix 1. Structural studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Adams et al. (2008). Retrospective; EP-controls	MRI 1.5T	312: **212 MTS** Age: 37 yrs **TLE (other lesions)** Age: 35.5 yrs **TLE (non-lesional)** Age: 36.8 yrs **ETLE (lesional)** Age: 37.7 yrs **ETLE (non-lesional)** Age: 34.5 yrs **Controls:** -	**Duration, yrs:** - **Onset, yrs:** -	**Onset:** - **Duration:** - **Assessment:** DSM-IV *(not all pts had neuropsychiatric assessment)* **Symptom type:** **Lifetime diagn.** **MTS** Depression: 26.4% Psychosis: 8.3% **TLE (other lesions)** Depression: 27.6% Psychosis: 8.6% **TLE (non-lesional)** Depression: 41.9% Psychosis: 5.4% **ETLE (lesional)** Depression: 35.7% Psychosis: 8.6% **ETLE (non-lesional)** Depression: 41.2% Psychosis: 4.8% **Pharmacological intervention:** -	-	-

Appendix 1. Structural studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Adams et al. (2008). Retrospective; EP-controls	-	-	Non-surgical study	1. No sig. difference between the prevalence of any psychiatric disorder (depression/psychosis) & TLE vs ETLE 2. Pts with non-lesional EP (both TLE & ETLE) had sig. higher prevalence of psychiatric disorders (69.2%) than those with lesional EP (inc. TLE & ETLE pts) (52.9%) 3. No sig. differences in the prevalence of *any* psychiatric disorder & pts with TLE vs ETLE 4. In multivariable analyses, the odds of any psychiatric diagn. were 2.4 times *higher* for pts with *non-lesional* focal EP vs lesional EP (MTS & other lesions); although this was due to pts with a lifetime diag. of depression 5. The laterality of the seizure foci (R/L/bilateral) were not sig. predictors of psychopathology 6. No sig. difference between the lifetime prevalence of depression between TLE (31.2%) & ETLE (37.9%) pts 7. Pts with non-lesional EP exhibited higher prevalence of depression (41.6%) compared to those with lesional EP (28.5%) 8. Lifetime psychiatric diag. was not predicted by MTS or another lesion 9. Multivariable analyses indicated that a lifetime diag. of depression was only sig. predicted by *non-lesional* EP. The odds of a lifetime diagnosis of depression was almost double (OR: 1.96, 95%CI: 1.16-3.31, p=.01) for pts with non-lesional vs lesional EP 10. Lifetime diag. of depression was not predicted by MTS or another lesion 11. The laterality of the seizure foci (R/L/bilateral) were not sig. predictors of depression 12. There were no sig. relationships between any of the EP variables & a history of psychosis 13. Similarly, logistic regression did not find any sig. EP variables (laterality/TLE vs ETLE/lesional vs non-lesional/pathology type) predicted psychosis

Appendix 1. Structural studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Sundram et al. (2010). Retrospective; controlled	MRI (VBM) GE Signa 1.5T; 1.5mm **Customised templates:** Y **IGK:** 8mm **ROI:** N (whole brain analysis)	20 TLE: **10 TLE+SLP/PIP** Age: 35 ± 5.2 yrs 50% = IP; 50%=PIP **10 TLE-only** Age: 33 ± 6.1 yrs **Controls:** 10 TLE-only	**Duration, yrs:** **TLE+SLP/PIP** 23 ± 12.4 **TLE-only:** 17 ± 8.6 **Onset, yrs:** **TLE+SLP/PIP** 12 ± 11 **TLE-only:** 16 ± 8.2	**Onset:** **TLE+SLP/PIP** 30 ± 5.6 yrs **Duration:** **TLE+SLP/PIP** 18 ± 9.9 yrs **Assessment:** ICD-10; OPCRIT **Symptom type:** **TLE-only:** All pts were free of co-morbid psychopathology in the preceeding yr **Pharmacological intervention:** -	-	-

Appendix 1. Structural studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Sundram et al. (2010). Retrospective; controlled	-	-	Non-surgical study	1. No sig. differences in total brain/ GM/WM volumes between between the groups 2. TLE+psychosis group had sig. ↓ GM volume in unilateral TL structures (L parahippocampal gyrus & hippocampus). 3. TLE+psychosis group had sig. ↓ GM volume in lateral temporal lobes (bilateral inferior, middle & superior temporal gyri & fusiform gyri) 4. TLE+psychosis group had sig. ↓ extratemporal bilateral GM atrophy (insula, cerebellum, caudate nuclei). Unilateral GM volume loss seen in the R cingulum and L inferior parietal lobule. 5. TLE+psychosis group had sig. ↓ WM in bilateral hippocampus, parahippocampal gyrus, lateral temporal lobes (middle & inferior temporal gyri & fusiform gyri). 6. TLE+psychosis group had sig. ↓ WM in unilateral R superior temporal gyrus. 7. TLE+psychosis group had sig. ↓ WM extratemporally (bilateral cingulum, corpus callosum, thalamus. Unilateral reductions: L lingual gyrus & R midbrain) found between age & bilateral frontal & temporal reductions in both groups 7. Negative symptom score sig. predicted L FL FA reductions

Appendix 1. Structural studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Psychiatric details	EEG	Pathology
Gutierrez-Galve et al. (2012). Prospective; controlled	SBM (FreeSurfer) GE Signa 1.5T; 1.2mm **Customised templates:** Y **IGK:** 10mm **ROI:** 22 cortical parcellations used **Whole brain correction:** Y	45: **22 TLE+IP** Age: 38.9 ± 9.7 yrs **23 TLE-only:** Age: 38.7 ± 12.1 yrs **Controls:** 20 Age: 36 ± 11.3 yrs	**Duration, yrs:** **TLE+IP:** 39.1 ± 11.1 **TLE-only:** 25.7 ± 14.2 **Onset, yrs:** **TLE+IP:** 7 ± 7 **TLE-only:** 12.5 ± 7.2	**Onset:** **TLE+IP:** 26.7 ± 6.3 yrs **Duration:** **TLE+IP:** 12.1 ± 9.1 yrs **Assessment:** Clinical interview; (DSM-IV-TR) PANSS **Symptom type:** **PANSS (TLE+IP):** Positive: 16.4 ± 3.5 Negative: 24 ± 7.1 **Pharmacological intervention:** **TLE+IP:** 15 (68%) = anti-psychotics **TLE-only:** None = anti-psychotics **HC:** None had a formal psychiatric history	-	**TLE+IP:** Normal: 10 (46%) LHS: 6 (27%) RHS: 4 (18%) Bilateral HS: 2 (9%) **TLE-only:** Normal: 10 (44%) LHS: 6 (26%) RHS: 4 (17%) Bilateral HS: 3 (13%)

Appendix 1. Structural studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Findings
Gutierrez-Galve et al. (2012). Prospective; controlled	-	**NART:** TLE+IP: 90.6 ± 14.9 TLE-IP: 94.8 ± 14.2 **Current IQ:** TLE+IP: 76.1 ± 10.7 TLE-IP: 85.6 ± 14.3 **Working memory span:** TLE+IP: 4.2 ± 1.2 TLE-IP: 5.3 ± 1.4 **Working memory manipulation:** TLE+IP: 60.6 ± 24.8 TLE-IP: 43.4 ± 23.7 **Story recall (immed):** TLE+IP: 16.5 ± 11.1 TLE-IP: 21.9 ± 11.8 **Story recall (delayed):** TLE+IP: 13.6 ± 10.6 TLE-IP: 16.4 ± 12.2	Non-surgical study	1. TLE+IP pts had a sig. earlier age of EP onset/higher prevalence of SE/reduced current IQ/reduced working memory span & working memory manipulation, compared to TLE-only pts 2. TLE+IP pts had sig. reduced cortical thickness in the IFG, specifically the pars opercularis, compared to HC (after FDR correction) 3. No sig. trend (p=.06) between TLE+IP and TLE-only pts in IFG cortical thickness 4. Age of EP onset/duration of EP/ history of SE/age or duration of psychosis/dose of neuroleptic meds were not significantly associated with cortical thickness in either pt groups 5. Cognitive scores were not sig. associated with cortical thickness 6. Sig. left-sided reduction in cortical area in the IFG (pars opercularis) in TLE+IP pts compared to TLE-only pts 7. In TLE+IP pts only, current IQ was positively associated with frontal & (superior frontal & rostral middle frontal) & temporal (superior temporal) cortical surface area (after FDR correction) 8. In TLE pts only, current IQ was positively associated with cortical frontal (superior frontal & rostral middle frontal), temporal (superior temporal & fusiform gyrus) and inferior parietal volumes (after FDR correction)

Appendix 1. Functional studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Epilepsy Onset, yrs	Psychiatric details	EEG	Pathology
Gallhofer et al. (1985). Prospective; controlled	PET (oxygen-15 inhalation) **ROI:** Y	12 EP+SLP **6 EP+SLP+meds:** Mean age: 42.3 yrs **6 EP+SLP-meds:** 38.2 yrs **Controls:** 5=EP-only 5=HCs	**Duration, yrs:** - **Onset, yrs:** -	-	**Onset:** - **Duration:** - **Assessment:** PSE **Symptom type:** 4 (67%)=nuclear schizophrenia 1 (17%)=psycho-tic depression 1 (17%)=schizo-phrenia with 1st rank symptoms **EP+SLP+meds:** 2 (33%)=nuclear schizophrenia 2 (33%)=depressive psychosis 1 (17%)=paranoid psychosis 1 (17%)=improved & not psychotic **Pharmacological intervention:** Of the EP+SLP pts, 6 (50%) were free from anti-psychotics at the time of scanning	**EP-only:** 3 (60%): R-sided abn 2 (40%): L-sided abn **EP+SLP:** 3 (25%): R-sided abn 1 (8%): L-sided abn 8 (67%): Bilateral abn	*CT scans of the EP pts did not reveal clear structural lesions*

