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What is the patient and carer burden of LGI1-autoimmune Limbic Encephalitis and its associated cognitive and behavioural changes; a mixed methods study using a neuropsychological test battery, semi-structured interviews and digital diaries

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What is the patient and carer burden of LGI1-autoimmune Limbic Encephalitis and its associated cognitive and behavioural changes; a mixed methods study using a neuropsychological test battery, semi-structured interviews and digital diaries

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Declaration of any previous submission of the work

The material presented here for examination for the award of a higher degree by research has not been incorporated into a submission for another degree.

Candidate's signature……*Rhea Zambellas*……………………………

Declaration of Authorship

I am the author of this thesis, and the work described therein was carried out by myself personally.

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Abbreviations

ACE-R	Addenbrooke's Cognitive Examination-Revised
AE	Autoimmune Encephalitis
aLE	Autoimmune Limbic Encephalitis
AMI	Apathy-Motivation-Index
B-ADL	Bayer Activities of Daily Living
BDI	Beck's Depression Inventory
CIS	Carer Information Sheet
CASPR2	Contactin-Associated Protein 2
CSF	Cerebrospinal Fluid
CI	Chief Investigator
DS	WMS-III Digit Span
EEG	Electroencephalogram
FSS	Fatigue Severity Scale
FBDS	Faciobrachial Dystonic Seizures
FINER	Feasible, Interesting, Novel, Ethical, and Relevant.
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression Scale
HC	Healthy Control
HRA	Health Research Authority
ICF	Informed Consent Form
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IS	Interview Schedule
IPA	Interpretive Phenomenological Analysis
LARS-Caregiver	Lile Apathy Rating Scale_Caregiver
LE	Limbic Encephalitis
LESS	Limbic Encephalitis Sub Study. (Used as a participant patient and carer code)
LGI1	Leucine-rich Glioma Inactivated Protein
MAXQDA	Software for qualitative and mixed method analysis
MM	Mixed Methodology
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis

MTL	Medial Temporal Lobe
NMDA-R	N-Methyl-D-Aspartate-Receptor
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory Caregiver Distress
NBM	Narrative-Based Medicine
NPI	Neuropsychiatric Inventory
NPTB	Neuropsychological Test Battery
PD	Parkinson's Disease
PIS	Patient Information Sheet
PICO	Patient problem, Intervention, Comparison or control, Outcome
PSQI	Pittsburgh Sleep Quality Index
PROMS	Patient Reported Outcome Measures
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SHAPS	Snaith Hamilton Pleasure Scale
SPIDER	Sample, Phenomenon of Interest, Design, Evaluation, Research type
TBI	Traumatic Brain Injury
WMS-III	Wechsler Maximal Span-III
WHO-5	World Health Organisation- Five Well-Being Index
ZBI	Zarit Burden Interview

Dedication

This thesis is dedicated to my mother, Rosemary.

Acknowledgements

First and foremost, I would like to thank all the participants who took part in my research. For those diagnosed with autoimmune limbic encephalitis, my appreciation is not only for the requirements of the neuropsychological testing in Oxford, but the time, effort and dedication they provided during the interviews and for the digital diaries. I will always feel honoured and humbled that they shared their openhearted experiences on the effects of the disease, for the purposes of this doctorate. My immense appreciation also reaches out to the 'carers' (spouse/partner/sibling), who have all shown courage and strength in, not only recalling traumatic and distressing experiences, but sharing the realisation that the impact could continue for years to come.

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Abstract

Background: Autoimmune Limbic Encephalitis (aLE) is a rare condition, targeting parts of the limbic regions of the brain. Instead of the immune system producing antibodies to destroy foreign invaders such as infections, the antibodies attach to healthy body tissue, in this case, the tissue in the limbic brain. This occurs when the antibodies target the LGI1 (leucine-rich glioma inactivated protein) or the CASPR2 (contactin-associated protein 2). There is still a need to learn how the symptoms and behavioural changes associated with these proteins, affect the patient long-term. This research is two-fold. First it identifies the negative sequelae of LGI1-aLE and determines the extent of the patients' cognitive and emotional impairment, together with an overview from the carers' assessment. Second, it investigates the patient and carer experiences of living with LGI1-aLE. With the current literature predominately focusing on the symptoms, diagnosis and appropriate treatment of the disease, this research has bridged the literary gap to integrate mixed methodology (MM) and add an original synthesis using interpretive phenomenological analysis (IPA) to provide an insight into the patient and carer perspectives on the burden of living with the chronic negative sequelae of LGI1-aLE.

Methods: A MM approach incorporating a triangulation method was used for 10 patients and 10 carers. A neuropsychological test battery (NPTB), which assessed the patient's memory, apathy, anhedonia, depression, fatigue and sleep quality, also used carer assessments on neuropsychiatric symptoms, apathy, carer burden, activities of daily living and memory/intelligence changes over ten years. Together with semi-structured interviews and digital diaries, these methods formed the three phases of data collection.

Results: Descriptive and inferential statistics demonstrated the severity of symptoms and comparisons at group level. There was very little evidence for group-level deficits across the tests/questionnaires administered. However, there were several patients that scored in the impaired range, especially in episodic memory, fluency and sleep quality. The interviews represented in five themes, revealed shared patterns and unique experiences which contribute markedly to the impact on daily

lives. Using Interpretative Phenomenological Analysis (IPA), some narratives showed consistencies with the NPTB findings, whereas others demonstrated contradictions. The direct effect of the acute symptoms illustrated a range of feelings including shock, fear and disappointment. The chronic symptoms demonstrated sadness and frustration with the patients' decline in motivation and confidence, and an increase in irritability and apathy, requiring adjustment from both the patient and carer. The impact on relationships varied in extent and severity, together with the degree of reliance and coping strategies in place. Returning to work in a different capacity and reduced grade evoked feelings of loss, yet a few patients embraced their new roles with pride. A final theme exposed a variety of feelings regarding the uncertainty of making future plans, although possibly attributable to old age and other pre-existing health conditions.

Conclusions and implications: The impact of LGI1-aLE leaves many patients with residual, long-term impairment after treatment. The knowledge produced from this thesis has enhanced the knowledgebase beyond traditional measurable datasets and emphasised the need for health professional learning, by exploring the narratives of those impacted by the disease.

Please note: The thesis will refer to these terms throughout: Autoimmune Encephalitis (AE) which is not antibody specific, Limbic Encephalitis (LE) which is not autoimmune specific, Autoimmune Limbic Encephalitis (aLE) which is not specific to LGI1, and LGI1 Autoimmune Limbic Encephalitis (LGI1-aLE), which is specific to the cohort of patients in this research.

CHAPTER ONE

Introduction

1.1 Background of Autoimmune Encephalitis

The human immune system plays a vital role in protecting the body from disease or threatening foreign bodies such as viruses, bacteria and parasites. It can also identify foreign bodies from the body's own healthy tissue. Antibodies are also known as immunoglobulins, which are a type of protective protein that are present in the bloodstream. The antigen is a molecule that activates leucocytes to bind to the outside of a pathogen, which in turn stimulates an immune response to produce antibodies. Antibodies are named according to the antigen they target. In 'autoimmunity' the body's immune system fails to recognise its own cells and tissues, therefore releasing proteins called 'autoantibodies' that attack healthy cells as if they were foreign. When the autoantibodies target the antigen on nerve cells in the limbic regions of the brain, they are known as 'LGI1' or 'CASPR2' (leucine-rich glioma inactivated protein or contactin-associated protein 2). These autoantibodies cause an encephalitis termed autoimmune limbic encephalitis (aLE) (Irani et al., 2011). This is a rare disease, characterised by inflammation of the limbic brain (primarily the hippocampus and amygdala) (Finke et al., 2017). The scope of this thesis examines LGI1 and not CASPR2 aLE, as each autoantibody carries specific symptoms which warrant separate research.

More recently, aLE has been rapidly recognised as a result of improved clinical experience and knowledge in neurological autoimmunity, which has distinguished and identified the many different causes of encephalitides (being the plural of one encephalitis). Although the incidence rate of aLE is expected to increase dramatically due to this improved knowledge, incidence data remain sparse (van Sonderen et al., 2016). One reason for this may be due to the frequency of aLE being underestimated in potentially unrecognised cases in elderly patients, with similar neurodegenerative symptoms (Guan, 2016). Another reason may be due to

misinterpretation of manifested symptoms showing similarity with some psychiatric symptoms (Herken & Prüss, 2017). There are different incidence rates for aLE across countries. It has been suggested that approximately 0.83 LGI1-aLE cases per million are present in people in the Netherlands (van Sonderen et al., 2016). Dubey et al. (2018) reported an incidence rate in the USA (between 1995-2015) for combined autoimmune and infectious encephalitis as 0.8 per 100,000 people. The incidence rate for any form of autoimmune encephalitis (AE) has been suggested as 13.7 per 100,000 people in Germany (Macher et al., 2018). These rates possibly remain underestimated, as knowledge continues to increase and improve across the clinical fields of neurology and psychiatry, together with improved antibody detection (Dubey et.al., 2018).

This increased and improved knowledge is based on the recognition that clinical diagnosis of aLE remains difficult, due to the similarities in the brain imaging and symptoms with other forms of autoimmune and infectious encephalitis (Lancaster, 2016). Therefore, by applying an understanding of the different types of autoimmune encephalitides, this demonstrates the differentiation between a paraneoplastic encephalitis associated with a cancerous tumour, a viral encephalitis, a bacterial encephalitis (infectious encephalitis), or even caused by a fungi or parasite. Notably, these encephalitides may share general symptoms such as headaches or confusion, but under closer inspection each type presents with very specific and unique symptoms

To further complicate an understanding of encephalitis, there are different autoimmune diseases such as vasculitis of the central nervous system which cause encephalitis (Berlit & Kraemer, 2014), and add to an already difficult diagnosis. To consider the different types of encephalitis, correct diagnosis is guided not only by the clinical examination of patients, but also by specialised tests including a lumbar puncture or cerebrospinal fluid (CSF) test and antibody tests to detect the specific antibody in the serum, (Graus et al., 2016). Incidentally, patients with new-onset

seizures or already established epilepsy, were not routinely tested for autoimmune antibodies until recent years (Kambadja et al. 2021), thus highlighting the importance of this testing to assist in correct and prompt diagnosis. Magnetic Resonance Imaging (MRI) of the brain may show a decreased T2 signal. This detects an abnormal electromagnetic signal, which is associated with intracranial pathologies and seizures. However, despite the cruciality of MRI characteristics in different encephalitides, researchers have discovered that MRIs may be in fact present nonspecific findings in certain cases. In anti-N-methyl-D-aspartate receptor –(NMDA-R) encephalitis, an autoimmune encephalitis, the brain scan was normal in approximately 60% of the patients they studied (Granerod et al., 2016). For the purpose of excluding the cause of seizures, an electroencephalogram (EEG) may also be useful in diagnosis.

By investigating the specific clinical symptoms of LGI1-aLE, using a tailored approach, this achieves a correct and prompt diagnosis, supports immediate treatment, and ultimately improves outcomes conducive to the patient's health. LGI1-aLE ischaracterised as the subacute onset of frequent seizures, cognitive impairment, and behavioural changes (Binks et al., 2018). Not only can these manifestations mimic similar clinical presentations in other autoimmune encephalitides, such as changes in behaviour, seizures, or memory deficits, but it is important to note that each autoantibody can present with different clinical findings. Hence, the two mentioned autoantibodies LGI1 and CASP2 are recognised and differentiated by specific findings, even though they are both associated with inflammation of the limbic brain (Lancaster, 2016). Table 1 below summarises the acute symptoms associated with LGI1-aLE, which are already established within the literature.

Table 1: Acute symptoms associated with LGI1-aLE

Faciobrachial dystonic seizures (FBDS).
Memory deficits
Psychiatric disorders such as altered personality and behaviour
Sleep disturbances

Given the importance of correct and prompt diagnosis of aLE, early consensus across neurology, neuropsychiatry and neuropsychology expertise can lead to the appropriate evaluation of the correct treatment, which ispredominantly presented in scientific literature as indicating improved outcomes for the patient. However, the patient experience and interpretation of the delayed or misdiagnosed disease, is rarely documented. In order to raise awareness of encephalitis, stories and narratives are presented from sufferers as encouraging and inspiring to other sufferers, to help understand the 'wounded brain'. This awareness of patient insight is successfully captured through their narratives, which are often portrayed on charity websites (The Encephalitis Society https://www.encephalitis.info/ and The Autoimmune Encephalitis Alliance https://aealliance.org/). However, there is a need for health professionals to recognise how narratives synthesise scientific and patient-carer communication.

1.2 Significance of the research

An overarching conceptual framework employing the mixed methodology (MM) approach and using the 'triangulation method', demonstrates the complexity of complementing the quantitative research with the qualitative research. The framework not only clarifies the design process, but conceptualises the multidimensional impact of the disease, by searching for further meanings, interpretations and comprehension of LGI1 aLE. Despite the lack of literature on the role of a conceptual framework in MM (Johnson and Onwuegbuzie, 2007), or an absence of ideas to guide its use (Evans, Coon and Ume, 2011), using a conceptual

framework helps direct the research inquiry, design, analysis and resources for this thesis. Furthermore, a conceptual framework is likely to demonstrate the purpose and significance of quantitatively evaluating the negative sequelae on LGI1-aLE patients, and also focus on the patients' experiences and perspectives through their narratives.A patient's narrative is a tool that can enrich scientific knowledge by offering valuable perceptions and adding a therapeutic aspect for the patient (Morris, 2008), and provide an individual perspective into experience, enabling a better understanding and insight for professionals and families (Easton, 2016). By investigating the impact of the longer-term features of cognitive and behavioural changes in LGI1-aLE, these perspectives are important. However, due to the patients' cognitive deficits, this may lead to less articulate and shorter narratives. Therefore, carers of patients offer a supplementary relevance in the recollection of events and provide an added benefit in the qualitative data collection of LGI1-aLE.

The use of a MM approach, and more specifically applying a triangulation method which combines both quantitative and qualitative methods to examine different aspects of an overall research question, is yet to be incorporated within LGI1-aLE research. Therefore, the strength of this thesis is that it offers   MM to understand the human experience of the impact of LGI1-aLE for both patients and carers, and not just the measurable symptoms. Informed by IPA, the data from semi-structured interviews and digital diaries raises awareness of the ongoing symptoms to the patient, together with the distress and burden to the carer, through the immersion of narratives and the researcher's reflective interpretation. The impact of the disease on the daily lives and altered relationship dynamics for the couple and the wider family, highlights ways to manage and enhance health professionals' and families' understanding.

1.3 Research Questions

The MM approach used here was designed to respond to the following research questions:

1. What are the negative sequelae on LGI1-aLE patients?

2. What is the carer interpretation of these negative sequalae?

3. How do the patients' and carers' narratives inform us of a truthful depiction of the impact of the disease?

1.4 Structure of thesis

Chapter Two provides a review of the various literary sources associated with aLE, offering a comprehensive understanding of the diagnosis and treatment. Much of the literature investigates the neuroscience background to the autoantibody LGI1, together with disease symptoms and treatment. However, limited evidence exists describing other key sources such as the use of neuropsychological assessments and narrative-based medicine (NBM) in LGI1-aLE patients. Furthermore, the patient experiences and carer perspectives using IPA to interpret and identify specific aspects of the disease's impact are rarely presented. The review accentuates the gap in qualitative research, and the need to incorporate the patient and carer narrative.

Chapter Three describes the aims and objectives. This is followed by a description of the philosophical, epistemological, and ontological foundations which seek to explore the meaning of LGI1-aLE through quantitative and qualitative paradigms. An overview of the triangulation method illustrates its rationale in this thesis to undertake a Phase 1 quantitative data collection (neuropsychological test battery -NPTB) and analysis, which endeavours to capture the self-reports and assessments of the

patient in real-time, together with the perspectives of informants (carers) who live with them and know them well. In addition, the Phase 2 qualitative data collection (semi-structured interviews) and analysis, pursues a further exposure to the patient and carer perspective, allowing their voice to be heard through their own narratives. Phase 3 represents the qualitative data collection of digital diaries. Ethical considerations together with recruitment, and the informed consent process are detailed. Finally, this chapter endorses the MM approach using the triangulation method to complement both the quantitative and qualitative data.

Chapter Four examines the quantitative research findings to identify the extent of the patients' cognitive and emotional impairment, together with an overview of the carers' assessments. The impact of LGI1-aLE is complex and therefore, seeking an accurate representation is demonstrated using descriptive and interferential statistics. The areas of focus represent the symptoms causing the most impairment individually and at group level. Several patients lost points in memory and fluency tests, scored in the impaired range for sleep quality, and some experienced moderate apathy. There was no evidence for problematic fatigue or anhedonia reported by the patients themselves. Phase 1 NPTB patient and carer data summarise the clinical and neuropsychological variables of interest, which identify positive associations in domains such as fatigue/apathy, apathy/anhedonia, and the ability to undertake daily activities/carer burden.

Chapter Five seeks to capture the personal impact of LGI1-aLE through the perspectives of the patient and carer, derived during Phases 2 and 3 qualitative findings. This chapter illustrates the data collection process, and through the process of IPA identifies five themes. These themes represent the core concepts and experiences of the disease, where IPA was key in the interpretation and description of meanings, using the phenomenological approach to capture the complexity of LGI1-aLE. Furthermore, this chapter symbolises engagement and reflection with the patient and carer, though their personal narratives offering unique and shared

experiences. In addition, any relevant digital diary data is highlighted and incorporated into the themes to add a third frame of reference.

Chapter Six presents the discussion on the MM findings, organised using quantitative and qualitive results across aspects of acute and chronic symptoms of the disease. Through the unique insight of the patient and carer experiences, living with memory loss, fatigue, apathy and behavioural changes, the onus is demonstrated through the inevitable adjustment in problematic areas of returning to work, relationships and future planning Finally, the increased responsibility on the carer together with the adjustment to living with LGI1-aLE for the patient, carer and families, is discussed. Any consistencies and variances are highlighted across both methodologies.

The final chapter, the conclusion, draws the results from MM to provide an overarching account of LGI1-aLE. The quantitative data supports current evidence of memory loss, apathy and fatigue, together with fluency impairment and poor sleep quality. The qualitative data captures the personal impact of the disease on the patient, and a 'silent suffering' amidst their memory, fatigue and emotion dysregulation. The carer perspective highlights levels of distress and burden, previously unreported. Finally, the implications for professional practice and research are shown, together with the summary of the thesis' contribution to knowledge.

CHAPTER TWO

Literature review

2.1 Introduction to the literature review

The literature available on aLE is extensive and stretches across multiple, broadly conceived disciplines, such as neuroscience, neuropsychiatry and neuropsychology. However, due to the rarity of the disease, focus is seldom extended to patient and carer experiences and narratives, nor represented in MM, leading to a noticeable methodological gap between neuroscience/quantitative and person-centred/qualitative approaches.

Clinical features, neuroimaging, diagnostic testing, and the use of neuropsychological assessments, are useful for the correct diagnosis and prompt treatments employed in evidence-based medicine, which considers empirical and scientific research as exemplar standard. Within this scope, the literature review is divided into five key sections which encompass the neuroscientific/quantitative to the human-centred/qualitative evidence: 1) the neuroscience background to the autoantibody LGI1 combined with diagnosis and treatment; 2) neuropsychological assessments; 3) NBM; 4) patient experiences in AE and Interpretive Phenomenological Analysis (IPA); and 5) carer perspectives in AE. Collectively, these sections underpin the rationale for using a range of search strategies available on LGI1-aLE.

2.2 Literature review process

A detailed database search in neuroscientific and clinical journals, used the FINER criteria (feasible, interesting, novel, ethical, and relevant) (adapted by Aslam and Emmanuel, 2010), to formulate the focused research question, "what is the patient and carer burden of LGI1-autoimmune Limbic Encephalitis and its associated

cognitive and behavioural changes?" Due to the growing knowledge-base on antibody testing, diagnosis and current treatment over the last decade, articles within the last ten years were included. The focus of key words in the search strategy relied on the effective composition of criteria, such as including research published within a certain timeframe or in a certain language (Pautasso, 2013). Using PICO, an evidence-based model (see Appendix 1), allowed for refinement of key areas and categories for the search strategy (Appendix 2). Both PICO and SPIDER models (Cooke, Smith, & Booth, 2012) (Appendix 3) are recommended for greater specificity in MM and qualitative experiences respectively (Menthley et al., 2014). A full database search record is available in Appendix 4, together with the review summary (Appendix 5). Database access included SOLO advanced (2009-present), Embase (1974-present), PsycINFO (all years), MEDLINE (1946-present), PubMed (2009-present), Scopus (2009-present), and CINAHL (2009-present). The PRISMA Statement (Appendix 6) was used as a comprehensive critical appraisal of the literature, (Moher et al., 2009). In addition, neuroscience conferences were also useful sources of information for current clinical treatment and research. An online IPA support group, and online encephalitis charities provided evidence-based information to help with recognising and managing the acute symptoms and the effects of an acquired brain injury.

Regarding the emerging practice of using MM as a source of new knowledge to possibly influence disease intervention or policies (Bradshaw, Atkinson, and Doody 2017), this review revealed little evidence of drawing from multiple paradigms in aLE. According to Jason and Reed (2015), using MM combines the quantitative data to describe the magnitude of the illness, with the qualitative data to enhance understanding of the unique challenges that patients and families experience. This review also established the absence of encephalitis studies using digital diaries. Existing knowledge on digital diary use has demonstrated their effective use when self-reporting recordings of seizures (Fisher et al., 2012), their benefit when documenting self-administration of medications in neurology (Zettl et al., 2013), and capturing greater accuracy of real time daily symptoms in Parkinson's Disease (PD)

(Vizcarra et al., 2019). It has been suggested that sensitive information may benefit from the protected nature of electronic assessment, compared with paper diaries or personal interviews (Broderick, 2008). For LGI1-aLE patients and carers, making diary entries in the privacy of one's home was also beneficial when capturing sensitive or traumatic data. Furthermore, Page et al. (2018) advocated the use of digital diaries in a prospective study capturing the true impact of the disease over time. The five key sections below emphasise the sources of the existing body of literature, and its importance in the context of this research.

2.2.1 The diagnosis and treatment of LGI1-aLE

Most literature in the field of LGI1-aLE is based in neuroscience. Evidence suggests there are several challenges in making a correct and prompt diagnosis of LGI1-aLE, which precedes the decision to offer the most appropriate treatment. This includes firstly avoiding mistaking symptoms with other diseases or conditions, and distinguishing between similar clinical findings in other encephalitides, and secondly, commencing the recommended treatment. Despite some variability in the type of method used and the sample size in the reviewed literature, most of the published articles were case studies or retrospective case reports from around the world, including France (Aupy et al., 2013), Spain (Leypoldt, Armangue, and Dalmau, 2015), Canada (Vollmer and McCarthy, 2016) and Brazil (Simabukuro et al., 2016). The largest sample sizes of LGI1-aLE patients ranged from 16 to 30, which highlights the rarity of this disease, and places the sample size in this research as a justifiable number. Below are the subsequent findings on examination of the diagnosis and treatment.

Mistaking symptoms and distinguishable clinical/imaging findings: The majority of participants in this research experienced delayed diagnosis, and many were wrongly diagnosed. Therefore, in order to avoid misdiagnosis, the emphasis was on the combined importance of clinical, laboratory and MRI findings, together with shared

expertise across specialities. LGI1-aLE which presents with rapid neuropsychiatric decline, together with memory deficits and seizures, is sometimes mistakably diagnosed (Ramanathan et al., 2019). Therefore, differentiating patients with psychiatric presentation requires expertise and transparency of knowledge across specialities, before any treatment can be decided upon. It has been argued that immunotherapy could potentially help in patients with an autoimmune origin to their psychosis (Lennox et al., 2019), whereas patients with an AE would not benefit from antipsychotic mediation (Dalmau, 2019). Other conditions such as dementia may be initially suspected as they carry similarities in cognitive impairment. However, dementia carries a slower, chronic progression (Perera, Mueller & Stewart, 2020), unlike LGI1-aLE with its acute onset of frequent seizures, cognitive impairment, and behavioural changes.

Regarding other forms of autoimmune and non-autoimmune encephalitides, literary evidence distinguishes between similar clinical, imaging and laboratory findings found in the larger retrospective studies (Körtvelyessy et al., 2018; Macher et al., 2018). These articles reiterate the importance of starting treatment prior to antibody testing, even though symptoms may differentiate between other autoimmune diseases (Nosadini et al., 2015; Lancaster, 2016; Macher et al., 2018). Another form of AE, anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis, presents with psychotic behaviours such as delusions or hallucinations, and different epileptic characteristics (Al-Diwani et al., 2019). In contrast, it is associated with a coexistent teratoma, needing surgical removal, as well as immunotherapy and anti-epileptic medication. This illustrates the importance of distinguishing features during full body imaging.

On examination of viral infectious encephalitis such as tick-borne or herpes, this may present with fever, headaches, confusion and seizures (Kennedy, 2004), but will not present with specific symptoms associated with an AE (Lancaster, 2016). This emphasises the importance of an accurate medical history including recent travel

and activities. One of the specific symptoms patients typically present with LGI1-aLE, is faciobrachial dystonic seizures (FBDS). These have been reported in approximately 50% of patients (Irani, 2011). This 'dystonic posturing of the upper limb and face', presenting with a slight 'twitching', is not always recognised as LGI1-aLE, yet it has been suggested that any presentation of FBDS offers guidance to clinicians awaiting antibody testing results, to recognise the distinct features of the disease (Patira et al., 2016). In addition, the literature describes a transient loss of awareness or a vague staring into space following a FBDS, which provides further evidence in the differentiation in specific symptoms across encephalitides.

Despite the extensive literature available on prevalent symptoms, a reasonable approach would be to focus on any uncommon symptoms. A rarely reported symptom of AE (not specific to LGI1 aLE), is collective changes to smell and taste, due to damage to the olfactory and gustatory pathways in the inflamed limbic brain. Geran et al. (2019) confirmed findings of olfactory and gustatory dysfunction in 32 patients with AE, using functional testing on age and sex matched healthy controls (HCs). Their research identified 6 LGI1-aLE patients and acknowledged the small sample sizes in each antibody status sub-group was due to the rarity of the disease. Although, this thesis' methodology does not use HCs when examining symptoms, exploring reduced gustatory function has been reported by a few patients. Therefore, a strategy to enhance diagnosis would be to include questioning on changes to taste and smell.

Regarding literary evidence on MRI, a key notion not commonly known to inexperienced neurologists, is that some types of encephalitis may not show any neuroimaging abnormalities (Finke et al, 2017). In fact, Heine et al. (2018) studied 27 LGI1-aLE patients using matched HCs to suggest that up to 60% of these patients did not exhibit MRI abnormalities in the acute disease stage. This may well have played a role in the prolonged or misdiagnosis of the patients studied in this thesis. In addition to the distinguishable clinical features of LGI1-aLE, some researchers

have studied the video-electrographies of seizures to describe the characteristics associated with these patients. Not only do their findings suggest higher seizure frequency recognition is a useful component in correct diagnosis but can predict a limited long-term recovery (Aurangzeb et al., 2017), indicating the importance of close monitoring and treatment for patients.

Despite close physical examination, history from family, important diagnostic tools such as MRIs and antibody testing, delays in correct diagnosis are inevitable without local expertise. Overall literature suggests that antibody testing is paramount, not only to determine specific autoantibodies, but to make that differentiation with other diseases and conditions. In addition, antibody testing enhances diagnosis when imaging and lumbar puncture, for example, produce nonspecific findings (Ganesh and Wesley, 2018). However, specialist antibody testing is not available at many hospitals, and results may produce false positive or negative detection (Ganesh and Wesley, 2018). In addition, the sensitivity or specificity of the antibody test depends on the type of test performed in the laboratory. Therefore, the increasing challenge in diagnosis is further complicated by considering both the clinical manifestations and the antibody testing. Neurologists with expertise in aLE agree that clinical presentation of the disease and other diagnostic tests predominantly drive the correct early diagnosis and treatment, while waiting for the interpretation of autoantibody testing (Irani et al., 2014; Lancaster, 2016). This suggests the delay of diagnosis is not associated with whether the hospital has antibody testing assays, but whether its clinicians and neurologists recognise the complexities of aLE, thus proposing a major determinant of delayed or misdiagnosis in this cohort of patients.

Recommended therapy: Further evidence is based on the best choice of therapeutic treatment and recommendations. Although, some neurologists differ in their immunotherapy preference, the worldwide consensus is to prevent severe complications by following immediate first line therapy of steroids and therapeutic plasma exchanges while waiting for the antibody testing (Graus et al., 2016).

However, affordability may be an issue for many patients around the world, where plasma exchange and intravenous immunoglobulin may not be covered in health insurance (Ganesh and Wesley, 2018). There is a lack of evidence suggesting the benefit of clinical trials to evaluate early treatment with delayed treatment, due to its unethical nature. However, neither is there evidence for clinical trials using different treatment options. One method employed for the first randomised controlled trial (RCT) evaluated the effect of early intravenous immunoglobulin treatment in paediatric encephalitis which carries high rates of morbidity (Iro et al., 2016). Despite early immune treatment demonstrating a beneficial role in disease outcome, the results of this RCT are not yet published. Furthermore, it has been suggested that prospective RCTs are needed with adult patients, to confirm the efficacy and safety of current immunotherapy, as well as investigating new therapeutic options (Shin et al., 2017). As early diagnosis is synonymous with early treatment, these existing studies offer substantial evidence for the importance of trying to reduce permanent brain damage and cognitive change. Further evidence suggests that reversing the symptoms with early treatment reduces the extent of residual cognitive changes (Vincent et al., 2004; Butler and Zeman, 2005; Shin et al., 2017; Macher et al., 2018). Regardless of the benefits of prompt treatment following correct diagnosis, significant residual cognitive deficits persist (Irani et al., 2010; Lai et al., 2014; Vincent et al., 2004). Incidentally, clinical information obtained retrospectively from medical records and telephone interviews, showed persistence in memory dysfunction and behavioural deficits (Thieben et al., 2004). However, treatment options may have changed since then, with self-reporting of ongoing symptoms possibly open to retrospective bias. Therefore, more recent research evaluated 54 patients over four years using a clinical assessment scale for AE undertaken by neurologists (Abboud et al., 2021). This scale correlated with poor outcomes, and despite not being specific to LGI1-aLE, the assessment of long-term improvement rates would be beneficial when evaluating the residual cognitive deficits in this cohort.

Whilst neuroscientific articles continue to focus on the symptoms and treatment for aLE (Patira et al., 2016, Van Sonderen et al., 2016; Aurangzeb et al., 2017 and Bien, 2019), the importance of retrospectively auditing for those diagnosed and treated for AE (not specific to LGI1-aLE), was highlighted by Kinsella et al. (2018). In contrast, Van Sonderen et al. (2016), Arino et al. (2016) and Aurangzeb et al. (2017) stated that application of treatments was only relevant by potentially monitoring the outcomes of these patients longitudinally. Despite the advantage of longitudinal monitoring being beyond the scope of this research, there is almost a certain need in future studies. Arino et al. (2016) found prompt treatment enabled only 35% of 76 patients to return to their baseline cognitive function using a 'cognitive performance score' designed for the purpose of their retrospective analysis. Furthermore, it has been suggested that using patient reported outcome measures (PROMS) highlights both the distinct features of LGI1 and CASPR2 aLE, and quality of life for the patient (Binks et al., 2018). Their research was conducted at a median of 41 months after symptom onset, once more illustrating the relevance of early therapy for optimal outcomes. Though qualitative analysis was not used to capture in-depth, lived experiences, it did however, include short patient quotes which were useful for highlighting the extent of the impact of the disease on their quality of life.

The next section demonstrates the neuropsychological element. This contributes to the understanding of this complex disease and shapes a significant part of this thesis.

2.2.2. Neuropsychological assessments

The relevance of neuropsychological evaluation has been demonstrated to provide either a diagnostic workup to appropriate treatment, or monitoring of the disease (Harvey, 2012). It has been suggested that neuropsychological performance testing, such as the collective NPTB should be considered to identify cognitive deficits (Tanner-Eggen, 2015). The test battery itself can include different cognitive and

behavioural assessments which are tailored to individual research areas or projects. As cognitive and behavioural changes are key in LGI1-aLE, the neuropsychological assessments allow for quantitative measurement of both the patient and carer scores. The key role of the NPTB in assessing the patient's cognitive functioning, is its use in domains of memory, attention/concentration, language, fluency, behavioural changes such as mood, apathy, anhedonia, and depression, together with sense of wellbeing. Whilst research supports addressing the negative neuropsychological aspects of LGI1-aLE, the strength of existing research often lies with base-rates and HCs to produce an interpretation of the neurological deficit.

Regarding the management of acute viral encephalitis, it has been suggested that test batteries are useful tools in diagnosis (Ellul & Solomon (2018). Research conducted using neuropsychological assessment with a comprehensive test battery on LGI1-aLE patients, remains limited to a few studies (Frisch et al., 2013; Malter et al., 2014; Butler et al., 2014; Finke et al., 2017; Miller et al., 2017; Heine et al., 2018). However, the carer assessments which create a new opportunity to study the neuropsychological performance of the patient who may lack insight, have been mainly limited to other neurological condition such as dementia and PD. Therefore, the direct, objective nature of carer reporting may maximise the understanding of neurodegenerative disorders (Eggins et al, 2022). A possible area of future research would be to include carer accounts as part of the NPTB in aLE, to gain a fuller picture of the cognitive performance

By repeating neuropsychological assessments to determine long-term outcomes and clinical associations in patients (Donders, 2020), this could be applied to the LGI1-aLE cohort in future studies. Therefore, neuropsychology not only contributes to the diagnosis, but it plays a significant role in monitoring the course of the disease and the level of success of the treatments offered (Witt and Helmstaedter, 2021). However, different studies use different measures of neuropsychology, and so comparisons across studies are not straightforward. The NPTB in this thesis

captures data cross-sectionally, ranging from a few months to several years since diagnosis was made, without the scope to monitor aLE at different timepoints.

Memory loss: One of the primary symptoms of LGI1-aLE is memory loss. Memory loss together with fluency deficits are predominantly shown in neuropsychological evaluation, whereas language and attention impairments are relatively spared (Binks et al., 2021). Using memory tests, highlights the association of hippocampal atrophy with episodic memory impairment, hence the importance of early recognition and treatment (Malter et al., 2014). Interviewing patients with hippocampal damage not specific to LGI1-aLE, showed a delayed memory recall as the most significant feature of the neuropsychological testing (McCormick et al., 2018). Similarly, research on aLE patients (non-antibody-specific), presenting with hippocampal damage showed episodic memory impairment (visual and verbal recall and recognition impairment), in terms of anterograde memory (Argyropoulos et al., 2019). This was also explained by Loane et al. (2019), who used neuropsychological assessments with age- and sex-matched HCs to investigate the relationship between residual memory impairment and hippocampal abnormalities. Although their work determined brain abnormalities and its role in residual memory impairment, the sample size was limited and disease controls were not included, perhaps limiting the generalisation of findings to other types of LE.

Consistent with extensive research on the acute phase where patients have shown impairment across several domains of memory including executive function, fewer studies have shown the long-term cognitive decline outcome. According to Butler et al. (2014), anterograde episodic memory impairment has also been identified to show residual impairment in the chronic phase, with decreased ability to retain new information. Other literary evidence using a NPTB, established cases of retrograde amnesia where many patients recalled events prior to the disease with poor episodic specificity, (Miller et al., 2017; Argyropoulos et al., 2019). The LGI1-aLE patient cohort in this thesis have typically presented with both forms of amnesia, involving

the partial or total inability to remember past events, together with some impairment in recent events.

Verbal fluency: Overall literature demonstrates that impaired verbal fluency is part of the neuropsychological profile of encephalitis patients (Frisch et al., 2013; Gross et al., 2016). LGI1-aLE patients typically demonstrate mild cognitive deficits in fluency, but more so at disease onset. Some case studies have demonstrated moderate deficits in fluency tasks improving post morbidity, at 3 months (Krastinova et al., 2012). Long-term impairment has been described by Finke et al. (2017) using HCs, but other research has claimed no impairment compared to standardised norms, thus introducing some conflict (Miller et al., 2017). In a systematic review, neuropsychological testing on NMDA-R encephalitis suggested certain abnormalities such as fluency could be overlooked by more prominent symptoms such as psychiatric symptoms (Nicolle and Moses, 2018).