Appendix 1. Functional studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Ictal	Interictal	Findings
				Blood flow/glucose metabolism	Blood flow/glucose metabolism	
Gallhofer et al. (1985). Prospective; controlled	-	**Mean IQ:** EP+SLP+meds: 97 EP+SLP-meds: 96 EP-only: 98	Non-surgical study	-	**HC vs. EP groups:** rCMRO2: HC > EP in L & R TL, L basal ganglia rCBF: HC > EP L TL, R TL, FTCB, basal ganglia & limbic strip rOER: HC < EP in L FTCB, R TL, FTCB & limbic strip **EP-only analyses:** rOEF: EP-only < EP+SLP in limbic strip & TL, FTCB, basal ganglia bilaterally rOER: EP+SLP-meds < EP+SLP+meds in L TL, limbic strip & bilaterally in the FTCB & basal ganglia	1. HC had higher values of oxygen utilization & cerebral blood flow than the EP groups, with the most sig differences in the mid & posterior TLs 2. EP pts with psychosis had sig reduced oxygen extraction (rOEF)in fronto-temporal regions

Appendix 1. Functional studies: Interictal Psychosis in epilepsy

Study	Imaging modality/ details	Sample (n)	Epilepsy details	Epilepsy Onset, yrs	Psychiatric details	EEG	Pathology
Marshall et al. (1993). Prospective; controlled	SPECT ^{99M}Tc-HMPAO (av. dose: 550 MBq). **ROI:** Y	**5 EP+SLP** Age: 37.6 ± 7.7 yrs **Controls:** **5 EP-only** Age: 38 ± 8.7 yrs	**Duration, yrs:** - **Onset, yrs:** **EP+SLP:** 12.5 ± 12.1 **EP-only:** 9.9 ± 10.4		**Onset:** - **Duration:** - **Assessment:** RDC; SADS **Symptom type:** **EP+SLP:** No pt was psychotic at the time of scanning **Pharmacological intervention:** EP+SLP: 100% on neuroleptics	*Groups were matched*	**EP+SLP:** 3 (60%): atrophy on CT scans (groups were *not* matched on gross cerebral pathology)
Mellers et al. (1998). Prospective; controlled	SPECT ^{99M}Tc-HMPAO (av. dose: 550 MBq). **ROI:** Y (6 cortical regions defined)	**12 EP+SLP** Age: 43 ± 9.7 yrs **Controls:** **16 EP-only** Age: 40.5 ± 9.7 yrs **11 SCZ** Age: 38.7 ± 10.4 yrs	**Duration, yrs:** **EP+SLP:** 32.5 ± 10.4 yrs **EP-only:** 24.8 ± 12.2 yrs **Onset, yrs:** -		**Onset:** - **Duration:** **EP+SLP:** 13.5 ± 10.4 yrs **SCZ:** 24.8 ± 12.2 yrs **Assessment:** DSM-III-R; BPRS **Symptom type*:** **BPRS:** EP+SLP: 5.5 ± 5.4 SCZ: 5.4 ± 5.2 EP-only: 1.4 ± 2.3 (assessed immediately prior to scanning) **Pharmacological intervention:** All SCZ & EP+SLP pts were taking neuroleptics	*Groups were matched*	-

Appendix 1. Functional studies: Interictal Psychosis in epilepsy, continued

Study	Neuropathology	Neuropsychology	Post-surgical psychiatric outcome	Ictal	Interictal	Findings
				Blood flow/glucose metabolism	Blood flow/glucose metabolism	
Marshall et al. (1993). Prospective; controlled	-	**VIQ range:** EP+SLP: 85-98 EP-only: 96-116 **PIQ range:** EP+SLP: 80-107 EP-only: 76-118	Non-surgical study	-	**EP+SLP vs EP-only:** SLP pts had sig reduced rCBF in the L medial TL region	1. EP+SLP pts had sig reduced rCBF in the L hemisphere, circumscribed to the medial TL compared to EP-only pts 2. Groups differed sig in gross brain pathology & IQ
Mellers et al. (1998). Prospective; controlled	-	**NART:** EP+SLP: 105 ± 14 EP-only: 111 ± 9 SCZ: 112 ± 6	Non-surgical study	-	1. SCZ pts showed greater activation of the ACC compared to the EP groups 2. EP+SLP pts showed reduced activity in the L STG during verbal fluency compared to SCZ & EP-only pts	1. EP+SLP pts had lower rCBF in the L STG during a verbal fluency task compared to EP-only and SCZ groups 2. SCZ group had greater increase in rCBF in the ACC than both epilepsy groups 3. The EP+SLP group performed sig worse on the verbal fluency task compared to the other groups (EP-only & SCZ)

Abbreviations for Appendix 1: * hippocampal volumes recorded, refer to paper for further details; cRBF, Cerebral regional blood flow; CT, Computerised tomography; d, days; DEP, Depression; DES-II, Dissociative Experiences Scale version II; diagn, Diagnosis; DLPFC, Dorsolateral prefrontal cortex; DSM, Diagnostic Statistical Manual; DTI, Diffusion tensor imaging; EP, Epilepsy; ETLE, Extra-temporal lobe epilepsy; ETOH, Alcohol; EZ, Epileptogenic zone; F/U, Follow-up; FA, Fractional anisotropy; FC, Febrile convulsions; FDG, Fludeoxyglucose; FDR, False discovery rate; FFG, Fusiform gyrus; FG, Frontal gyrus; FL, Frontal Lobe; FLRx, Frontal lobe resections; FSIQ, Full scale IQ; FTCB, "Fronto-temporal bridge"; GM, Grey matter; GTC, Generalised tonic clonic; HADS (D/A), Hamilton Depression Rating Scale (depression/anxiety); Hcau, Head of caudate; HC(s), Healthy controls; HS, Hippocampal sclerosis; HV, Hippocampal volume; ICD, International classification of Diseases; ICV, Intracranial volume; IDD, Interictal dysphoric disorder; I.E.D, Intermittent Explosive Disorder; IED, Interictal epileptiform discharges; IF, Inferior frontal; IFG, Inferior frontal gyrus; IG, Idiopathic generalised epilepsy; IGK, Isotropic Gaussian Kernel; IHC, Ipsilateral hippocampal volume; ITL, Inferior lateral temporal; immed, immediate; IMT, Inferior mesial temporal; incl., including; IP, Interictal psychosis; ISWM, Increased T2-weighted signal in anterior temporal white matter; ITG, Inferior temporal gyrus; L, Left; LOI, Leyton obsessional inventory inventory; LTG, Lamotrigine; m, month; MADRS, Montgomery Asberg Depression Rating Scale; MCST, Modified Card Sorting Test; MD, Mean diffusivity; MDD, Major depressive disorder; meds, Medication; MF, Mid-frontal; MFG, Middle frontal gyrus; MINI, Mini International Neuropsychiatric Interview; MT, Mid-temporal; MTG, Middle temporal gyri; MTI, Magnetization Transfer Imaging; MTLE, Mesial temporal lobe; MTLRx, Mesial temporal lobe resection; MTR, Magnetization Transfer Ratio; MTS, Mesial temporal lobe sclerosis; N, No; N.S, Not significant; N/A, Not applicable; NAA, N-acetyl-aspartate; NART, National adult reading test; NMTRx, Non mesial temporal lobe resection; No., Number; NOS, Not otherwise specified; NS, Nuclear schizophrenia; NTL, Neocortical temporal lobe lesions; NTLRx, Neocortical temporal lobe resections; OFC, Orbitofrontal cortex; OL, Occipital lobe; OLRx, Occipital lobe resections; OPCRIT, Operational Criteria Checklist for Psychotic Illness; OXC, Oxcarbazepine; PANSS, Positive & Negative Syndrome Scale; PET, Positron emission tomography; PHG, Parahippocampal gyrus; PHG LesX, Parahippocampal gyrus lesionectomy; PIM, Postictal manic; PIP, Postictal psychosis; PIQ, Performance IQ; PL, Parietal Lobe; PNES, Psychogenic non-epileptic seizures; POMS, Profile of Mood States; Pre-TLE-op, Before temporal lobe epilepsy surgery; PSE, Present State Examination; psych., Psychiatric; pts, patients; PVC, Partial volume correction; QOLIE-89, Quality of Life in Epilepsy Inventory-89; R, right; RAM, Radial atrophy mapping; rCBF, Regional cerebral blood flow; rCMRO2, Regional oxygen metabolism; RDC, Research Diagnostic Criteria; rOER, Regional oxygen extraction ratio; SADS, Schedule for Affective Disorders and Schizophrenia; SBM, Surface-based morphometry; SCID, Structured Clinical Interview for DSM-IV; SCIP-P, Adapted SCID for patients with epilepsy; SCZ, Schizophrenia; SDAS-21, Social Dysfunction and Aggression Scale; SDQ-20, Somatoform Dissociation Questionnaire-20; SE, Status epilepticus; secs, Seconds; SF, Superior frontal; sig., Significant; SMA, Supplementary motor area; SPECT, Single-photon emission computed tomography; SPM, Statistical parametric mapping; SSSI, Social stress & support interview; ST, Superior temporal; STAI, State-Trait Anxiety Inventory; STG, Superior temporal gyrus; SWM (BE), Spatial working memory (between errors), sz, Seizure; sz freq, seizure frequency; TH, Thalamus; TL, Temporal lobe; TLE, temporal lobe epilepsy; TMT, Trail Making Test; Uni-, Unilateral; VBM, Voxel-Based Morphemetry; VIQ, Verbal IQ; Wmem, working memory; WM, White matter; Y, Yes; yr(s); year(s).

Appendix 2.

University College London Hospitals NHS
NHS Foundation Trust

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The National Hospital for Neurology and Neurosurgery
Neuropsychiatry Department
Queen Square, London, WC1N 3BG

Telephone: 020 7837 3611
Department Facsimile: 020 7676 2051

PATIENT INFORMATION SHEET

Version: 1.2 - Oct 2009
Project ID: 08/0220

1. Study Title: Psychiatric outcome of surgery for temporal lobe epilepsy and relationship to cognitive function

2. Invitation

We would like to invite you to participate in a project investigating psychological and cognitive problems following surgery for epilepsy. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

3. What is the purpose of the study?

The main purpose of this study is to investigate whether psychological symptoms such as depression or anxiety are influenced by cognitive function (e.g. memory, planning, decision making skills) after surgery for temporal lobe epilepsy.

4. Why have I been chosen?

You have been invited to take part because you are on the waiting list to have surgery for epilepsy.

5. Do I have to take part?

It is entirely up to you to decide whether or not to take part.
If you do decide to take part you will be asked to sign a consent form, of which you will keep a copy.
You will still be free to change your mind at any time and without giving a reason.
Your decision not to take part, or a decision to withdraw, will not affect the medical care you receive.
Unless you disagree, we will inform your general practitioner that you have agreed to participate in this study.

6. What is involved in the study?

If you agree to take part in this study, we would like to ask you to attend appointments with a research psychologist once before surgery and at 6, 12 and 24 months after your surgery. During these appointments, the following procedures will be conducted:

(i) The research psychologist will interview you about details in your medical history and any psychological symptoms you may be experiencing. We would like to ask you to fill in questionnaires about your emotions and behaviour. This takes approximately an hour. If possible, we would also like to ask a family member or friend who knows you well to fill in questionnaires about your emotions and behaviour, but only if you agree.
(ii) We will also administer some tests of memory, attention, planning, decision making skills which should take about an hour.

A copy of both the signed consent form and this information sheet will stay with you.

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PATIENT INFORMATION SHEET

7. What will happen to me if I take part?
We will arrange appointments for you to attend The National Hospital, London or National Society for Epilepsy (NSE), Chalfont St Peter. You will be met by the research psychologist when you arrive, who will explain the study again. You will be asked to sign the consent form of which you will be given a copy. You will also have the opportunity to ask any questions. You will be with us for about 2 hours on each occasion. Travel expenses will be refunded.

8. What are the possible risks of the study?
There are very few risks as this does not involve any invasive procedures. If at any stage you find the clinical assessments or cognitive testing too stressful, you are free to stop the interview or withdraw from the study.

9. What are the possible benefits of taking part?
There is no direct clinical benefit to you in taking part. However, if information is found that is likely to affect your treatment, this will be passed on to your Consultant.

10. What information is held about me?
Information about you will be stored on a computer during this research project. This will include your name and contact details to allow us to keep in contact with people we have recruited. Clinical information (your diagnosis, drugs you are taking and any relevant medical or family history) will be kept separately on paper records and coded on computer to allow us to study any relationships between your diagnosis or medication and the study results. All information will be kept secure and strictly confidential, accessible only to those involved directly in this research. No information will be passed to any third parties or outside the EU for any reason without your explicit consent. The data will be kept securely at the National Society for Epilepsy in a locked cabinet and secured computer under the supervision of Dr. J Foong and Dr P Thompson. Your personal information will be anonymised, this means that your name will not be with the research data but linked by a separate code. All data will be stored under password-protection.

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

11. What if the findings affect me during the study?
If during the course of the study, we are concerned that you are experiencing serious psychological problems, such as depression or anxiety, we would like to inform your GP and discuss with you any arrangements for appropriate psychological support/treatment.

12. What will happen to the results of the research study?

A copy of both the signed consent form and this information sheet will stay with you.

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PATIENT INFORMATION SHEET

The results of this research may be published in the scientific literature, however this will never include any identifying details and your identity will always remain anonymous. Details of publications by the Department of Clinical and Experimental Epilepsy and National Society for Epilepsy can be obtained from our website. All personal data will be destroyed at the end of the study and you may be contacted if further research is planned.

13. Who is organising and funding the research?

This study is organised by researchers from the Department of Neuropsychiatry at the National Hospital for Neurology and Neurosurgery and the Department of Clinical and Experimental Epilepsy of the Institute of Neurology, University College London. The study has been funded by the Henry Smith Charity.

12. Who has reviewed the study?

All proposals for research involving human subjects are reviewed by an ethics committee before they can proceed. This project has been reviewed by The National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee.

13. What if something goes wrong?

If you are not happy with any aspects of the study, you have the right to complain through the UCLH complaints procedure: UCLH NHS Foundation Trust Patient Advice and Liaison Service (PALS) located at the Ground Floor Atrium, University College Hospital, 235 Euston Road, London NW1 2BU. Telephone: 020 7380 9975. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns of this study, the normal National Health Service complaints mechanisms should be available to you.

14. Feedback

If you participate in this research project we would like your feedback afterwards. Please give us feedback of what we should change and what could be improved. Please also indicate whether you would be willing to be invited by phone, e-mail, mail or personal contact to participate in a research project again.

15. Further Information

If you, your relatives or friends have any questions about participating in this study, please contact Dr Jacqueline Foong, Consultant Neuropsychiatrist, NHNN on 0207 8373611 Ext 3425 or Dr Pam Thompson, Senior Lecturer, Department of Clinical and Experimental Epilepsy, ION and NSE on 01494 601346.

Thank you.

A copy of both the signed consent form and this information sheet will stay with you.

University College London Hospitals NHS
NHS Foundation Trust

The National Hospital for Neurology and Neurosurgery
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CONSENT FORM

Centre Number:
Patient Identification Number for this study:

UCLH Project ID number: 08/0220
Form version: 1.2 – October 2009

Title of project: **PSYCHIATRIC OUTCOME OF SURGERY FOR TEMPORAL LOBE EPILEPSY AND RELATIONSHIP TO COGNITIVE FUNCTION**

Principal Investigator : **Dr Jacqueline Foong**

	Please initial box
1. I confirm that I have read and understood the information sheet dated Oct/09 (version 1.2) for the above study and have had the opportunity to ask questions.	☐
2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study.	☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
4. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from UCLH NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
5. I understand that my GP will be informed of my participation in the study.	☐
6. I agree to take part in the above study.	☐

Name of participant	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher (to be contacted if there are any problems)	Date	Signature

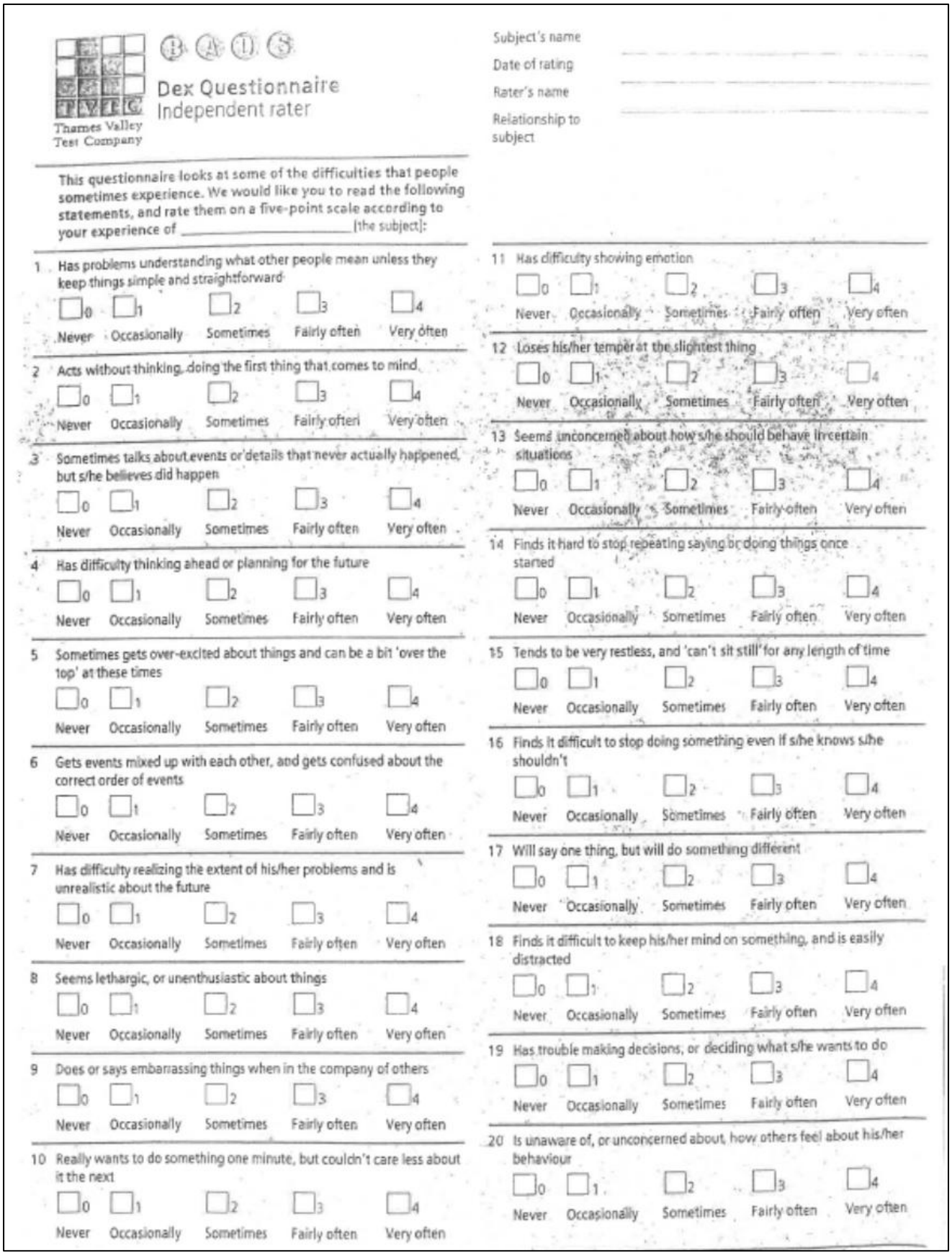
Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCLH project number at the top this consent form.