Social cognition: Existing literature recognises that the damage in limbic brain structures, in particular the amygdala, is associated with impairments in social cognition abilities such as basic emotions, but also in interpreting other's emotions (Dodich et al., 2016). Moreover, the affected amygdala is involved in the perception and understanding of emotion which causes difficulty in recognising and understanding non-verbal social cues (Bannerman et al., 2004). Studies applying assessments for recognition of emotion and intensity of emotion in aLE using pictures of facial expressions are rare. Notably, Mueller et al (2022) demonstrated pronounced difficulties in tests to recognise fear, but less so with disgust, anger and sadness. Recent research acknowledges pathological tearfulness and emotionality in aLE, using questionnaires, MRIs and age and sex matched HCs (Argyropoulos et al., 2020). Although a significant difference lies in the methodology used in this thesis, the strength of using MM has allowed for patient and carer descriptions of sudden episodes of tearfulness during the acute stage of the disease. In addition,

MM has added detailed carer accounts of changes in the patients' emotionality since disease onset, which cannot be defined using questionnaires.

Rehabilitation: Rehabilitation can focus on cognitive and emotional wellbeing, using an integration of services from a multidisciplinary team to address and manage difficulties experienced by the autoimmune neurology patient, including activities of daily living, return to work and driving (Abbatemarco et al., 2021). Few studies have drawn on effective rehabilitation for aLE patients, yet Corallo et al. (2018) highlighted the role of cognitive rehabilitation in LE using neuropsychological and imaging status. Although Corallo's atypical case study was not autoimmune related, it recognised the use of rehabilitation and offered useful interventions to patients.

2.2.3. Narrative Based Medicine and Interpretative Phenomenological Analysis

By evaluating the differences and similarities between NBM and IPA, the literature search allowed for a better understanding of the values each term holds. Both NBM and IPA focus on the person's own stories and experiences. NBM is commonly viewed as a patient-centred method, focusing on the patient as a storyteller of their experience of the physical illness, thus promoting empathy and self-reflection in the clinician and leading to a more holistic quality of care (Zaharias, 2018). Therefore, NBM is not directly addressed in this thesis, as the practice of acquiring clinical expertise based on patients' narratives to reach an accurate diagnosis, was not studied. However, there is scope for neurologists to validate patient narratives in future encephalitis research to enhance scientific certainties and acqure more awareness to the patient and carer voice. In contrast, IPA takes the story-teller's experience to try to understand what the experience is like for an individual and analyse this personal and accurate account of a complex and emotionally laden illness or disease. Moreover, the researcher attempts to make sense of how the storyteller makes sense of what they are feeling by considering researcher individuality and intuition (Smith, Flower, & Larkin, 2009), together with the

interpretation of people's meaning-making of experiences (Mortari, 2015; Cannella and Lincoln, 2007). A doctoral thesis using IPA to analyse the parents' narratives of children with aLE, incorporated their perspective of adjustment to the disease (Sharples, 2016). In one of the rare qualitative documentations of aLE, a neurologist and aLE sufferer, narrated his own moving experiences (Morrow, 2015). His prior professional experiences included treating his own patients with aLE, yet his narrative portrayed his own personal account of 'sketchy recollections' before diagnosis to his slow recovery and adaptation.

Both NBM and IPA, therefore, are fundamentally drawn on the subjectivity of the data collection (Kalitzkus and Matthiessen, 2009). Despite the argument that NBM is less esteemed as evidence-based medicine, its benefit to our knowledge and learning is demonstrated through the perspectives of patients and carers, and hence the personal experience of living with an illness (Kalitzkus and Matthiessen, 2009). Furthermore, the application of narratives complements the dominant biomedical model by recognising the role of the patient in their own illness experience (Kalitzkus and Mattiessen, 2009). This review has highlighted the lack of literature pertaining to aLE narratives, in particular from the carer.

Despite extensive available literature on NBM, the use of narrative in neurology which is the fundamental basis for patient assessment, obtaining a history and later a diagnosis through examination of cognition, emotion, speech and language, is less documented. Although neurologists use a narrative component to interpret and respond to the patient narrative, supported by a clinical significance based on their word choice, sentence structure and vocal patterns such as rhythm and speed (Alcauskas and Charon, 2008), there are few studies that capture the encephalitis experience. Moreover, the consequential 'dehumanisation' effect on patients with a neurological disease, is often caused by their unique impairments in function, which other health conditions do not generate (Alcauskas and Charon, 2008). Only through understanding the patient's story, can the neurologist comprehend the feelings

associated with cognitive decline, and hence the realistic quality of life expectations. In order to understand the valuable contribution of narrative, it is suggested that clinical practice needs to include the stories of those who are suffering from the condition or disease (Charon, 2001). Fioretti et al. (2016) suggest that research protocols should include NBM to focus on the patient and carer experiences. In addition, it is recognised that researchers can benefit from enhancing their professional empathy by reflecting and understanding the human reality of living with a disease (Chen and Forbes, 2014). In a study exploring dementia through narratives, patient and relatives were presented with an opportunity to assert their personal accounts of living with the disease (Hillman et al., 2018). Their research accurately produced reflections through narratives on how dementia changed the lives of the patient and carer at two time points to explore changes over time. Whilst extensive narratives in Hillman's dementia research identify themes that have covered the complexity of relationships, coping, self-identity, and future planning, few narratives are available to illustrate these themes in LGI1-aLE. Distinct portrayals are also represented in studies on TBI (Morris, 2008) and dementia (Benbow and Kingston, 2014), where authentic insight was achieved through storytelling or illness narratives. Although difficult to fully understand the extent of memory loss in these conditions, narratives served to make sense of the distress and created a hope for a future. Considering that NBM complements the patient-clinician relationship as a valuable tool in developing empathy, understanding and communication, this is likely to contribute towards future research in LGI1-aLE. So too can NBM inform the current neuropsychological interpretations of aLE through its beneficial and enlightening insight, at different timepoints.

Although the similar qualitative focus that NBM and IPA draw on, mainly the personal knowledge and expertise of one's own illness, there are differences to the evidence they produce. Some articles suggest narrative is comprised of stories that essentially have a beginning, middle and end, which uses chronological sequencing to explain events leading up to an illness (May, Griffin and Seale, 2012). Whereas, other evidence suggests that narrative offers a biographic context to the illness, perhaps

highlighting cultural influences, or coping strategies (Aronson, 2000). IPA, which uses coding and themes to produce an analysis of the phenomenon being studied (Smith, Flowers and Larkin, 2009) can also be an effective approach for patient narratives to be thematised (Malterud, Siersma and Guassora, 2016). However, the use of themes in IPA has been criticised, suggesting common themes from the codes may reduce the core meaning of idiography (Brocki and Wearden, 2006). This thesis represents idiography in each patient and carer single-case narrative offering a unique perspective, which does not seek to generalise results to others. By integrating the strengths of narratives using IPA to provide a valuable interpretation, this thesis has provided an opportunity for LGI1-aLE patients and carers to offer the additional personal-based knowledge to a disease and described how that disease affects their lives through their experience of suffering or burden. To make sense of their suffering, people are not only described as victims of a disease, but as 'wounded storytellers' of their disease (Frank, 1995).

Despite the gap in literature using narratives on aLE patients, evidence of 'neuro-narrative', a term based on the personal experiences of having a brain injury, offers the subjective account on the impact of a disease such as LGI1-aLE on the carers and families (Morgan, 2016). Further evidence of neuro-narratives was found primarily in books and charity websites. In contrast, three prevalent neurological diseases (stroke, spinal cord injury, and MS) demonstrated the benefit of NBM, to gain a better knowledge of the patient perspective (Soundy et al., 2013). The literature suggests that within neurological rehabilitation narratives revolved around the patient's hope by managing diseases in a multidisciplinary team process approach, thus placing importance on the patient experience, choice and involvement in decision-making (Department of Health, 2010). '

The strength of NBM is further enhanced by capturing the carer's experience discussed in 2.2.5. First, the carer adds an outside perspective to the patient's symptoms and reality. Second, the carer's experiences which often remain hidden in

the broader context of the encephalitis sufferer, offer narratives reflecting the feelings and emotions attached to these experiences. Third, without carer narratives, strategies to minimise or avoid difficult or stressful situations remain unexposed and external support cannot be offered. It is suggested that the carer's unique insight into the experiences of encephalitis sufferers, enables the reader to share powerful narratives (Easton, 2016). In contrast to Morrow's (2015) narrative, his wife's recollections featured descriptions of irritability, disorientation, confabulation and lack of insight. Thus, the focus on the carer's voice allowed for details that the patient could not remember due to their memory loss. Remarkably, the neurologist described how he dismissed his partial seizures and overtiredness, as did patients in this thesis who did not have his neurological knowledge. His presentation was typical of aLE and illustrated the importance of a patient, carer, and clinical insight into the disease. A notable 'key point' of his was, 'listen to your partner', and his acknowledgement of thanks to his wife as 'not having signed up to be a carer', was nevertheless a single case-study, in which the experience of his wife may be different to that of others. Furthermore, as the neurologist's narrative was not anonymised and was published, it is possible that the carer's description of her experiences, may have been altered.

Other sources have emerged within the search, which support the importance of narratives. Charity websites provided book titles and support information for the carer (https://www.encephalitis.info/Pages/FAQs/Category/helpful-books) (https://shop.headway.org.uk/caring-for-someone-with-a-brain-injury-45-p.asp). Wilson, Robertson and Mole (2015) offered a series of narratives which focused on the families and carers of those affected by a brain injury including encephalitis. These narratives have opened an opportunity to understand the early days of diagnosis, and the cognitive, emotional and psychological effects of the brain injury. In addition, patient and carer narratives are further explored, in monthly bulletins from two charities, Headway and Autoimmune Encephalitis Alliance (USA). The overall literary confirmation that narratives are beneficial to patients, carers and

professionals, emphasises the importance of this thesis. Patient and carer experiences in AE are now discussed in turn as search terms, in the next sections.

2.2.4 Patient experiences in autoimmune encephalitis and IPA

Notably, the extensive literature on patient experience overlaps with NBM in the previous section offering co-occuring ideas, yet the search terms were originally separated for the literature review. Current research using patient experiences as a search term, tends to focus on three areas. First, patient experiences are recognised as an assessment around satisfaction of patient care delivery and clinical decisions. Second, their experiences offer an understanding of the illness through the eyes of the sufferer, and third, experiences act as a tool for interprofessional working to plan individualised care. This thesis uses the concept of patient experience founded on narratives of LGI1-aLE collected post-acutely, recognising individual experiences of the illness journey, together with the importance of family and health professionals' recognition.

Patient experience is positively associated with health outcomes, clinical effectiveness and patient safety (Doyle, Lennox and Bell, 2013). Furthermore, patient experience is widely recognised as integrated with ratings of the quality of healthcare and making improvements based on patient ownership in clinical decision-making. Research suggests the concept of patient experience gives context to the clinical evidence by directly informing our understanding of the effects and burden of the health condition to both patients and carers (Rand et al., 2019). Ultimately, the strength of incorporating the patient experience with NBM adds to research evidence and provides a 'holistic' overview to capture insights to the existing clinical knowledge.

For the qualitative inquiry to illustrate what it feels like to experience a health condition, the use of IPA, melds with both terms of narrative and patient experience to make sense of the impact on patient's quality of life through robust analysis to highlight the likelihood of improvements to care and support. Despite absent evidence on using IPA to capture the lived experiences of aLE patients, there are sufficient texts within other neurological conditions, such as PD, where the IPA's idiographic focus is on the individual patient's experience (Eatough and Shaw, 2019). Rabanal et al. (2018) captured literature on the needs and experiences of young patients with dementia, using semi-structured interviews and IPA. However, some critics of IPA raise doubt on the efficacy of the researcher's descriptive opinion of the patient's experience as not representing the true meaning of the experience (Tuffour, 2017). Furthermore, Willig (2013) argued whether both the patient and researcher have the essential communication skills to enable them to interpret experiences. If IPA is only successful in eloquent patients who can relay their narrative effectively, then the success of IPA is refuted. To address this criticism of using IPA on LGI1-aLE patients who most commonly exhibit cognitive deficits in memory and fluency, this thesis has successfully added another data collection component: the carer. By directing sensitive questioning of cognitive and behavioural changes to the carer, enrichment of lost or inarticulate narratives from the patient, is provided. On the contrary, evidence critiquing the common use of the caregiver narrative in dementia research, preferred the focus to come from the overlooked patient perspective (Hill et al., 2018; Larsson et al., 2019). Aldridge, Fisher, and Laidlaw (2017) used IPA in dementia patients to capture an understanding of their experiences, sharing some aspects of cognitive decline such as difficulties in concentrating or agitation, with LGI1-aLE patients. Resonating with this research, common symptoms they described of memory loss and fatigue, were more likely to produce less narrative. Evidence by Nicolle (2017) has also considered the importance of not overlooking the experience of patients with NMDA-R encephalitis, as part of her thesis, and therefore recognised the relevance of the person-centred approach to healthcare, a predominant focus to this research. Finally, a qualitative study using IPA, explored the essence of young adults' lives with various chronic neurological conditions (Kola, Turner and Dhingra, 2015). This article highlighted the

worth of analysing a small sample of participants, together with the detailed exploration of their lived experiences.

The benefit of using IPA to interpret these experiences, is two-fold. Firstly, it makes sense of the patients' experiences on how LGI1-aLE impacts on their lives, and secondly, it incorporates unique examinations of complex, intimate and emotional topics, which the quantitative analysis cannot capture.

2.2.5 Carer perspectives in autoimmune encephalitis

Using the search terms 'carer perspective' and 'AE' highlighted several case reports in the literature on carers of patients with other neurological conditions, but few emphasised the resulting impact of AE. However, a notable spectrum of support offered by the Encephalitis Society website, comprises of virtual meetings, support on the challenges of caring, and a qualitative insight on the consequences of AE amongst other types of encephalitides, using narratives as further evidence. The accompanying acute symptoms of LGI1-aLE are often more distressing to the carers than the patients, yet their perspectives on the patient's journey from initial symptoms, diagnosis, treatment and ongoing symptoms, are rarely documented. Existing literature fails to illustrate the carer's voice through qualitative data collection, whilst quantitative measurement of carer burden and quality of life has been addressed by using self-report questionnaires in AE research (Tomlinson et al., 2020; Wang et al., 2020). On the contrary, the Encephalitis Society provides a platform for carers to share their perspectives with other carers, decreasing feelings of isolation in the challenging recovery period, and offering support on carer's rights as well as tailored advice on their needs.

Despite evidence suggesting MM's increased overall use in recent years (Tashakkori and Teddlie, 2010; Creswell & Plano Clark, 2011; Timans, Wouters and Heilbron,

2019), its use in autoimmune neurological conditions to gain a carer perspective remains less common, further limited on the carers of encephalitis sufferers. Research on carers using MM has been limited to other neurological conditions, such as dementia, illustrating the management the patient's symptoms, the complexities of relationships between the carer and patient, the carer's coping and wellbeing and resources (Stirling et al., 2010). Regarding the carer perspective in other neurological conditions, such as multiple sclerosis (MS), there are substantial qualitative aspects incorporated into the research methodology (Fallahi-Khoshknab et al., 2014). Their qualitative study highlighted the necessity of information sharing with families and nurses, regarding the patient's reaction to their diagnosis, yet the study was limited to the culture and context in Iran and other research would be needed in other countries to improve the transferability of findings. Moreover, studies on MS have addressed the experiences of carers who faced a life-changing challenge and acknowledged their ongoing needs (Corry and While, 2009). A review of these MS studies has shown the negative impact upon the carers' psychological wellbeing and the need for professional recognition.

Further evidence has been presented on case studies on the parents (carers) of paediatric encephalitis patients (two viral cases, one not specific to LGI1- aLE), whose experiences using semi-structured interviews were identified during different stages of the disease trajectory (Lemon et al., 2019). The strength of the research embraced a qualitative component to enhance triangulated (multiple) methods of data collection. Further evidence taken from a thesis on parental coping with paediatric brain injury, in collaboration with the Encephalitis Society, incorporated semi-structured interviews to show the impact of the disease on parents (Bainbridge, 2005). Obtaining understanding and support from relatives and friends, is problematic for LGI1-aLE patients, as memory deficits and behavioural changes are not always obvious to others outside of the home environment. Therefore, the carer's perspective based on their insight is of significant value in this thesis and provides a powerful tool to identify problem areas and suggest ways of support from health professionals, family members and friends.

2.3 Chapter summary

With aLE gaining importance in neurology over the last ten years, articles reinforced the focus upon LGI1-aLE symptoms, diagnosis and treatment. Drawing on the broad range of symptoms can be significantly challenging for early and correct diagnosis, and prompt treatment to provide the most appropriate management of these patients. The available articles using neuropsychological assessments on LGI1-aLE, although limited, have produced some significant findings on FBDS, memory deficits, social cognition abilities, and behavioural changes. This review, however, reveals two shortcomings. Firstly, there is a lack of qualitative research to gain insight into the patient perspectives and secondly, there is a further lack of evidence on the carers' imperative accounts, which contribute to cognitive impairment research.

CHAPTER THREE

Methods

3.1 Overview of methods

This chapter demonstrates the reasons for using the MM as the most effective strategy to address the research questions [1.3] incorporating the primary and secondary objectives. The rationale for choosing a triangulation method [3.3.2] as a recommended and comprehensive choice where both the quantitative and qualitative components carry significant weight in this research, is also shown. Subsequently, the theoretical foundations showing the essential differences in the quantitative and qualitative paradigms are explored, together with how the characteristics of the chosen MM methodology sit within the philosophical assumptions of epistemology and ontology. Finally, this chapter describes the processes of the quantitative and qualitative data analyses.

3.2 Study aims, objectives and the research questions

The aim of this thesis is to understand the longer-term impact of LGI1-aLE, captured by MM. This thesis addresses three questions [1.3] guided by the objectives below: -

> Objective 1: To identify the negative sequelae of LGI1-aLE and determine the extent of the patient's cognitive impairment, and behavioural changes, using the NPTB. In addition, an overview from the carer's assessment is evaluated.

> Objective 2: To use IPA to investigate the patient and carer experiences of living with LGI1-aLE.

3.3 Methodology: MM

The characteristics of the chosen methodology and design were relevant when considering the aims and objectives of this research. First the quantitative dataset gathered the test/questionnaire scores of patients and carers. Second, the qualitative dataset used semi-structured interviews and digital diaries. Some qualitative researchers believe that aspects of human behaviour and experience cannot be quantitatively measured (Bryman, 2016. Therefore, the qualitative dataset provided a human interpretation on experiencing LGI1-aLE. The goal here was not to seek a full understanding of the disease, but instead to provide a rich analytically informed description of the experiences. This methodology contains an element of learning from the participants' recollections, which can be used as a source of new knowledge to possibly influence disease intervention or policies (Bradshaw, Atkinson, and Doody 2017). MM addressed the complexity of researching LGI1-aLE by adding the participants' experiences in Phases 2 and 3, to the measurable test results of Phase 1 [3.3.2]. Several researchers have suggested that the value of MM lies in its strong contribution to methodology development (O'Cathain, Murphy, and Nicholl, 2007; Shorten and Smith 2017), and enhances the integrity of the findings (Bryman, 2016). Giovannetti et al. (2018) suggest the combination of methods creates a more 'exhaustive analysis'; and other authors refer to a 'synergistic approach' to MM research using the strengths of both types of approaches to make vital research design decisions (Hall and Howard, 2008). Furthermore, MM research allows for skills and expertise enhancement, as well as encouraging 'practical thinking outside the box' across different methodologies (Guetterman et al., 2017, p.7). Moreover, the purposeful mixing or integrating of both datasets can provide a 'more panoramic view of the research landscape' (Shorten and Smith, 2017, p. 2), and is described as a 'powerful tool' when investigating health and healthcare (Fetters, Curry, and Creswell, 2013, p. 2134). Some researchers advocate the concept of triangulation of methods as it can achieve the aims that a single paradigm cannot (Silverman, 2004), as well as facilitating different ways to explore the phenomenon. What is more, some researchers emphasise the benefit of drawing on the dual strengths and advantages of both methods (Creswell and Plano Clark, 2011). Critics, however, believe triangulation assumes that the data from two

research methods may not be of equal weight in the research question and using the term 'triangulation' is confusing as it has different meanings (Heale and Forbes, 2013). In addition, supporters of MM could suggest that neurologists with access to neuropsychological datasets together with transcription datasets, can allow results and acquired expertise to be shared with other stakeholders such as the encephalitis charity websites and patient groups.

As well as providing an opportunity for advancements in methodology, MM can possibly carry risks for researchers (Brannen, 2005). Brannen highlights that researchers may over-report one set of data collection and under-report the data set from the other. Critics of MM highlight that researchers may find difficulties in being theoretically knowledgeable and experienced in both methods (Tariq and Woodman, 2013). To strengthen data collection and analysis skills, additional training and funding may be necessary, which could be beneficial, as it presents an opportunity for skills enhancement, which is particularly useful and highly valuable for the researcher's career.

Regarding the concept of combining two databases, it has been suggested as conducive for the most effective analysis (Castro et al., 2010; Creswell and Plano Clark, 2011). Two databases, Open Clinica for the NPTB quantitative dataset and MAXQDA for the qualitative dataset were employed in this research.

3.3.1 Philosophical foundations

Essential differences in quantitative and qualitative approaches exist within epistemological and ontological lines. The fundamental understanding of research terminology begins with a paradigm that represents a distinct set of concepts, beliefs and ideas which include the theories and research methods contributing to the field of interest being studied. Each paradigm is based upon its own ontological and

epistemological assumptions, which enable the researcher to view knowledge holistically. This work relates to a holistic approach to the negative sequelae of LGI1-aLE. Ontological assumptions are concerned with what constitutes reality. In other words, what is truth based on our knowledge and relative to the researcher (Parahoo, 2014). Therefore, the ontological assumptions of the disease are based on our knowledge of the disease-the reality.

To understand epistemology is to understand the scope of knowledge-what it is, how it is acquired, what is known, and how it can be created and communicated (Denzin and Lincoln, 2011). Within a quantitative paradigm, epistemology attempts to explain what we know through objective knowledge, summarised by truth, data and facts. Quantitative methodologies hold the paradigmatic orientation of positivism, where the ontology of truth and explanation can only be reached through measurable methods adopting a deductive logical approach. In this thesis, ontology gains further knowledge about the 'reality' of LGI1-aLE, using the assessment of symptom severity and neuropsychological changes. In contrast, within a qualitative paradigm epistemology, we attempt to know by immersing ourselves in the data through the narratives and experiences of other people. It has been proposed that epistemology in qualitative research has three main influences, which shape the data collection and analysis processes (Carter and Little, 2007). Firstly, it is influenced by the relationship between the researcher and participant, where meaning is constructed differently. Secondly, it is influenced by the way in which the quality of methods is demonstrated through effective interviews and subsequent transcriptions and interpretations. Thirdly, it is influenced by how the researcher communicates the findings through interpretation. Certainly, these three influences are fundamental in IPA which uses an epistemological bearing based on the person's subjective account of their unique experience. Moreover, this knowledge-making evolves into the researcher making sense of the participant's sense-making as the double hermeneutic (Smith and Osborn, 2008). Within phenomenology, there are multiple versions of reality (ontology), which recognise the subjectivity of a person's views, perspectives and experiences. To understand 'experience', this refers to everyday

parts of people's lives and events that become part of their memory. Several theorists played an important role in the development of phenomenology along exploration of the concept of lived experience and reflection, like Dilthey, Husserl, Heidegger and Merleau-Ponty (cited in Alase, 2017). Husserl considered science to be secondary knowledge dependent on the person's primary personal experience, by using reflection and placing less emphasis on previous assumptions and preconceptions (Öktem, 2009). Husserl's focus on reflection and bracketing is commonly used in qualitative research approaches today, to address any possible preconceptions that may be detrimental to the research process (Tufford and Newman, 2010). However, critics argue that it may not be feasible for the researcher to disengage from past experiences and emotions during the interview, as this can distort engagement with the participant (Tufford and Newman, 2010).

Philosophical foundations have shown a significant influence on choosing MM within a pragmatic paradigm, focusing on what is the most pragmatic way to obtain the truth regarding the research question (Archibald, 2015). MM within pragmatism is presented in positivist and interpretivist terms, by validating findings and exploring meanings, and has been identified as the flexible approach and most appropriate paradigm for many researchers (Guba and Lincoln, 1994; Johnson, Onwuegbuzie and Turner, 2007; Creswell and Plano Clark, 2007; Morgan, 2007; Denscombe, 2008; Bazeley, 2009; Teddlie and Tashakkori, 2009; O'Cathain, Murphy and Nicholl, 2009; Johnson and Gray, 2010). However, critics suggest that it is not philosophically compatible to combine epistemologies. On the contrary, Sale, Lohfeld and Brazil. (2002) suggests that MM can incorporate both approaches for a complementary purpose if the differences are acknowledged. Hence this thesis took a pragmatist approach to investigate the reality of living with LGI1-aLE through a combination of innovative and complementary phases, to gain a richer understanding of the disease.

3.3.2 Research design

It has been suggested that MM research can use one of four basic types of research design, including 'convergent parallel', 'sequential exploratory', 'embedded' or 'sequential explanatory' (Halcomb & Hickman, 2015). However, as this thesis does not strictly fall into any of the above categorised designs, then it seems more appropriate to use the'triangulation method'. Therefore, the interaction or integration between the quantitative and the qualitative components can generate the data that one approach could not yield if undertaken independently (O'Cathain, Murphy and Nicholl, 2010).

Figure 1 below shows, where quantitative data is collected and analysed first, followed by the collection and analysis of qualitative data (Onwuegbuzie, Johnson and Collins, 2011). In addition, Phase 3 data was later collated, which enabled the investigation from diverse viewpoints. Furthermore, it can facilitate the collaboration between health professionals and researchers, by enriching their experiences, based on different perspectives (Wisdom and Creswell, 2013).

Figure 1. Diagram to show the triangulation method
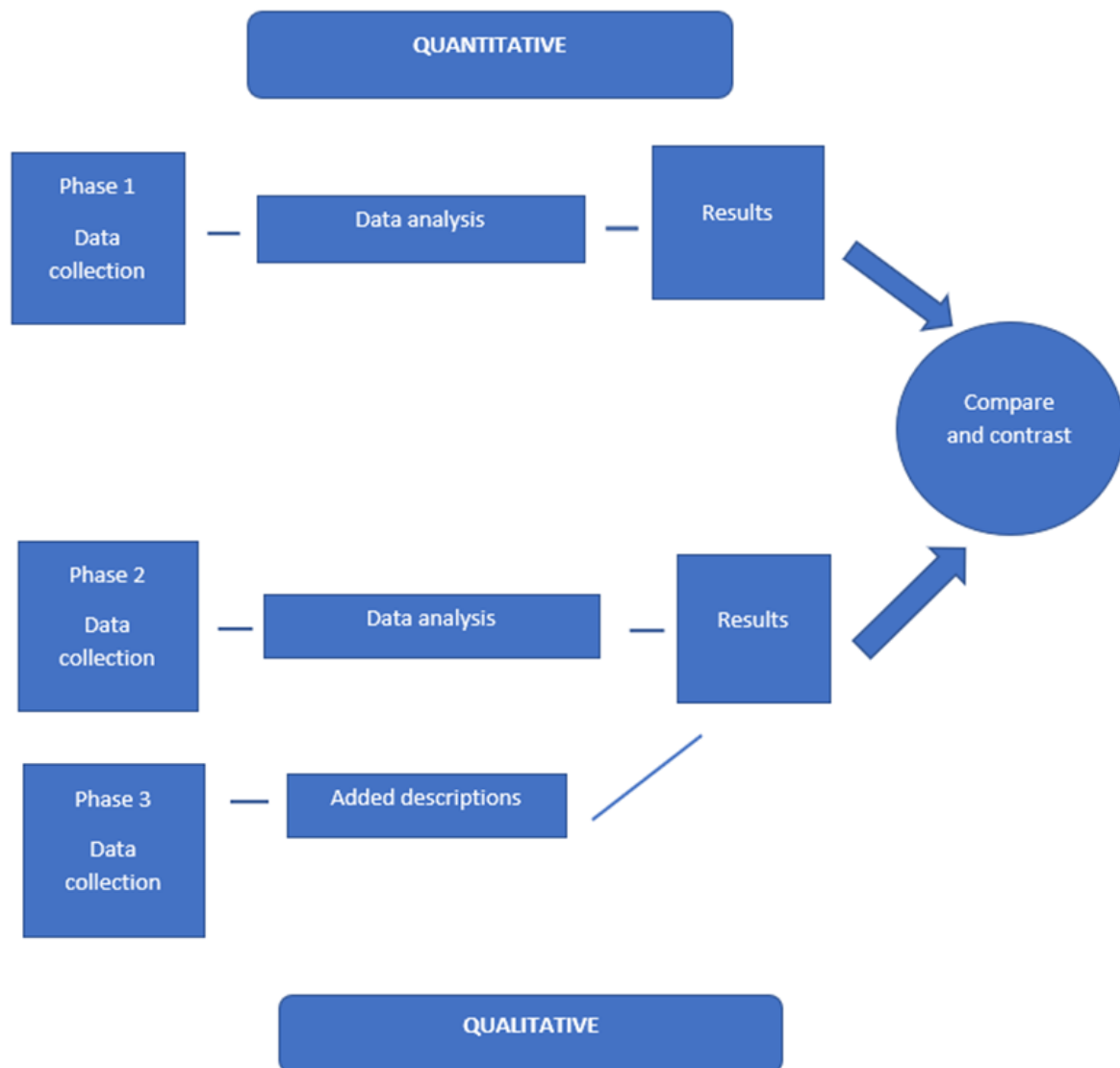
Figure 1: Data collection and analysis using triangulation method

As well as considering the rationale, theoretical influence, and point of integration, when designing a MM study, timing is also important in order to establish whether the quantitative and qualitative methods are employed concurrently or sequentially (Creswell & Plano Clark, 2007; Tashakkori and Teddlie, 2010; Johnson, Onwuegbuzie, and Turner, 2007; Greene et al., 2008; Schoonenboom, Johnson and Koln, 2017). The MM components in this thesis were implemented sequentially,

where the later components (Phase 2 interviews and Phase 3 digital diaries), took place after the earlier component (Phase 1 NPTB). The point of integration occurred when the components were brought together for comparison and contrast, focusing on six aspects of the disease (symptoms, professional support, the consequences on carer burden, relationships, returning to work, and future planning). These were extracted from Phases 1-3, from the results of the patient and carer testing, the developed themes and description of significant diary entries, to examine the data as a whole.

In addition, data collection included some MRI reports and findings on the local Electronic Patient Records (EPR) where available.

3.4 Study setting, study population and timeframe

The study setting was based at the Oxford Autoimmune Neurology Clinic in Oxford University Hospitals and the Department of Experimental Psychology, University of Oxford. The study population consisted of 10 patients who were diagnosed with LGI1-aLE, together with their carers (9 spouses, 1 sibling). The flow diagram shown in Figure 2 below, demonstrates the recruitment process. Participant study identifiers are represented as 'LESS' (Limbic Encephalitis Sub Study) and numbered '1-10'.

Figure 2: Flow diagram for aLE MM study screening and recruitment process
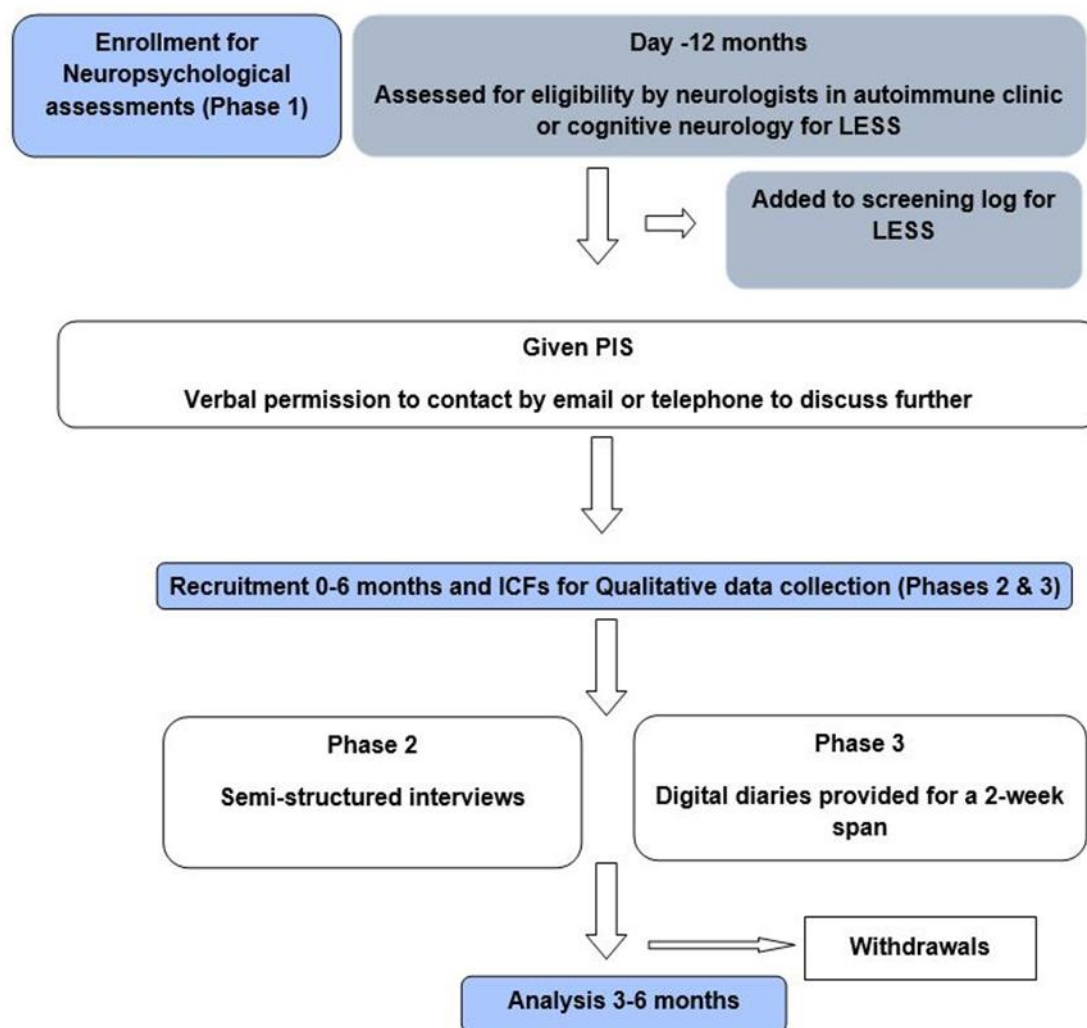
Figure 2: Flow diagram to show enrolment, and recruitment process, including timelines.
LESS=Limbic Encephalitis Sub Study. ICF=Informed Consent Form. PIS=Participant Information
Sheet.

Phases 1-3 were undertaken over a period of two years. The data obtained from the
NPTB, were used to write the Interview Schedule (IS) for the semi-structured
interviews in Phase 2, which were undertaken by telephone from autumn 2019 until
spring in 2020. Consequently, during Phase 3, participants were sent the digital

diaries to their homes for a total period of two weeks, after they had completed the interviews.

3.5 Quantitative and qualitative sampling

An identical sample of participants was used in both the quantitative Phase 1 and the qualitative Phases 2 and 3. Other studies have referred to recruiting the same sample of participants in a sequential explanatory design (Lalor et al., 2013). In this thesis, using a triangulation method, thehe sampling for the NPTB informed the purposive sampling for the qualitative data collection. There are no clear guidelines for conducting purposeful sampling using MM, particularly when there are two objectives (Palinkas et al., 2015). However, it is recognised that most MM studies incorporate non-random samples as a sampling strategy (Teddlie and Yu, 2007). Traditional quantitative methodologies consist of larger samples to represent a larger population (Salvador, 2016). Although there is no consensus on what forms a sufficient sample size for qualitative studies (Malterud, Siersma and Guassora, 2016), literature favours small samples for conducting in-depth qualitative analyses (n = 20–40), against larger samples for the quantitative considerations and reliable multivariate statistical analyses (n ≥ 40-200) (Castro et al., 2010). The rationale for this thesis' chosen sample size was based on the incidence of the disease and access to adequate potential participants at Oxford, which is a major recruitment specialist area for autoimmune neurological referral.

3.5.1 Phase 1: Quantitative Screening and Recruitment

Adult patients attending the Oxford Autoimmune Neurology Clinic, the Neurology Cognitive Disorders Clinic or admitted into the neuroscience wards in Oxford, were screened by consultant neurologists. The potential patient participant was approached by the Chief Investigator (CI) to obtain verbal consent to be contacted by telephone or email. Carers were invited to participate simultaneously in the same

manner. Inclusion criteria procedures were based on their consultation, symptoms, available antibody test results, CSF and MRI results. The CI provided the Participant Information Sheet (PIS) and the Informant/Carer Information Sheet (CIS) (see Appendices 7 and 8), to read in an unhurried, timely manner. Participants consented for the use of their NPTB data to be included in this LE sub-study, during the chronic phase of LGI1-aLE, taken to correspond to > 2 year since diagnosis and treatment onset, as in studies referring to 'long-term follow-up' (Rodriguez et al., 2021). Of the 10 carers, 9 were spouses, and 1 was a sibling. 7 patients were male and 3 were female.

3.5.2 Phase 2: Qualitative Screening and Recruitment

The same sample was used for the qualitative data collection. Informed Consent Form (ICF) (see Appendix 9) was sent to both patient and carer participants for initialling and signatures. It was subsequently returned in a pre-paid stamped addressed envelope to the CI directly, who is suitably qualified and experienced. A copy of the signed ICF was returned to the participant, and the original signed form was retained at the study site.

3.5.3 Study visits

There was one study visit where the participants undertook the NPTB. The subsequent semi-structured interviews were conducted by audio-video call or telephone call. Digital diaries with instructions were sent in the post, with additional instructions (see Appendix 10). The screening log (see Appendix 11) provided information on those who declined to take part, the dates of assessments, and those who returned the digital diaries unused. There were no withdrawals or deaths.

3.5.4 Phase 1: Quantitative Data Collection (a. NPTB Patient Assessment, b. NPTB Carer Assessment)

This section describes the quantitative method using the NPTB and its contents (see Appendix 12). The NPTB is a set of performance-based assessments and standardised questionnaires, structured to require participants to demonstrate their skills and self-rating in the presence of the researcher, who assigns scores and measurements to patients and their carers. Neuropsychological assessment is usually performed with a battery approach, involving a variety of cognitive tests (Harvey, 2012). The assessment used for LGI1-aLE participants in this research evaluated the patients' cognitive function and the carers' evaluation.

The time span from diagnosis to the NPTB assessments varied per individual. The measurements fell into two categories: behavioural measures, such as the working memory capacity using the digit span (Wechsler, 1997), and self-report measures, such as the apathy scoring questionnaires The NPTB took around two hours to complete. Below the patient and carer assessments are described in turn.

3.5.4.1 a) NPTB Patient Assessment

This incorporates nine measurements in total of the patient's cognitive impairment, apathy scoring, hedonic state, severity of depression, fatigue level, quality of sleep and wellbeing.

The Addenbrooke's Cognitive Examination-Revised (ACE-R) (see Appendix 13), is a diagnostic test used in mild cognitive impairment, specifically developed to incorporate tests of attention, memory, verbal fluency, language and visuospatial function (Mathuranath et al., 2000). The total ACE-R has a maximum score of 100, with higher scores indicating better cognitive functioning (Beishon et al., 2019). The ACE-R is only one component to the NPTB to distinguish the degree of cognitive deficit. Takenoshita et al. (2019) found the internal consistency, test-retest reliability,

and inter-rater reliability of ACE-R to be excellent. Although there are no cut-off scores available for encephalitis patients, cut-offs have been suggested in PD patients with mild cognitive impairment, with suggested scores for each ACE-R domain (Berankova et al., 2015).

The Digit span (DS) (see Appendix 14) was used for the assessment of verbal short-term and working memory (Wechsler, 1997; cited by Saklofske, Rum and Schoenberg, 2017). This is the subtest from the Wechsler Memory Scale, 3rd edition (WMS-III) (Wechsler, 1997) and comprises the forward span and the backwards span to measure capacity to recall a maximum number of digits. The simpler forward span requires short-term memory and attention memory, and the backwards span tests verbal working memory, often considered a component of executive function. It has been suggested that LGI1-aLE patients show pronounced working memory impairment versus controls (Finke et al., 2017). This thesis uses age-scaled standardised scores derived using norms tables (see Appendix 15), to compare the LGI1-aLE patients DS scores.

The Apathy-Motivation-Index (AMI), and AMI for carer (see Appendices 16 and 17), are a novel and reliable measure of individual differences in apathy presented as self-report questionnaires designed to identify sub-types of apathy: behavioural, social and emotional (Ang et al., 2017). Every AMI subscale consists of six items scored from 0-4. Proposed cut-offs in the AMI are > 1.91 for 'moderate' and > 2.38 for 'severe' apathy.

The Snaith Hamilton Pleasure Scale (SHAPS) (see Appendix 18) *is* a 14-item scale that assesses hedonic tone or the ability to experience pleasure (see Appendix 18), recommended for psychopathological research (Nakonezny et al., 2010). Its validity and reliability were found to be satisfactory (Snaith et al., 1995). SHAPS was scored

as the sum of the 14 items so that the total scores ranged from 0 to 14, with a timeframe for the last few days. A score of <2 constitutes a "normal" score, while an "abnormal" score is defined as >3, for hedonic experiences (Snaith et al., 1995). Even though SHAPS may lack validation in encephalitis patients, it has been used in PD, to score hedonic symptoms after therapy (Leentjens et al., 2008), where anhedonia focussed on the subjective emotional experience of the patient rather than as a symptom.

The Beck's Depression Inventory (BDI) (see Appendix 19) is a 21-item scale that measures the severity of depression (Beck et al., 1996). It measures key symptoms of depression such as mood, pessimism, sense of failure, self-dissatisfaction and guilt, self-dislike and suicidal thoughts. Smarr and Keefer (2011) proposed interpreting the BDI-as: 0–13 for minimal depression; for mild depression, a range of 14-19; a range of 20-28 for moderate depression, and a range of 29-63 for severe depression. There are no available cut-off values for encephalitis patients. The cut-off score in medical patients varies according to the patient sample (Wang and Gorenstein, 2013). Other studies have concluded that this is a reliable and valid tool for detecting depressive symptoms in MS (Sacco et al., 2016) or non-autoimmune encephalitis (Corallo et al., 2018). In addition, Knapskog, Barca and Engedal (2014) suggested depressive symptoms are common among patients with memory problems, and therefore the inclusion of this scale was important in this cohort. Argyropoulos et al. (2019) used another questionnaire for depression, the Hospital Anxiety and Depression Scale (HADS), developed by Zigmond and Snaith (1983) which showed higher scores for depression in patients in the post-acute phase of aLE.

The Fatigue Severity Scale (FSS) (Appendix 20) (Krupp et al., 1988) facilitates research in conditions where fatigue is a prominent disabling symptom. The 9-item scale provides a basic understanding of fatigue symptoms. There is a cut-off score of >36 considered indicative of problematic fatigue in MS (Krupp et al., 1988). The

detrimental impact of fatigue with LGI1-aLE, has been linked to depression (Binks et al., 2021), and to anhedonia and apathy (Ang et al., 2017). Therefore, while correlation does not necessarily reflect a causal relationship, evidence of increased fatigue scores with low motivation and increased apathy will be investigated.

The Pittsburgh Sleep Quality Index (PSQI) (see Appendix 21) (Buysse et al., 1989) measures the quality and patterns of sleep in adults. The PSQI is an important subjective sleep quality measurement, as sleep dissatisfaction accompanies many illnesses and is associated with an impaired quality of life. A proposed cut-off score above 5 distinguishes poor sleepers (Grandner et al., 2006). Research on four LGI1-aLE patients' sleep quality post hippocampal damage (mean of 9 years), matched with HCs, showed a mean score of 3.5, which was not indicative of poor sleep quality (Spanò et al., 2020). This research not only investigates whether patients experienced poor sleep, but whether there was a negative association between poor quality of sleep and apathy, which is demonstrated in aLE (Blattner et al., 2019).

The World Health Organisation- Five Well-Being Index (WHO-5) (see Appendix 22) is a short self-reported measure of current mental wellbeing and has been found to have adequate validity measuring well-being in some studies (Topp et al., 2015). '0' represents the lowest imaginable quality of well-being and '100' represents the best imaginable quality (WHO-5, 1998).

The Cantrill Ladder is a subjective scale, where respondents are asked to think of a ladder, and rate the best possible life for them being a '10', and the worst possible life being a '0' (Cantrill, 1965, cited in Tay and Diener, 2011). No cut-off has been suggested for encephalitis patients.

3.5.4.2 b) NPTB Carer assessment

The carer assessment was undertaken in parallel to the patient assessment. It measured the carer's scoring of the patient's behavioural symptoms, apathy, performance of daily activities, together with the patient's performance in memory and cognitive intelligence compared to ten years ago. It is recognised that carers can notice cognitive changes before any psychometric testing is undertaken, as they have previous knowledge about the patient's habits and behaviours. In addition, the carer assessment distinguishes two components: the carer burden and the carer distress. The carer assessment consists of the following scales or and scores:

The Neuropsychiatric Inventory (NPI) (see Appendix 23) was developed by Cummings on Alzheimer's Disease (AD) (2020) and the NPI-Questionnaire (NPI-Q) was later developed for the carer to assess changes in the patient's behaviour over the last month, which retrospectively assessed 12 behavioural disturbances occurring in dementia patients (Kaufer et al., 2000). Each of the 12 NPI-Q domains asks whether the disturbance is present, and if 'yes', the informant rates the severity of the symptoms present within the last month using a 3-point scale (mild, moderate, severe), with the total NPI-Q severity score represented as 0-36. Any factors such as delusions or hallucinations indicate the presence of an abnormality, with no cut-off score. Carers rated symptoms by frequency and severity of distress to themselves, using the Neuropsychiatric Inventory Caregiver Distress (NPI-D), incorporated into the NPI-Q. The associated impact of the symptoms on the carer rates their own distress on a scale of 0 to 5 (not at all, minimal, mild, moderate, severe and extremely distressed).

The Lille Apathy Rating Scale - Caregiver (LARS) (see Appendix 24) was initially validated for patients with PD but was later developed to include a carer's version (Dujardin et al., 2008). The questionnaire contains multiple queries which fall into nine domains, each relating to the clinical manifestation of apathy. The higher the

score, the most apathetic the patient is. The carer uses this questionnaire to rate the patient's apathy. The cut-off scores are: -36 to -22 absence of apathy, -21 to -17 for slight or mild apathy, -16-to -10 moderate apathy and >-9-+36 severe apathy (Sockeel et al., 2006). This scale has since been used in other neurological conditions and has excellent psychometric properties. In one study, scores on the LARS for the patient and carer were highly correlated, with apathy rated significantly more severely by the carer than by the patient (Dujardin et al., 2008).

The Apathy-Motivation-Index AMI caregiver (Appendix 17) is adapted from the patient version, already mentioned with the same questions and scoring, but identifies the characteristics of apathy from a carer's perspective. Pfeifer et al. (2017) acknowledged that carer reports of apathy tend to be overrepresented (caregiver-rating bias), as the cognitively impaired patient has less insight. Carers may report apathy as a symptom but lack an understanding of the reasons for apathy. This may lead to misjudgement of the patient being withdrawn, insensitive or lacking empathy. Any association between the AMI patient and carer scores, and whether there is a level of concordance between patients' own self-reflections and the carers' observations on patients' levels of motivation will be investigated.

The Bayer Activities of Daily Living (B-ADL) Scale (Nagaratnam, Nagaratnam and O'Mara, 2013) was developed to record deficits in the performance of ADLs (see Appendix 25). It comprises 25 items to be completed by the carer, or someone who knows the patient well. The higher the score, the more difficulty the patient has with the activity. Coping with unfamiliar or new situations is a known feature of encephalitis patients, yet this scale is a helpful measurement of the challenges the LGI1-aLE patient faces which used to be familiar to them, such as maintaining a conversation or concentrating when reading. A correlation between the patients' cognitive status (total ACE-R score) and their carers' evaluation based on the B-ADL scores, will be explored to show to what extent deficits in daily activities are correlated with a decline in cognitive status. Notably, the B-ADL has been used to

compare apathy, cognitive decline and carer burden in LE patients, concluding the higher the dependency the patient had with daily activities, the higher the carer rated the patient's apathy (Klar et al., 2021).

The Zarit Burden Interview (ZBI) includes a revised 22-item self-reported measure of burden for the carer, and each item uses a 5-point scale ranging from 'never' to 'nearly always' to describe their feelings when caring for their relative (Zarit, Reever and Bach-Peterson, 1980) (see Appendix 26). The ZBI revised version involves suggested cut offs of 0-21 (little or no burden), 21-40 (mild to moderate burden), 41-60 (moderate to severe burden) and 61-88 severe. The advantage of using this self-reported measure, on diseases such as encephalitis, is its internal consistent reliability at different points in time.

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (see Appendix 27), is a questionnaire which asks carers to determine whether the patient has declined in cognitive functioning 10 years ago compared with now. It included situations where they had to use their memory or intelligence and whether this had improved, stayed the same or deteriorated. It is an alternative cognitive test which is often used as a complementary screening tool for dementia (Harrison et al., 2016), who suggested that consideration must be given to its usefulness when using the IQCODE as a follow-up assessment in other neurological diseases. Having shown the various components of the NTPB data collection for the patient and carer, the qualitative data collection components are now described.

3.5.5 Phase 2: Qualitative data collection (semi-structured interviews)

Phase 2 consisted of the data collection from semi-structured interviews. Not only are semi-structured interviews predicted to generate valuable insight into specific, detailed experiences (Edwards and Holland, 2013), but they are also the most

common qualitative data collection method in health services research (DeJonckheere and Vaughn, 2019). The semi-structured interviews were guided by the adaptable IS for patients and carers (Appendix 28). The aim of the IS was to develop questions which could produce rich, individualised data using a combination of open and closed questions. The questions in the IS were derived from observation during previous consultations in the autoimmune neurology outpatient clinic, and from significant findings from the NPTB. Care was taken not to interpret findings during the interview, but only to keep notes on the IS. Good interviewing essential to IPA, was developed here by a) using a well-prepared IS which provides a tool for the researcher to probe and to maintain optimal narrative; b) using Patient and Public Involvement participants to review documents and c) obtaining the senior qualitative supervisor's review on the content of the IS. The IS covered both patient and carer participants' perspectives, and their common understandings and experiences living with the impact of LGI1-aLE. Interview questions were descriptive, asking participants to tell their story. For some of the patient participants, expressing their feelings in a descriptive way was difficult, sometimes needing prompting or reminding of the question to keep the conversation flow. A separate IS was used for the carer, with similar structure and some adapted questioning in areas of impact, coping, relationships and future planning. For example, carers were asked to describe how their spouse's behaviour had changed due to the aLE. Interview times were on average 30 minutes for the patient, and 50 minutes for the carer. The flexible nature of the interviews not only enriched data collection, but provided an opportunity to explain or clarify any misunderstandings, which in turn, increased the accuracy of the data

3.5.6 Phase 3: Qualitative data collection (digital diaries-dictaphones)

Phase 3 consisted of the use of a digital diary over a two-week period. As a supplementary qualitative method, digital diaries were generated using dictaphones. The patient and carer were sent the device in the mail together with the digital diary instructions (Appendix 10), to use as and when they wished to record their narratives

related to the impact of the disease. The device was mailed after the interview had taken place. Only seven out of the ten dictaphones were returned with data. Despite the response rate not as strong and robust as hoped, nor the quality of data from patients lower than anticpated, the diary entries were transcribed verbatim and provided useful anecdotes of participant feelings and experiences incorporated into Chapter Five.

3.6 Quantitative data analysis

The collected data from the NPTB administered in Phase 1 is described statistically, using means, standard deviations (SDs) and ranges of scores, using GraphPad Prism 9.1.1. All patient and carer scores from the NPTB, are presented in spreadsheets in Appendices 29 and 30. Open Clinica software was used to collect NPTB data (Appendix 31). Before analysis, data cleaning and preparation of data, ensured the accuracy of the data.

The patient assessment was based on the severity of symptoms which were scored on various cognitive, behavioural and emotional domains, together with the carer's scoring on different domains of burden and distress. Correlation analysis was undertaken using Pearson correlation coefficient to demonstrate the strength of the relationship between two domains. The Spearman's rho was used where the scores were not normally distributed (nonparametric correlation). Correlations between variables are presented, together with comments on their significance to practice, and possible relations to other studies. In order to determine whether a raw score for each patient participant reflected impairment or near-normal performance, cut-offs were used from articles and similar evidence-based research literature. Z-scores (also known as standard scores) were useful in showing the patient's performance, comparable with means and SDs from HCs in original research studies where there were no available cut-offs to indicate impaired performance. However, these were not demographically matched to the aLE patients. By using one-sample t-tests

versus cut-off scores from published research, group-level deficits were identified for each test or questionnaire. The steps in quantitative data analysis are shown in Table 2, below.

Table 2: Summary of the quantitative analysis process

i. Administer the NPTB for Patients and Carer participants, in Oxford or in their homes.
ii. Data entry onto Open Clinica/Clinical Conductor
iii. Data exported using Excel spreadsheet for analysis using GraphPad Prism
iv. Provide summary statistics on demographic, clinical, and neuropsychological variables of the patient group.
v. Provide demographic, clinical, and neuropsychological information separately for each individual patient participant
vi. Provide summary statistics on demographic, clinical, and neuropsychological variables of the carer group
vii. Run one sample t-test to indicate level of impairment at using cut-offs
viii. Conduct bivariate correlation analyses between variables

Table 2. To show quantitative analysis process.

Normal distribution was assessed using Shapiro-Wilk normality test in GraphPad Prism (V8.4.0), with p-value >0.05 reflecting data variables that assume normal distribution of the NPTB data (see Appendix 32 for the GraphPad Prism text version of the normality tests). For one-sample t-tests, when the assumption of normal distribution was violated, the one-sample Wilcoxon signed rank test was used instead. In summary, a combination of tabulated description, graphical description, and statistical commentary to discuss results, was applied.

3.7. Qualitative data analysis

Qualitative analysis was undertaken using IPA. Timing of analysis is paramount to ensure that interpretation is not hurried (Smith, Flower and Larkin, 2009). Therefore, interpretation was done methodically and accurately, over months. Notes made on

the IS were also useful in determining whether the flow and content of the schedule needed adjusting and reviewing.

All interviews were transcribed verbatim, anonymised and organised using MAXQDA 2018. Full versions of de-identified transcripts are available on request. IPA was undertaken using guidance from Pietkiewicz and Smith (2014). During the initial stage of 'immersion' or total pre-occupation with the narratives, the researcher considered each transcript in turn to get an initial sense of the flow of the interview. Non-verbal communication was included in verbatim transcriptions when they were interpreted as meaningful within the conservations, such as a sigh or laughter added as emoticodes on MAXQDA. Linguistic comments such as pauses, degree of fluency ('articulate' or 'hesitant'), were also documented as useful reflections on the narratives. A detailed illustration of capturing coding using colour coding, code favourites, code matrix, cross-tab across texts to compare codes, coded segments and other features useful in managing the qualitative data, such as using memos and reflection, is demonstrated through screenshots from MAXQDA (Appendix 33). Using Gibbs' (1988) 'reflective cycle' and Schon's (1983) 'model of reflection', any areas of interest during Phase 1 were re-addressed in Phase 2 interviews. Gibbs (1988) believes that without reflecting on the experience, its learning potential will be lost. Furthermore, reflective notes are considered vital when interpreting the setting and the relationship with the interviewees (Smith, Flowers and Larkin, 2009; Korstjens and Moser, 2018). Regarding reflexivity of one's findings, a different approach has been suggested to divide the narrative into separate phases, in respect of a 'sequencing of interpretation' (Alvesson and Skoldberg, 2000).

Although there is no single method for conducting qualitative analysis (Miller and Daly, 2013), the common processes are highlighted by reading techniques used by other experts and authors. The analytic process to make sense of the participants' experiences, is shown below using guidelines on IPA based on a practical guide by Pietkiewicz and Smith (2014). However, it can be argued that the distinctness of IPA

lies in its approach to capturing the person's concerns accurately and honestly, as opposed to following set steps in the analysis process (Larkin, Watts and Clifton, 2006).

> Stage 1. Multiple reading and making notes/comments
>
> Stage 2. Coding
>
> Stage 3. Memo writing (reflection, bracketing, researcher's feelings, how the interview went and additional documents)
>
> Stage 4. Identification of themes
>
> Stage 5. Identification any sub-themes; patterns or unique
>
> Stage 6. Writing up the findings, retaining the participant's personal experience
>
> Stage 7. Use of supervision from a senior qualitative researcher for the first transcripts

Despite these stages being beneficial in the facilitation of analysis for novice researchers, experienced researchers may prefer not to follow stages precisely, but instead to embrace the whole process, and use the stages as guidelines. Over the period of analysis, every code and theme were examined and re-examined. Every subsequent re-read of the text using the exploration of key words, phrases, quotes and emotional responses, subsequently allowed for the interpretation of how the participant was making sense of the impact of LGI1-aLE (double hermeneutics). Using IPA enabled a shift from introducing topics to obtaining accounts of experiences and feelings, such as, 'can you describe how that felt for you?'. Summarising, reflecting or sharing the researcher's understanding is good IPA practice, such a 'so you felt fearful?' (Holloway and Jefferson, 2005; cited in Smith, Flower and Larkin, 2009). Comments were marked as memos (Appendix 34 for a more concise referral to coding and memos). Coding involved interpretation of the data to open possible channels to the participants' feelings and understandings. Furthermore, 'reflective memos' included some comparisons, similarities and patterns that had been observed concerning participants' experiences, feelings and symptoms. Memos described the researcher's thoughts and 'how the interview

went', which was useful in analysing any interruptions, flow of conversation, or the ability of the participant to express themselves. Finally, memos noting additional documentation from participants were added (not used in the analysis but are available as Appendices 34, 35 and 36). LESS1 wife provided a useful diary entry of events. Presentations by LESS6 patient and wife and LESS8 wife, demonstrated further accounts of the impact of the disease.

IPA involved seeking out patterns or differences by bracketing assumptions and biases (using bracketing memos), including the acknowledgment of recall bias due to memory loss. It has been suggested that bracketing any influence or bias emerging from the first transcript analysis, should be undertaken before analysing the second and third analysis (Smith, Flower and Larkin, 2009). Notably, direct quotes provided an extended representation of narratives. Data collection was built on trust and rapport with the participants, demonstrating professional empathy and developing skills to probe further, when appropriate. Essentially the balance of the IPA was maintained between giving a voice to the participant and making sense of what they said through the researcher's interpretation and engagement with their narrative. Following each interview, the digital diary was sent out with instructions. The recordings of the diaries were transcribed using the MAXQDA transcription function, as soon as data was received.

The organisation of themes was revealed after initial coding, with case-by-case analysis demonstrating how relevant the theme was to each participant, what was important to them, their concerns and the key features of their experiences. Important themes were identified from the data, and differentiated using symbols and emoticons, but colour-coded text was also available. Retrieval of coded segments was easy by using the search options and 'favourite coding'. Purposeful themes were already considered to ensure data collection remained focused and relevant. By removing duplicated codes this reduces them to a manageable list of themes, which are the major ideas emerging from the data (Creswell, 2012). To address the

quality of the transcriptions, the first two transcriptions and coding were sent to an experienced supervisor in qualitative methodology. Some research suggests that the use of investigator triangulation when more than one researcher is involved in analysis, can provide further trustworthiness of the coding, themes and interpretation of data (Carter et al., 2014). For this thesis, however, the supervisor did not undertake any analysis. Instead, improvements in interview techniques, such as the flow of the interview plan and probing, were recommended.

3.8. Measuring data quality: Phase 1

During Phase 1, 'validity' is concerned with whether this research is true, by measuring and evaluating what it is supposed to (Heale and Twycross, 2015).

The concept of the psychometric NPTB uses closed-ended self-report patient and carer questionnaires or researcher-led patient questionning to provide quantitative or numerical data. Each questionnaire has been extensively explored and tested by experts to measure what it intends to measure, by comparing individual performance-based measures with normative data. Standardised instructions ensured that researchers were trained to undertake the assessments in a standardised manner. 'Internal validity' is defined as the NPTB measuring its intended scores, and not on other confounding factors, therefore making the causal relationship more credible. 'External validity' refers to the extent to which the NPTB can be used in other settings, on different populations and over time. Heale and Tywcross describe three types of validity. 'Content validity' refers to whether the tool used covers all the content, in this case a self-report or researcher-led questionnaire. 'Construct validity' refers to the extent to which the tool measures what it intends to, such as apathy. 'Convergent validity', a kind of 'criterion validity', shows that a tool correlates with a tool measuring similar variables. The questionnaires used in the NPTB were already decided upon under the original protocol 'Memory and Motivation', of which an amendment was made to add the qualitative aspect of my thesis (Limbic Encephalitis Sub Study). Therefore, I did not have the opportunity to

consider the above validity elements for the questionnaires used per se, but instead commented on validity and reliability in section 3.5.4.

'Reliability' represents the accuracy, consistency and replicability of the results (Heale and Twycross, 2015). Within the employment of psychometric testing, reliability can be assessed by obtaining the same results on repeated administrations to the same participants and by more than one researcher obtaining the same results. Reliability refers to the consistency of the NPTB measurements, where the test-retest method has assessed the stability and reproducibility of the questionnaires and scales. The selection of well-standardised tests to use for neurological patients is based on specialist knowledge and experience, and comparable published norms from other research (Miller and Rohling, 2001). Furthermore, these standardised tests were undertaken using interpersonal skills, necessary to build rapport with the participants, enhance cooperation and maximise effort during testing.

3.9. Defining data quality: Phase 2

Unlike quantitative research, the overall trustworthiness of the qualitative data collection is considered to contribute to the credibility, confirmability and dependability of the research (Lincoln, Lynham and Guba, 2018). Trustworthiness was demonstrated in this thesis by engaging with senior researchers and supervisors, gaining significant literary knowledge on LGI1-aLE, as well as obtaining complex and sensitive information shared by patients and families in outpatient's clinic, or at research events. First, the credibility of the data which refers to the confidence of the findings, or reality, can be compared to the internal validity of quantitative research. Credibility, known as the 'truth value ((Lincoln and Guba 1985, cited in Korstjens and Moser, 2018), was enhanced by building a good rapport and trust with the participants. Furthermore, reflexivity enhanced the transparency and quality of the data, by critically self-reflecting on the analysis. In addition,

triangulation of methods added another aspect of credibility. Second, confirmability refers to the findings being explored and confirmed by other researchers, in this care thesis supervisors. However, supervisor subjectivity, may lead to different judgment, opinions and experiences. Another form of confirmability refers to the steps taken to ensure data represents the participant's thoughts rather than the researcher's own views. This can be done by asking participants to comment on the preliminary analysis via focus groups or to comment on a written account of their experience (Probyn, Howarth, and Maz, 2016). For this research, all the participants were given a copy of the transcriptions from both the semi-structured interviews and the digital diaries to confirm the true likeness to the conversations and recordings, but they were not given a copy of the analysis. Other studies invite participants for a post-interview meeting to enable them to respond to their transcripts, but arguably these discussions could influence the researcher's subsequent interpretation (Wagstaff and Williams, 2014). Transferability refers to how the data collection can be applied to other participant groups who have similar neuropsychological changes, such as to different forms of encephalitis, for example (viral or non-autoimmune). Third, dependability has been likened with quantitative reliability, as it leads the way for other researchers to replicate the research (Saunders et al., 2018). However, this does not imply that the same results will be expected, but that the design and data collection methods could be repeated in the future.

Regarding the saturation of data, this can be conceived as a tool to collect adequate and quality data. However, over recent years, the consensus on saturation has been in dispute. Some researchers argue that data saturation or sufficiency in qualitative research is a criterion to stop data collection when no new ideas or concepts emerge (Glaser and Strauss 1967, cited by Probyn, Howarth and Maz, 2016). This is supported by Fusch and Ness (2015) stating that failing to reach saturation as a gold standard for qualitative rigour, can affect the quality of the research. On the contrary, other researchers raise uncertainties about how to conceptualise saturation, and have proceeded to critically examine the concept. Starks and Trinidad (2007) offered a third model of saturation where data is never completely explicit but is enough to

illustrate the individual narrative. Furthermore, Legard, Keegan and Ward (2003), stated that saturation is not obtained at the point of the complete data collection, but for that individual participant and that specific interview. This thesis follows the position that data saturation can never be entirely reached, as any future interviews or diary entries could yield new feelings and experiences.

3.10. Ethics

The use of the NPTB data, for Phase 1 of data collection, was approved by the local Research Ethics Committee (REC Ref: 18/SC/0448), HRA and Sponsor (see Appendices 37 and 38). The Sponsor for this the University of Oxford.

3.11 Risks

Part of the ethics process was to maintain the participants' safety and wellbeing within clinical research. The NPTB for this research was not associated with any risks to participants. The qualitative data collection extracted sensitive and traumatic information, but there were no risks. Ethical considerations addressed anonymity, confidentiality and informed consent (Sanjari et al., 2014). In addition, ethics approval included the reviewing of the IS and Digital Diary Information Sheet, which addressed the issue of sensitive data and taking a break if the participant felt tired.

3.12 Data handling and participant confidentiality

Under the General Data Protection Regulation (GDPR), guidelines for the collection and processing of participants' personal information were followed. The process of collecting and storing personal data was undertaken using electronic databases, which were password-protected on university computers. Participants were fully informed of the use of the NPTB data for the additional purpose of this doctorate,

when signing and dating the ICF. The CI and research staff are obligated under Good Clinical Practice guidelines to ensure that the participants' anonymity is maintained. Participants were only identified by a study identifier on all databases and documents, including transcriptions.

3.13 Chapter summary

This chapter has outlined the essential differences in the quantitative and qualitative paradigms, together with the pragmatic stance using MM. Having explained the triangulation method to maximise integration of analysis, together with the rationale for design implementation, screening, recruitment and data collection methods, the next two chapters will show the findings from Phases 1-3.

CHAPTER FOUR

Quantitative Results (Phase 1)

4.1. Introduction to the chapter

This chapter presents the quantitative results, using descriptive statistics to summarise the NPTB data from Phase 1. Patient and carer data are shown, using means, SDs and ranges of findings. Regarding inferential statistics, one-sample t-tests were conducted versus the available cut-off scores. In addition, bivariate correlations were undertaken on possible associations of interest to the researcher.

4.2. Participant demographics: patients and carers

Table 3 below summarises the demographic data. This sample has a consistent characteristic in terms of mean age with other research, such as a retrospective study of 118 patients with LGI1-aLE (median age at disease onset was 66 years) (Rodriquez et al., 2022). The mean age of patients in this sample was 64.4 years of age. The mean number of years from diagnosis of the LGI1-aLE to the time of the NPTB assessments, was 5.4 years, with a range from 2-10 years, indicating the application of the NPTB as a long-term, chronic assessment of patient symptoms. The mean number of months from the patient's first symptoms to their diagnosis date, was 13.7 months, which ranged from 2-77 months. This demonstrates how the cohort of patients experienced a considerable delayed diagnosis. The outlier of 77 months accepted the misdiagnosis of menopause for an extended period. Without this outlier, the mean was 6.67 months. This is comparable with a study by Macher et al. (2018), where 38 aLE patients' (seven of which were LGI1 patients) demonstrated a mean delay in months from first symptoms to diagnosis as 5 months.

Table 3: Demographical data

Study Subject	Sex	Age (years) at NPTB assessment	Years from diagnosis to NPTB	Months from first symptoms to diagnosis	Left/right-handed	Years of full-time education
LESS1	m	60	7	5	left	10
LESS2	f	62	2	5	right	16
LESS3	m	74	2	4	right	11
LESS4	f	47	3	77	right	11
LESS5	f	53	3	23	left	13
LESS6	m	81	7	3	right	17
LESS7	m	55	5	3	right	11
LESS8	m	66	9	8	right	11
LESS9	m	77	10	2	left	10
LESS10	m	59	6	7	right	17

Table 3. Demographic data for patient participants. m: male, f: female. LESS=Limbic Encephalitis Sub Study.

All patients satisfied the diagnosis criteria as described by Graus et al. (2016), including subacute onset, referred to as less than 3 months, working memory deficits (short term memory loss), FBDS, altered mental status or psychiatric symptoms. Furthermore, all patients had positive LGI1 antibodies when recruited. In addition, consistent with existing criteria and guidelines to include routine bloods and CSF analysis (Venkatesan et al., 2013), all patients had undertaken these tests.

60% of patients were not working at the time of the NPTB. 5 patients had retired and 1 had taken early retirement. Those under the retirement age, did not receive any sickness pay and continued to work part-time.

4.2.1 NPTB self-report symptoms

Overall, symptoms were reported in all the patients at the time of their assessment in Oxford. 40% of patients reported the encephalitis as having 'no impact', on their lives, but this was not consistent with what the carer had described, during their assessment. This question was presented as part of the NPTB. This was not a separate questionnaire. It simply gave four options ('not at all', 'slightly', 'moderately' or 'a lot').

Table 4 shows the patient-reported first symptoms prior to diagnosis, when asked as part of the NPTB, equating to the acute phase.

Table 4: Patient-reported first symptoms prior to diagnosis and at the time of the NPTB in Phase 1

Study ID	First Symptoms prior to diagnosis	Patient reported symptoms at time of the NPTB (Phase 1)
LESS1	Absent moments. Had a tonic clinic, heart arrhythmia	Memory worse. Relapsed twice 2013 and 2018
LESS2	Got up, felt like they had hit a brick wall. Sensations down left side. Right side head heard clear voices. Memory loss. Tremors. Fell and broke right hip.	Tremors. Occasional sensations. Fatigue. No energy.
LESS3	Was told they were away in [country]. Memory loss. Did not recognise long-term friend. Unconscious for 3 days in ITU.	Memory loss.
LESS4	Funny feelings in hand-felt numb and not strong holding something. Horrible feelings in stomach (temporal lobe epilepsy 30 a day) Anxious feeling- locking the windows.	Still has abnormal sensation/strength in left hand. More emotional.
LESS5	Memory loss repeatedly asking questions. Irritable	Lack confidence. Feelings of being overwhelmed. Less attachment to material things.
LESS6	Fainting. Dizziness. Seizures	Occasionally tingling feeling in left arm, ranging from 3 times a day or none for 3-4 days.
LESS7	Does not remember.	Memory loss. Find difficult to empathise with wife. Easily frustrated.
LESS8	Seemed vague. Staring aloof. Leg shaking before absent moments. Dropped coffee. Staring when driving.	Memory loss.
LESS9	Headaches and fits (seizures) his wife says.	None.
LESS10	My wife says psychotic. Headaches Seizures	Headaches. Memory loss.

Table 4. As reported by patient. LESS=Limbic Encephalitis Sub Study number

A broad range of symptoms was identified at the time of the NPTB (see Table 3). Memory loss was the most common patient reported symptom. However, in most instances, due to memory loss the patient was told by the carer of these first, acute symptoms. Patients reported abnormal sensations, likely focal seizures, which took the form of a rising feeling in the stomach, a jerking, tingling or twitching in the extremities or fiddling. These descriptions were consistent with a general difficulty in describing the feeling (Wang et al., 2017). Some carers reported the patient as staring blankly into space or demonstrating a brief absence.