/N 1/1 CF Version 1.2 - November 2009

1 form for Patient; 1 to be kept as part of the study documentation, 1 to be kept with hospital notes

Appendix 3.



Thames Valley Test Company

B A D S

Dex Questionnaire
Independent rater

Subject's name
Date of rating
Rater's name
Relationship to subject

This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements, and rate them on a five-point scale according to your experience of _____ [the subject]:

1 Has problems understanding what other people mean unless they keep things simple and straightforward
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

2 Acts without thinking, doing the first thing that comes to mind
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

3 Sometimes talks about events or details that never actually happened, but s/he believes did happen
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

4 Has difficulty thinking ahead or planning for the future
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

5 Sometimes gets over-excited about things and can be a bit 'over the top' at these times
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

6 Gets events mixed up with each other, and gets confused about the correct order of events
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

7 Has difficulty realizing the extent of his/her problems and is unrealistic about the future
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

8 Seems lethargic, or unenthusiastic about things
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

9 Does or says embarrassing things when in the company of others
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

10 Really wants to do something one minute, but couldn't care less about it the next
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

11 Has difficulty showing emotion
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

12 Loses his/her temper at the slightest thing
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

13 Seems unconcerned about how s/he should behave in certain situations
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

14 Finds it hard to stop repeating saying or doing things once started
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

15 Tends to be very restless, and 'can't sit still' for any length of time
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

16 Finds it difficult to stop doing something even if s/he knows s/he shouldn't
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

17 Will say one thing, but will do something different
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

18 Finds it difficult to keep his/her mind on something, and is easily distracted
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

19 Has trouble making decisions, or deciding what s/he wants to do
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

20 Is unaware of, or unconcerned about, how others feel about his/her behaviour
☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

BADS

Dex Questionnaire
Self-rating

TVTC Thames Valley Test Company

Subject's name _____

Date _____

This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements, and rate them on a five-point scale according to your own experience:

1 I have problems understanding what other people mean unless they keep things simple and straightforward

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

2 I act without thinking, doing the first thing that comes to mind

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

3 I sometimes talk about events or details that never actually happened, but I believe did happen

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

4 I have difficulty thinking ahead or planning for the future

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

5 I sometimes get over-excited about things and can be a bit 'over the top' at these times

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

6 I get events mixed up with each other, and get confused about the correct order of events

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

7 I have difficulty realizing the extent of my problems and am unrealistic about the future

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

8 I am lethargic, or unenthusiastic about things

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

9 I do or say embarrassing things when in the company of others

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

10 I really want to do something one minute, but couldn't care less about it the next

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

11 I have difficulty showing emotion

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

12 I lose my temper at the slightest thing

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

13 I am unconcerned about how I should behave in certain situations

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

14 I find it hard to stop repeating saying or doing things once I've started

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

15 I tend to be very restless, and 'can't sit still' for any length of time

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

16 I find it difficult to stop myself from doing something even if I know I shouldn't

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

17 I will say one thing, but will do something different

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

18 I find it difficult to keep my mind on something, and am easily distracted

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

19 I have trouble making decisions, or deciding what I want to do

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

20 I am unaware of, or unconcerned about, how others feel about my behaviour

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

Appendix 4.

BDI®-FastScreen for medical patients

Today's Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

BDI–FastScreen

This questionnaire consists of groups of statements. Please read each group of statements carefully, then pick out the one statement in each group which best describes the way you have been feeling during the past 2 weeks, including today! Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle the statement which has the largest number.

1.
- **0** I do not feel sad.
- **1** I feel sad much of the time.
- **2** I am sad all the time.
- **3** I am so sad or unhappy that I can't stand it.

2.
- **0** I am not discouraged about my future.
- **1** I feel more discouraged about my future than I used to be.
- **2** I do not expect things to work out for me.
- **3** I feel my future is hopeless and will only get worse.

3.
- **0** I do not feel like a failure.
- **1** I have failed more than I should have.
- **2** As I look back, I see a lot of failures.
- **3** I feel I am a total failure as a person.

4.
- **0** I get as much pleasure as I ever did from the things I enjoy.
- **1** I don't enjoy things as much as I used to.
- **2** I get very little pleasure from the things I used to enjoy.
- **3** I can't get any pleasure from the things I used to enjoy.

5.
- **0** I feel the same about myself as ever.
- **1** I have lost confidence in myself.
- **2** I am disappointed in myself.
- **3** I dislike myself.

6.
- **0** I don't criticize or blame myself more than usual.
- **1** I am more critical of myself than I used to be.
- **2** I criticize myself for all of my faults.
- **3** I blame myself for everything bad that happens.

7.
- **0** I don't have any thoughts of killing myself.
- **1** I have thoughts of killing myself, but I would not carry them out.
- **2** I would like to kill myself.
- **3** I would kill myself if I had the chance.

1 1 2 A B C D E

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_____ Total

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Appendix 5.

BAI®

AME _____ DATE _____

elow is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by each mptom during the PAST WEEK, INCLUDING TODAY, by placing an X in the corresponding space in the column next to each symptom.

	NOT AT ALL	MILDLY It did not bother me much.	MODERATELY It was very unpleasant, but I could stand it.	SEVERELY I could barely stand it.
1. Numbness or tingling.				
2. Feeling hot.				
3. Wobbliness in legs.				
4. Unable to relax.				
5. Fear of the worst happening.				
6. Dizzy or lightheaded.				
7. Heart pounding or racing.				
8. Unsteady.				
9. Terrified.				
10. Nervous.				
11. Feelings of choking.				
12. Hands trembling.				
13. Shaky.				
14. Fear of losing control.				
15. Difficulty breathing.				
16. Fear of dying.				
17. Scared.				
18. Indigestion or discomfort in abdomen.				
19. Faint.				
20. Face flushed.				
21. Sweating (not due to heat).				

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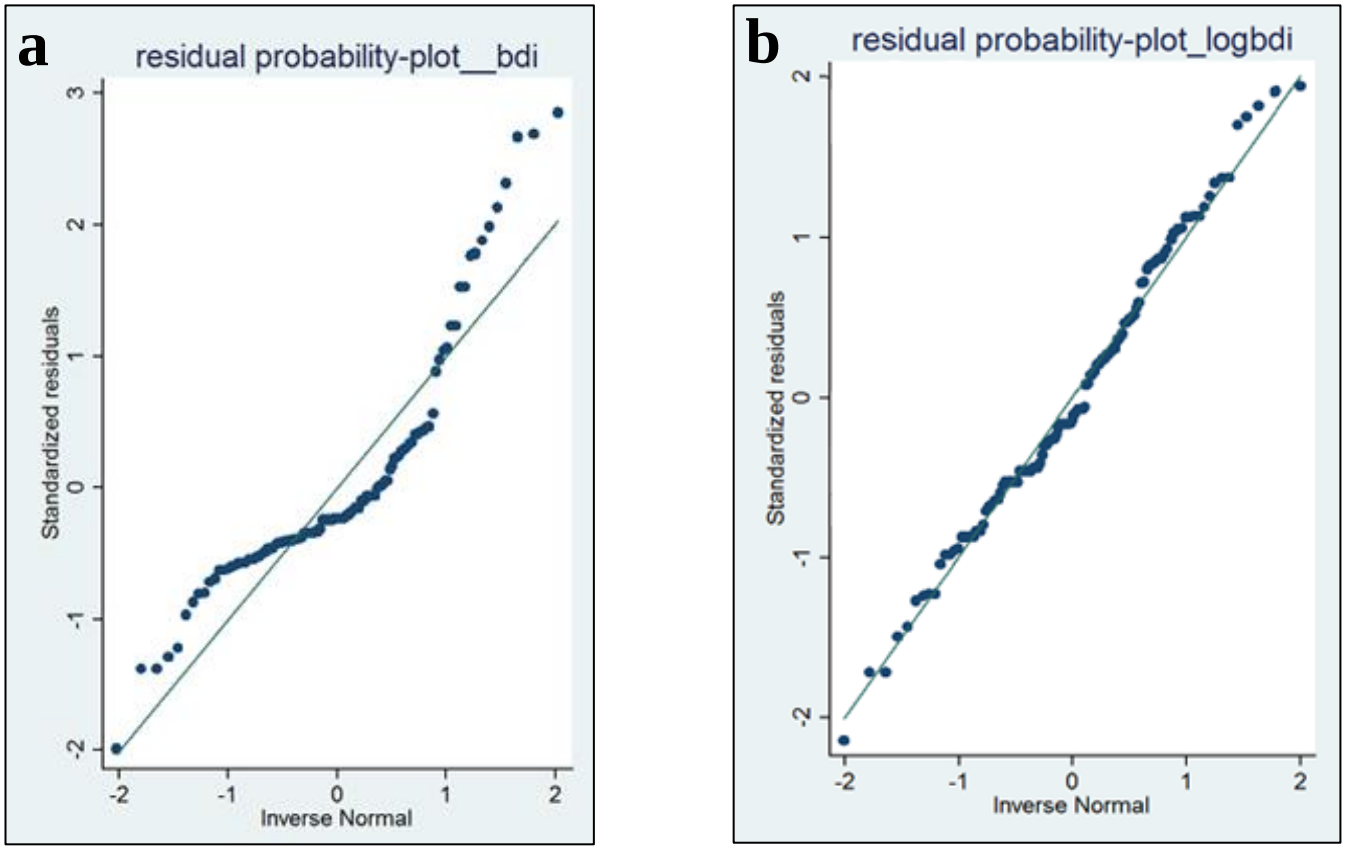
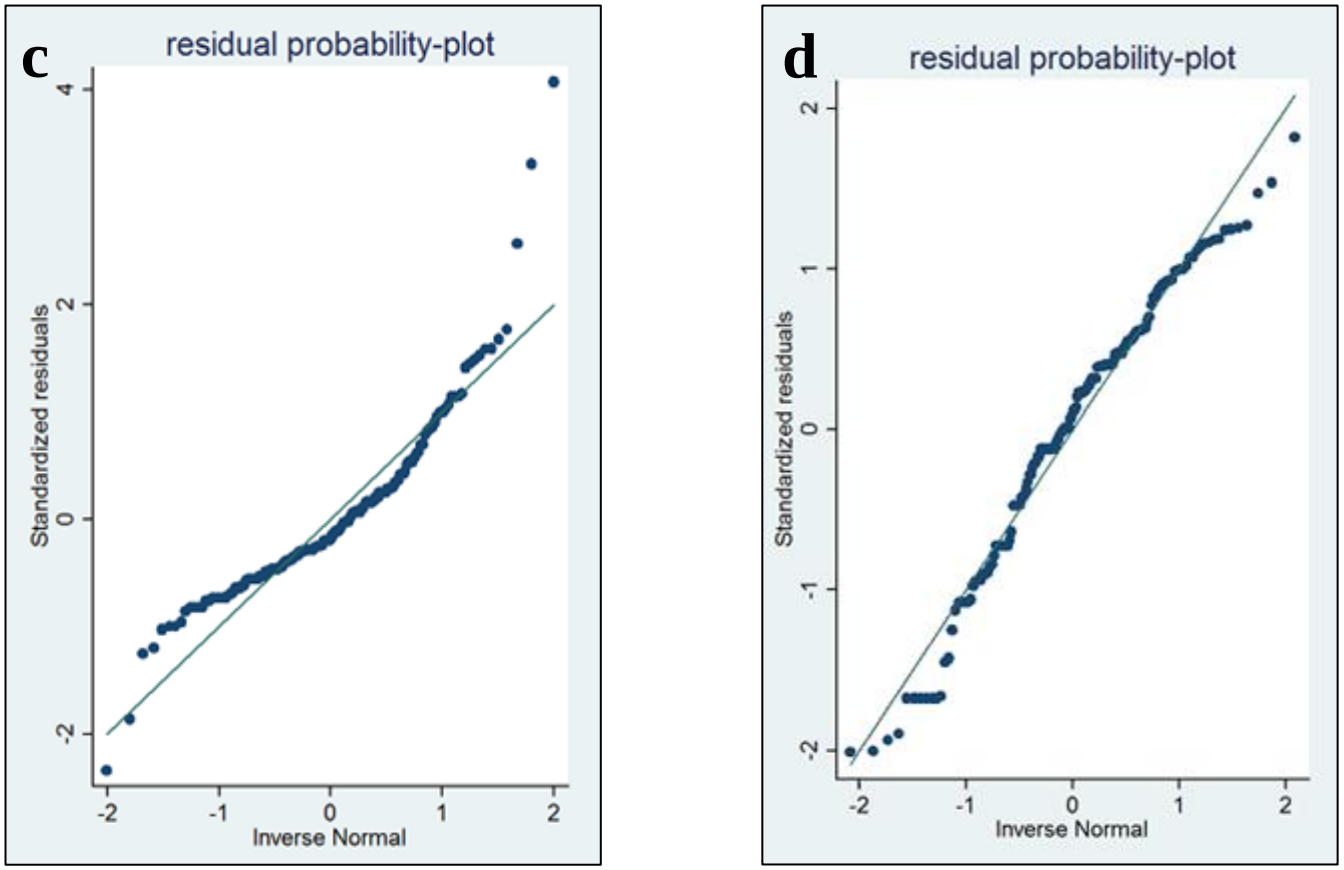
Appendix 6.

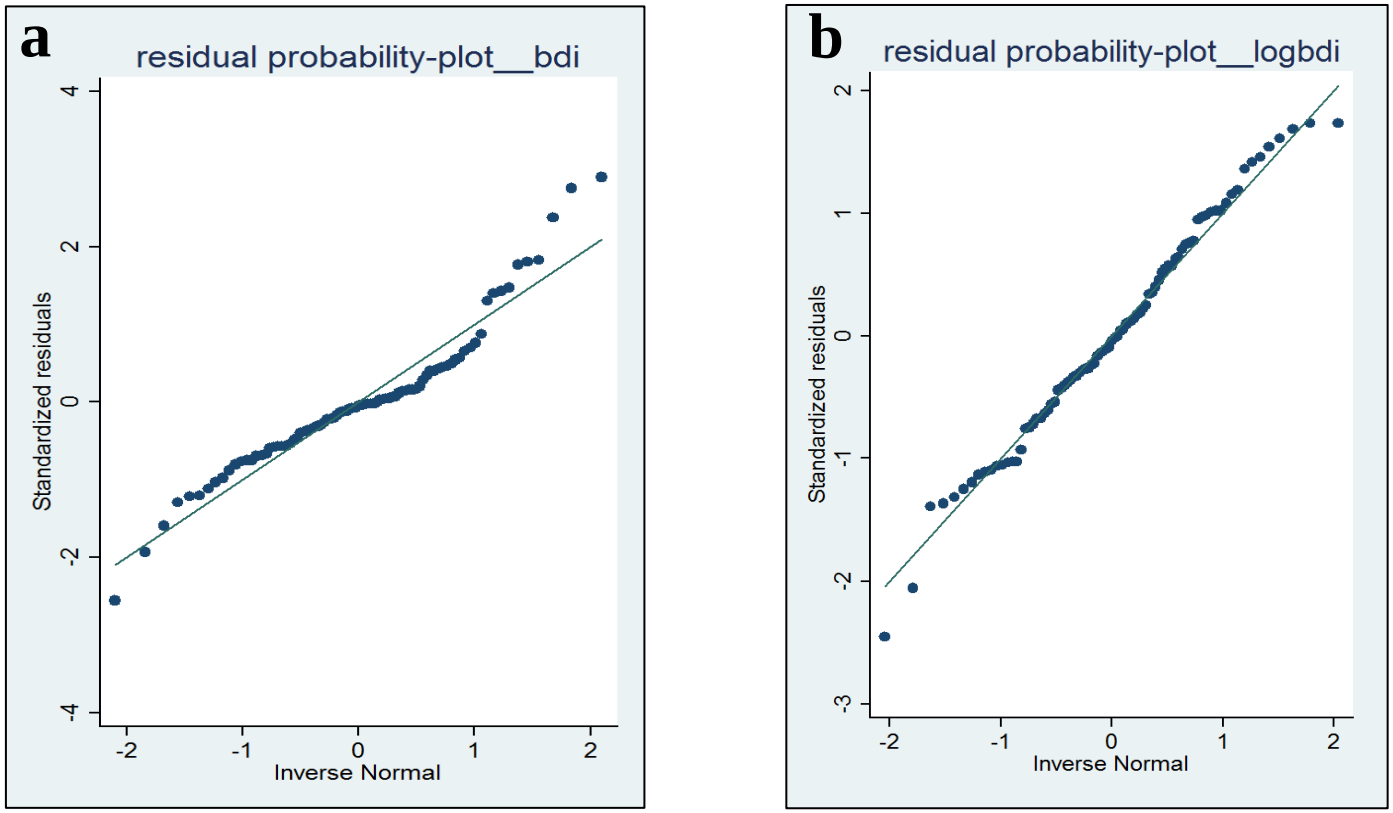


BDI-FS probability plots. *a) Indicating that there were marked deviations from the predicted line; the assumption of normally distributed residuals has been violated. b) Normally distributed BDI-FS residuals following a logarithmic transformation*