One participant stated he did not have any symptoms. At the time of the NPTB, 90% of patient participants were taking anti-seizure drugs, possibly indicating seizure control. However, de Bruijn et al. (2019) stated that most patients with AE do not need long term medication for seizures. Interestingly, research reporting 1 out of 13 LGI1-aLE patients were still receiving anti-seizure medication following a median of being 5 years seizure free (Lyas-Feldmann, Prüß and Holtkamp, 2021).

4.2.2 NPTB findings: patient participants

Table 5: Descriptive statistics for all patient assessments.

Variable	Domain	Mean	SD	Minimum	Maximum	Maximum possible score of test	Cut-offs <impaired	Participants performing in the impaired range (cut-off score based on mean and SD of scores from healthy participants)
Age at assessment (years)		64.40	9.75	53.00	81.00			
Years from diagnosis to NPTB in Oxford		5.40	2.87	2.00	10.00			
Delay from first symptoms to diagnosis (months)		13.70	23.05	2.00	77.00			
ACE-R Attention	Cognition	16.80	2.15	12.00	18.00	18	<17.5	LESS1 (16) LESS9 (14), LESS10 (12)
ACE-R Memory	Cognition	21.90	3.28	16.00	26.00	26	<22.5	LESS1 (16), LESS2 (19), LESS4 (22), LESS7 (21), LESS9 (19), LESS10 (22).
ACE-R Fluency	Cognition	10.00	1.94	8.00	13.00	14	<11.5	LESS4, LESS8, LESS9, LESS10 (all scored 8), LESS1 (10), LESS3 (10), LESS6 (11).
ACE-R Language	Cognition	25.60	0.97	23.00	26.00	26	<24.5	LESS1 (23)

ACE-R Visuospatial	Cognition	15.50	0.67	15.00	16.00	16	<15.5	
ACE-R Total		90.00	6.15	80.00	98.00	100	> 88.5 normal	LESS1 (80), LESS9 (82), LESS10 (84)
WMS-III Digit Span Total	Cognition	13.20	2.53	8.00	16.00	30	>10 aged related mean	
AMI Behavioural Score	Apathy/Motivation	1.22	0.62	0.17	2.00	*4	>2.34 moderate	LESS4 (0),
AMI Social Score	Apathy/Motivation	1.78	0.967	0.67	3.33	*4	>2.43 moderate	LESS6 (0.83)
AMI Emotional Score	Apathy/Motivation	1.17	0.44	0.33	1.83	*4	>1.68 moderate	LESS5 (0.33)
AMI Total Score		1.39	0.53	0.61	2.17	4*	>2.31 severe, >1.91 moderate	LESS1 (2.11), LESS9 (2.17)
SHAPS Total Score	Anhedonia	0.80	1.23	0	4	4	Cut-off >2	LESS7 (4 Total))
BDI Affective Sub score	Depression	2.50	2.63	0.00	8.00	13		
BDI Dysphoric Mood Factor	Depression	3.50	2.80	0.00	9.00	19		
BDI Loss Interest Pleasure	Depression	1.30	1.64	0.00	5.00	28		

BDI Total		9.60	7.10	1.00	24.00	63	>20 moderate, >29 severe	LESS10 (24)
FSS Score	Fatigue	30.0	1.60	9.00	54.00	63	>36	LESS2 (45), LESS9 (46), LESS10 (54).
PSQI Total Score	Sleep quality	5.20	2.57	2.00	10.00	21	>5 poor quality	LESS2 (9), LESS4 (6), LESS5 (10), LESS7 (5), LESS8 (5) and LESS10 (5).
WHO5 Percentage Score	Wellbeing	68.80	17.26	40.00	92.00	100	No cut-off*	
Cantril Ladder	Life satisfaction	7.50	1.51	5.00	9.00	10	No cut-off*	

Table 5. ACE-R=Addenbrookes Cognitive Examination Revised. ACE-R cut-offs taken from PD study comparing normal cognition to mild cognitive impairment (Berankova et al., 2015). , WMS-III DS=Digit Span, AMI=Apathy Motivation Index * Three domains of apathy-motivation are assessed with the mean score, which ranges from 0-4 (with 0 being motivated and 4 being apathetic) 1) Behavioural:Q5, 9, 10, 11, 12, 15 2) Social: Q2, 3, 4, 8, 14, 17, 3) Emotional: Q1, 6, 7, 13, 16, 18. SHAPS=Snaith Hamilton Anhedonia Pleasure Scale, BDI=Becks Depression Inventory ** Total scores available 0-7 = Minimal level of anxiety, 8-15 = Mild anxiety, 16-25 = Moderate anxiety 26-63 = Severe depression. FSS=fatigue Severity Scale, PSQI=Pittsburgh Sleep Quality Index, WHO=World Health Organisation quality of life, Cantril=life satisfaction. Empty cells=not possible to ascertain impairment based on this test, as sub-scores do not have cut-offs.

Having shown the descriptive statistics for all patient scores (individual patient scores are found in Appendix 29), each test/questionnaire is examined in turn.

4.2.2.1 Cognition (ACE-R)

The cognition test has revealed two important things in neurological research. First, regarding total scores in early onset dementia, Elamin et al. (2016) showed a total score of > 88 as normal, with people over 75 years of age scoring less. This younger cohort's scores ranged from 80-98, showing that that some patients demonstrated cognitive impairment (See Appendix 39 for the scoring instructions). However, using a one-sample t-test showed that patients did not score significantly lower than the cut-off total score of 88 (mean = 90; SD = 6.18; t = 0.92, p = 0.38). Hence, there was no evidence for overall cognitive impairment in this group.

Second, comparable to research on PD differentiating normal cognition with mild cognitive impairment, a cut off of 88.5 was used (Berankova et al., 2015). Overall, memory was one of the significantly affected domains as demonstrated in this cohort of patients, showing a range of 16-26/26 and a mean score of 22. 40% of patients lost points pertaining to the memory domain. This is comparable with a study, where cognitive testing revealed 32% of the LGI1-aLE patients with a median age of 64 demonstrated an impaired total ACE score using <88 as a cut-off (Binks et al., 2021). Furthermore, their study showed 16% of LGI1-aLE patients scored less than healthy elderly individuals in memory and fluency and 9% of patients scored less in attention. In comparison to this thesis cohort, the mean fluency total was 10, with a range of 8-13/14, where all patients lost points in fluency, and 30% lost points in the sub-domain attention, where they showed a range 12-18/18 and a mean score of 16.7 (see Table 6 below). In summary, deficits in fluency and attention were predominant factors in the ACE-R cognitive test.

Table 6: ACE-R scores

Study.Subject.ID	Attention	Memory	Fluency	Language	Visuospatial	Total
LESS 1	16	16	10	23	15	80
LESS 2	18	19	12	26	16	91
LESS 3	18	26	10	25	15	94
LESS 4	18	22	8	26	16	90
LESS 5	18	25	13	26	16	98
LESS 6	18	26	11	26	16	97
LESS 7	18	21	12	26	16	93
LESS 8	18	23	8	26	16	91
LESS 9	14	19	8	26	15	82
LESS 10	12	22	8	26	16	84

Table 6: Sub-tasks for the ACE-R=Addenbrookes Cognitive Examination Revised. LESS=Limbic Encephalitis Sub Study number

4.2.2.2 Cognition: short-term and working memory (WMS-III DS)

The test to recall digit sequencing had an interesting result. Running a one-sample t-test at group level, patients scored significantly higher than the age-scaled mean being 10 (mean = 13.2; SD = 2.53; t = 4.00, p < 0.03). Furthermore, z-scores were derived by using the psychometric conversion table (see Appendix 40) with the corresponding scaled scores. Notably, none of the patients scored below an age-related score of 5, which corresponds to the 5th percentile. This indicated no impairment in short-term and working memory, reflected in both forward and backward DS performance.

4.2.2.3 Apathy-Motivation (AMI)

In terms of the apathy-motivation self-report, this has revealed two distinct findings. First, the cohort scores ranged from 0.61-2.17, illustrating no patients scored within the severe apathy range (>2.38). Second, two patients scored within the moderate apathy range. Furthermore, a separate one-sample t-test against the moderate score

cut-off of 1.91 for total scores showed most patients did not show evidence of moderate apathy at group level (mean = 1.39; SD = 0.53; t = 3.13; p = 0.01). LESS1 and LESS9 exhibited the most apathy within the moderate range.

Having establish the total score findings, a separate one-sample t-test for the three sub domains of apathy against the moderate cut-offs for behavioural apathy (>2.34), social apathy (>2.43) and emotional apathy (>1.68) was also undertaken. Behavioural apathy which demonstrates a lack of self-initiated activities, was not demonstrated by most patients (mean = 1.22; SD = 0.62; t = 5.71; p <0.1). For social apathy indicating a lack of initiation or engagement in social activities, and emotional apathy, which is characterised by both negative and positive emotions, most patients' self-reported scores did not show evidence in these domains (social score mean = 1.78; SD = 0.97; t = 2.12; p = 0.06, emotional score mean = 1.17; SD = 0.44; t = 3.66; p<0.01). In summary, the evidence should be interpreted with caution due to the small sample size, and the forthcoming contradictory qualitative findings in the next chapter.

4.2.2.4 Hedonia (SHAPS)

This scale has not disclosed a lack of pleasure for LGI1-aLE patients. The total scores for this cohort ranged from 0 to 4, with a mean score of 0.8. For one-sample t-tests, when the assumption of normal distribution was not fullfilled, the one-sample Wilcoxon signed rank test was used instead. Several patients scored significantly lower than the cut-off total score of >2 (W = -40; p = 0.04), hence, there was no evidence for overall anhedonia in this cohort.

4.2.2.5 Depression (BDI)

Regarding the test for detecting depression, findings did not expose any depression amongst patients. Running a one-sample t-test using the total BDI scores, also included the sub scores of affective mood, dysphoric mood and loss of interest. There was no evidence of moderate depression disclosed at group level, as 90% of LGI1-aLE patients scored significantly lower than the cut-off score of 20 for moderate depression (mean = 9.60; SD = 7.10; t = 4.63, p < 0.01). Furthermore, no patient participants reported taking anti-depressants at the time of the NPTB or later during the interviews. However, the score of one patient (LESS10) indicated moderate depression (24). The next chapter illustrates patients' expressions of irritability or mood swings rather than depression, with one patient attributing his occasional depression to the winter seasons.

4.2.2.6 Fatigue (FSS)

Interestingly, this score did not disclose prominent patient fatigue as a chronic symptom. The LGI1-aLE cohort ranged from 9-54/63 with a mean score of 30.0 (SD = 1.60, t = 0.34, p = 0.26), therefore not indicative of a problematic fatigue at group level, using >36 as a cut-off. Often patients did not report a fatigue problem, whereas the carer perspective described fatigue as very significant during the interviews. 20% of LGI1-aLE patients scored in the impaired range, higher than the cut-off of 4, indicating problematic fatigue. Comparable with other research, where fatigue has remained prominent long-term (Binks et al., 2021), future research with a larger sample size could be applied to this cohort of patients to strengthen the interpretation of results.

4.2.2.7 Sleep quality (PSQI)

Assessing the patients' sleep quality during the month leading up to the NPTB, the findings have demonstrated that 60% of patients scored the cut-off of 5 and above

indicating poor sleep quality. The range of scores for this cohort was 3-10/21. Despite the mean scores of the cohort being 5.20, there was no evidence for group-level impairment (mean = 5.20; SD = 2.57; t = 0.25, p = 0.81). LESS2, LESS4 and LESS5 suffered with the poorest sleep quality above the cut-off score. None of the patients were taking sleeping medication at the time.

4.2.2.8 Wellbeing (WHO-5)

This is a subjective measure of positive mood, vitality and general interest, which is useful as part of the NPTB. The LGI1-aLE scores ranged from 40%-92%. With a cut-off of <50% identified using the WHO-5 (Gao et al., 2014 cited by Topp et al., 2015), a one-sample t-test using the total WHO-5 scores, showed there was good self-reported wellbeing at group level, as patients' scores were on average higher than the cut-off score (mean = 69.00; SD = 17.26; t = 3.44, p = 0.01). LESS10 scored 40%, the lowest representation of the best possible quality of life, which is later reflected in his narrative.

4.2.2.9 Cantrill ladder

This measurement of the patients' life satisfaction on a scale of 0-10; where 10 is the best possible life imagined, is another subjective test. A cut-off using the median score of 5 has been used in research studying older people with apathy (Groeneweg-Koolhoven et al., 2014). Using a one-sample t-test there was good self-reported life satisfaction at group level, as LGI1-aLE patients' scores were on average numerically higher than the cut-off score of 5 (mean = 7.40; SD = 1.43; t = 5.31, p < 0.01). This cohort ranged from 5-9/10, with a mean score representing a relatively high life satisfaction score, which will be further explored in the qualitative data analysis.

4.2.3 NPTB findings: carer participants

9/10 carers were spouses, and 1 was a brother (see Table 7).

Table 7: Descriptive statistics for all carer NPTB questionnaires

Variable	Domain	Mean	SD	Minimum	Maximum	Maximum score possible	Cut-offs	Which participants performed in the impaired range if cut-off available and their score
NPI-Q Total	Neuro-psychiatric symptoms reported by carer	18.40	12.49	0.00	39.00	144	>11	LESS1 (12), LESS3 (32), LESS4 (14), LESS5 (26), LESS6 (12), LESS7 (15), LESS8 (16), LESS10 (39)
NPI-D Caregiver Distress Score	Distress of carer	12.50	8.87	4.00	30.00	60	No cut-off	LESS9 (30)
LARS Carer Total	Apathy reported by carer	-15.60	14.67	-33.00	5.00	36	>-9 severe apathy -16 to -10 moderate -21 to -17 mild	LESS1 (-8) LESS3 (3), LESS9 (5), LESS10 (1)
ZBI Total	Burden for carer in providing care	32.10	18.28	7.00	62.00	88	>21 mild to moderate>41 moderate burden, >61 severe burden	LESS3 (54), LESS7 (47), LESS10 (62)
B-ADL Carer Total Score	Difficulties in everyday activities reported by carer	3.82	2.55	1.00	8.84	10	>3.12 mild to moderate	LESS 1 (3.76) LESS4 (3.12) LESS 5 (4.12) LESS 9 (6.35) LESS 10 (8.84) with increased possibility of cognitive decline

| IQCODE Score | Cognitive decline | 3.89 | 0.58 | 3.19 | 5.00 | 5 | >3.51 moderate decline | LESS5 (4.44) LESS10 (5.00) |

Table 7.NPI=Neuropsychiatric Inventory, LARS=Lille Apathy Rating Scale, ZBI=Zarit Burden Interview, B-ADL=Bayer-Activities of Daily Living, IQCODE=

Carer, Informant Questionnaire on Cognitive Decline in the Elderly.

The carer questionnaires below are colour-coded with the Table above (Table 6); blue relates to questions about the patient, and light green relates to questions about the carer (individual carer scores are available in Appendix 30).

4.2.3.1 Neuropsychiatric Inventory (NPI-Q)

This questionnaire has exposed three critical findings. First, most carers stated that these symptoms had occurred in the acute phase and that only some had persisted during the time of Phase 1 NTPB data collection. Second, as few studies have proposed cut-offs for the NPI, any neuropsychiatric score is interpreted as an abnormal one. However, one dementia study determined a cut-off of 11 (Nunes et al., 2019). Third, using a one-sample t-test, carer-reported neuro-psychiatric symptoms over the last month for the LGI1-aLE patients were on average higher than the cut-off score of 11 (mean = 19.40, SD = 11.58; t = 2.23, p < 0.05). These persistent symptoms included agitation, anxiety, irritability, disinhibition, apathy and appetite changes, which will be described in the subsequent qualitative data. The range of total scores was 0-39/96, notably with one husband scoring zero.

4.2.3.2 Carer distress (NPI-D)

This distress score associated with the patients' psychiatric symptoms and behavioural changes in the NPI-Q over the last month, has revealed two important findings. First, although there is no cut-off score for carer distress, research has suggested a mean total distress score of 3.3 for carers of PD, showing greater distress to recently diagnosed patients (Dlay et al., 2020). Second, the mean score for each carer's distress score was derived first, then by using a one-sample t-test, carer-reported distress was on average lower than the mean used in Dlay's research (mean = 1.12, SD = 0.68; t = 10.14, p < 0.01). This could be explained by the knowledge that PD progressively worsens, whereas AE stabilises. Two female carers stated the most distress (25 and 30/60), and one male carer reported the

least distress (2/60) with influences expressed during their narratives. Future research into gender differences may be thought-provoking. In general terms, the lower than average distress score may be attributable to the time that has passed since diagnosis, allowing the carer to adjust and place less importance on their distress levels.

4.2.3.3 Apathy (LARS)

The apathy scale has indicated ratings for this cohort ranged from -33 to +5, with 40% of patients rated as severely apathetic by the carers (-9 to +5). A one-sample t-test against -21 (scores between -21 and -17 indicate mild apathy), showed that on average patients scored numerically higher than the cut-off which indicates at group level there was no evidence for mild apathy, according to the carers' ratings (mean = -15.6, SD = 14.67, t = 1.16, p < 0.27). These findings support current research on apathy remaining a chronic symptom in LGI1-aLE patients and are confirmed in the qualitative data collection.

4.2.3.4 Carer burden (ZBI)

This test has revealed some interestesting findings. First, using 21 for the cut-off score for mild burden, a one-sample t-test at carer group level showed scores were marginally higher (mean = 32.1, SD = 17.09, t = 2.22, p = 0.05). Three carers rated their perceived burden in providing care to the patient, as moderate to severe (LESS3 wife, LESS7 partner and LESS10 wife). Second, referring to the scale asking patients whether the symptoms impacted on their daily lives, two patients LESS3 and LESS9 reported their symptoms as 'not impairing' their daily lives at all. However, they were represented by the highest carer's burden (ZBI) scores of 54 and 62, contradicting the patient reports of 'not at all' and 'mild' impairment respectively. Further exploration for reasons for this high burden are described in the qualitative data.

4.2.3.5 Activities of daily living (B-ADL)

This scale has disclosed 50% of carers reported mild to moderate difficulties in patients performing daily activities. LESS10 wife reported the highest impairment in undertaking daily activities (8.84). The cut-off for mild to moderate difficulty reported by the carer, is >3.12. The scores for this cohort ranged from 1 - 8.84. A one sample t-test against 3.12 indicated that patients at group level did not score significantly lower than the cut-off, and thus the presence of moderate difficulties cannot be rejected (mean = 3.74; SD = 2.62; t = 0.74, p = 0.47). Details on which activities patients had difficulty in, are discussed later.

4.2.3.6 Cognitive decline (IQCODE)

This test has exposed 50% of patients with severe cognitive decline over the last ten years. Jorm (1994) proposed a cut-off point of >3.51 for moderate decline and >4.01 for severe decline. The LGI1-aLE cohort displayed a range from 3.19-5.00, indicating most patients showed some cognitive decline. A one sample t-test showed that, on average, carers scored higher than the cut-off value of 3.51 (mean = 3.85; SD = 0.60; t = 1.78, p = 0.12), but this was a non-significant trend. This supports current literature on long-term poor cognitive outcome in this disease.

Finally, the violin plots in Figure 3a and 3b below illustrate the distribution and density of the patients' and carers' scores. These show the median line and interquartile range, and any outliers. In addition, a complete overview of the data's distribution provides a powerful insight of scores, reviewing the thicker parts containing the highest frequencies and the thinner parts containing the lower frequencies.

Figure 3a: Violin plots to show distribution of patients' scores.
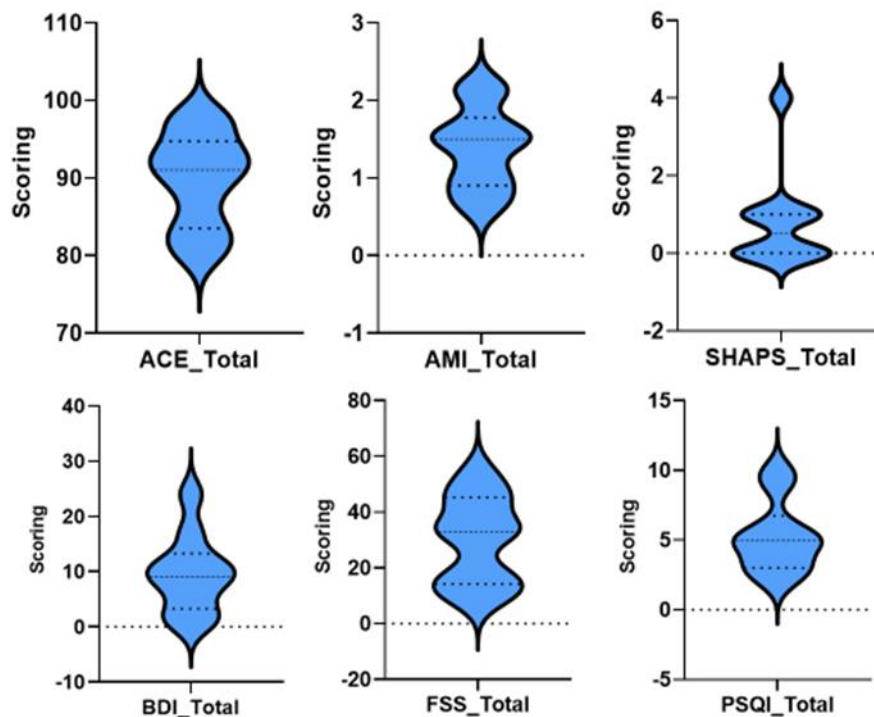
Figure 3a: Violin plot showing distribution of patients' scores: ACE-R – Addenbrookes Cognitive Examination Revised, AMI=Apathy Motivation Index, SHAPS=Snaith Hamilton Anhedonia Pleasure Scale, BDI=Becks Depression Inventory, FSS=Fatigue Severity Scale, PSQI=Pittsburgh Sleep Quality Index. The wider sections represent the highest frequency of the scores, and the dotted lines represent the interquartile ranges.

Figure 3b: Violin plots to show distribution of carers' scores
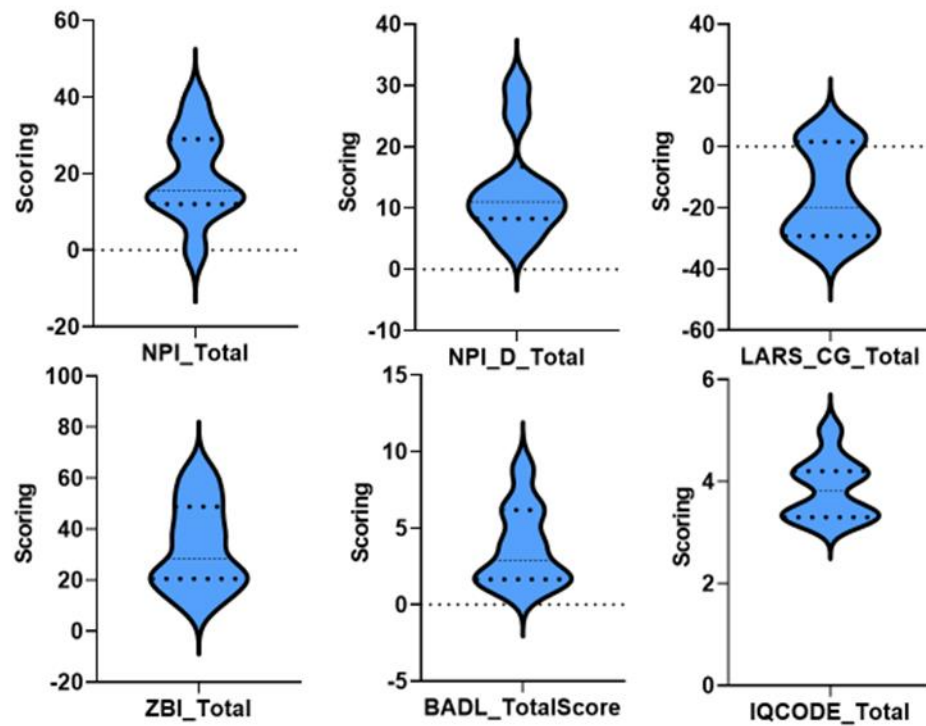
Figure 3b: Violin plot showing distribution of carers' score: NPI=Neuropsychiatric Inventory,
LARS=Lille Apathy Rating Scale, ZBI=Zarit Burden Interview, B-ADL=Bayer-Activities of Daily Living,
IQCODE=Carer, Informant Questionnaire on Cognitive Decline in the Elderly. The wider sections
represent the highest frequency of the scores, and the dotted lines represent the interquartile ranges.

4.2.4 Correlations

These are shown using Pearson's correlation coefficient (r) and Spearman's rho, to investigate any associations of interest between two scores. The value of the effect size of Pearson r correlation varies between -1 (a perfect negative correlation) to +1 (a perfect positive correlation). The effect size is low if the r value is around 0.1, medium if around 0.3, and large if more than 0.5 (Cohen, 1992). Spearman's correlation interpretation is like that of Pearson's, ranging from -1 to +1. describing the strength of the correlation as 0.00-0.19 very weak, 0.20-.039 weak, 0.40-0.59 moderate, 0.60-0.79 strong and 0.80-1.0 very strong. (https://www.statstutor.ac.uk/resources/uploaded/spearmans.pdf). Table 8 below shows the correlation matrix of all the measured variables.

Table 8: Correlation Table for main variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Addenbrooke Cognition Examination	--															
2. Digit span	0.24	--														
3. Apathy-Motivation Index	**-.83	-0.46	--													
4. Snaith Hamilton Pleasure Scale	-0.18	-0.59	**.79	--												
5. Becks Depression Inventory	-0.70	-0.26	*.65	0.42	--											
6. Fatigue Severity Scale	*-.66	-0.12	*.66	0.32	***.90	--										
8. Apathy-Motivation Index_Carer	**-.76	-0.16	0.60	0.51	**.77	**.74	0.91	--								
9. Pittsburg Sleep Quality Index	0.29	*.69	-0.29	-0.13	-0.27	-0.12	-0.15	-0.40	--							
10. Neuropsychiatric Inventory_Carer	-0.15	0.01	-0.18	-0.02	0.47	0.21	0.25	0.48	-0.23	--						
11. Neuropsychiatric Inventory_Carer Distress	-0.31	-0.47	0.19	0.02	0.34	0.32	0.42	*.64	-0.62	0.53	--					
12.Lille Apathy Rating Scale _Carer	*-.68	-0.01	0.38	-0.11	*.66	*.70	*.73	0.90	-0.36	0.57	*.72	--				
13. Zarit Burden Interview_Carer	-0.23	-0.21	0.00	**0.20**	0.56	0.48	0.60	*.74	-0.22	*.71	0.62	0.62	--			
14. Bayer Activities of Daily Living_Carer	-0.46	0.10	0.11	-0.07	*.69	0.50	0.51	*.69	-0.22	***.91	0.51	**.79	*.66	--		
15. Informant Questionnaire on Cognitive Decline in the Elderly	-0.35	0.29	0.03	-0.03	0.57	0.33	0.35	0.59	-0.01	**.84	0.20	0.55	0.50	***.91	--	
16. Months from first symptoms to diagnosis	0.11	0.25	-0.08	-0.03	-0.09	-0.12	-0.39	-0.60	0.30	-0.11	-0.52	-0.31	**-0.19**	-0.08	-0.03	--

Note: $*p < .05$, $**p < .01$, $***p < .001$, two tailed. $N = 10$. (Bold type = Spearman's rho)

Critical value for correlation co-efficient: $p < 0.05$ $r > 0.63$, $p < 0.01$ $r > 0.76$, $p < 0.001$ $r > 0.87$.

Table 8. Shows the bivariate correlations for variables analysed from the NPTB.

4.2.4.1 Relationship between the patient and carer for apathy and motivation

Regarding the self-report index of apathy and motivation, there was a large positive but non-significant correlation between the AMI patient and AMI carer scores across patients (r = 0.60, p = 0.21) shown in Figure 4 below. The AMI Carer score was only introduced to the NPTB in 2019, therefore, data was only available for the six carers who completed this questionnaire. This demonstrated a non-significant positive relationship. Furthermore, patients' and carer's scores were not significantly different (paired-samples t-test: t = 1.84, p = 0.12) therefore, rating the patient's apathy and motivation similarly, where the same questions were asked from two perspectives.

Figure 4. AMI Patient and AMI Carer Totals
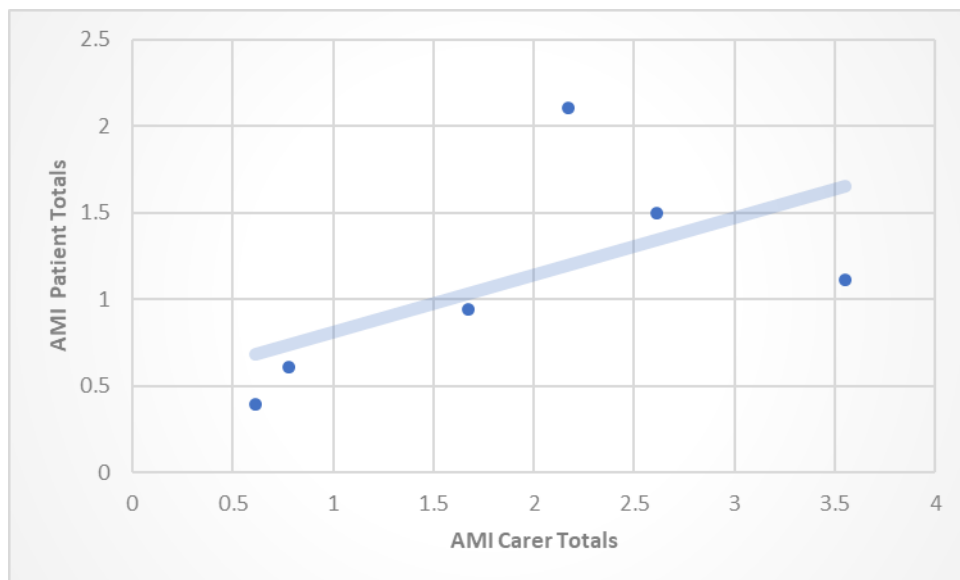
Figure 4: Scattergram to show correlation between Patient and Carer AMI=Apathy Motivation Index totals.

4.2.4.2 Relationship between fatigue with apathy/motivation

The correlation between the FSS and AMI indicated a large positive but non-significant relationship between fatigue and apathy/motivation across (r = 0.61, p = 0.06; Figure 5). Although these are common persistent symptoms in LGI1-aLE

research, these results may reflect the lack of problematic fatigue and apathy and motivation at group level, reported earlier.

Figure 5.FSS and AMI Patient Totals
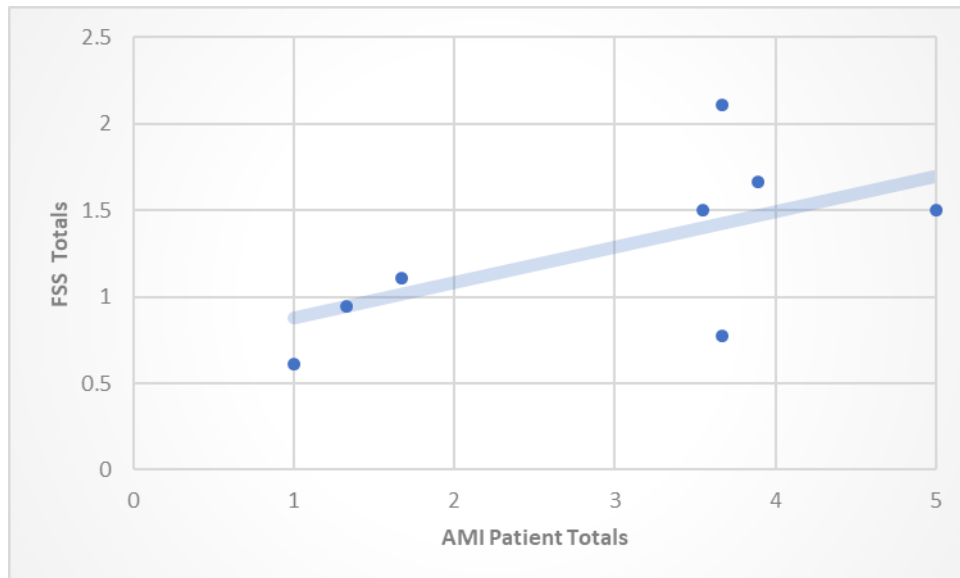
Figure 5. Scattergram illustrating the relationship between FSS=Fatigue Severity Scale and AMI=Apathy Motivation Index across patient

4.2.4.3 Relationship between apathy and hedonia

This nonparametric correlation showed an increase in apathy was accompanied by an increase in anhedonia across patients (rho = 0.79, p < 0.01 (Figure 6), indicating a moderate positive and significant correlation. This positive interrelationship was reflected, despite there being no overall evidence of apathy and motivation, nor anhedonia at group level. Perhaps, by nature of the disease, the combination of apathy based on reduced emotional indifference and goal-directed behaviour, together with the lack of drive to pursue these activities in anhedonia, was already incorporated into the patients' attitudes towards the questionnaires.

Figure 6. AMI Patient and SHAPS Totals
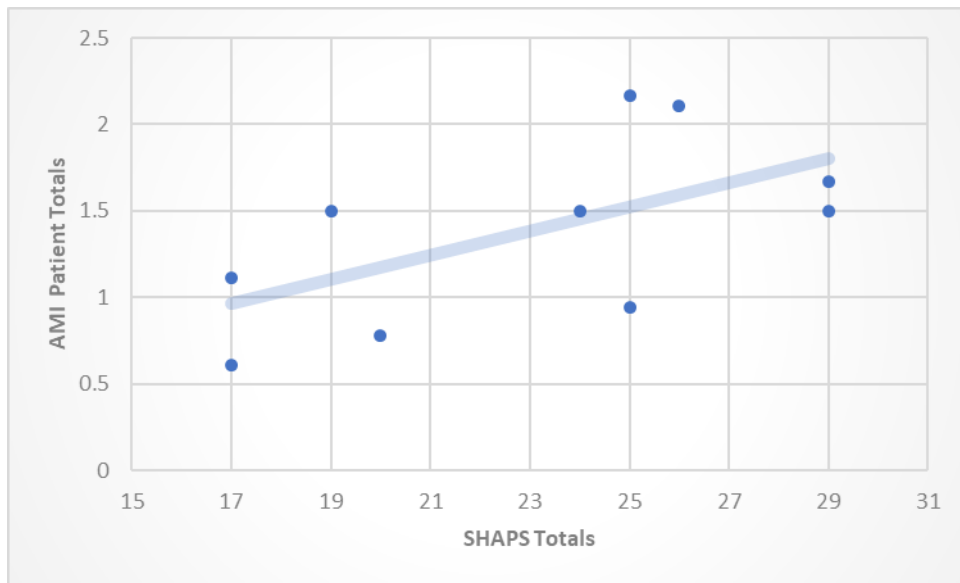
Figure 6: Scattergram illustrating the relationship between AMI=Apathy Motivation Index and SHAPS=Snaith Hamilton Anhedonia Pleasure Scale across patients.

4.2.4.4 Relationship between hedonia and burden

Figure 7 below indicates a weak positive nonparametric correlation of non-significance between the level of the patient's hedonia and the carer burden (rho = 0.20, p = 0.45). This suggests the amount of anhedonia reported by the patient is not interrelated with the increased scores for the carer's levels of burden. Their burden, therefore, may inadvertently be indicated by other causes.