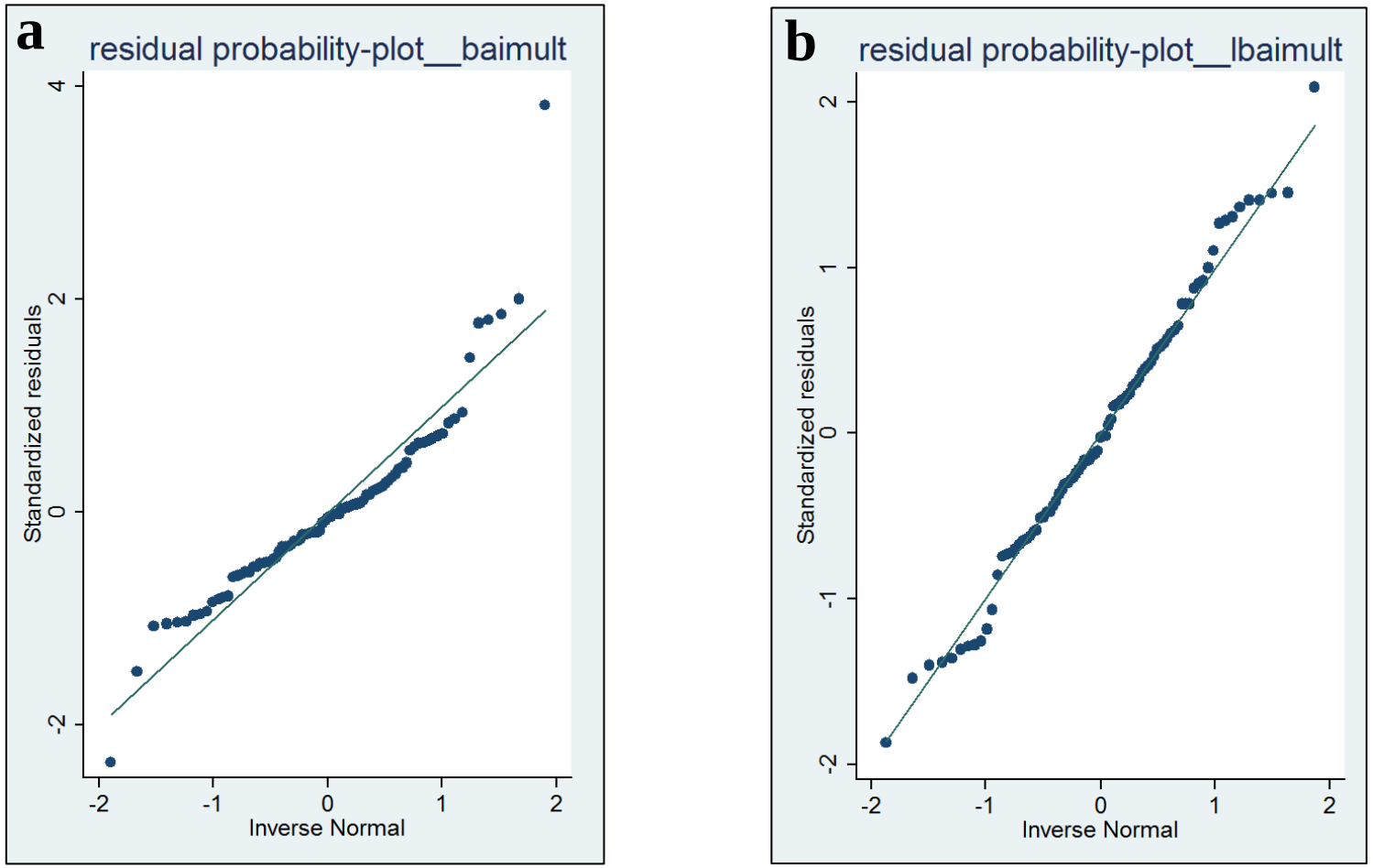
BAI probability plots. c*) Indicating that there were marked deviations from the predicted line; the assumption of normally distributed residuals has been violated. d) Normally distributed BAI residuals following a logarithmic transformation*

Appendix 7.



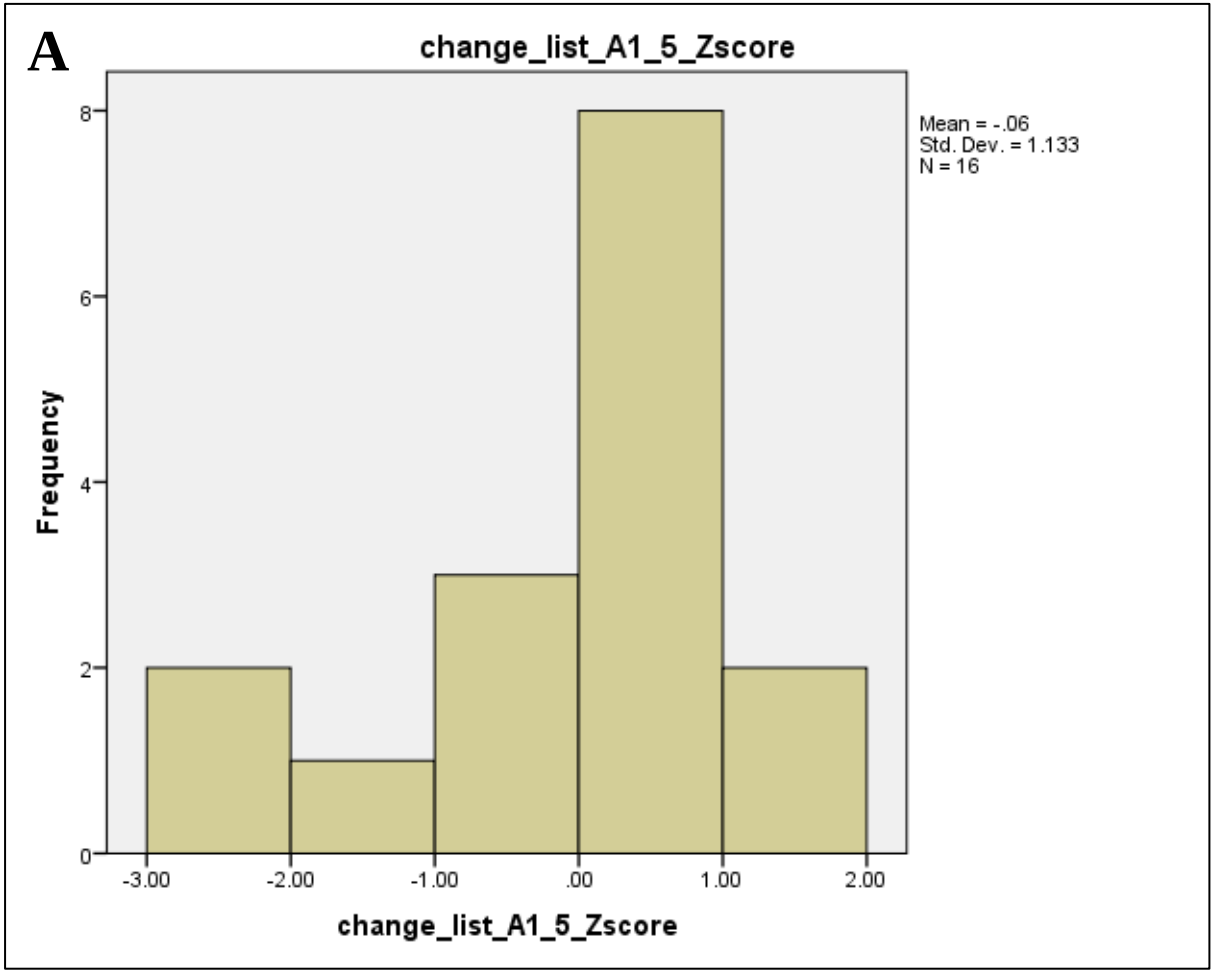
Multivariable (a) non-log and (b) log- BDI-FS random intercept only models.

Appendix 8.



Multivariable (a) non-log and (b) log- BAI random intercept only models.