Figure 7. SHAPS and ZBI Totals
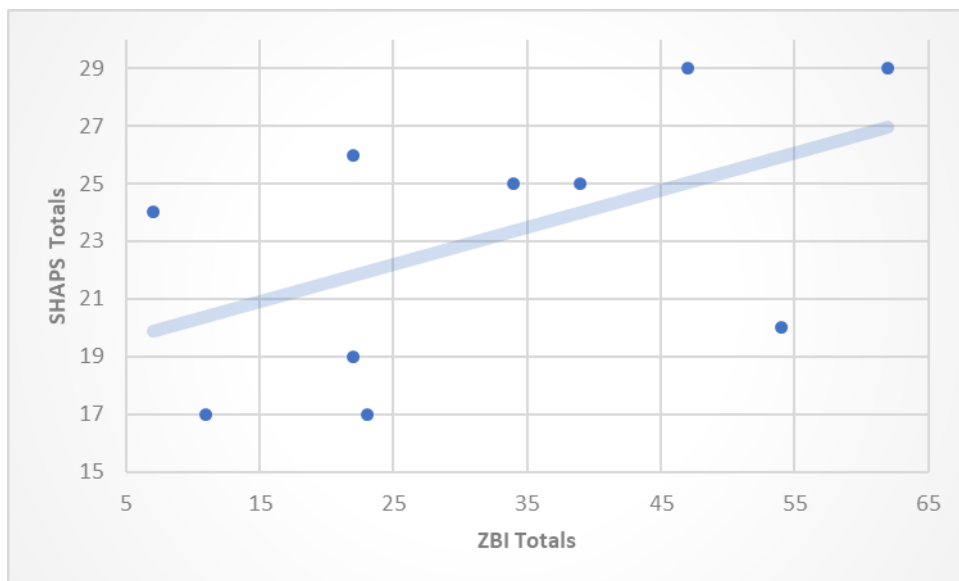
Figure 7: Scattergram illustrating the relationship between SHAPS=Snaith Hamilton Anhedonia Pleasure Scale and ZBI=Zarit Burden Interview.

4.2.4.5 Relationship between depression and burden

In the LE cohort, there was a large positive but non-significant relationship between the patient reported depression scores, and the carer reported burden score (r = 0.60, p = 0.06) (Figure 8). Although the 9/10 patients who scored significantly lower than the cut-off score for moderate depression did not show a positive association with carer burden, the carer with the highest burden score was the wife of the one patient that scored as moderately depressed. The accompanying burden may therefore not pertain to the patient's depression alone, but possibly to other factors.

Figure 8: BDI and ZBI Totals
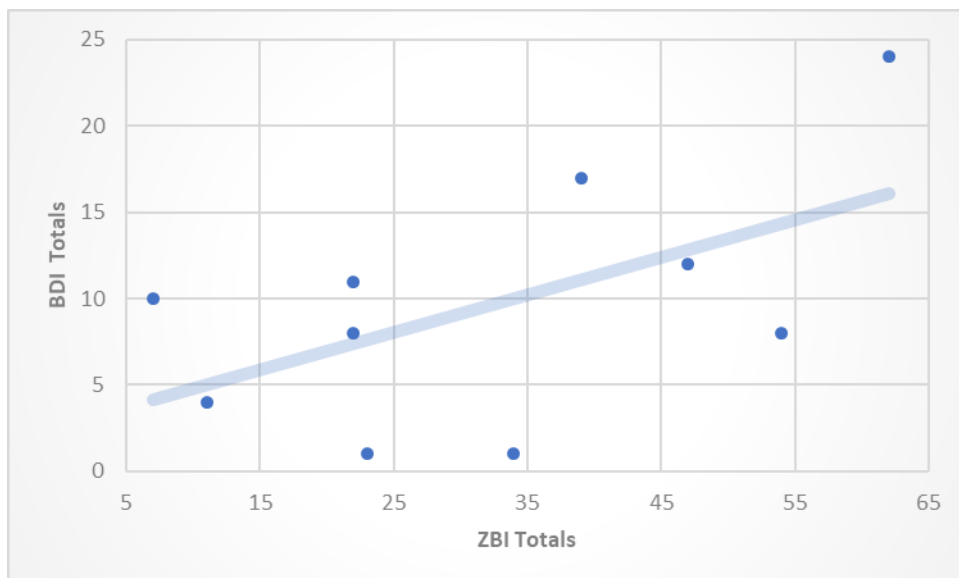
Figure 8: Scattergram to show the relationship between BDI=Beck Depression Inventory and ZBI=Zarit Burden Interview.

4.2.4.6 Relationship between fatigue and burden

Patient-reported fatigue and carer burden showed a large positive but non-significant correlation across patients (r = 0.60, p = 0.07; Figure 9). As the patient-reported scores for fatigue did not show problematic fatigue, this is likely reflected below. As shown previously in Table 4, only 2/10 patients scored above the cut-off of >4 for problematic fatigue. However, the carer perspective is explored further in the qualitative interviews, where fatigue together with other domains, adversely affected the patient's everyday functioning, hence causing an increased burden on the carer.

Figure 9: FSS and ZBI Totals
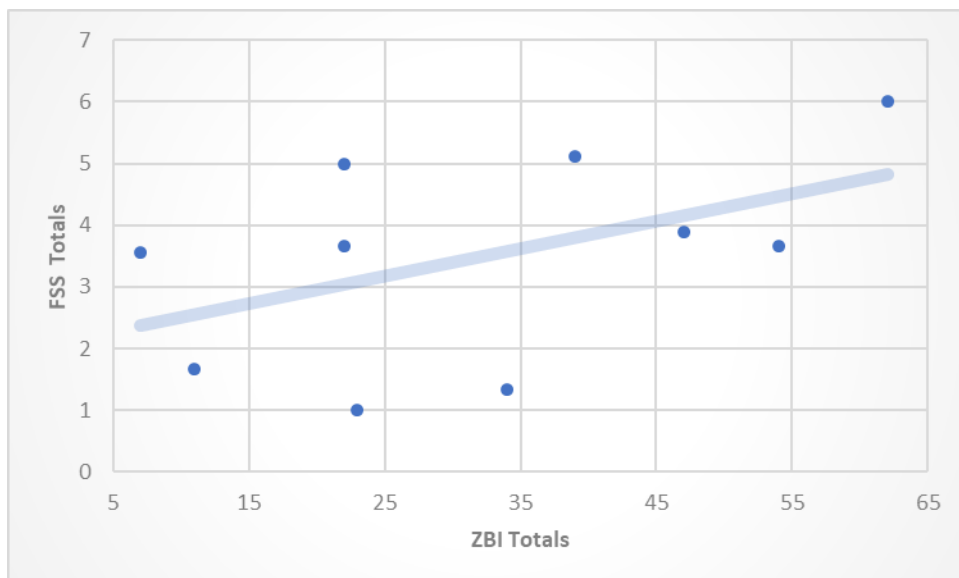
Figure 9: Scattergram to show the relationship between FSS=Fatigue Severity Scale and ZBI=Zarit Burden Interview.

4.2.4.7 Relationship between the carer reported daily activities with burden

The correlation between the B-ADL and ZBI indicated a large positive and significant relationship between the patients' ability to perform daily activities and the carers' burden (r = 0.72, p = 0.02) (see Figure 10). 50% of carers reported mild to moderate difficulties in the patients performing daily activities. However, the three carers who rated their perceived burden in providing care to the patient as moderate to severe, were different carers, suggesting the importance of the qualitative data collection to provide details on this relationship.

Figure 10: B-ADL and ZBI Totals
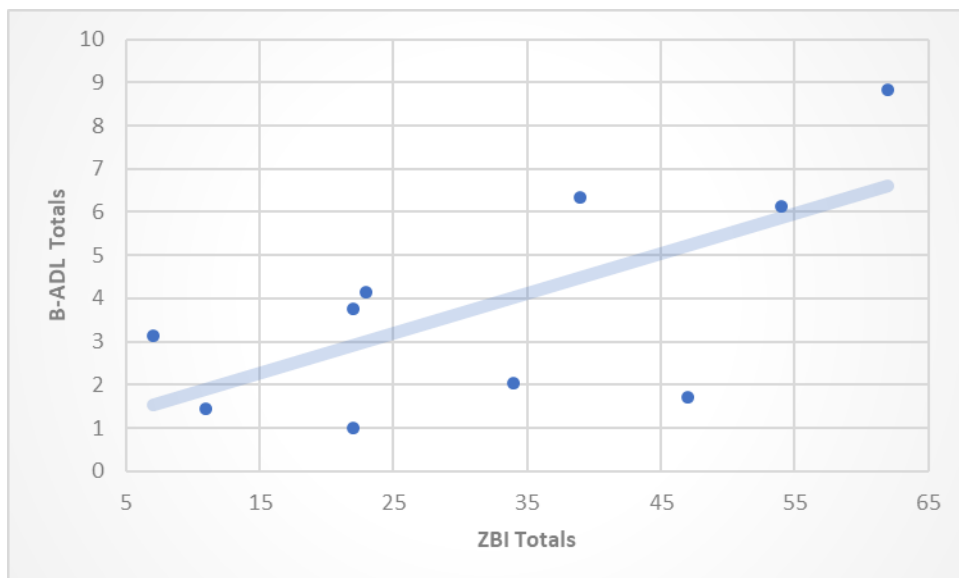
Figure 10: Scattergram to show the relationship between B-ADL=Bayer Activities of Daily Living and ZBI=Zarit Burden Interview.

4.2.4.8 Relationship between depression and fatigue

The correlation between the BDI and FSS indicated a large positive and significant relationship between depression and fatigue across patients (r = 0.86, p < 0.01, see Figure 11). Although depression was less common than fatigue in this cohort, the association with fatigue is uniquely captured. The two patients with the highest depression scores also scored highest for fatigue. However, confoundering factors to be considered in depression and fatigue in the LGI1-aLE patient may include age, sleep quality, and the general status of their recovery.

Figure 11: BDI Totals and FSS Totals
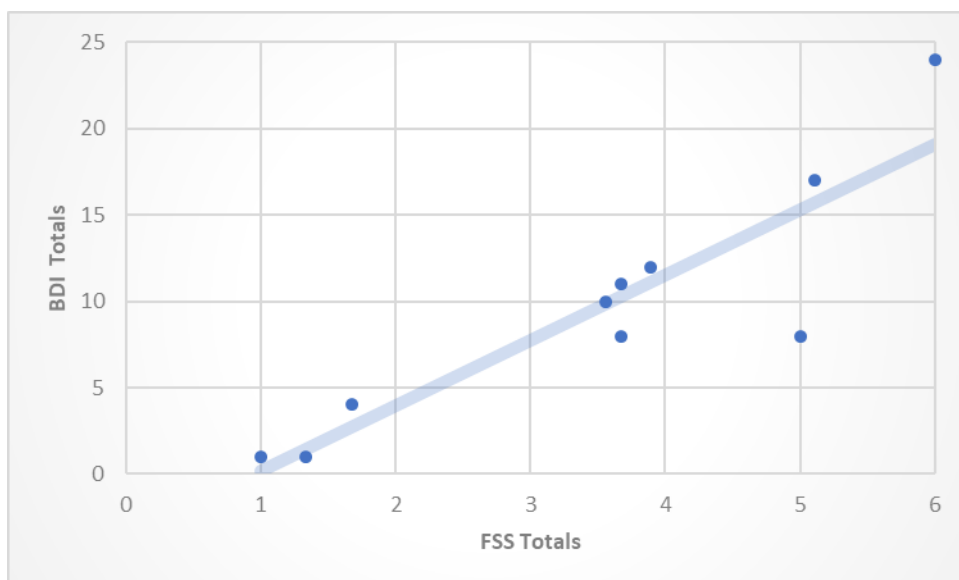
Figure 11: Scattergram to show the relationship between BDI=Beck Depression Inventory and FSS=Fatigue Severity Scale.

4.2.4.9 Relationship between sleep quality and motivation

Given that a subset of patients (n=6) reported poor sleep quality (PSQI score > 5; Table 4), a correlational analysis was conducted between PSQI and AMI scores across patients, in order to investigate the relationship of sleep quality with apathy and motivation across patients. PSQI and AMI scores showed a low negative and non-significant relationship across patients (r = -0.29, p = 0.41, see Figure 12). With 6/10 patients having a compromised quality of sleep, it is possible that other counfounders such as age and nocturnal fragmentation of sleep were contributory factors.

Figure 12: PSQI Totals and AMI Totals
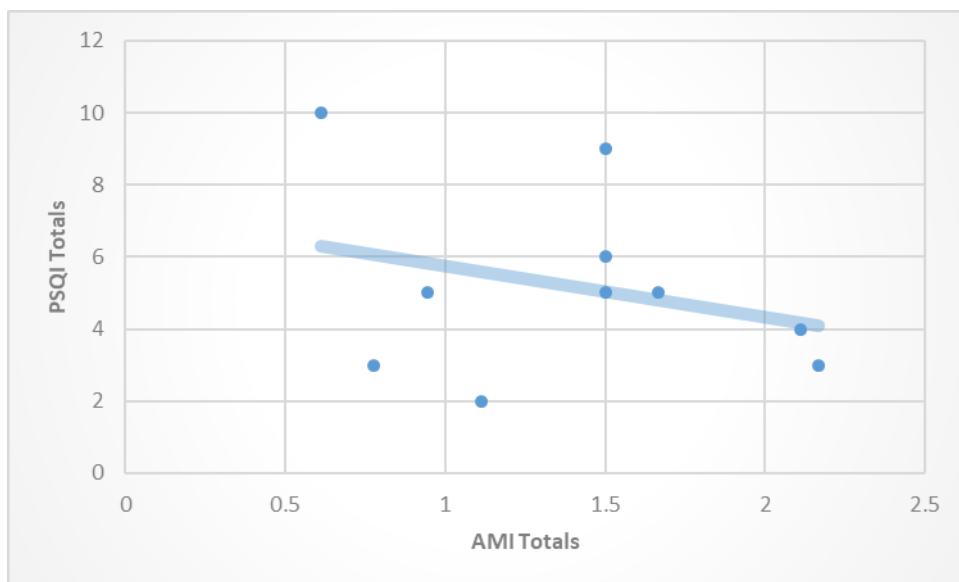
Figure 12: Scattergram to show the relationship between PSQI=Pittsburg Sleep Quality Index and AMI=Apathy Motivation Index.

4.2.4.10 Relationship between burden and months awaiting diagnosis

There was non-significant relationship between the self-reported carer burden (ZBI) and the time between symptom onset and diagnosis, with a very weak negative correlation (rho = -0.19, p = 0.59, see Figure 13). This indicates that despite the

prolonged time to reach a correct diagnosis, the detrimental effect on the 3/10 carer's mild to moderate burden, was not associated.

Figure 13: ZBI Totals and months from first symptoms to diagnosis
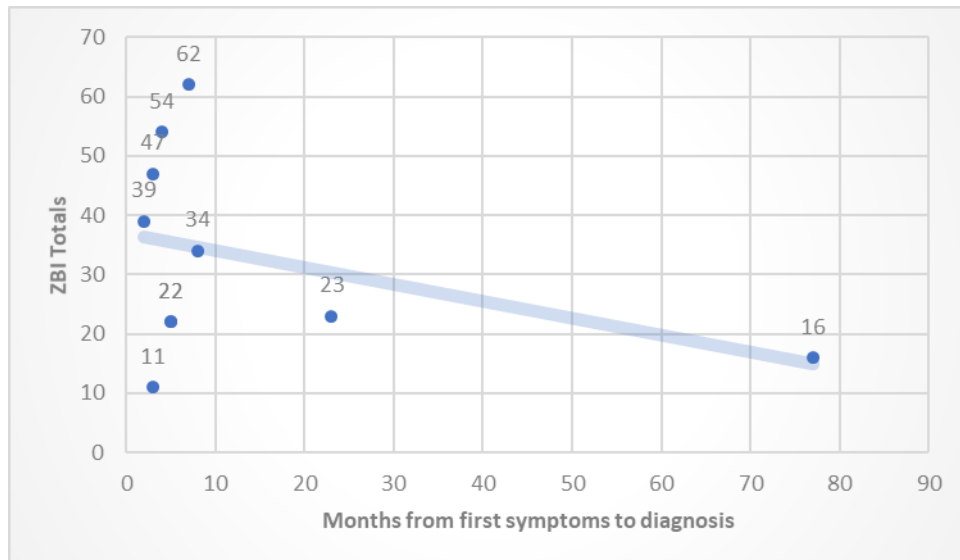
Figure 13: Scattergram to show the relationship between ZBI=Zarit Burden Interview and months from first symptoms to diagnosis.

4.2.4.11 Relationship between cognition and burden

The correlation between the patient ACE-R totals and the ZBI carer burden demonstrated a weak negative but non-significant relationship between patients' cognition and carers' burden (r = -0.23, p = 0.52, see Figure 14). With the 6/10 patients who lost points pertaining to the memory domain, it was not indicative of an increased carer burden in this cohort. Correlating a chronic symptom such as memory loss on carer burden may have incurred different results during the acute stage following the impact of sudden memory loss. These results are reflected qualitatively in the next chapter, in coping and adaptation to memory loss.

Figure 14: ACE-R Totals and ZBI Totals
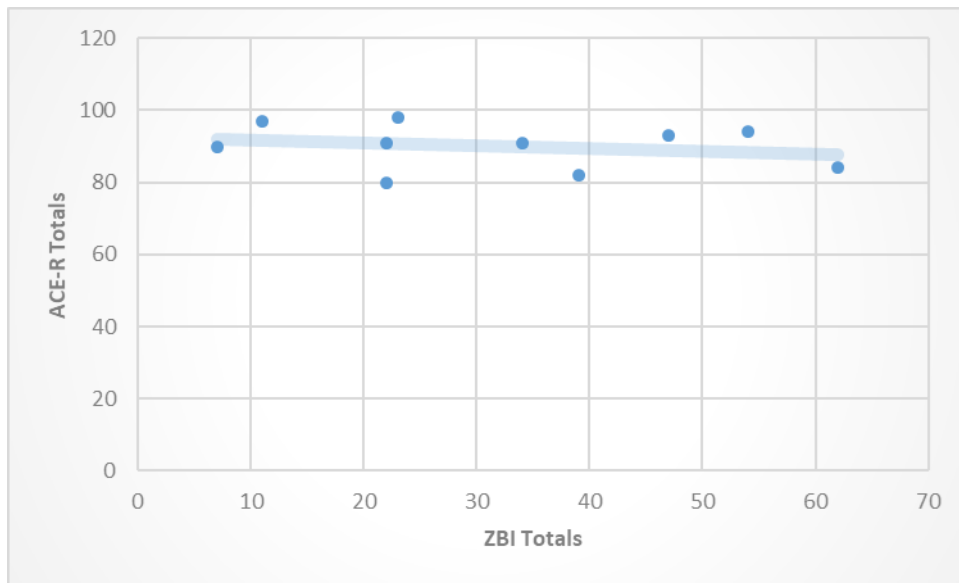
Figure 14: Scattergram to show the relationship between ACE-R=Addenbrookes Cognitive
Examination Revised and ZBI=Zarit Burden Interview.

4.2.4.12 Relationship between the patients' daily activities and cognition

The correlation between the patient's ability to perform daily activities (B-ADL) and
cognition represented in the total ACE-R scores (r = -0.43, p = 0.22), showed a
medium negative but non-significant relationship (see Figure15). With 6/10 patients
presenting difficulties pertaining to cognitive decline, this was not bound to the
memory loss scores in this cohort.

Figure 15: B-ADL Totals and ACE-R Totals
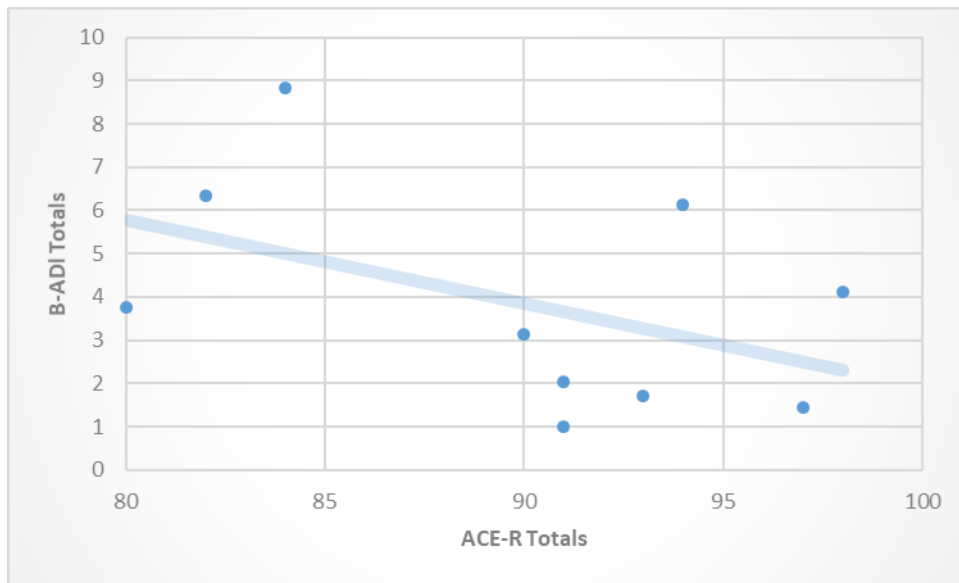
Figure 15: Scattergram to show the relationship between B-ADL=Bayer Activities of Daily Living and ACE-R=Addenbrookes Cognitive Examination Revised

4.2.5 MRI reports and Electronic Patient Records (EPR) findings

Not all patients were diagnosed locally and therefore their MRI results were not available on the EPR locally. However, some participants had results from their local hospitals which were sent to the researcher. Clinical MRIs of 4 patients disclosed structural abnormalities in the hippocampus (Appendix 41).

4.3 Chapter summary

The negative sequelae of LGI1-aLE have been identified and the extent of the patients' cognitive and emotional impairment has been determined. The NPTB successfully gathered quantifiable data to primarily produce descriptive statistics, and secondly to identify group-level impairment in specific functional domains, as well as examining correlations. The mean age of the patients was 64 years of age,

with a mean period of five years since their diagnoses were made. Using cut-offs derived from published research, 60% of patients showed forms of cognitive deficit, with the most points lost in memory and fluency. 30% of patients reported moderate apathy and reduced motivation, yet 40% of carers reported severe patient apathy using a separate score. Most patients experienced poor sleep quality (60%) and 30% rated problematic fatigue. Carer's assessments revealed that 90% reported some form of neuropsychiatric symptoms within one month of the NPTB, mainly relaying domains of agitation, apathy/indifference, irritability and a change in eating behaviour/weight change. Testing on the patients' daily living activities, revealed 50% of carers reported difficulties. In addition, cognitive decline comparing the patient to ten years ago, was noted by half of the carers.

There was little evidence for group-level deficits across the tests and questionnaires administered. However, several patients scored in the impaired range for certain domains. Finally, the interrelationships between fatigue/apathy, apathy/anhedonia, ability to undertake daily activities/carer burden, and depression/fatigue, all showed positive associations. By examining the qualitative results from Phases 2 and 3, in the next chapter, further exploration highlights the symptoms and impact in more detail.

CHAPTER FIVE

Qualitative Results (Phases 2 and 3)

5.1 Introduction to the chapter

Analysis of Phase 2 was conducted using the role of the researcher to offer an insight into participants' experiences through IPA's distinguishable exploration and interpretation. Participants are referred to by their study ID numbers, showing consistency across the MM. Collectively, these themes have created a detailed insight and exploration of the meaning of LGI1-aLE. Theme One 'Acute symptoms and a correct diagnosis of LGI1-aLE' [5.2], represents the experiences of the acute symptoms and the impact these created. Theme Two 'the chronic symptoms and personal impact' [5.3], exemplifies the continuous impact the disease has. Theme Three 'relationships' [5.4], introduces significant changes in relationship dynamics with the carers, children and friends. Theme Four 'return to work and leisure' [5.5], highlights the difficulties and challenges involved. Theme Five 'future plans' [5.6], addresses concerns by participants, and recognises adjustments around the patients' capabilities. All participant couples are introduced under Theme One. When referring to the years the participants have been together or the years since diagnosis, this pertains to the point of recruitment into Phase 1 for the NPTB. Providing accurate data was dependent on the participants' generosity in sharing and reflecting upon their experiences and feelings. The themes, with occasional overlap, contain a powerful testimony on the impact the disease has had, has, and continues to have.

An additional contribution to the analysis of data was provided in the digital diaries. These provided enhanced information, some of which was already discussed in the interviews, but some presented new and unique experiences. The diary data was

incorporated into this Chapter, as there was a lack of robust data for further individual analysis, but instead was described to support the IPA.

5.2 Theme One: Acute symptoms and a correct diagnosis of aLE

The first theme generated explores the experience of patient and carer journeys waiting for a correct diagnosis of LGI1-aLE. Generally, participants shared experiences oriented around symptoms during the acute phase, hospitalisation and professional support, which formed the basis of the over-arching theme. Whilst acknowledging commonalities amongst participants, it is important to recognise that experiences of symptoms not only differered for the patient and carer but were also affected by the wider environment of friends, family and occasionally the public.

Evidence recognises the positive impact of a prompt and correct diagnosis of aLE, discussed in Chapter Two, yet does not ascertain the delay in diagnosis in months/years as a comparison to this cohort. The acute phase personified a period of cognitive changes, seizures and memory loss, which were not always recognised and concisely associated to LGI1-aLE at the time, causing a delay. For the patient, the common representation of their narratives was drawn from expressions of their marked difficulties in recall during this period.

LESS1 patient and carer are a married couple who have known each other forty-four years. The husband was diagnosed seven years prior to the NPTB, five months after his symptoms first started. He had no memory of that period:

> "I can't remember that bit of my life at all, even though I was in hospital for 6 months, I can't remember a single day of it." (LESS1 patient interview)

This quote expresses the extent of his memory loss and is representative of most patients, who could not remember this period at all. For some patients, they referred

to their memory loss as 'a blur' or as 'a bit sketchy' and stressed their reliance upon their carers' accounts of events:

> "I have had to ask [carer's first name], my wife, what actually happened to me." (LESS6 patient interview)

Placing trust in the carers' portrayal was commonly conveyed. Even for LESS9 patient who was diagnosed reasonably quickly within two months, she had absolutely no memory of this time. For those patients with some recollection, they inferred feelings of confusion, frustration and anticipation (LESS6 and LESS7). Moreover, a sense of dependence on the carer was compounded by their trust and faith in them. However, it also heightened aspects of helplessness and powerlessness.

For the carer, witnessing disturbing scenes of unusual behaviour, together with psychiatric symptoms such as hallucinations or extreme anger, heightened their fear and shock. This incurred common feelings of distress amongst carers. LESS3 patient and his wife have known each other for over ten years, and this is their second marriage. He was diagnosed two years prior to the NPTB having waited four months for a correct diagnosis. Incidentally, the manifestation of his rapid behavioural changes, associated with waiting for a correct diagnosis, caused the couple to experience a period of separation. The initial symptoms and behavioural changes heightened her sense of fear and isolation, as the couple were abroad at the time:

> "One morning he sat up in bed asking 'who are you and where am I." (LESS3 wife interview)

As with many carers, she was shocked and unprepared for this unpredictable behaviour, and she tried to comprehend the sudden, unforeseen irritability and aggression, which most probably was intensified by being alone with him on holiday. LESS7 patient and partner have been together thirty-seven years. The patient was diagnosed five years prior to the NPTB, having waited three months for the correct

diagnosis. For LESS7's partner, it was only when his hallucinations and strange behaviour began that she become really concerned:

> "He could not sleep, he did not let me sleep, he said that people were coming out of the TV to get them; that they were being watched. At some point when he got angry with me, I was afraid... I know that sounds...[sighs].. I have never been afraid of him, but I felt he might do something… he was confused, his eyes were glazed all the time." (LESS7 partner interview)

There was a sense of feeling isolated with him in the house, and unable to cope with this increasingly frightening and disturbing situation alone. Her sighing perhaps resonates having to encounter her feelings at that time, once more during the interview.

Referring to LESS10 and his wife who have been together thirty-four years. The patient was diagnosed six years prior to the NPTB and waited seven months for a correct diagnosis; a prolonged period. His memory loss was exemplified by his wife's description of her sense of bewilderment when her husband had returned from abroad:

> "He's bought me a perfume I used to wear when we first got married. I don't wear that anymore." (LESS10 wife interview)

This indicated to the carer that his memory had been affected, and she became concerned, yet tried to find a reason for his 'strange behaviour'. At the time, LESS10 wife attributed his affected memory to a possible nervous breakdown. Furthermore, she ascribed the breakdown to his unusual reserved and disengaging manner towards the family. Another carer described the memory loss as presenting itself 'subtly'. For the brother of LESS5, he described a sense of guilt that he perhaps had not given adequate notice to her 'goldfish memory', which possibly started five years prior. Furthermore, the memory loss had caused her agitation which he could have addressed earlier on. It is possible that two factors played a role in not instigating his

concerns earlier on; living together as siblings, and he, himself suffering with a debilitating neurological condition.

Regarding patient memory loss, LESS10 wife described how her husband phoned her to say he was using his Sat Nav (satellite navigation) to go to work, which demonstrated atypical behaviour. This was further compounded when he came home after work that day:

> "Where do I sit?" She replied "in the normal place", "where is that", he asked?" (LESS10 wife)

Other carers have also described feeling disbelief linked to the patient's disorientation. Referring to the patient' sudden memory loss in finding their way back to the car, or to a friend's house (LESS2 and LESS4), also evoked feelings of apprehension for the patients.

Regarding the carer's experience of misdiagnosis, for LESS1 wife, there was a sense of confusion and frustration with the initial misdiagnoses:

> "They were struggling to find a definite diagnosis. It took ages, months, and during that time we didn't know what was happening." (LESS1 wife interview)

Furthermore, she felt tearful when her husband was discharged home on two occasions. This led to feelings of abandonment and invisibility. Other couples drew attention to the misdiagnosis as precipitating a fusion of resentment, isolation and abandonment. The youngest patient in this cohort, LESS4 patient and her husband have been together for forty-three years. She was diagnosed three years prior to the NPTB. There was a period of over six years (77 months) before she was correctly diagnosed. She shared:

> "They said it was the menopause the whole time, yet my body wasn't having hot flushes, it was coming out in goose bumps. Of course, these goose bumps, we later found out were the seizures." (LESS4 patient interview)

This quote depicts a prolonged misdiagnosis, perhaps confounded by contributory factors of gender and age. In fact, her enduring nature and trust in the clinician's diagnosis possibly disguised her sense of discernment with the hormone replacement therapy (HTR) given to her. During the interview she remained cheerful and accepting of how the many years of HRT had failed to ease her symptoms. It was not until she developed more acute symptoms of memory loss that her husband refuted this diagnosis:

> "She had been working quite a few years at the same place and then suddenly couldn't remember how to get there, or to walk to her friend's house which is a couple of streets away. (LESS4 husband interview)

This quote personifies the severity of her memory loss and induced his decision to seek further consultation. As demonstrated by other carers, a persistence in challenging clinicians was exhibited following dissatisfaction and loss of trust in their initial diagnosis. Incidentally, other misdiagnoses included stroke and then herpes simplex encephalitis for LESS1, post-traumatic stress disorder for LESS2, migraine for LESS6, and Creutzfeldt–Jakob disease for LESS9.

Evidence suggests FBDS can occur frequently during the acute phase, resulting in dystonic movements of the leg and falling, which is often overlooked by clinicians (Morano et al., 2020). LESS2 patient lost her balance getting out of the car, fell, and broke her hip. Although her husband was concerned by her falling, he also noticed it was unusual, and described it as:

> "Not like a tripping or stumbling, but like a tree being felled." (LESS2 husband interview)

Falls were also described by LESS9's wife. LESS9 and his wife have known each other thirty-five years. He had been diagnosed ten years prior to the time of the interview. She also stated her husband had stumbled for no apparent reason, which the family initially laughed about. In fact, they had joked that he was 'clumsy'. Although LESS2's fall led to an injury and surgery, there was a commonality of the unrecognition of FBDS, iterated across both accounts. Further evidence of the FBDS presented in the form of the involuntary facial movements:

> "It looked a bit like cerebral palsy kind of look...., and he was sort of moving his arms and his face...grimacing. A very, very strange look a very manic look." (LESS9 wife interview)

For her, the grimacing represented her sense of 'fear and panic'. Other carer narratives highlighted facial movements, twitches, falls and feeling cold with goose bumps, but did not understand them as a type of seizure. This unrecognition was heightened by apprehension. Regarding these seizures, a unique and detailed account may not be reported to the clinician if the significance of them is unknown. Furthermore, recognition by the clinician is equally paramount. Fortunately for one patient, her consultant witnessed one of her seizures and told her:

> "That's not stress, that's autoimmune encephalitis." (LESS2 husband interview)

This linked to feelings of relief, yet still instigated a sense of fear of the unknown consequences of this disease, regarding length of treatment and chances of a full recovery.

Regarding the presentation of a patient's challenging behaviour, disinhibition and indiscretion were commonly acknowledged by carers. LESS6 patient and his wife have been together forty-four years. He was diagnosed seven years ago, having waited three months for a correct diagnosis- a considerably quick diagnosis. Her sense of loathing of his indiscretion, is exemplified here:

> "In company, he had no discretion, and now he has this obsession with people who are massively overweight. I have a very close friend who is very, very overweight, and he would always scathe overweight people and come up with jokes, and I had to be very honest with my friend, please don't take offense." (LESS6 wife interview)

This reflected her hurt, not only for her friend, but for the way others judged her husband, as he used to be diplomatic and supportive. She also felt a sense of disapproval and helplessness.

In addition, this quote has now become a joke shared by the family:

> "When the doctors were examining him in the acute stage, he told the doctor he wanted to have sex with her", and I said "and you're telling me he is OK, that's not my husband saying that?" (LESS6 wife interview)

As a researcher, it was pleasing to hear her laughter, as narratives most commonly described considerable distress to the carer. She also recalled his newly founded childish sense of humour and a tendency to laugh inappropriately, joking at things other people did not find funny. In addition, his acts of impulsivity without thinking of the consequences, lead to saying hurtful or insensitive remarks, speaking crudely and speaking to strangers. These changes in his behaviour revealed her sense of shock, hurt and disapproval, which has been mirrored in other carer accounts.

A subtle aspect for consideration within this theme was how some patients resumed a child-like sullen mood if criticised. LESS8 patient and wife have been together for thirty-eight years. He was diagnosed nine years prior to the time of the interview, after a period of eight months since his first symptoms. One pertinent perception of her husband's state of mind at the time, was captured:

> "It was like he was a little child again. If you told him off, he sulked." (LESS8 wife interview)

This has been echoed in one other carer narrative:

"I try and deal with him like he is one of my teenage children, because that is the way he behaves; he gets resentful and wants to please himself, he doesn't like me telling him anything." (LESS3 wife interview)

The carers' feelings of irritability and stress are linked to their coping strategies in a later theme.

For most carers, waiting for a correct diagnosis was wearisome. LESS8's wife commented that:

"That time felt very desolate, because we didn't know what we were dealing with, and the not knowing to me, was awful." (LESS8 wife interview)

The essence of these poignant moments of realisation were reiterated in all carer accounts, as a fear of the unknown and consequently having to deal with the complexities of awaiting a correct diagnosis. Despite the uncertainness of this period for the carer and family, the patient had to deal with elements of powerlessness, lack of confidence and entrusting all decision making over to the carer, while in an often confused or psychotic state. For some carers, emerging from the manifestation of feelings associated with the acute symptoms, a correct diagnosis triggered some relief, which is linked in with hospitalisation.

Hospitalisation itself evoked a range of feelings for patients and carers based on the reasons for being hospitalised; as a result of misdiagnosis, receiving a correct diagnosis, or being discharged home sooner than they had hoped. Despite events of hospitalisation predominately communicated by carers, some patients portrayed traces of insight and feelings. LESS2 patient and her husband are a married couple, who have known each other for forty-seven years. The patient was diagnosed two years prior to the NPTB, following a five-month period since symptoms first started. Following hospitalisation for hip surgery, her subsequent transfer to the neurology

ward led to a 'chance' seizure being recognised. From never hearing of the disease, her husband described how they adjusted to it:

> "It comes off our tongue as if we had talked about it all our lives. The clinician held his hands out like a fisherman does when he catches a large fish, and he says your disease will take that long to cure." (LESS2 husband interview)

This draws attention to some aspect of fear due to the unknown implications and severity of the disease. Two carers expressed feelings of gratitude to the clinicians, acknowledging that the disease had only recently been recognised and discovered by neurologists (LESS1 wife, LESS2 husband). For LESS5's brother, there was a sense that the correct diagnosis had at least secured a confirmation and realisation of the 'toll the symptoms had taken, during this period of uncertainty'. However, for others, the diversion of being presented with a name for the disease, was not enough to avert feelings of apprehension for the level of recovery and future expectations.