Appendix 9.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Std. Dev. = 1.133
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Frequency
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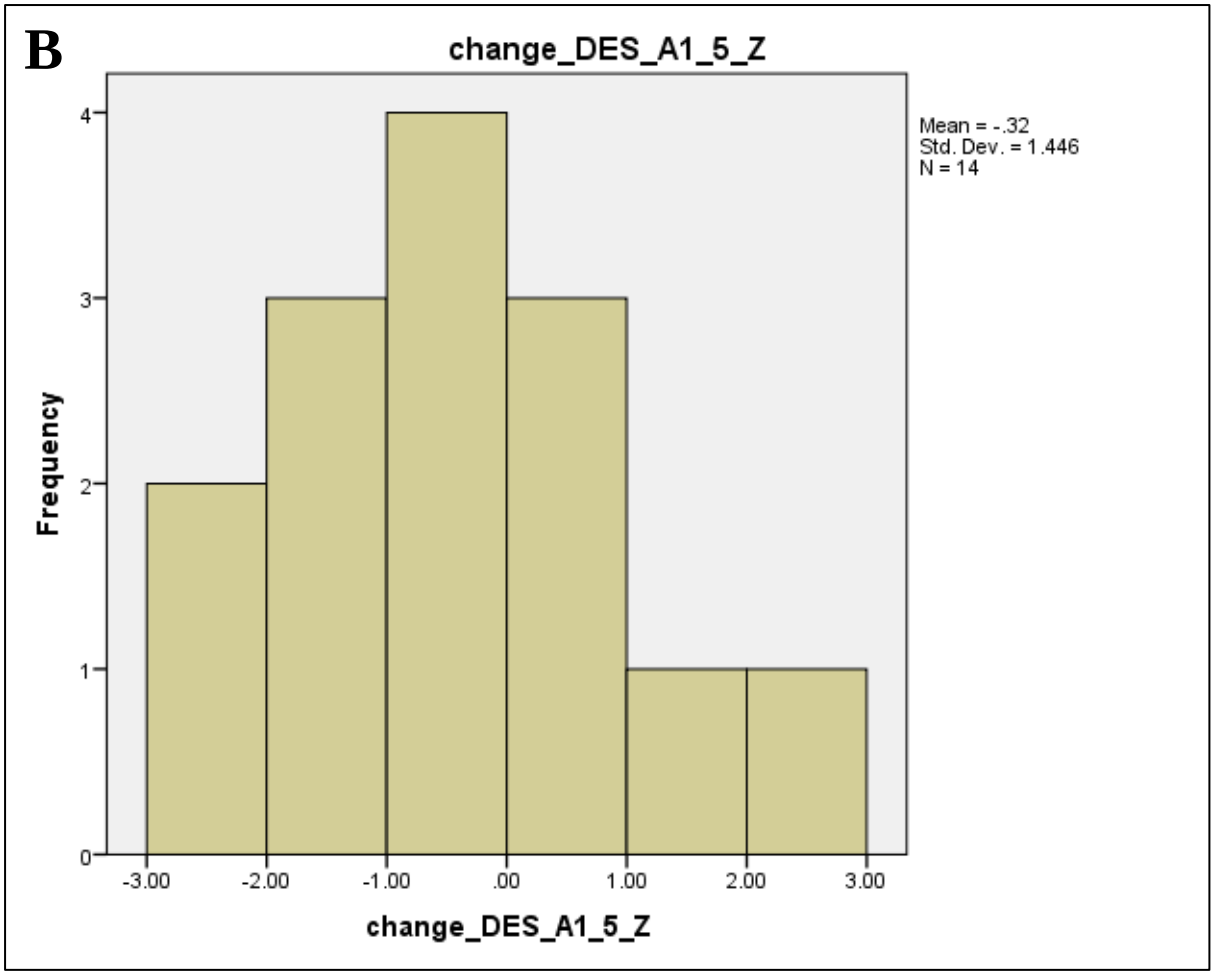
2
4
6
8
-3.00
-2.00
-1.00
.00
1.00
2.00
change_list_A1_5_Zscore


B
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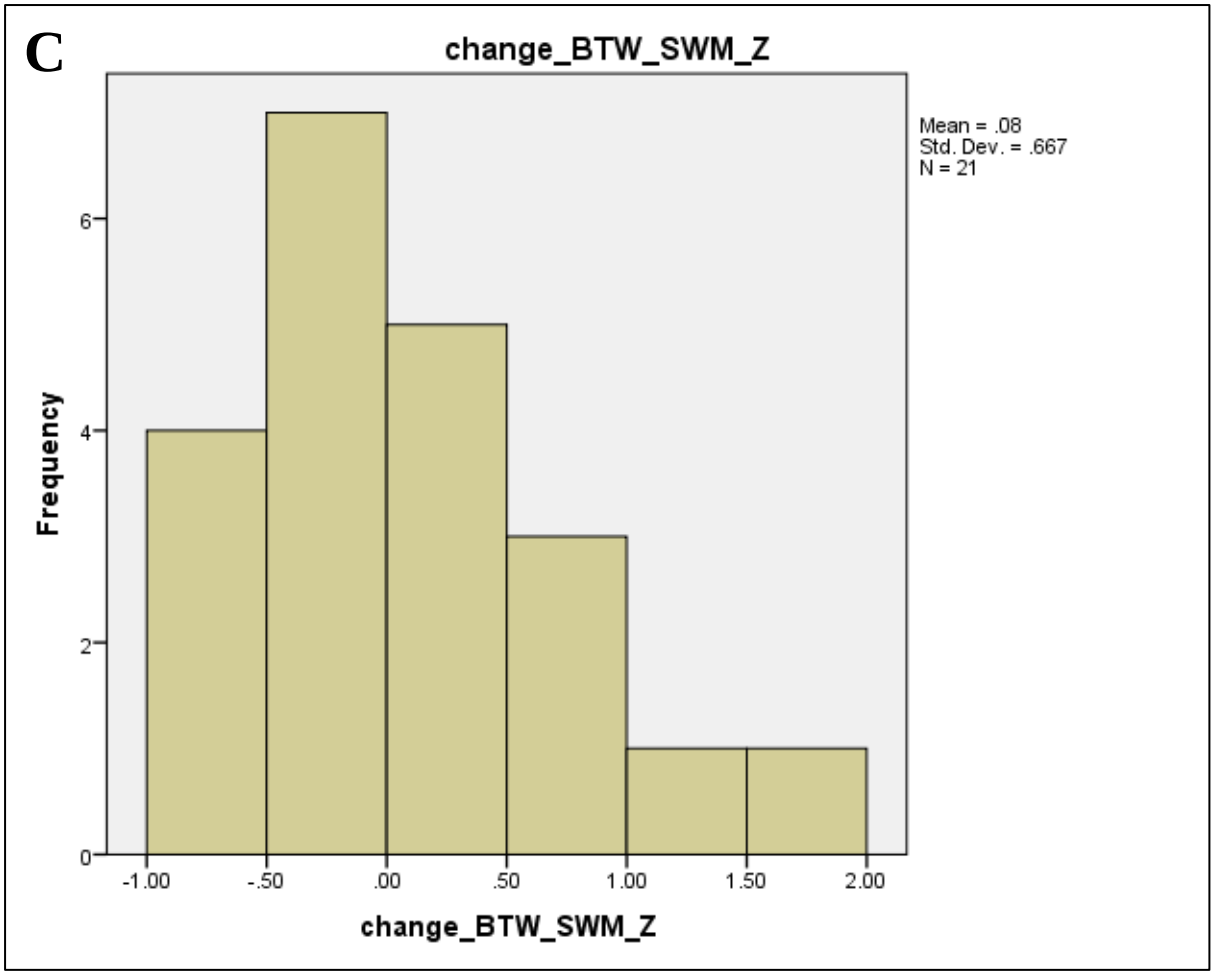
.00
1.00
2.00
3.00
change_DES_A1_5_Z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Std. Dev. = .667
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2
4
6
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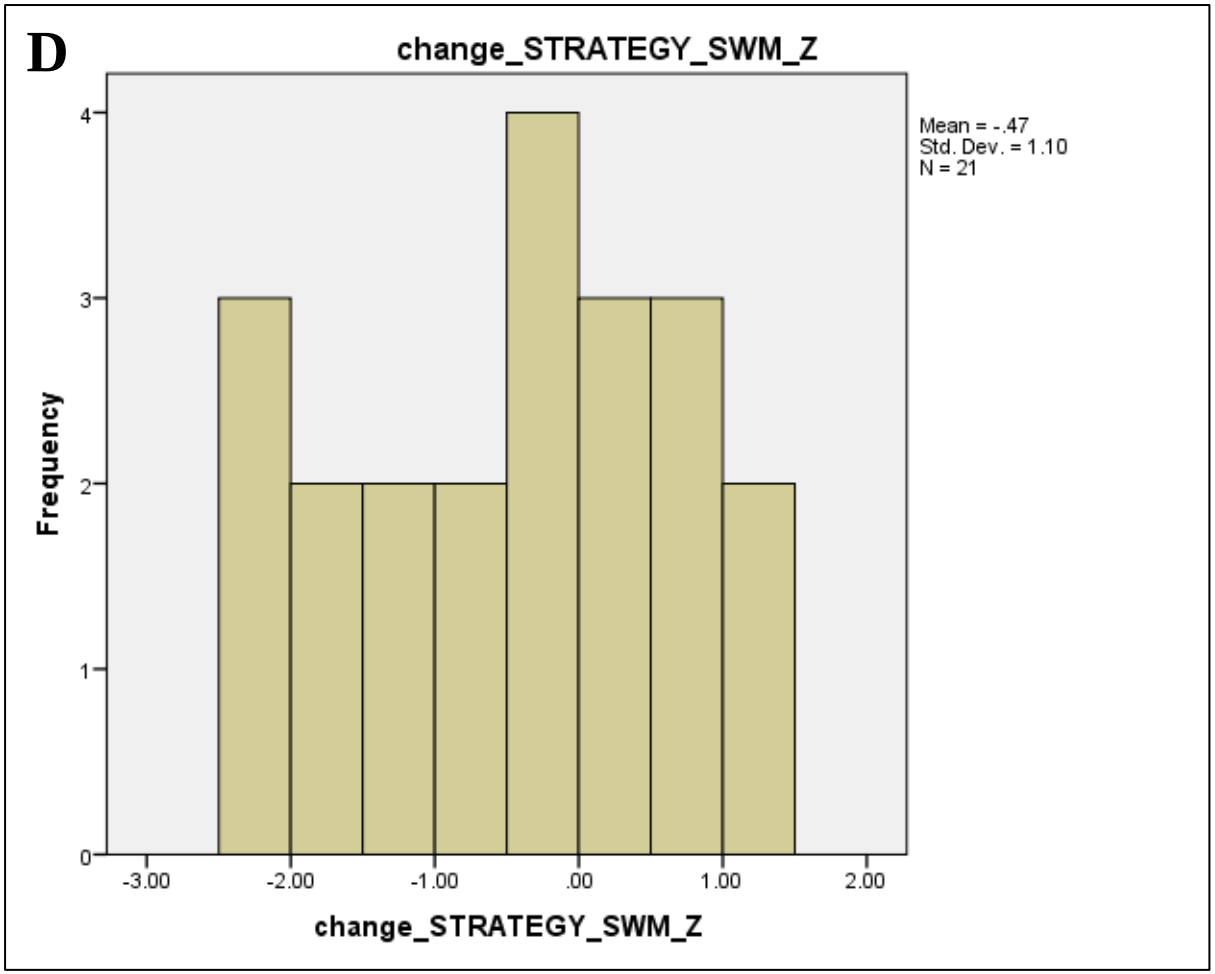
.00
.50
1.00
1.50
2.00
change_BTW_SWM_Z