Although carers experienced a sense of relief when receiving a correct diagnosis, on reflection, the delay had already caused some an irreconcilable resentment. LESS6's wife exhibited feelings of frustration and anger based on the hospital's dismissive attitude and wanting to discharge her husband. However, amidst her anger directed at the NHS, and being placated and reassured by their consultant, she did however believe they had to fight for a correct diagnosis, and not all carers felt in a position to dispute professional opinions.

During hospitalisation, some patients suffered with hallucinations and periods of aggression, recounted by carers. During LESS10's hospitalisation and subsequent seizure, he exhibited psychotic behaviour, shouting aggressively and throwing objects.

> "'Nobody's fucking listening to me, nobody's fucking listening to me', he was quoting binary numbers constantly, and they were giving him pens and papers to calm down, and he was literally and completely insane. A nurse, came to me and said to me, 'is

your husband normally like this?' ...and I just felt the ground could have opened up and I fall in." (LESS10 wife interview)

This evokes feelings of shock, disgust and embarrassment at his psychotic behaviour. During this time, their young children had experienced their father's changed behaviour, which LESS10 wife shares:

> "He was a gentle giant always........he was a problem solver, his life was about pleasing people, and ensuring everyone was treated fairly, it was about resolving issues…, but he became aggressive, a complete bully, and very assertive, and very rude, he came out with some awful comments regarding a book on slavery…sexist, horrible, almost the complete reverse of the person he was." (LESS10 wife interview)

Sadly, as with other carers, she described 'feeling mortified' that the person she had married, had dramatically changed. One carer described 'fleeting' moments as glimpses of recognising her partner's former self (LESS7 partner). This perception is commonly highlighted by carers who displayed a 'grieving' for the patients' former selves. Some patients recalled feeling confused, frustrated and angry, however they lacked the understanding of what was wrong with them and why they were feeling 'different'. Therefore, in addition to the carers' feelings accompanying this period of hospitalisation, patients elicited a comparable 'silent suffering' and inability to recall or express their feelings.

With reference to the final component of this theme, professional support during hospitalisation, this was essentially underwhelming for both patients and carers. Most carers felt frustration, disappointment and isolation, yet they also accepted that due to the disease's rarity and unrecognition among professionals at the time, a structured pathway for support was not in place. However, only a few carers had been made aware of the charitable organisations that provided information and support for encephalitis.

> "I think we felt quite isolated in a way, because there was no support for any of us at all. I think we felt abandoned and ignored." (LESS1 wife interview)

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Furthermore, many carers felt further isolation once the patient was discharged home without ongoing support or guidance. LESS1 was the only person to be offered additional professional support for the incorrect diagnosis of stroke, which was consequently deemed unnecessary. Some carers mentioned their greatest source of support was from the consultant who had made the correct diagnosis, as they had shared in the relief together. Yet, there was a strong essence of hope amongst participants that future patients and carers would be offered the support that was, unfortunately, unavailable to them.

5.3 Theme Two: chronic symptoms and personal impact

The second theme demonstrates how chronic symptoms continued to impact on the personal lives of patients and carers. Three sub-themes form the basis of the over-arching theme: 1) the ongoing impact on the patient; 2) the ongoing impact on the carer; and 3) coping strategies and support. Given the nature of the unhurried interviews, the data capture from the patient relays valuable elements which are often underrepresented during busy clinical consultations.

5.3.1 Ongoing impact on the patient

Some patients demostrated an awareness and understanding of the ongoing behavioural and emotional changes, with many feeling a sense of impatience, frustration and irritability, possibly mounting from the inability to express oneself in an articulate and constructive manner or making decisions confidently. For other patients, these feelings arose from a reduced ability to undertake their usual activities. However, for the majority of patients, frustration manifested from their memory loss, and having to rely more on their carer for 'lost' information. This subsequently affected their confidence and self-value.

For some, the opportunity to use a digital diary was beneficial. LESS5 made twelve entries in the diary. By recording her thoughts, it enhanced her sense of coping and positivity.

> "I always feel I miss the old me, and little things like that remind me the old me is still here and the illness hasn't taken that part away from me." (LESS5 digital diary)

Although her entries added valuable evidence on her improvement and how she was enjoying life, they also continued to illustrate her impaired memory. Unfortunately, her brother was not able to make diary entries, due his MS decline. She spoke about this tearfully in the diary entries. The researcher felt a sense of her underplaying her own symptoms, and instead, empathising with his situation. This conforms with evidence from her brother elsewhere in the interviews, when he described her as very uncomplaining and selfless. Notably, as siblings they are unique to this cohort, both having a neurological condition.

Regarding ongoing mood changes, LESS6 patient made three diary entries. He expressed concern that his mood changed according to the weather; not mentioned previously in the interview. In addition, the digital diary reiterated his memory loss, providing scenarios of forgetfulness. As echoed in his interview, he felt that his memory loss resonated in his wife's loss of confidence in his decision-making. In general, this is a perplexing position to be in for the carer, not wanting to hurt the patient's feelings, yet considering safe and appropriate decisions are made.

With regards to the patient's lack of motivation, many patients reflected a general lack of enthusiasm and letting others take responsibility in certain activities. This was possibly a consequence of their lost capabilities due to the memory loss and poor decision-making. One patient illustrated her sense of a calm and acceptance of the disease:

> "It is hard work … it's like I'm talking myself into doing things and then once I'm there its fine." (LESS5 interview)

On the contrary, for other patients, making excuses not to do something felt easy and demonstated a degree of defiance.

Concerning one patient's perspective on taking longer to get up and shower in the mornings:

> "From getting up, I just felt my body like lead, my head in particular, my eyes just wouldn't seem to open." (LESS2 patient digital diary)

To some this could be classed as decreased motivation or lethargy, but here, the reader can sense the impact of the disease on the patient, emphasising the credibility of using the diary.

Some patients reported the continuation of subtle features of FBDS. However, for those not experiencing current FBDS, there was still an eminent fear of another significant seizure occurring again in the future. For LESS6 patient, his concerns were not expressed in the interview, and provided additional evidence:

> "These uncontrollable muscular contractions are mainly in my arms, but there are facial twitches as well." (LESS6 patient digital diary)

This ongoing symptom of LGI1-aLE may make the patient feel self-conscious of how others look at them when in public, even though the movements are sometimes subtle and hardly noticeable to the untrained eye.

All patients commented on memory loss and its negative effect on the whole family. The loss of precious memories of one's own wedding, family holidays and family

events, caused a significant sense of frustration, sadness and disappointment. Many patients tried to recall events when prompted with photos from the carer. However, some patients perceived the photo just as an image, often feeling disconnected to the experience. Hence, they felt powerlessness in not being able to reconnect to certain events and holidays. One patient's memory loss affected the ability to learn new tasks at work, relaying a sense of frustration and despondency; and in her words, making her look forward to retirement even more so. LESS5 cannot remember recipes she once knew by heart and had to resort to recipe books now. In addition, she described the inability to remember a book chapter the next day, which has also been highlighted by another patient. In fact, LESS2 patient turned her scenario jokingly around byillustrating the amount of money saved on reading the same book repeatedly. Any devastating impact of LGI1-aLE, that caused some laughter in the participant, resonated an astonishing joyous feeling which was shared through narratives. Her diary entries encompassed the coping strategies she used at work, by writing notes, then taking photos on her mobile phone to use later as an aide-mémoire. It was clear from her entries that memory loss represented a constant worry for her. Diary evidence reinforced how the encephalitis made it difficult for her to deal with unknown circumstances, yet on the contrary with familiar circumstances, she functioned well.

Regarding some patients' impaired navigation skills when driving, one patient explained using Google Maps more, as he could not recall the local roads (LESS7). One patient described how his wife's awareness of his impaired navigational skills, caused tension between them when she questioned the route he chose, which incidentally took longer (LESS6). Many carers summed up the patients' concentration difficulties, as well as anxiety and irritability whilst driving. However, with the revoking of driving licences after a history of seizures, many patients exhibited a sense of frustration, loss of independence and role reversal, resulting in tension placed on the couple and family often due to the reliance on others. LESS9 who used to be a London black cab driver, felt embarrassment that his wife had to learn to drive at 69, affecting his confidence and position in their relationship.

5.3.2 Ongoing impact on the carer

Unlike the acute stage, where treatment offered some improvement and hope, the chronic stage encapsulates feelings of adaptation and resilience. Most carer narratives conveyed a profound sense of distress induced by the patient's ongoing symptoms.

Many carers highlighted the post-morbidity inability of the patient to sympathise or empathise, who struggled to 'read' or understand emotions. This inability to recognise facial expressions or react to the carer in a way they would have expected, led to a re-occuring complaints of 'self-centredness' expressed in the interviews and diaries. One digital diary entry described how her husband would appear self-centred to others and behave like a child or teenager (LESS7 carer digital diary). This presented resentfulness and irritability in most female carers' accounts, taking these scenarios personally. Furthermore, many carers conveyed the patient's insensibility and their inability to apologise:

> "I had the flu for two weeks, but he never asked how I was." (LESS9 wife interview)

This quote depicts her sense of resentment. Other carers described the patient's emotional detachment towards them:

> "There is no sentimentality at all. I find him devoid of emotion, if I get to the stage
> when I am bursting into tears, he will say to me, when you are finished shall we put
> the rubbish out or go out and do something. He would never comfort me." (LESS10
> wife interview)

This illustrates the hurt and disappointment she felt. Besides these examples of emotional detachment, some patients exhibited emotion excessively, through tearfulness, over a trivial news article or TV programme. Some carers reported inappropriate joking, which presented as a childlike sense of humour, leading to evoked feelings of irritation and embarrassment. Furthermore, accounts of using inappropriate language, were sometimes portrayed as heightened garrulous talking-

an extrovert behaviour they acquired after the onset of the disease. Others have lost their inability to regulate impulsive temper outbursts, or some patients showed an overfamiliarity with strangers, interrupting conversations or waiting impatiently for their turn. This was the case with LESS2 who showed her anger:

> "'Put the bloody phone down and supervise your kid." (LESS2 husband interview)

This quote was relayed in the GP practice waiting area where his wife spoke out completely out of character, to a mother not paying enough attention to her child. It made her husband feel uncomfortable that his wife would be perceived in that atypical manner, by members of the public.

Whether a patient's anger was the direct effect of the damaged limbic brain, or a result of frustration, many carers have to learn to cope and take hold of the subsequent behavioural changes resulting in outbursts, impatience and extreme irritation:

> "One of the things I do now, as he tends to be more verbally aggressive, I say to him, I can't talk to you when you are like this, and I will wait until you calm down so we can have a conversation and I try and leave the room." (LESS3 wife interview)

This gives the carer a sense of taking control in an unmanageable situation.

LESS9 wife made five diary entries. As in the interview, she reiterated how her husband becomes agitated very quickly, and this is linked to coping:

> "This can be a bit embarrassing if you are out somewhere or amongst company. In general, I try to avoid that situation by dealing with most things myself, rather than letting him deal with them." (LESS9 wife digital diary)

LESS2 husband made fifteen diary entries, describing daily occurrences and feelings. His wife made three diary entries. He explained that his wife needed a

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distraction daily to leave the house for some retail therapy. Sometimes he described how trying to get his jobs done in the house could be problematic, when she became frustrated staying at home. He describes this as a 'typical offshoot of the encephalitis'. Although relaying his sense of exasperation at her frustration, there was a general feeling of resilience from him.

Concerning fatigue, many carers supported its ongoing impact, highlighting how patients remained late in bed and needed encouragement to get up and shower in the mornings, which resonated in their feelings of irritability. LESS4 husband has noticed a 'subtle shift' in her motivation and increased fatigue. However, he did not express irritation or resentment. For one carer, her husband's continual fatigue, was a cause of her isolation and boredom:

> "He doesn't feel like doing anything, and that can be quite boring for me, as he lays in bed a lot. I just have to go and find my own things to do. We never seem to do anything together. We used to do a lot together." (LESS9 wife digital diary)

Despite her sense of resentment and frustration, the quote suggests her adaptation. With fatigue being synonymous with lethargy, some carers disclosed how the husbands' lethargy impacted on their personal hygiene. LESS9 wife spoke of his lack of hygiene, in the digital diary, but not at the interview.

> "His understanding of hygiene is virtually nil. I have to keep reminding him to change is clothes." LESS9 wife digital diary)

Furthermore, with the need for constant reminding to keep his environment around him clean, and the constant 'nagging' to clean up after himself, this is reflected through her sense of frustration and feeling trapped with the perpetual situation. This was echoed by another carer:

> "He relies on me for his socks and pants, getting him in the shower is a real hassle. I have to entice him to have a shower, entice him to brush his teeth, and it is just

constant, constant, constant, like pushing water uphill, constantly." (LESS10 wife digital diary)

This embodies a sense of an irresolute burden on her together with her irritability in ensuring her husband undertakes basic daily activities. She provided further examples as diary entries, which reiterated his poor hygiene skills. One task she found very challenging to deal with, was cutting his toenails:

> "He's normally screaming that I am hurting him so much and the children find it hysterical. I have to set it all up, do the foot spa, get my scissors ready, and I normally have to give him a piece of cake or coffee to keep him occupied. Cleanliness and cutting toenails is just awful." (LESS10 wife digital diary)

Her quote encapsulated a comical scene, yet this burdensome task heightened her feelings of anxiety, displeasure and stress.

Regarding a less common symptom of LGI1-aLE, only one carer described how the patient confabulated. This refers to a belief that an incorrect memory is real, however in reality, it did not actually happen.

> "So, in conversation if he is confabulating and it doesn't matter I leave it, but sometimes it does, so then I have to intervene and set the record straight which is a horrible thing to have to do really." (LESS1 wife interview)

This quote raises a unique sense of placing her in a difficult conundrum: to intervene and cause confrontation, or to say nothing.

Many carers relayed how the patient's lack of confidence, initiation and inability to make decisions incurred feelings of frustration; be it navigating a parking machine or deciding on what to eat for dinner. Other carers have expressed the lack of confidence in meeting people and social situations. One post-morbidity scenario described how the patient had become unsociable and solitary, in contrast to how the couple previously enjoyed friends and social events together, which led to resentment and feelings of isolation, depicted below:

> "He is just not interested anymore. That is one of the worst things I think, as it has affected out social life which is virtually nil now, apart from anything to do with the family." (LESS9 wife digital diary)

With reference to the patient's disinhibition, this was described by some of the carers in the interviews, as demonstrating less 'tact'. One carer described:

> "There are still embarrassing moments when he says things he shouldn't or does things he shouldn't, especially to do with his hygiene." (LESS9 wife digital diary)

These disinhibited behaviours appear rude or even offensive to onlookers. To the carer, they induce a sense of strain and embarrassment. Furthermore, there was a common pattern with patients not wanting to take the advice of the spouse, and insistence on making their own detrimental decisions:

> "We have had instances where we have been out shopping and I asked him to put a belt on around his trousers and he refused...anyway we were in the shop and his trousers fell down which he thought was hysterical."

> "When we go shopping, he'll get the trolley and he will hide from you. So, you are busy trying to get shopping together then trying to trace him all the time." (LESS10 wife digital diary)

LESS10 has displayed disinhibited behaviour in other ways, causing his wife extreme strain yet resilience towards the public's attitudes and reactions towards him.

> "We once had a situation and I was driving through London, and he decided to get out of the car in the middle of London, and it was absolutely awful. He has done that in Bath, in Bristol, and those are really, really difficult moments." (LESS10 wife digital diary)

In addition, she provided further unique evidence of disinhibited behaviour in the diary:

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> "If we go out and have a coffee, he will go to the sugar sachets, and stash his pockets full of sugar, and try and eat sugar whilst we are there. We constantly try to either take it away from him. I made a sticky toffee pudding the other week, and we all had lunch, and whilst we were watching this film he had eaten all 16 pieces. We leave fruit out, which he doesn't touch." (LESS10 wife digital diary)

Her quote illustrated a unique experience of his gluttony, and her astonishment at how his whole life had changed post morbidity, to "revolve around food". This suggests unique evidence on a patient's food cravings. Sugar cravings are often seen in patients with hippocampal damage, and it is believed the processing of hippocampus signals control this ultimate decision to binge eat or to refrain.

As in two carer interviews, post-morbidity hoarding habits were also expressed through the digital diary entries. Although the carers transmitted a sense of annoyance, sometimes it was easier to remain unconfrontational and give unwanted hoarded items away instead. However, for the patient, the items may have represented a way of maintaining some control of what they decided to keep.

Concerning memory loss, most carer accounts described aspects of frustration and annoyance when having to repeat information. Some patients needed regular prompting to remember where objects were kept at home, or to read the memos they had written as aide-mémoires, or certain forthcoming important dates. However, they all expressed the necessity of adjustment and acclimatisation as a consequence of the LGI1-aLE. A final entry captured a sense of disappointment due to the patient's memory loss. It also consolidates the pure frustration and sadness the carer felt:

> "He recognised Valentine's Day on the radio, on the car, and so he was insistent that he needed to get me a card, and I checked he had some money and I dropped him off at the shops, but he walked past all the roses and cards, got himself a paper and chewing gum, and came back out again, minus any flowers or card or anything to do with Valentines whatsoever." (LESS10 wife digital diary)

This sub-theme has highlighted some of the carer's feelings associated with the experiences of the ongoing symptoms of LGI1-aLE. However, in order to fully understand the participants' adaptability to the disease, the dilemma posed by coping versus confrontation, needs to be explored further.

5.3.3 Coping strategies and support

Coping strategies essentially related to the level of cognitive deficit in the patient, their shared emotional stability as a couple and with the wider family, and with the general quality of life experienced together. In addition, coping may be regarded as a personality style, displaying gender differences in perception and reflection, or personal expectations. With coping being open to individual interpretation, the interviews illustrated many ways in which both the patient and carer displayed resilience. To some extent, there was a self-preservation adopted by patients since the onset of the disease to manage activities and scenarios as best as they can. Although full recovery had not been achieved for most patients, the concept of coping involved developing new habits or skills to address the ongoing challenges. It is suggested that for carers, advanced adaptation and adjustment of their coping strategies over time could have further benefited from an understanding of the neurological reasons behind the symptoms. With a lack of professional support and self-management advice for both the parent and carer, their personal strategies were fundamentally based on self-initiated advice, or through other support systems.

Patients primarily employed various coping strategies for their memory loss. These consisted of using prompts and reminders in the form of diaries, photo albums or notepads. One patient and her husband have a coping strategy, 'a game' for her repetitive conversations and memory loss, which amuses them:

> "If I have asked him something before, I say don't look at me that way, just say 'ding'.
> It's quite funny, and sometimes he'll say "ding, ding, ding, ding, ding (laughs)."
> (LESS4 patient interview)

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This quote exemplified using laughter and joking as their joint strategy, not to dwell on the negative impact but to adjust their expectations. In addition:

> "I write everything down, it's just a joke, I have pens and paper everywhere in every handbag in every room (laughs)." (LESS4 patient interview)

Her husband confirms that her strategy worked well, and prepared her for future meetings:

> "When she's seen friends, she'll come home write up some notes…she'll reread her notes before she sees them again." (LESS4 husband interview)

In fact, this highlights a valuable tip to share with other patients, to restore a sense of control and boost their confidence. In contrast, some patients filtered out the memories they thought were unnecessary, as another coping strategy:

> "If the information is useless, then I do not bother trying to remember it." (LESS4 patient interview)

She described how having to remember where the car was parked, was redundant information to her if she was with someone else. Similarly, another patient said:

> "Why would I need to remember that. That's mundane." (LESS7 interview)

This suggests a dilemma where useless or mundane information did not compete with necessary information. In contrast, some carers expressed an increased responsibility, having to also make sense of the changed priorities post-morbidity. Interestingly, they used self-reflection over time, learning to deal with scenarios differently.

One carer's coping strategy established the importance of learning new memories, instead of dwelling on the sadness incurred by lost memories (LESS5 brother). He and other family members promoted going on holiday together so that they could all build new memories. This induced feelings of hope and positivity.

Regarding the avoidance of arguments, there was a commonality amongst carers that agreeing with patients sometimes seemed an easier option than disagreeing with them. To avoid disputes and confrontation, LESS3 wife explained that these scenarios induced a sense of exhaustion, as she tried to work out which strategy worked well. Moreover, if decision making was a challenge for the patient, reducing choices or making decisions for them seemed an easier option for some carers. This was often upsetting for the carer, taking away the patient's control, but in some cases, it was deemed necessary. One carer described how he would look back on one of the more argumentative days, as:

> "We're just sort of treading water, just keeping our lips above water." (LESS5 brother interview)

However, patients too, will try to avoid an argument. Some patients described avoiding situations which they knew would have caused them irritability and intolerance. For example, LESS1 tried to 'take a reality check', as he calls it. He now reflects on a situation, instead of being on the defensive and taking things personally.

With regards to one carer's coping strategy for her husband's spending and impulsivity to hoard items under the bed:

> "I feel quite helpless to stop him. I have to limit…keep a check on the bank and have stopped him taking money from the joint account." (LESS9 wife interview)

Although the quote illustrates her sense of feeling helpless to some degree, she found a 'middle-ground', which is often what carers have to do.

Finally, concerning one patient's increased desire for retail therapy:

> "There are at least two new coats that have not come back out of the cloakroom since she bought them, so it is the act rather than the need." (LESS2 husband interview)

As a couple, this strategy to go out clothes shopping works two-fold: by satisfying her frustration and desperation at staying in the house for too long, which her husband believed was a product of the encephalitis, and by breaking up the long, sometimes monotonous day indoors for them both.

The benefit of personal support systems was highlighted in numerous narratives. This is different to the support discussed in Theme Two, which centred around professional support during the acute stage and hospitalisation. For most patients and carers, there was an aspect of support associated with their religion, friends and family. As well as the benefit of connecting to others which relieved feelings of isolation for the couple, it also improved motivation, decision-making skills and confidence for the patient. Furthermore, those in a supportive environment were more likely to have an improved quality of life.

LESS5 was diagnosed three years prior to the NPTB and waited the second longest period to be diagnosed (23 months). She lives with her brother who has MS. She repeatedly expressed her siblings' support, cohesion and encouragement following diagnosis.

Some patients included their church as an additional support option. One patient attended a Buddhist spiritual retreat twice a year, where they practiced techniques for serenity and managing stress. This not only provided an added form of support but improved his sense of calm and acceptance at home. This was reflected in his narrative, where he offered to ease the atmosphere when tense, instead of becoming confrontational.

Regarding friendships, one patient with decreased motivation, had tried to delay or make excuses when meeting friends, yet she admitted feeling a sense of relief in having met up with them afterall. However, not all patients were persuaded to meet up with friends. Instead, they made decisions to stay home and avoid social situations.

Further evidence from this sub-theme suggests that although some friends have tried to remain loyal and close, for others the consequences of LGI1-aLE were difficult to manage.

> "[Patient's name] had a very good friend, but he found it exceptionally hard because of all the things, times, memories they had…and jokes, but he had forgotten all that information." (LESS10 wife interview)

Many carers expressed the need to have time on their own, or a break from the situation at home. One carer joined crafts groups which helped provide her with additional support, together with some time away from the routine at home.

> "I do get that guilty feeling when I go to my daughter, I shouldn't be out so much, but if I didn't do it, I would go crazy. If I didn't do things, I would be alone here." (LESS9 wife interview)

This personifies her guilt in leaving him, together with her strategy to cope with the isolation she felt. In fact, during her interview, she described having a 'breakdown' and having to give up work, several months after her husband was diagnosed. This sense of feeling overstretched, struggling with the additional responsibility and feeling unsupported in her workplace, was intertwined with feelings of guilt leaving her husband alone in his vulnerable state.

Referring to the relevance of family support, most patients and carers expressed a pride and gratitude for their children's or close family's love and empathy. This sub-

theme has enhanced our knowledge on how coping strategies have developed alongside the ongoing impact of LGI1-aLE. For both the patient and carer, each individual circumstance necessitates a degree of negotiation between their expectations, their coping, and the actualisation of achievable goals.

5.4 Theme Three: Relationships

The third theme generated, explored the challenging experiences within relationships. As most patient and carer participants are spouses who have been married for a significant amount of time, the carer knows the patient very well. Post-morbidity behavioural changes have either strengthened the relationship or incurred barriers. These barriers have stemmed from the patient's ongoing symptoms of reduced sensitivity and affectionateness, their increased irritability, or from the carer's attitude and resilience towards the changed situation they find themselves in. The ongoing impact of LGI1-aLE not only affects the quality of existing relationships but continues to impact on the quality of future relationships. However, this quality is sometimes compromised in friendships, where there is less insight and understanding of the disease. The following sub-themes form the basis of the over-arching theme: 1) the relationship with the spouse/partner/brother;2) the relationship with family and friends.

5.4.1 Relationship with the spouse/partner/brother

Unveiling the impact on personal relationships has been mostly detrimental and bound to the physical and emotional bond the couple had pre-morbidity. Furthermore, their expectations moving forward held different challenges and contrasting perspectives on the coping strategies to achieve the outcomes they both wanted. Although one couple experienced a period of separation directly attributable to the impact of the disease, and failure in their relationship, they have since reunited and are enjoying a healthy and fulfilling relationship once more. For other couples,

there was a joint sense of stoical determination to accept their situation and manage as best as they could. Most patients felt fortunate to have a loving, supportive relationship stating the LGI1-aLE has not changed this, but instead had strengthened their relationship. For example, although LESS1 acknowledged his behaviour, he also divulged his love for his wife:

> "Character wise, I have changed a little, because I am more defensive. I am probably not as warm as I used to be. Our love is still as deep, and I am grateful that we can still build and have a future together. There are no issues in our marriage." (LESS1 interview)

His wife's quote below, captured her feelings and exemplified a sense of loyalty and acceptance:

> "He's still [patient's name], he's still the same man, although things have changed, but the root man is still there and that's the deepest part of our relationship, it's still there." (LESS1 wife interview)

Another patient's quote illustrated the wife's devotion:

> "He is my rock. I mean I think it frightens him sometimes that I rely on him so much but I do, I just love him to bits. And we've always been good pals, you know, as well as husband and wife. I'm very lucky there." (LESS2 patient interview)

Her husband's account suggested adapting and learning to be more forgiving, yet he relayed some disappointment on her behalf. There was a sense of hope, as he described her persona was still there, but her energy had diminished.

The emphasis for couples who were having an intimate relationship up until the onset of the aLE, placed significant strain and tension on the carer. One couple was experiencing a difficult time at the time of the interviews. The patient felt 'the love and respect were there', yet his partner's perspective offered a stark contrast. It relayed a sense of loss in their relationship, of love and spontaneity. As a result of

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the disease, the changes in the dynamics of the relationship made her now feel like his carer:

> "We have been intimate and close for 37 years, but I don't know if he remembers the feelings we had, when we used to look at each other, and he had a twinkle in his eye." (LESS7 partner interview)

This sense of sorrow and disappointment persisted throughout her narrative, and she became tearful. Evenings passed by, without a word spoken, without any affection, causing feelings of sadness and mourning of the relationship they once shared. Instead, she faced a 'blankness':

> "I look at him in the eyes…the eyes are different. Have I got to put up with this forever? I don't know if I can and that sounds selfish, but then I feel guilty…if I suppress it, I get depressed." (LESS7 partner interview)

Despite this quote offering a sense of the antipathy towards their relationship post-morbidity, it also exhibits her guilt when questioning whether she could contemplate this scenario for ever.

Regarding the traditional male role of making the financial decisions some male patients illustrated a sense of struggle with the role reversal:

> "Now, I am in a situation at home where she can question me, and I have doubt in my mind, whether I am doing the right thing. That knocks confidence out of you and you tend to question yourself a bit more…. basically, we have almost had a role reversal, and this has sometimes caused issues." (LESS6 interview)

This evoked a feeling of failure in him, putting his wife in a position to question him. Although questioning a patient's decision-making is often deemed as a personal criticism not intended that way by the carer, it nevertheless produced friction in many couples. Furthermore, his wife described:

> "He can get very upset and angry at things. I feel maybe he feels he has lost a little bit of control, as a father and a husband, I think maybe that's an issue for him." (LESS6 wife interview)

For some patients, the sexual drive or libido had decreased, possibly due to the damaged or scarred tissue in the limbic brain, or perhaps explained by fatigue and apathy:

> "Since I've had that, this encephalitis you know, the sex side of it has gone." (LESS9 patient interview)

However, one patient blames his decreased libido on the role reversal and its harmful effects on their relationship (LESS10 patient), with his wife's perspective offering a sense of disappointment, yet acceptance:

> "I probably felt like a carer, as opposed to a wife. Personally wise, nothing happens in the bedroom now and hasn't for a couple of years. Since the encephalitis, he has not been very loving...I don't know if it's just age." (LESS10 wife interview)

For couples who enjoyed an intimate relationship pre-morbidity, the abrupt challenge on a spouse becoming a carer and taking on all or increased decision-making for them both, placed them under unprecedented strain.

Furthermore, the theme has highlighted an awareness of one patient's insensibility towards his partner who felt when she got upset, there is no empathy. If she touched his hand, he pulled away. Their loss of connection and intimacy stimulated feelings of hurt:

> "Breaks my heart, breaks my heart, because I feel like I have done something wrong, and I know I haven't. I don't think he misses me if I wasn't in bed at all, you know...." (LESS7 partner interview)

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This illustrates the sadness felt by the carer, but also a sense of hopelessness. For some carers, the loss of the warmth and satisfaction in their relationship was linked to the loss of sexual desire. However, it was also possible that decreased libido was affected by other factors such as the side-effects of medication, growing older and other co-morbidities.

5.4.2 Relationship with family and friends

This sub-theme highlights how the impact of LGI1-aLE often reflected negatively on the relationships with family and friends, depending on their level of understanding and insight of the seriousness of the disease. Potentially, children living at home at the time had a deeper knowledge of the consequences, whereas there was evidence within this theme to suggest that some children living away from home, failed to fully understand, and even joked or trivialised the effects:

> "I will say to our daughter your mum is getting much better, and my daughter will say that's lovely, when can she come and babysit for us." (LESS2 husband interview)

For those children who played a pivotal role in the patient's recovery, they also provided support to both parents. LESS1 patient's daughter had personal experience of epilepsy and was able to give her father valuable support. Some children also experienced an aspect of role reversal in caring duties for their parent (as expressed by the carer). However, this could have been interrelated to the parent getting older and perhaps was not a direct result of the disease. For some children there was a sense of grief for the loss of their parent's usual behaviour and character, having witnessed the changes first hand, causing them shock and anguish.

For one patient's daughter who was not living with him, she did not understand the full impact of the LGI1-aLE. However, his stepdaughters who lived with him,

experienced his changed behaviour and expressed a powerlessness to help. Regarding the way LESS7 sometimes spoke unacceptably to his partner, their daughters took different approaches towards him. One daughter tried not to confront him or make him angry, perhaps reiterating her mother's technique, whereas another daughter was firm with him:

> "You can't speak to mum like that', and he will say 'yes sorry, it's the brain injury' and then she'll say ' that's an excuse." (LESS7 partner interview)

She felt irritated that he used the aLE as an excuse and found this unacceptable. Most patients felt their relationship with their children was possibly stronger, although some carers indicated a contrasted perspective of disinterest towards their children and grandchildren, and a lack of enthusiasm which had occasionally highlighted feelings of sadness (LESS8 and LESS9 carers).

Pertaining to friendships, there was an awareness by carers that some had dwindled or been lost all together, which evoked feelings of sadness and disappointment. The narratives expressed how close friends had sometimes found it difficult in dealing with the behavioural changes and memory loss. LESS1 wife accentuated the concept of LGI1-aLE being 'hidden' and a formidable task for friends to take on and adapt to. In other cases, the friendship dynamics remained strong, yet the logistics of visiting friends was problematic especially if the driving licence had been withdrawn.

Two female patients in this cohort indicated that their close circle of friends had remained unchanged. Yet for some wives of patients, they demonstrated heightened resentment due to the loss of their joint friendship circles:

> "The worst scenario is, if anyone is physically injured, you will have empathy, sympathy and understanding from people. With this, you will lose your friends, you don't get invited anywhere, you will be excluded, you have to really go out and find your own life." (LESS10 wife interview)

This quote reflects the loss of friendships from a carer's perspective, evoking exclusion and isolation. However, from a patient's perspective, some found it difficult to keep up with, and contribute to the conversations due to their decreased confidence, with linkages to memory loss, decreased motivation and increased fatigue. It is plausible that the lack of understanding of the disease amongst friends has also contributed to the detrimental interactions with them.

5.5 Theme Four: return to work and leisure

The fourth theme explores the experiences which impinge on returning to usual activities, for patients and carers. Two sub-themes form the basis of this arching theme. These are: 1) the return to work; and 2) the return to leisurely activities. Often the effect of the limbic brain damage and its related deficits, forced the patient to seek new employment and abandon their existing career path. Finding new employment entailed accepting a new job role to suit the patient's post-morbidity capabilities, including reduced hours due to fatigue or less responsibilities due to their memory impairment and altered decision-making skills. Regarding leisurely activities, associated symptoms of fatigue and demotivation hindered the patient's plans to exercise and undertake household and garden chores.

5.5.1 Work

This sub-theme has highlighted the impact LGI1-aLE has on employment status. Three patients were below retirement age and had to face the challenge of returning to work hampered by their memory problems, reduced motivation, fatigue and reduced concentration span. They subsequently had to seek new employment with entirely different roles. Only one patient was consequently able to get company early retirement benefit. Essentially, returning to work with ongoing symptoms was extremely difficult, and the challenges associated with changes in job role status and responsibilities incurring a variety of feelings.

One patient (LESS1) who previously worked as a magistrate had to resign from the bench after twenty years' service, due to his memory impairment that compromised his capacity to make decisions and his fear of making mistakes. The dramatic decline in recall and decision-making abilities was accompanied by a sense of sadness and disappointment. He subsequently tried to set up his own business which he since had to close due to his memory issues. He found it difficult to make conversations with new customers and had lost his confidence in business meetings. Therefore, the situation forced his wife to work full time instead, leading to a significant loss of income and role reversal, which subsequently incurred feelings of frustration and despair for the patient, and increased pressure on the carer:

Losing confidence not only stemmed from the associated cognitive deficits, but it also affected the patient's individual personality causing anxiety. This was common amongst patients who focussed on what they could no longer achieve, instead of what they have accomplished despite the limitations of the disease. LESS2 patient described a sense of feeling burdensome, as she lacked confidence and completely relied on her husband. Losing confidence was a common complaint amongst this cohort, and perhaps reflected some gender differences associated with traditional roles they assumed in their relationship, pre-morbidity. One patient gave up a senior residential social worker due to the encephalitis:

> "I wouldn't have the foggiest where to start now. I would not feel comfortable, I would not be confident that I could not do the job properly." (LESS5 patient interview)

This quote reinforces the lack of confidence common in other LGI1-aLE patients, yet, remarkably she showed such positivity in her interview, and has since started a new role as a supermarket cashier:

> "I've got back some of the can-do attitude." (LESS5 patient interview)

The sense of pride in her achievement was evident, despite the decrease in salary and job status. Another patient changed job status from a contract's manager to a labourer and felt content in his new role. Despite the complexities of seeking new

employment, those patients showed unquestionable courage and determination, appreciating newly acquired skills and camaraderie from colleagues.

For one patient who took early retirement from his position as chartered accountant, felt he now lacked initiation and relied on his wife:

> "If I hadn't had this, we'd have .....she wouldn't have been my carer......we would have been in a financially different situation because I could have still been working... we would have done a lot of travelling." (LESS10 patient interview)

This possibly depicts a sense of letting his wife down in what 'would have been' without the onset of aLE.

Regarding carers giving up work, two carers described giving up work to remain home with their spouse, yet they did not display resentment. LESS3 wife described how she was forced to stop working as a GP and took six months off to look after her husband, and then finally only returned part-time. Eventually, the stress associated with her husband's illness led her to take early retirement from a career she loved, evoking a sense of disappointment. LESS9 wife was unsupported in her workplace, and eventually had a 'breakdown' due to the additional burden and duties as a carer.

In general, the loss of self-esteem and confidence caused by memory loss and fatigue, made returning to work with the exact responsibilities as pre-morbidity, near impossible. In addition, the financial strain caused by loss of work or a change in work status with the associated reduced salary, personified distress and tension for the couple. For those male patients who assumed the traditional role of bread winner, this proved especially devastating as they felt they had let their spouse down, perhaps revealing an incompetence on their behalf. Feelings associated with

additional burden to the carer, included disappointment and tension, yet as in other themes, formidable stoicism.

5.5.2 Leisure

The patient's usual activities including taking holidays, were predominantly linked to their capabilities to undertake them. Partly based on patient recollection and partly from the carer's account, this sub-theme illustrates common associated feelings such as disappointment and frustration. The experiences are also reflected in the activities shared with friends, some of which have changed or ceased completely. For many patients, their wellbeing was enhanced with their pre-morbidity leisurely activities such as DIY, gardening, attending football matches, and church groups. One retired patient spoke of his interest in Buddhist workshops and retreats, which played a significant role in his spiritual wellbeing.

One patient who loved swimming regularly and visiting friends and family with her husband, admitted to lacking motivation. However, her husband reiterated that once she has finally decided on meeting her friends, her confidence grew and she reaped the reward the experience gave her. For the carer, any opportunity for the patient to be with others allowed him some respite also. Her husband has expressed feeling 'claustrophobic', 'housebound' and not having enough 'me time'.

Regarding leisurely activities, one patient expressed his lack of motivation to play golf, and easily made up excuses not to go. Although he and his wife had taken cycling holidays, he now felt 'lazier' and there was a sense of de-motivation. As for his volunteering work at the golf club, he described some enjoyment with the social interaction with the workers, including 'the crack and the banter'. Other patients' narratives evoked a lack the motivation and decreased confidence to undertake activities. For some carers this was concerning, however, for other carers, there

were feelings of annoyance and frustration that the social life they used to have together, has declined or no longer exists [5.3.2]. The quote below regarding holidays, portrays these feelings:

> "I won't go on holiday with him alone, because I get so bored. He is in bed a lot of the time, and I am on my own, and go to breakfast on my own. So that's why I won't go away with him alone anymore." (LESS9 wife interview)

Other patients felt frustration in not being able to remember a holiday and feeling sadness for the carer who may be forfeiting holidays away. For other patients there were feelings of acceptance and adaptability. Incidenatlly, at the time of the qualitative data collection, not all participants were aware of an innovating 'connection scheme' to share feelings, in operation through the Encephalitis Society.

5.6 Theme Five: future plans

The fifth and final theme focused on how making future plans with family and friends was problematic, due to the uncertainty of the recovery, or due to co-existing health conditions. One patient expressed the futility of future planning:

> "What's the point spending a lot of money on the holiday, because within a couple of weeks I can't remember it." (LESS4 patient interview)

This elicits a sense of practicality in saving money. This was evident in other interviews, talking about past holidays. Even if the patient was prompted by a photo, the memories and feelings were often lost.

Some carers illustrated a sense of fear when planning to go abroad and having sole responsibility for their spouse. One couple viewed getting travel insurance to the States as problematic, and therefore resorting to travel within Europe.

For many patients, even planning short-term was difficult, but LESS5 brother iterated:

> "…because we don't live by next week, next month, next year, we live by day, the only time we plan ahead is for our holidays. The only decent thing that came out of this…. [sister's name] was claustrophobic for over 20 years. Now she'll sit on a plane 10 hours no problem (laughs)." (LESS5 brother interview)

His quote highlighted a unique, positive outcome since the diagnosis, maybe due to a personality change. Be it was rare 'coincidental' benefit, it reflected also some amusement.

One patient and his wife were preparing to present at the Encephalitis Research Day in Oxford. For his wife, it was not just the encephalitis that changes future plans, but also their resilience and getting older.

One patient who highlighted his uncertainty about the future and his fear of possible reoccurrence of a seizure, talked of buying a property near the coast. However, his partner had her doubts and concerns, as she relayed a somewhat reluctance and indecisiveness regarding moving away with him. This would lead to feeling isolated when being away from her friends and family.

Finally, one carer emphasised the children's role in her future:

"There are no future plans. I work around the children, playing carer with [husband's name] and mother with the children." (LESS10 wife interview)

There was a sense of affliction on her future plans. Admittedly, future planning for all participants was not only dependent on the impact of the disease, or on other interchangeable and inevitable factors such as getting older, but also on the general outlook on future planning they shared pre-morbidity.

5.7 Chapter summary

All five themes have represented new evidence surrounding the core concepts and experiences of LGI1-aLE. Through the hermeneutic underpinnings of IPA, insightful and descriptive accounts made sense of how the participants made sense of their experiences and feelings, through their engagement with the disease. Most narratives revealed considerable commonality in acute and chronic symptoms consistent with published findings, yet diverse and unique experiences were also discovered. However, these themes were not conclusive in any way and can be developed further in future research. Direct quotes offered transparency, credibility and trustworthiness, representing participants' narratives. All patients and carers have had to adapt and accept the situation, inciting courage and stoicism for some, but for others, a sense of exasperation and intolerance.

Theme One demonstrated awareness of the direct effects of the acute symptoms on the patient and carer. Narratives successfully illustrated a range of joint feelings of shock and fear of the unknown. Due to the persistence of some carers to keep their spouse in hospital until a correct diagnosis was made, a sense of determination and courage was demonstrated. Lack of professional support induced a feeling of anger and disappointment for some carers. For the patient, unable to recall and relay certain acute symptoms, including neuropsychiatric symptoms, this theme

represented an 'unpreserved time' for them, with heavy reliance on their spouse and family.

Theme Two demonstrated the persistence of symptoms and their continuous impact on both the patient and carer. The significant impact of memory loss caused patients sadness, disappointment and frustration, concerning lost events and family memories. Many carers noticed a decline in motivation, confidence, emotionality and sensitivity, and an increase in fatigue, irritability, impatience and apathy. Furthermore, this theme yielded unique accounts of the less common ongoing symptoms, such as the hoarding of overpurchased and unwanted items, accounts of poor navigation or decision-making skills, disinhibited behaviour, poor hygiene and prominent sugar cravings.

Theme Three highlighted the impact on relationships. Some relationship problems were attributed to the patients' post-morbid behavioural changes such as increased frustration and irritability, which may have been further exaggerated by the resulting negative impact of role reversal, loss of earnings and reduced job prestige. In addition, many patients felt their independence had been compromised, due to their reduced decision-making abilities and lack of confidence, placing heavy reliance on the carer. Many couples understood their traditional roles and faced a sense of shock when their roles were dissembled. For some carers, the experiences relating to their new role also evoked feelings of stress, due to the added responsibilities and burden of additional 'duties' put on themselves. Some carers expressed the need for some respite and feeling trapped within their homes, evoking a sense of guilt when they left home to meet friends or undertake outside interests alone. Regarding relationships, some patients spoke of decreased libido, possibly associated with lack of confidence, fatigue and apathy. However, many female carers outlined their feelings of hurt and frustration with the patient's post-morbid lack of empathy, emotionality, sentimentality, and the loss of physicality. This was possibly attributable to gender account differences, but further research would be necessary to

investigate this. The impact varied across the carer cohort in regards to severity, and to an extent the digital diaries helped understand the frequency of certain symptoms.

Theme Four demonstrated a significant impact on the patient and carer, with some transferrable feelings from other themes. For some patients who were not retired, continuing work in a different capacity and reduced grade evoked feelings of loss, frustration and disappointment. However, two patients embraced their new job roles with a sense of positivity and pride. Regarding activities outside work many patients believed lack of confidence caused by memory loss, fatigue and demotivation hindered their pursuit in leisurely activities which they enjoyed pre-morbidity. Regarding social activities, there was some resentment and loss with some carers, who once shared an active social life as a couple.

Finally, Theme Five exposed a variety of feelings regarding making future plans. Couples mostly attributed the inability to make plans to the disease, associated with the uncertainty of a full recovery. However other pre-existing health conditions also affected decisions to make plans, together with getting older. Most couples acknowledged that making concessional plans was possible and provided hope and enjoyment.

CHAPTER SIX

Discussion

6.1 Introduction to the Chapter

This original research project offers a comprehensive understanding of LGI1-aLE, using a triangulation method to identify the negative sequalae of aLE, which are the associated complications of the disease such as long-term memory and behavioural changes, together with their impact on patients and carers. This method provided a useful approach, requiring quantitative and qualitative analytical skills to uncover specific ongoing clinical characteristics of the disease, predominantly of amnestic and behavioural presentations in line with existing research. Where the quantitative findings of the NPTB in Phase 1 could not capture the detail and extent of the disease's impact, the qualitative findigs in Phase 2 and 3 have added the participant voice to answer the research question holistically.

These findings have provided the long-term neuropsychological outcomes during Phase 1. Phases 2 and 3 have yielded reliable data obtained through interviews and digital diaries for in-depth exploration of patient and carer experiences. Recognising the impact on patients and carers has relied on the subjective relationship between the researcher and interpretation of the participants' narratives in order to make sense of the disease's impact on them. Rich, everyday accounts of participants' experiences analysed with IPA confirmed distinctions between common or unique patterns of symptoms across patients, and common or unique patterns of burden and distress across carers. Furthermore, the facilitation of MM clearly contributed towards our knowledge on the long-term outcomes of LGI1-aLE, which leads to the improvement of the recovery expectations for both the patient, carer and whole family. The implications of the MM findings are presented by organising quantitative and qualitative results compared across six aspects of the disease: symptoms, professional support, the consequences on carer burden, relationships, returning to work, and future planning.

6.2 Symptoms

Despite the rarity of the disease, the small study sample has captured a neurocognitive profile characterised by chronic symptoms which support existing research. The chronic symptoms include memory loss, apathy, fatigue, behavioural changes and poor sleep quality. The acute symptoms at disease onset were reported retrospectivly as part of the NPTB, and included memory loss, FBDS and psychiatric symptoms. Whilst the personal impact of these symptoms on the patient and carer are understudied, these MM findings illustrate any similarities, contradictions and inconsistencies across both datasets, which are discussed below in each sub-section.

6.2.1. Acute symptoms

As mentioned, findings resonate with current literature on acute symptoms, demonstrating prominent observations of memory loss, FBDS and psychiatric symptoms such as aggression and disinhibition. During the period of acute symptoms, three carers experienced somewhat dissatisfaction with the delayed correct diagnosis by their local NHS clinicians and sought a second opinion from a private neurologist. However, these second opinions did not offer correct diagnoses, but instead confirmed the complexity and difficulty of diagnosis for experienced neurologists working in the private sector. Incidentally, it is likely that second opinions are less sought after now in developed countries as they were ten years ago, due to improved knowledge and expertise in AE, but further research would be needed to confirm this.

By reflecting on the acute period, the qualitative data collection highlighted feelings associated with the disturbing and shocking experiences at that time. Waiting for a correct diagnosis not only resulted in confusion, dissatisfaction and distress for the carers, but left the patient feeling reliant and vulnerable. Moreover, one carer was

frustrated and angry at the dismissive health professionals who referred to her husband as a 'bed blocker'. Overall, the carers' determination to find a correct diagnosis is consistent with accounts shared on the encephalitis websites. The significant acute symtpoms are described below.

6.2.1.1 Memory loss

Regarding acute memory loss, these findings confirm it continues to be reported as one of the principal symptoms in aLE, in line with previous studies (Bien, 2019; Kinsella et al., 2018; Aurangzeb et al., 2017; Van Sonderen et al., 2016; Patira et al., 2016). This thesis reveals both patient and carer recounts of acute memory loss, as the patient's ability to provide substantial recall on the acute symptoms was insufficient, and hence a second perspective was necessary. Although previous LGI1-aLE research quantifies the extent of acute memory loss using test scoring, these qualitative findings distinctively affirm the personal suffering of the patient with acute memory loss through narratives. As mentioned, patient narratives may have been compromised due to the recall deficit, consistent with research on patients with hippocampal damage who may present with difficulties when asked to narrate about events that happened pre-morbidity (Miller et al., 2017). Furthermore, research by Dede et al. (2016) where patients with medial temporal damage (not LGI1-aLE) and HCs were asked to produce detailed narratives about recent and remote events, suggests that difficulties in remote autobiographical recall were alleviated when patients were assisted in staying focused in their narratives, by using frequent supportive questioning. This research could not ascertain whether patients' narratives were compromised because of retrograde amnesia, or because their anterograde amnesia prevented them from staying focused on the narratives they provided. In contrast to these findings, impairment of recent episodic memory, but less so of remote episode memory with preservation of personal and autobiographical memory, has been suggested in aLE patients (Lad et al., 2019). Memory loss was addressed using prompting and guidance to maintain the flow of the patient narrative. Qualitative findings highlighted the patients' incurred feelings of

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severe frustration, sadness and loss. In addition, loss of confidence in the patient was a common factor associated with acute memory loss, leading to reliance on carer accounts to provide and substantiate information. Therefore, the carer accounts were essential in providing an additional unique insight. For all carers, the the severity and escalation of the sudden memory loss was both concerning and shocking.

Some unique findings regarding sudden memory loss during the acute stage, came from LESS10 wife's narratives. Examples included the time her husband exhibited unusual behaviour such as buying her a perfume she had favourited several years prior, suddenly needing a Sat Nav to get to and from work, and the inability to recall his usual place at the dining table. The MM approach has subsequently offered a new element to our current knowledge on acute memory loss in LGI1-aLE, by demonstrating the personal insight on feelings. Moreover, carers sometimes assigned other reasons for the sudden memory loss, in LESS10 wife's case a 'nervous breakdown' due to pressures at work. It is possible that carers' speculations may even have delayed seeking medical advice on the sudden memory loss. Furthermore, research suggests patients and carers may delay seeking advice if memory loss or behavioural changes have occurred gradually over weeks (Budhram et al., 2019). Together with careful history-taking by an experienced clinician, any subtle deterioration in memory and the recognition of focal seizures may have been detected earlier. Furthermore, any aspect of denial of memory problems initiated by the patient, could have misinformed its severity to the carer. This is consistent in a blog by an NMDA-R sufferer, she explained that her 'reduced insight and denial of memory problems' created challenges for her family (Dawson, 2018).

6.2.1.2 Faciobrachial Dystonic Seizures (FBDS)

Regarding FBDS, these were commonly unrecognised by health professionals during the acute stages, pre-diagnosis. Despite current neurological literature on

LGI1-aLE showing early FBDS seen in up to 71% of LGI1-aLE cases, occurring up to two hundred times a day (van Sonderen et al., 2016) amongst the primary symptoms (Lancaster and Dalmau, 2012; Irani et al., 2010), not all neurologists had the knowledge or experience to recognise and differentiate these characteristic seizures at the time of diagnosis. During the qualitative data collection, patients and carers described a variety of sensations and movements ('goose bumps', 'jerks', 'twitches', 'grimacing'), which are all suggestive of seizures in LGI1-aLE, but in hindsight were thought to be the result of other factors, such as the menopause or work-related stress. According to Finke et al. (2016), 17% of 30 LGI1-aLE patients in their study reported shivers or flushing during the acute stage, but data was obtained through assessments and not narratives. 'Goose bumps' or piloerection were also explained by Rocamora et al., (2014), where three LGI1-aLE patient case studies retrospectively presented this form of seizure. Incidentally, sudden falls were also noted in two patients, but were not initially linked to the FBDS, where temporary loss of sensation or muscle weakness in the legs can occur and cause a fall. Consistent with findings by Iyer et al. (2017), FBDS were responsible for patient falls in a case study. However, the contribution of narratives to existing research using clinical assessments, has valued the participants' descriptions of the seizures together with descriptions of any characteristics which were present leading up to diagnosis. Further evidence is revealed in a patient narrative on the Encephalitis Society website, describing how an AE sufferer remembers feeling 'prickling, buzzing and burning' in her limbs, and compared this to 'walking on broken glass or gravel'. She described her hand going numb and dropping objects, or her leg feeling heavy before a fall. By volunteering accurate accounts, patients have substantively improved our understanding and awareness of FBDS. The presentation of seizures as involuntary or unusual movements, but without the detailed narratives, had led to often unrecognised or missed incidences of FBDS by the health professional, contributing towards a delayed diagnosis in LGI1-aLE.

Despite the rarity of qualitative accounts of FBDS in the current literature, research on the patient's subjective narratives of the seizure experience has been

demonstrated by Thompson et al. (2009), who studied patient perspectives of having non-epileptic seizures (not AE), using semi-structured interviews and IPA. Such research improves the communication process with patients, which in turn heightens our understanding of their symptom experience.

6.2.1.3 Psychiatric symptoms

Results herein are indicative of typical psychiatric presentation during the acute stage of aLE shown in other studies (Dalmau, 2019; Herken and Prüss, 2017; Ramanathan et al., 2019). This has also been identified in other types of encephalitis, emphasising the importance of correct diagnosis (Al-Diwani et al., 2019). Insight into these acute symptoms was supported by some carers' narratives during the period awaiting diagnosis and during hospitalisation. Although the NPI to assess neuropsychiatric symtoms was completed during Phase 1, carers' descriptions often reflected on the sudden onset of hallucinations, aggression and confusion during the acute stage. Narratives available here described feelings of shock, fear and distress for the carer and especially for those children living at home. In one example, a carer felt a sense of disgust and shame in her husband's verbal and physical aggression while in hospital. At that time, the carer focus was often on the disturbing psychiatric presentation rather than the indicative signs of less known symptoms, such as FBDS. On reflection, this focus could have unintentionally contributed to misinforming the clinician's decision making in reaching a correct diagnosis. Despite the majority of psychiatric symptoms reported in case studies or as narrative reviews, patient and carer subjective narratives are rare and likely to be found on encephalitis websites. Research by McKeon et al. (2021) used semi-structured interviews to explore the experiences of seven NMDA-R encephalitis patients, to obtain a better understanding of their acute psychosis. However, patients often could not recall precise psychotic symptoms, and carer perspectives were not included, highlighting their beneficial contribution for future studies.

6.2.1.4 Indiscretion

The MM findings herein include narrative descriptions of indiscretion using insensitive and insulting speech, inappropriate laughter, exhibiting an almost childish sense of humour or sexual innuendos. Previous studies have not highlighted indiscretion as an acute symptom for LGI1-aLE, although inappropriate sexual behaviour has been shown in AE (Lancaster, 2016). This thesis has introduced reports of sexual indiscretion and social behaviour indiscretion, as expressed by carers. Similarly, findings from a case study on NMDA-R encephalitis have highlighted the patient's inability to recognise his own indiscretion (McKeon et al., 2016). Incidentally, chronic traumatic encephalopathy, a neurodegenerative syndrome, has been linked with inappropriate sexual behaviour (Antonius et al., 2014), suggesting an association with cognitive impairment. Despite narratives associated with indiscretion lacking in the current literature, these findings have reinforced the benefit of transparency of information amongst participants and inexperienced health professionals.

6.2.1.5 Other reported acute symptoms

One rarely reported acute symptom in non-antibody specific cases of AE was the change to smell and taste (Geran et al., 2019), which is consistent with unique findings in the qualitative data collection. LESS9 recalled strange tastes in his mouth of metallic or chemical/surgical smells, in addition to smelling fruit. It has been suggested that olfactory and gustatory dysfunction are detected symptoms in aLE, where essential parts of the pathways are located in the limbic system (Schmidt et al., 2019). The findings herein, although uncommon, suggest specific questioning on changes to smell and taste could be incorporated into assessments at diagnosis.

Despite the reference to onset of headaches during the acute stage of aLE (Graus et al., 2016), these are less widely documented than other acute symptoms such as

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memory loss, seizures and behavioural changes. Interestingly, prodromal headaches are commonly indicative of other AEs (Leypoldt, Armangue and Dalmau, 2015), but less prevalent in LGI1-aLE patients, supporting the results in Phase 1. Where the NPTB addressed the patient perspective on their initial symptoms, few recalled or had been told that they suffered with severe headaches leading up to diagnosis and treatment. Having examined the acute symptom findings, the following section will address the chronic symtoms of LGI1-aLE.

6.2.2. Chronic symptoms

This section presents findings of the chronic symptoms that continue to impact on lives. Although previous studies have highlighted the importance of prompt treatment to improve the chances of an optimal recovery, many LGI1-aLE patients experienced delayed treatment. Memory loss, reduced fluency, apathy, fatigue, FBDS, and poor sleep, show some consistency with van Sonderen et.al. (2016) and Ariño et al.'s (2016) retrospective research demonstrating residual symptoms of cognitive impairment, apathy and difficulties with spatial orientation. Comparative evidence on NMDA-R encephalitis suggests the most common behavioural changes in the chronic stage are fatigue, anhedonia, irritability, insensitivity and inability to empathise (Al-Diwani et al., 2019). Research suggests that sustained deficits across quality-of-life domains in LGI1 patients exist, compared with age-matched HCs (Binks et al., 2019). Despite the WHO-5 questionnaire being an effective tool for capturing detailed insight, the narratives have enhanced the illustration of the detrimental areas to quality of life experienced by the patients in this thesis.

The following sub-sections consider how the predominant chronic symptoms impact on the patients' and carers' lives, together with less commonly documented chronic symptoms such as reduced emotionality.

6.2.2.1. Memory (episodic vs short-term and working memory)

The chronic phase of aLE is recognised when applying neuropsychological assessments to measure levels of cognitive dysfunction, demonstrated in hippocampal atrophy in LGI1-aLE patients (Miller et al., 2017). Consistent with hippocampal damage (not specific to LGI1-aLE), patients fail to recall as many autobiographical event memories as HCs (McCormick et al., 2018). Whilst most literature reports cross-sectional findings using case studies (Morrow, 2016; Patira et al., 2016), some compare neuropsychological scoring longitudinally (Butler et al., 2014). A longitudinal investigation remained beyond the scope of this research. In the ACE-R, patients demonstrated the most impairment in memory (episodic recall), and fluency, part of executive function tests (attention and processing speed), consistent with literature (Kipps and Hodges, 2005; Graus et al., 2016; Lancaster, 2016 Finke, 2017). Although cut-off scores were not available for each domain of the ACE-R in encephalitis patients, age-related cut-offs were used from research in PD patients with mild cognitive impairment, shown in 4.2.1.1 (Berankova et al., 2015) Findings were comparable with aLE patients' scores, with the most deficits evident in fluency and memory. Using the ACE-R total scores, at group level patients did not score significantly lower than the cut-off total score, indicating that overall cognitive impairment did not characterise the group as a whole. Interestingly, anterograde amnesia demonstrated in the ACE-R (memory sub-test), showed how some patients found retaining new information problematic. Of the 8/10 patients who lost points in memory in the ACE-R, narratives from both patients and carers described memory loss as problematic and impacting significantly on their lives. However, of the two patients who did not lose any points in memory in the ACE-R, LESS6 inconsistently described the impact of memory loss as a daily re-occurrence in his interview. This could therefore suggest that the delays used for recall and recognition in the ACE-R are not long enough to capture the deficit, and more refined tests using longer delays for retrieval would be more valuable to establish the extent of the anterograde memory impairment. Regarding retrograde amnesia, the patient narratives consistently indicated its presence, described as losing the recollection of personal events in their past (autobiographical memory), such as weddings, birthdays, names of friends and family, or family holidays. Some patients in this research described

knowing they were married, but not being able to recollect the personal facts and self-knowledge of the event, suggestive of non-impaired semantic memory, but impaired episodic autobiographical memory. This dissociation has also been reported in a literature review of LGI1-aLE patients compared to HCs using an autobiographical interview to score memories (Griffith et al., 2020).

Similar to semantic memory, and in sharp contrast with episodic memory, patients showed no short-term or working memory impairment. In fact, the cohort in this research scored significantly higher than the age-related means in HCs on the WMS-III DS. This profile was consistent with the one noted in Bak et al. (2001), where two cases of nonautoimmune LE, showed average and higher than average DS scores.

This thesis has offered the added qualitative data collection to exhibit the personal and 'silent suffering' of the patient, together with an opportunity for the carer to express their feelings, which perhaps provided all participants with an incentive to take part. Qualitative findings herein not only confirmed the impact of ongoing memory deficit, but also illustrated its influence on social connections, including family and friends. Some carers described how new and old friendships had been damaged due to patient memory loss, and sometimes abandoned altogether, causing distress and disappointment to the patient. Forgetting major family events is not only saddening for the participants and family, but friendships have also been affected detrimentally. Another approach to future qualitiative analysis would be to investigate the unknown feelings of the friends. The patient narratives have also revealed common experiences of using coping strategies to manage memory loss, yet still relying heavily on their carers for guidance on a daily basis.

Investigating whether an association existed between cognition and carer burden, there was no relationship detected in this research, perhaps as it was underpowered

(small sample size), there was no such relationship in the first place, or because the questionnaires/tasks used were not refined enough to capture potential linkages. A study confirming an association between increased cognitive impairment and carer burden, suggested that carer wellbeing should be addressed, and the appropriate professional support offered (Black et al., 2018). As a result, qualitative findings herein are required to understand the most burdensome aspects of memory loss on carers' wellbeing, such as the patient's lack of confidence in decision-making.

By measuring the carer's perception of the patient's cognitive decline over the last ten years (IQCODE score), five carers indicated there had been severe decline, and a moderate decline was represented at group level. This is supported by the long-term follow up on various infectious encephalitides (non-autoimmune) (Mailles et al., 2012). All narratives verified the quantitative data, with reduced memory, decision-making and confidence post-morbidity However, the direct effect of aLE and aging could not be entirely separated. NBM using retrospective carer accounts to describe the impact of long-term management of a patient with cognitive decline, is rare. However, research to endorse patient experience of viral encephalitis was conducted using carers to 'co-produce' narrative interviews retrospectively (Cooper et al., 2017). Findings described the consequences of long-term memory loss and decreased concentration, comparable with post-encephalitis experiences in this thesis.

6.2.2.2 Fluency

These findings have demonstrated the sub-domain of verbal fluency sub-tests showed the most dramatic impairment for LGI1-aLE with all patients losing points. This is consistent with previous studies which indicated residual fluency impairment in LGI1-aLE patients (van Sonderen et al., 2016; Binks et al., 2021), advocating early treatment for optimal clinical outcomes. Fluency (verbal) has also been described as one of the most significant problems in encephalitis (not specific to LGI1-aLE)

(Hirayama et al., 2003; Lennox et al., 2017; Finke et al., 2017).). Nevertheless, Greenberg et al. (2009) argued that amnesic patients' performance in the fluency test may be compromised due to their anterograde memory impairment and is not a reflection on poor executive function. Therefore, it is not clear whether patients' low scores on this subtest demonstrate executive dysfunction reported in other research (Gibson et al., 2020) or should be attributed to anterograde amnesia. Despite, fluency tasks being a useful tool as part of neuropsychological testing, standard neurology follow-up consultations with the patient were also beneficial. During Phase 1, the researcher was sometimes present at neurology consultations in the out-patients clinic, where any chronic inconsistencies in the fluency of the patient's narrative, such as interruptions in speech flow, irregular speech rate and comprehension, were routinely observed. Existing literature fails to include NBM and fluency from the encephalitis patient or carer perspective. However, according to Callan et al. (2022), patient difficulty with word fluency and syntax using online focus groups to narrate the impact of the disease and the lived experience of 'brain fog', was demonstrated in long COVID-19 research. This may be a useful strategy for future research using an AE focus group approach.

6.2.2.3 Apathy

Findings herein partly resonate with other research describing apathy as indicative of behavioural disturbances in LGI1-aLE patients (Ariño et al., 2016), thought to be observed in up to 90% of patients (van Sonderen et al., 2016). LE research (non-autoimmune specific) has also reported the presence of apathy (Levy and Dubois, 2006). This suggests that apathy assessments as part of the NPTB in this thesis are important to target future behavioural interventions for the patient and address the implications for carer burden, which is less recognised (Wong et.al., 2020).

The quantitative findings on apathy using the AMI score confirmed that two patients scored within the moderate apathy range and no patients scored within the severe

apathy range. This was linked to the qualitative data, where the same two patients with moderate apathy described a lack of motivation and enthusiasm. One carer expressed her resentment in her husband's apathy. However, apathy was not indicative as characteristic at group level, reflecting the overall absence of apathy. In fact, the cohort scored significantly lower than the cut-off for moderate apathy. Nevertheless, some research proposes that self-reporting from LE patients can be misleading due to their lack of insight (Klara et al., 2020). This emphasises the value of adding the carer reports, which examine consistency with the patients' self-reports. Moreover, the investigation of apathy and motivation scores using the AMI for patient and carer, (albeit in 6/10 participant couples, due to the introduction of the questionnaire later in Phase 1), indicated that patients and carers interpreted the patient's apathy scores similarly.

Regarding the LARS-carer score, which also rated patient apathy, no significant levels of apathy were indicated by the carers, either highlighting an inconsistency with the AMI questionnaire, or was explained by the different questions and scoring used. Through the interpretation of narratives, apathy, possibly misconstrued by carers as disinterest, demotivation and lack of enthusiasm, had a common and distressing impact on them. Many carer narratives indicated a compelling level of patient apathy which affected their daily lives and future planning, suggesting the impact apathy has on carers of LGI1-aLE patients deserves recognition, and should be addressed. This leads to the benefit of explaining apathy to the carer and family as a consequence of the disease, and not to be regarded as disinterest in them personally. Regarding the patient interview, it is possible that apathy may have contributed to reduced qualitative data collection where some patients gave a shorter interview, or fewer digital diary entries. Despite the current literature on apathy which is predominately measured using patient or carer assessments, there is a lack of engagement with NBM. This prompts awareness to address patient and carer lived experiences, where often apathy determined by the carer is more prominent than the patient reports. Moreover, recent research suggests the link between apathy and carer burden is best explored using the carer's subjective experiences through

narrative (Chang et al, 2021). Carers' narratives herein often described strategies to manage the patient's lack of insight into their apathy, by negotiating a way to accept their disinterest and reduced ability to make decisions together, as they did pre-morbidity.

6.2.2.4 Anhedonia

In respect to anhedonia, previous studies have suggested this symptom as a behavioural disturbance in LGI1- aLE (Dalmau, 2019). By affecting the patient's thoughts and feelings of well-being, it can overlap with depressive disorders and perhaps be misdiagnosed, stressing the importance of autoantibody screening and communications across neurology and psychiatry (Hoffmann et al., 2016). With reference to measuring levels of anhedonia in this research, the cohort scored significantly lower than the cut-off indicating that anhedonia did not represent a problematic symptom to the group as a whole. This is reflected in the current literature, where anhedonia is not noted as a main characteristic feature of LGI1-aLE, but more so in NMDA-R encephalitis (Varley and Irani, 2015). Nevertheless, it is possible that under reporting anhedonia is a form of social desirability bias, associated with the participant's tendency not to respond accurately and to please the researcher. In terms of the correlation analysis, this indicated an increase in apathy was positively related with an increase in anhedonia across patients in this research, consistent with data demonstrating an overlap between apathy and anhedonia, as 15.4% in aLE in the studied cohort of neurology patients and carers (Klara et al., 2020).

Most patient narratives relayed some feelings of pleasure with regards to daily and future events, and with family relationships remaining mainly positive. However, incidences of social withdrawal and negative feelings in some personal relationships, were possibly attributable to anhedonia. Carers highlighted the patient's lack of initiation and demotivation, as opposed to the absence of pleasure. Regarding work,

patients still experienced pleasure from the interaction with colleagues, or ex-colleagues. Despite research on anhedonia being well investigated in other conditions using self-reports such as SHAPS, or laboratory-based assessments where patients are exposed to pictures and sounds to stimulate pleasure, little is known about the experiences associated with this symptom. Available narrative reviews enhance understanding of anhedonia as a neuropsychological concept, and a rare qualitative study has explored young people's experiences of anhedonia in the context of depression (Watson et al., 2020). Consistent with findings of LGI1-aLE patients in this cohort and participant experiences in Watson's research, both have captured similar experiences of feeling a loss of joy and positivity, a 'flattening of emotion', struggling with motivation and active engagement, and losing a sense of self-purpose, which highlights the extent of the subjective experience of anhedonia.

6.2.2.5 Fatigue

Whilst existing evidence suggests the long-term impact on patients with AE (non-antibody specific) after four years, essentially demonstrates fatigue, emotional lability, short-term memory loss and concentration difficulties (Yeshokumar et al., 2017), this thesis has shown that most patients did not report a fatigue problem using the FSS. Three patients scored higher than the cut-off showing evidence for problematic fatigue. Additionally, correlation analysis illustrated a significant relationship across patients, indicating that increased fatigue was associated with increased apathy. This identifies the importance of patient and carer education when managing these symptoms and understanding the impact of one symptom on another. However, the association between fatigue and apathy has not been addressed in other aLE research. Instead, it has been suggested that fatigue is a prominent feature of AE and screening would be useful to assess its impact on quality of life (Diaz-Arias et al., 2021).

As fatigue was predominately reported by carers in this thesis, indicating a discrepancy in patient and carer accounts, this once more recognises the value of carer narratives. Some carers described fatigue as very significant, noting that patients often napped in the day and appeared lethargic, which provided additional and contrasting data to the FSS. Some carers also described patient demotivation in getting up in the mornings, possibly related to fatigue. It is possible that patients failed to remember their level of fatigue, because of their anterograde memory impairment or felt ashamed reporting how much they slept during the day. It is possible that some self-report outcomes may present symptoms or behaviours more positively, in other words indicating symptoms are less problematic (Nolte, Elsworth and Osbourne, 2013). Furthermore, it is plausible that carers over-report the severity of symptoms, or underrate the quality-of-life scoring, such as in dementia research (Sands et al., 2004). This may depend on the patient-carer relationship, the level of care provided, the patient's sense of wellbeing and level of self-esteem, and the carer's feelings about their own quality of life.

Although NBM has failed to focus on fatigue in aLE, previous studies have used narratives to understand fatigue as a multidimensional symptom incorporating physical, emotional and cognitive components, which are not always captured in existing questionnaires (Mantri et al., 2020). This suggests another possible area for future qualitative research, investigating fatigue in aLE.

6.2.2.6. Depression

Overall, depression as a common symptom in LGI1-aLE has not been commonly presented. Previous studies have linked neuroinflammation and immune dysregulation with depression (Quaranta et al., 2015). Moreover, it has been illustrated as strongly correlated with fatigue in patients (Binks et al., 2021). Despite depression not strongly indicative in aLE, it does feature in the psychiatric manifestations associated with NMDA-R encephalitis (Quaranta et al., 2015). Only

one patient showed moderate depression using the BDI and there was no evidence for group-level depression in this cohort (including the sub scores of affective mood, dysphoric mood and loss of interest). Moreover, at the time of data collection during Phases 1 and 2 anti-depression medication was not being prescribed for any patients.

The narrative findings from this thesis provided little reference to depression as problematic. Only one patient narrative mentioned an aspect of feeling depressed, but he associated this with seasonal affective disorder (winter depression). One carer also described feeling depressed, which was linked to her own feelings of guilt and with her concerns for tolerating the situation between her and her husband post-morbidity. Desite the lack of evidence of depression in LGI1-aLE, it has been recently illustrated using NBM to promote the unheard experiences in mental health recovery (Ridge, 2021), and in other neurological conditions such as myalgic encephalomyelitis, where initial diagnoses of depression were made (Tucker, 2004).

Regarding Bink's link to depression and fatigue (2021), this was consistent with the findings herein, where the correlation between the BDI and FSS indicated a significant relationship across patients.