D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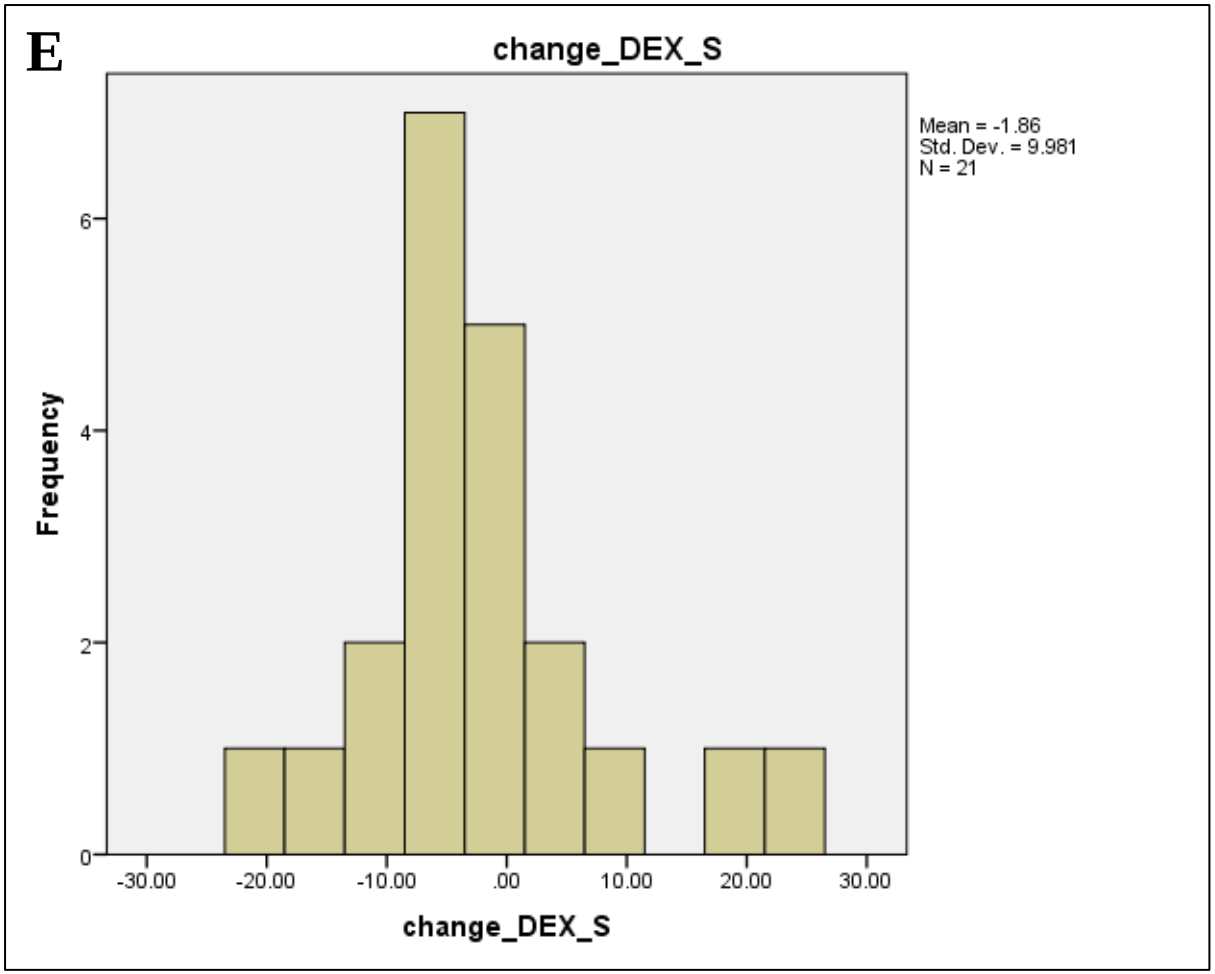
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10.00
20.00
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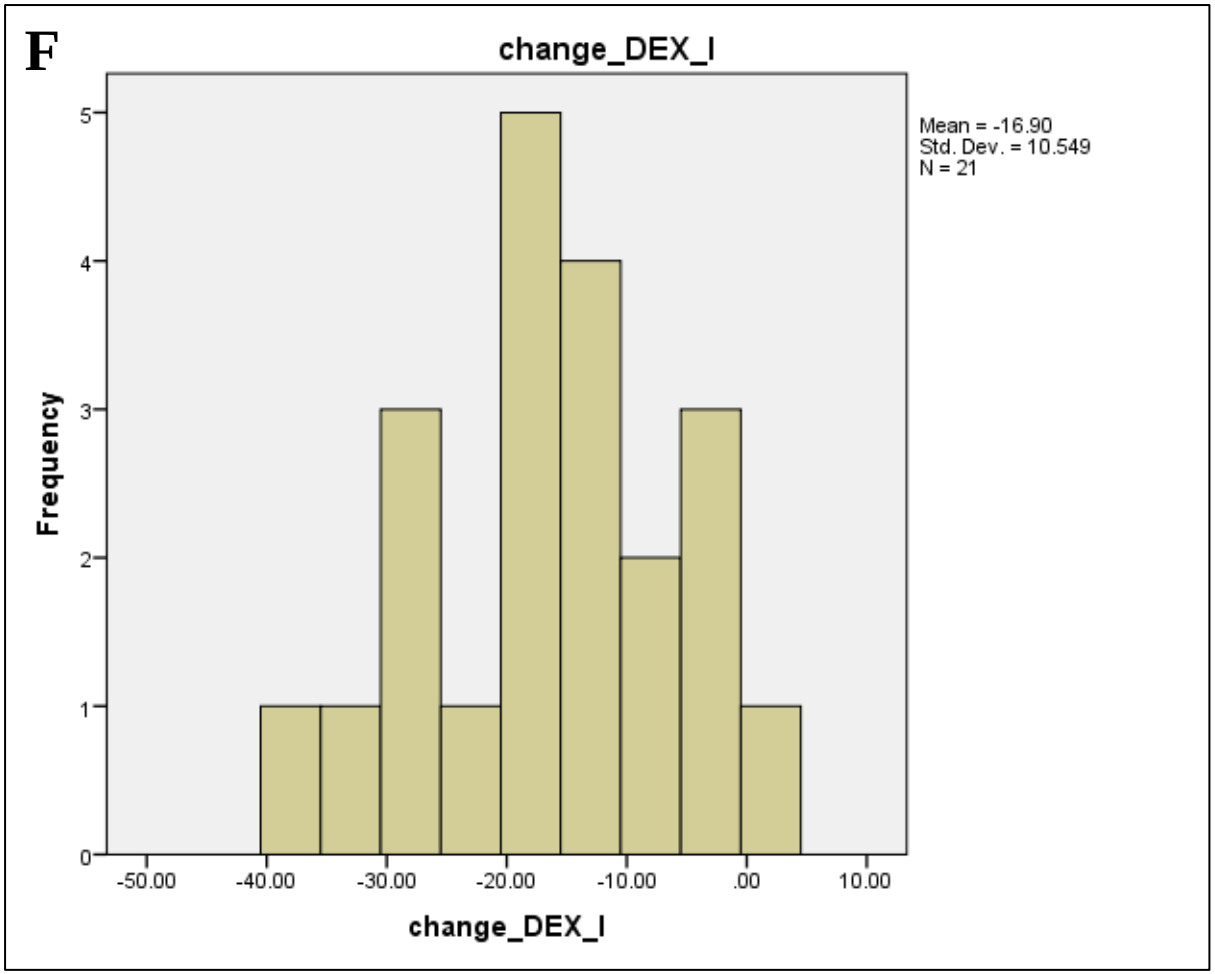
change_DEX_S

F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3
4
5
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-40.00
-30.00
-20.00
-10.00
.00
10.00
change_DEX_I

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