6.2.2.7 Emotionality and empathy

Previous research on LE (non-autoimmune) has highlighted alterations to patients' emotionality, evaluating for hypo and hyperemotionality during the early stages of diagnosis (Witt and Helmstaedter, 2021). However, the longer-term outcomes are not so well documented. Besides a prominent observation of emotional lability in previous studies where mood changes included aggression and severe agitation during the acute stages of the disease (Herken and Prüss, 2017), rarely has research on the long-term changes been conducted. In a recent study by

Argyropoulos et al. (2020), aLE patients diagnosed with pathologic tearfulness were compared with HCs. By using questionnaires and MRIs, their evidence suggested that patients scored higher than HCs in tearfulness, yet they found no difference in their empathy quotient. Furthermore, post acute tearfulness was found in 50% of patients with aLE, reflecting abnormal emotion regulation. Research has also demonstrated impairment of emotional responses with LGI1 patients and HCs, using videos and images as stimuli (Holtmann et al., 2018). However, the measurement of empathy using self-report questionnaires, must be analysed with caution, due to participant bias and wanting to appear empathetic to the researcher (Beadle and de la Vega, 2019). Regarding empathy accuracy tasks which have been used on healthy participants (Mackes et al., 2018), they have rarely been included in cognitive assessments for aLE. Moreover, critics argued that empathy cannot be compartmentalised in questionnaires alone (Hooker, 2015).

Turning to the impact on carers, some carers have described their spouse's inability to express their feelings, show sensitivity or be affectionate, which were traits that they possessed pre-morbidity. Distinguishable from emotionality, the findings available here have suggested that some patients have lost their ability to read others' emotions and to understand the carer's perspective. Interestingly, only the female carer narratives in this thesis placed significant importance in decreased emotionality and empathy. Whilst it has been suggested that there are biological differences in the capacity for empathy, as well as cultural or generation expectations (Christov-Moore et al., 2014), further research would be necessary to examine gender differences and empathy in aLE.

Despite empathy often represented in narrative literature as a core condition in a therapeutic doctor/nurse-patient relationship, or carers in the home exploring attitudes to active listening and sensitivity to patient cues, this research has contributed to an understanding of the carer's perspective on empathy and LGI1-aLE. Narratives on reduced post-morbid patient empathy, were often misunderstood

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as self-centredness, selfishness, childish behaviour and the inability to see the carer's perspective. Carers often interpreted changes in empathy as a loss in relationship quality and sometimes experienced anger and hurt. However, carer narratives available on neurological conditions with long-term residual changes in empathy have been commonly reported for patients with dementia and Alzheimers. Using questionnaires to explore carer wellbeing has highlighted the need for carer education in the disease process and empathy loss (Hua et al., 2021). Furthermore, it has been suggested that aging impacts on empathy, which could affect the quality of care given by caregivers, but more research is needed to explore age-related differences (Beadle and de la Vega, 2019).

6.2.2.8 FBDS

Despite seizures as predominantly acute symptoms of LGI1-aLE, research suggests they can persist as a chronic symptom without early treatment to improve outcomes (Irani et al., 2013). Furthermore, greater reduction in FBDS is produced by immunotherapies rather than anti-epileptics (Varley and Irani, 2015). Van Sonderen (2016) suggests long-term outcome is mostly favourable, but FBDS reoccurrence could indicate a relapse, and clinicians should be aware of this, even years after onset. Therefore, it is possible the choice of treatment during the acute stage of the disease may have affected the outcome in patients in this research. Perhaps adopting questionnaires on seizure description and activity could highlight chances of relapse in future research and thus provide support and reassurance to patients.

Regarding patient narratives and long- term seizures, various qualitative studies have provided useful insights into experiences (Rawlings and Reuber, 2016). However, narratives for long-term FBDS remain underrepresented in aLE research to date. As validated in the digital diaries in this thesis, some patients reported persistant FBDS by the type of sensation, the location on the body, their duration and frequency. Therefore, using MM could inform researchers of a detailed

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description of any persistent FBDS, together with an understanding of the patient experience.

6.2.2.9 Poor sleep quality

Despite sleep disorders commonly shown in both NMDA-R encephalitis and LGI1-aLE patients (Blattner et al., 2019), this relates to the acute phase which is usually more problematic. Findings herein suggest a compromised quality of sleep for patients. Using the PSQI, six patients scored within a range indicating poor sleep quality. With evidence suggesting the carer account often offers a more detailed insight into insomnia (Muñoz-Lopetegi et al., 2020), many carers in this cohort stated they slept in separate rooms, so could not offer a perspective on the patient's sleep quality.

In exploring a possible correlation with poor sleep and apathy-motivation, there was no positive correlation across patients, indicating that increased apathy and demotivation was not associated with poorer sleep quality. Furthermore, assigning poor sleep quality entirely to the disease is contestable, as confounding factors such as aging or any indirect effects of the disease (related stress caused by financial insecurity or change), may be attributable. Findings by Chang et al (2021), explored patient narratives in addition to using the PSQI in schizophrenia. Narratives enhanced an understanding of the sleep disruption experiences, useful in informing the family for possible reasons for fatigue in the daytime. In this way, narratives hold additional information that the PSQI cannot capture alone in some cases.

6.2.2.10 other chronic symptoms

The qualitative findings have divulged some less common chronic symptoms. A notable behavioural change regarding the hoarding of food and alcohol under the

bed was uniquely revealed by one carer. Despite, rarely identified hoarding associated with encephalitis, Butler and Zeman (2005) reported a case of hoarding in their case-series, but this was not specific to AE. While hoarding is characterised by not wanting to discard unwanted items, this patient only hoarded these items and only in the one place, which may reflect amnesia rather than a compulsive disorder, or it may reflect the need to keep a degree of control for certain possessions. Timpano et al. (2013) have explored the relationship between hoarding and impulsivity, suggesting that impulsivity contributes to hoarding symptoms. Moreover, rare cases of impulsivity may be explained by impaired executive function which results in poor planning and organisation, resonating in findings which strongly associate hoarding severity with executive dysfunction (Ayers et al., 2013). However, hoarding has not been widely described in encephalitis research, and the narratives available herein are associated with the experiences of family members. Future findings would be useful to obtain the LGI1-aLE patient perspective on hoarding.

A unique chronic symptom reported by a carer described a change in her husband's preference for sugary, sweet foods. She provided a detailed account in her diary entries of his compulsivity which were not discussed in the interview, justifying the use of Phase 3. LESS10 patient's increased appetite, gluttony, and sugar cravings affected the whole family. The wife described her astonishment and sometimes embarrassment. Their children had to store the foods they liked in their bedrooms, especially sweet items, to prevent their father from eating them first. Furthermore, some patients had indicated that they had put on weight post-morbidity, but they had not described any cravings. It is plausible that gluttony is linked to impulsivity, where the immediate benefit of a sugar craving outweighs any health detriment. Findings have linked gluttony with apathy and lack of empathy, to neurodegenerative disease in some cases (Ahmed et al., 2016). Furthermore, gustatory dysfunction and changes in food preferences in patients with AE are suggestive of damage to the amygdala (Geran et al., 2019). In addition, research by Davidson et al. (2019) not only suggests the hippocampus has a potential role in energy regulation, but that

there is a hippocampal-dependent learning and memory mechanism which might contribute directly to increased food intake.

Some narratives did report 'topographical disorientation'. This refers to the neurologically acquired inability to navigate one's environment, including recognising familiar routes, directions in their minds, landmarks and landscapes (Iaria and Slone, 2021). Literary evidence suggests the right hippocampus is involved in accurate navigation, and the left hippocampus uses episodic/autobiographical memory (Burgess et al., 2002). Furthermore, it is believed that hippocampal neurons play a role in spatial navigation and memory (Wood and Dudchencko, 2021). However, as current research reports this symptom during the acute stage only (van Sonderen et al., 2016; Aurangzeb et al., 2017), these findings complement the current findings, as disorientation continues to play a role in the chronic stages of LGI1-aLE.

6.3 Professional support

Some narratives added descriptions of a distinct lack of specialised professional support offered during the acute stage in hospital, and on discharge home. What is more, only some participants at that time described being guided towards the encephalitis charities, who offer recommendations on overall heathy lifestyle, relationships, disease management, and behaviour modification therapy. Whilst patients and carers in this thesis were supported by their consultants, being discharged home without ongoing support, often evoked feelings of disappointment and anger. In contrast, for those obtaining a correct diagnosis during the acute phase produced a sense of relief, gratitude and jubilation, with the realisation of forthcoming appropriate treatment and support.

Despite strong evidence of rehabilitative support for those suffering with cognitive impairment such as traumatic brain injury (Cullen et al., 2015), this is not routinely

offered to patients and families of AE. In fact, AE has been less likely than other acquired brain injuries to have its long-term impact recognised and addressed realistically to empower the patient and families in their management of the disease. Only relatively recently have GPs been offered guidelines to recognise different types of encephalitis and offer support in primary care (Encephalitis Society, 2018), illustrating an important change on the focus of this 'hidden' disease and its implications for ongoing support.

6.4 Consequences

Findings have indicated the long-term consequences of LGI1-aLE, which resonate with research on the experience of living with chronic encephalitis (Atkin, Stapley and Easton, 2010). Narratives have demonstrated the complexities of these consequences, within the four contexts below: -carer burden, relationships, returning to work and future planning. Compellingly, the consequences are not only bound to the extent of the patient's chronic symptoms reflected in neuropsychological test scores, but also to the carer's personality in discussing and dealing with them.

6.4.1 Carer burden

Whilst the patient remains the "wounded storyteller" (Frank, 1995) of the symptoms of LGI1-aLE, the carer burden is under-recognised in existing literature. Impairments in memory and behavioural changes such as apathy indicating a lack of initiation, decreased emotionality and lack of interest in daily activities, all have a profound effect on carers. These results using the carer assessment as part of the NPTB are rare, contrary to existing research on PD (Hagell et al., 2017) or dementia (Smith, George and Ferreira, 2018). Three carers perceived the burden as moderate to severe, yet there was no evidence for moderate burden at carer group level. These three carers also expressed corresponding feelings of frustration and resentment during the interviews and digital diaries. Patients did not self-report their ability to

perform daily activities for this thesis, but instead carers assessed the patient's ability. The carer's assessment using the B-ADL, indicated moderate levels of difficulties at group level. Five carers reported mild to moderate difficulties in patients performing daily activities. This suggests that not all patients became 'functionally independent' and returning to their pre-morbid activities was not possible for all of them, consistent with research by Chen et al. (2021). One patient who had the most difficulties in performing his usual activities, his wife reported the highest burden. However, it is possible that other factors may have contributed towards her burden. The corresponding carer narratives in this thesis essentially focused on the patients' lack of motivation with personal hygiene or household chores, when reflecting burden. This possibly suggests that apathy could have been misinterpreted as difficulty in performing activities. In addition, some carers described the burden associated with taking on the additional role of caring, and their feelings associated with this.

Given the moderate levels of difficulty, a correlation between the ability to perform activities of daily living and carer burden was anticipated, and the analysis indicated a significant relationship across patients. This is important and not to be overlooked; as there is a need for recognition of increased carer burden detrimental to mental health in other neurological diseases (Lwi et al., 2017). From the perspective of the carer, narratives provided additional details regarding the patient's lack of confidence, possibly influencing their ability to undertake certain tasks and make decisions (shopping, cooking). However, carers also described a lack of initiation and the need for prompting and 'nagging'.

Narratives support the quantitative findings, suggesting carer burden is apparent in daily lives, as a consequence of the additional responsibilities and ongoing symptoms. For some carers, burden was associated with constantly having to repeat information due to the patients' memory loss. For others, the decline in patient confidence and decision-making skills contributed towards the burden, causing

heavy reliance on the carer. Hence, carer wellbeing has been affected negatively in many cases. Although the essence of burden was common in qualitive data collection, the word 'burden' was never used. Studies in dementia and head injury have explored the carers' burden using ZBI, revealing a significant burden (Springate and Tremont, 2014; Harding et al., 2015). However, there is no comparable literary evidence for the carers of aLE patients.

Various correlation analyses were undertaken using the ZBI for carer burden, to explore patient scoring with possible associations. With regards to anhedonia and burden, the amount of anhedonia reported by the patient was not interrelated with the increased scores for the carer's levels of burden. Regarding patient depression and fatigue, both domains showed marginal correlation with the carer burden. With regards to an assessment during the NPTB, where patients were asked whether LGI1-aLE impaired on their lives using a Likert scale, one patient stated 'not at all' (LESS3), yet his wife presented the second highest carer burden score, contradicting the patient's perceptions/insight into impairment. It was anticipated that due to the fact that most patients waited a long time for a correct diagnosis, their outcome would have been worse overall, and therefore increasing the carer burden. A possible association with increased carer burden and the number of months from first symptoms to a correct diagnosis was investigated, yet there was no significant association demonstrated in these findings. The sample size was possibly underpowered with respect to such relationships.

Existing research suggests that gender influences coping strategies, which in turn mediate feelings of distress. Where men are traditionally less likely to ask for help, or to confide in others about their feelings, known as the 'emotional-focused coping', they are also more likely to use problem-solving approaches (Zygouri et al., 2021). Carer burden levels were reportedly reduced in this thesis, using adjustment and familiarisation to any traditional gender boundaries they shared with their spouse pre-morbidity. Carer narratives essentially represented strong coping strategies and

resilience, depending on expectations and obligations. Interestingly, some female carers described the additional burden of taking on the husband's traditional bread-winning and financial control roles, perhaps reflecting on an older generation presented in this cohort. In fact, handing over some additional responsibilities to the carer was sometimes more difficult for the husband to modify than for the wife to learn and adapt to as part of her new role. Future research into gender differences and coping with the impact of LGI1-aLE may therefore need consideration. Having indicated the consequences of LGI1- aLE on carer burden, the following section describes how relationships were affected.

6.4.2 Relationships

The investigation of intimate relationships and aLE is unreported. Despite existing knowledge on the impact of memory impairment on interpersonal relationships in other neurological conditions such as dementia and AD (Davies et al., 2010; Nogueira et al., 2015), information on relationship satisfaction and quality of life is lacking for encephalitis patients and families. Sexuality and intimacy have been widely researched where the patient is affected by memory loss, but rarely have carers also been given the opportunity to identify relationship issues (Davies et al., 2010). Although a reduced expression of affection has been commonly reported by female carers in this thesis, existing research only highlights a possible association with depression and schizophrenia (Martinotti et al., 2010). Furthermore, a loss of libido and loss of interest in physical intimacy, which was highlighted by two patient narratives, was not attributed entirely to the disease.

The impact of LGI1-aLE on patients' relationships is apparent, previously only addressed by anecdotes on charity websites. Some patients reported a change in the relationship dynamics, often attributable to their memory loss and their increased reliance on their partner. This subsequently caused loss of confidence, where their decision-making ability had been questioned. In addition, both patients and carers

stated that role-reversal has added to friction within their relationship, due to changes in expectations and responsibilities. Some male patients who were unable to continue taking on the same responsibilities, suffered feelings of inadequacy and incompetence. Role reversal has been explored in dementia and stroke research, where the caregiving role which started suddenly and unexpectedly, transitioned to long-term care (Morrison and Williams, 2020). Thus, taking on long-term adaptation to aLE offers a daunting onus on a relationship. Moreover, the carers' accounts herein have confirmed that some residual imbalances of temper and irritability, demonstrated by rapid and exaggerated changes in mood, have inevitably affected the feelings towards their spouse. One narrative highlighted how a carer learnt to drive at 69 years old, to fulfil her new responsibility. This relayed mixed feelings for the couple, with the anxiety of taking on a novel responsibility for the carer and raising issues of inadequacy and shame for the patient. Furthermore, the loss of confidence in the LGI1-aLE patient can be triggered by not feeling in control or not trusting their own abilities and judgment. This may lead to social anxiety and avoiding situations such as engaging, contributing or following in conversation, where scrutiny is probable and may further result in humiliation or embarrassment. One narrative described a disinterest in going out socially, to the detriment of the couple's relationship, especially when they used to be a sociable couple. On the contrary, one patient became more extroverted and enjoyed public talking and socialising. Reports of acute changes in introvert or extrovert behaviour are rare, with one such case study on NMDA-R encephalitis noting a patient's pre-morbid personality as extroverted (Roy et al., 2020). However, chronic introverted and extroverted behaviour changes are noted in the Encephalitis Society website (Dewar, 2020). Without the qualitative data collection used in this thesis, the opportunity to highlight feelings of decreased confidence and assertiveness, would have been lost.

The two male carers in this thesis were less forthcoming in describing any changes in their relationships than the female carers. Instead, they continued to balance their 'traditional' role, as well as taking on a caring role, employing optimal coping

strategies. Narratives illustrated a satisfaction in their relationships, and as carers, they scored numerically lower on the carer distress scores. This may suggest they employed different coping strategies or carried a gendered notion of being strong and dependable.

Additionally, this research has suggested that children were more likely to be affected and share the impact of the disease if living at home, even when the carer attempted to protect them from the full extent of the distress. To date, there is no research on children's perspectives on the impact of aLE. Existing studies on children who care for a parent with a neurological condition causing cognitive impairment, include caring for a parent with dementia (Deist and Greef, 2017). Furthermore, research by Lövenmark (2020) on children living at home as carers (up to 25 years of age) who have grown up with a parent with dementia, suggests they should express themselves through narratives. This thesis has raised concerns on the impact on children, marked by feelings of uncertainty, anxiety and misunderstanding of symptoms, as their roles and coping abilities change through to adulthood.

Some couples felt able to disclose and share sensitive information such as changes in post-morbid affection and physical intimacy, illustrating the benefit and value of MM, yet other couples claimed their relationships remained unchanged or had strengthened. While some LGI1-aLE patients were inarticulate in their narrative and expression of feelings, this does not imply that the impact on their relationship was less significant to them. Instead, the value in each narrative has improved our understanding on relationship changes.

6.4.3 Returning to work

Although research into LGI1-aLE patients returning to work is undiscovered, other neurological conditions such as stroke, has highlighted the proportion of patients returning to work together with the less visible factors such as mood and concentration changes affecting the ability to work or return to the same job post-morbidity (van der Kemp et al., 2017). It has been suggested that employment is regarded as a major contributor to a better sense of wellbeing and quality of life (Matérne et al., 2018). However, many patients in this cohort described a disrupted sense of wellbeing and an altered quality of life. Moreover, their narratives unveiled factors that made returning to work with the exact responsibilities as before the disease problematic, such as memory loss, loss of self-esteem, decreased confidence, decreased concentration levels, reduced energy levels and poorer organisational skills, all leading to detrimental effects on their wellbeing. These findings resonate with research on NMDA-R encephalitis, where some aspects of neuropsychological impairments remain, which are indicative of reduced confidence, resulting in re-evaluation of employment status, for example (McKeon et al., 2016). No patients worked in the same role as pre-morbidity, which incurred salary decreases and status changes in most cases. These changes have added financial strain on many couples. This research has therefore added to an understanding on returning to work for the LGI1-aLE patient and its consequences on the carer, which is currently limited to charity websites. This could not have been supported in the quantitative findings, due to the unavailability of return to work specific questionnaires.

6.4.4 Future planning

Finally, considering future planning, there has been considerable interest in conditions such as dementia or MS, which are often focused on care planning, and practical and financial planning. However, future planning for LGI1-aLE patients and their families has remained undiscovered. Regarding encephalitis, where there is a 'lack of continuity and order in one's life' (Atkin, Stapley and Easton, 2010, p. 387),

patients often struggle to adapt to the uncertainty of the future, when they already have difficulties coping with the complexities of memory loss.

Although future planning may be problematic due to aging and its associated altered competencies, the impact of LGI1-aLE needs to be interpreted with caution, as seven patients were below retirement age at disease onset with optimistic plans to retire and move forward with their lives together. Therefore, adaptation and resilience to the disease, and a determination to adjust to the patient's capabilities and needs, came through strongly in the narratives. Addressing narratives in the qualititative data has successfully provided an insight into future planning, which questionnaires alone could not have addressed.

6.5 Chapter summary

The MM approach has successfully described acute symptoms at disease onset and demonstrated the existence and severity of ongoing symptoms of LGI1-aLE, together with a unique insight into the experiences of those patients and carers based on shared, cherished and powerful narratives. Consistent with Teddlie and Tashakkori's (2009) description as 'the third methodological movement', the strength of this work was demonstrated through the adoption of a single pragmatic paradigm to answer the research questions. In keeping with the assumption that MM research can direct the research question more thoroughly than using either quantitative or qualitative methods alone (Creswell and Clarke, 2007; Tariq and Woodman, 2013), Phases 1-3 have successfully addressed both the primary and secondary objectives, to identify the chronic negative sequelae of LGI1-aLE during the NPTB, and to investigate experiences amongst patients and carers. Living with chronic residual symptoms may take months or years for the patient and carer to adjust to. Therefore, by understanding the clinical reason behind symptoms, patients and carers can benefit from this knowledge when addressing and coping with the long-term challenges associated with LGI1-aLE.

CHAPTER SEVEN

Conclusion

7.1 Restatement of research objectives

This thesis has sought to address three central research questions:

1. What are the negative sequelae on LGI1-aLE patients?

2. What is the carer's interpretation of these negative sequalae?

3. How do the patients' and carers' narratives inform us of a truthful depiction of the impact of the disease?

These were addressed and achieved by first, identifying the negative sequelae using the NPTB in Phase 1, and second, by investigating the patient and carer experiences of living with the ongoing symptoms of the disease during Phases 2 and 3.

7.2 Summary and contribution to knowledge

Overall, this thesis has not only contributed towards the literary and methodological gap, but it has strengthened our knowledge on the personal experiences related to LGI1-aLE. MM research on AE is rare, with prevalent published studies commonly covering disciplines of neuroscience, neuropsychiatry and neuropsychology alone. Therefore, this thesis' significance lies in demonstrating the benefits of using MM where shortcomings exist in using only one data collection method to predominantly illustrate symptoms, diagnosis and treatment. By addressing the use of the triangulation method, this has presented a unique opportunity to follow up the quantitative measurements of the NPTB with the qualitative data collection, and the subsequent interpretation. The resultant design has added entirety in the exploration of a complex disease.

Essentially, this thesis has offered a comprehensive and holistic understanding which supports the current literature on chronic symptoms of memory loss, apathy and fatigue (Graus et al., 2016; Lancaster, 2016; van Sonderen et al.; 2016, Ariño et al., 2016; Finke, 2017; Yeshokumar et al., 2017). Deficits in fluency are in line with published research (van Sonderen et al., 2016; Binks et al., 2021), although poor sleep quality commonly supported in acute aLE (Blattner et al., 2019), remained long-term in this research.

The NPTB's usefulness as a tool to assess the patient's cognitive functioning and performance was supplemented with the carer's reporting. This thesis has distinctively demonstrated that some of the deficits identified in Phase 1 are persistent in the qualitative data collected in Phases 2 and 3, with possible improvements for patients in certain domains over time. The qualitative dataset has illustrated the personal impact of LGI1-aLE for the patient, presented through five themes to successfully capture and interpret their shared and unique experiences. Although carer burden has been explored in areas such as dementia and head injury (Springate and Tremont, 2014; Harding et al., 2015), the carer perspective in this thesis has offered two important opportunities. First, it provided enhanced narratives, given that patients' anterograde memory impairment, fatigue and emotion dysregulation potentially limited the quality and quantity of their narrative data. Second, it has highlighted their levels of distress and burden, previously unreported.

The use of IPA was key in analysing rich narratives using the phenomenological approach to capture the complexity of LGI1-aLE. The life-changing participant journey and the overall 'silent suffering' has previously remained hidden in the published literature. These findings have addressed the 'unpreserved' acute period of LGI1-aLE where patients relied heavily on their carers' version of events, and carers themselves experienced feelings of shock and fear of the unknown diagnosis and toll on their abruptly changed situation.

The resultant persistence of cognitive impairment has yielded an adjustment for the patient to their capabilities and competencies, which are reflected in their levels of confidence and ability to make articulate decisions, socially and at work. This level of insight has validated the use of additional qualitative data, highlighted previously by Easton (2016) where the narratives add a personal perspective to the reality of living with the patient's symptoms. The resultant carer narratives have demonstrated examples of the patient's decreased motivation, confidence, emotionality and sensitivity. However, adaptation may still carry burden, in line with Lwi et al.'s (2017) research, stating a need for recognition of the increased carer burden which is detrimental to their mental health. Carer accounts of the patients' increased fatigue, irritability, impatience and apathy, have confirmed changes in the dynamics of their relationships, and have also illustrated the adverse emotional, social and financial effects. Husbands as carers, reported less burden than wives as carers, which was supported in the qualitative results. One explanation may suggest a gender difference in coping, resilience, reliance, personal expectations, or perhaps the difference lies in the decision to relay this burden during the interview. For all participants, a network of family and friends was vital in providing additional support, yet this was sometimes altered or severed completely due to the consequences of the disease. Overall, the qualitative data is of validated importance in this thesis, supplementing our knowledge of the detailed impact of LGI1-aLE for both the patient and carer.

The experience of having LGI1-aLE is not simply being part of a diagnosis, but it carries the participant's meaning of the disease, together with negotiating successful coping and self-management strategies, as suggested in Atkin, Stapley and Easton (2010). Access to the qualitative data not only makes a significant contribution but can be reviewed by clinicians and researchers as meaningful and transferable to other neurological conditions in the future by addressing relevant questions and previous assumptions. This does not imply that results will be consistent in other conditions, but that the knowledge obtained from patient and carer experiences, can be used alongside the quantitative datasets. Furthermore, the impact of chronic

symptoms can influence rehabilitation and education planning, to maximise the most favourable outcomes as addressed in other conditions with cognitive impairment (Cullen et al., 2018). Moreover, acquiring qualitative research training may enhance the professional-patient relationship, and improve the knowledge-base beyond traditional measurable datasets which are commonly used in neurology and neuropsychology.

7.3 Limitations

There are five distinct limitations to this research. First, although MM has been used in other areas of medicine it is still a relatively new approach to LGI1-aLE which predominantly uses quantitative oriented methods. The associated lack of academic understanding and methodological support compared with other neurological research such as on MS and dementia, could be viewed as a limitation. Furthermore, the MM triangulation method is very time-consuming which may not be a plausible choice for future researchers, in line with findings by Cresswell (2007).

Second, the purposive sampling technique presents limitations to this work through sample size and cross-sectional assessment. Undoubtedly, the experiences of participants within this cohort were likely to be different to those who did not take part, or who were not invited. However, due to the rarity of the disease, the purposeful sampling was justifiable, because the small population reflected an appropriate sample size to undertake IPA despite 'masking' potential group differences partly attributed to the low sample. From a quantitative perspective, sampling was underpowered with respect to detecting statistically significant differences and correlations, which could result in false positives /negatives. Unlike other research determining a pre-morbid performance or using neuropsychological assessments on large sample sizes and HCs, this thesis did not have the capacity for comparisons or repeated time ponts. Regardless of the NPTB demonstrating a variety of assessments cross-sectionally for the patient and carer, its repeated

administration in future research could demonstrate any deterioration in chronic symptoms over time and add to its reliability.

A third limitation exists in data saturation. Any future interviews or diary entries could unveil new experiences and new feelings that are not part of these findings. This could imply that data saturation can never be entirely reached, as any additional qualitative datasets could yield either similar or new experiences, feelings and themes. Furthermore, most patients waited many months from the first symptoms to the correct diagnosis. This range of time could have influenced the participants' performance results.

A fourth limitation is that the NPTB was used as a descriptive tool only. This means that results during Phase 1, did not lead to making assumptions that symptoms were entirely a result of the disease, but that they certainly represented consistencies with the literature on aLE.

A fifth limitation reflects the lower than anticipated digital diary data collection. Despite using digital diaries to facilitate a reduction in 'response bias' and an increase the reliability of the data, the quantity of data from patients was insufficient for its own analysis.

Finally, some critics suggest a limitation in using IPA and double hermeneutics, as it relies on the participants' unique perspective to communicate a narrative and to articulate possible complex thoughts and feelings (Chamberlain, 2011). This is a pragmatic limitation which some LGI1-aLE patients struggled with. If the patient is disadvantaged due to their memory loss, decreased motivational state and shorter attention span, this may compromise their performance and narrative, contesting the

researcher's 'sense-making'. Although the researcher's interpretation of the participant's experience does not necessarily lead to a complete understanding of the experience, any unique and common experiences still hold their own significance in the reader's comprehension of the disease.

Together, these limitations require consideration when undertaking future research in aLE or other neurological conditions using MM.

7.4 Implications to Practice

The findings of this thesis have shown the following implications for LGI1-aLE patients and their carers. First, the personal experiences and descriptions through narratives have confirmed the misunderstandings and misinterpretations of the acute symptoms leading to incorrect or delayed diagnoses. The less recognised symptoms such as FBDS and behavioural changes were often missed by health professionals. On the contrary, patients and those closest to them were the first to observe the subtle symptoms such as forgetfulness, body 'jerks, brief 'absences' where the patient glares into space, or unfamiliar mannerisms such as making inappropriate jokes or speaking out rudely. These symptoms were sometimes deemed insignificant and hence reporting them was delayed. Therefore, education and guidance on the awareness of significant symptoms is of the utmost importance to a range of health professionals, to aid a prompt, correct diagnosis. In line with previous evidence, this enables health professionals to ensure that appropriate health care decisions are made, and the best support is offered to the patient and the family (Sackett et al., 2000).

Second, the expectations for patients and carers are particularly relevant regarding chronic symptoms and behavioural changes. For the patient to facilitate their cognitive and emotional recovery, the possibility of rehabilitation and professional

support is a critical consideration. Cognitive rehabilitation therapy to encourage motivation and pleasure giving activities traditionally used in mood disorders (Dunn, 2012), could be applied to LGI1-aLE patients. Studies addressing strategies to improve memory by organising, planning and coping in the encephalitis patient (Harder and Mariano, 2018), as well as cognitive behavioural therapy to manage anxiety and low confidence in NMDA-R patients (Bach, 2014) are positive rehabilitative interventions. Furthermore, these could be tailored to the individual patient with a unique cognitive profile, personality and ways of coping. This has been supported in other conditions such as TBI, where findings suggest the longer-term benefits of a cognitive therapy programme enhance psychological wellbeing and improve problem focused coping (Arundine et al., 2012). In addition, cognitive therapy could offer some regulation and improvements to the consequences of emotional lability, such as exaggerated changes in mood and heightened irritability, or therapy to offer fatigue management.

A third implication is the quality of life for the carer. Evidence suggests that some carer participants found it helpful when a professional addressed common problems, challenges and solutions in a group therapy scenario (Geirdal et al., 2015). Focus groups could therefore be useful to establish transparency of knowledge about the disease, together with identifying some of the problems associated with chronic symptoms and building on coping strategies, in line with AD researcher on caregivers (Sanders et al., 2008). As noted in research to develop the ZBI (Zarit, Reever and Bach-Peterson, 1980), the strong association between visits from family and the carer's burden, is an important implication to practice. The focus on interventions to involve family members as the patient's natural support system, is vital to promote coping with problem behaviours, to share in the supportive care of the patient and carer, and lessen the responsibilities of the carer, where possible.

Finally, this thesis has successfully introduced a novel way of researching LGI1-aLE, using MM. As current evidence on the impact on the aLE patient is more common on

charity websites, a possible intervention for newly diagnosed patients would be to consult the web pages and to be better informed of the expectations and reality ahead. The novel addition of carer narratives has unveiled unique findings that have not been previously addressed, including detrimental changes which have affected the patient and carer relationship. By understanding the impact LGI1-aLE has on their lives, health professionals can promote an awareness, and achieve realistic goals together with the family. Therefore, this thesis has contributed considerably to the current knowledge, by adding personal and meaningful narratives to support the critical importance of correct diagnosis and treatment in the current evidence base.

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APPENDICES

Appendix 1: PICO
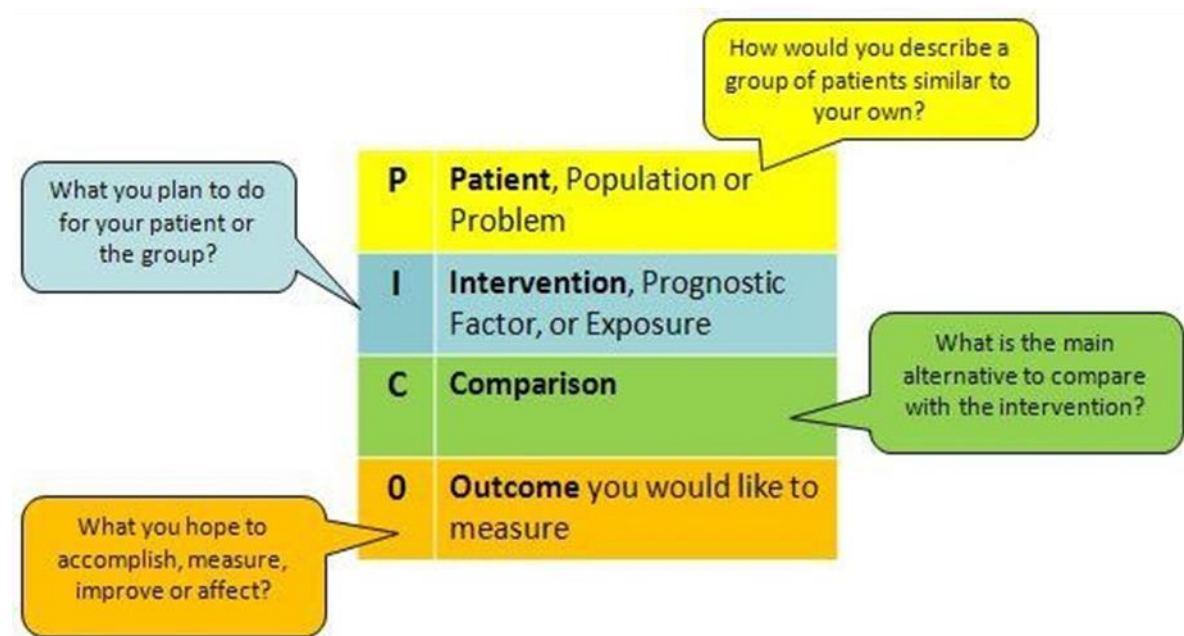
Appendix 2: SPIDER

SPIDER: Spinning a Web for Retrieval
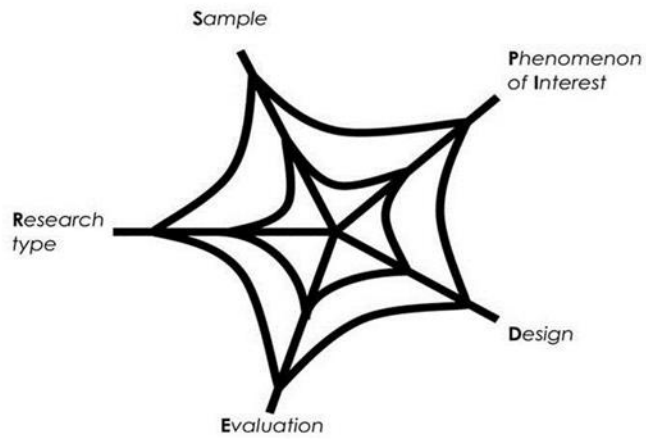
Cooke A et al. Qual Health Res 2012;22:1435-1443
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Appendix 3: Full database search tables

APPENDIX 2 FULL DATABASE SEARCH								
DATABASE & TIMESPAN	LANGUAGE	SEARCH DATE	SEARCH TERMS	BOOLEAN TERMS	NUMBER OF HITS	NUMBER DISCARDED	NUMBER REVIEWED TITLE AND ABSTRACT	NUMBER REVIEWED FULL TEXT
PUBMED CENTRAL PMC 2009-2019	ALL	2.3.19	AUTOIMMUNE ENCEPHALITIS	COMMA BETWEEN BOTH	259	219*	116	38
			NEUROPSYCHOLOGICAL					

*Reasons for discarding: not LGI1, paediatric cases, other syndromes, other antibodies, unavailable, poster abstracts only *Of these, 4 re-introduced for the neuropsychological aspect, but not LGI1*

CINAHL 2009-2019	ALL	2.3.19	AUTOIMMUNE ENCEPHALITIS	ANY	20	15	12	5
			EXPERIENCE					

Reasons for discarding: duplicated, not LGI1, paediatric cases, other syndromes, other antibodies, unavailable, poster abstracts only

OVID EMBASE 2009-2019	ALL	2.3.19	AUTOIMMUNE LIMBIC ENCEPHALITIS.mp.	AND	189	172	94	17
			NEUROPSYCHOLOGICAL.mp.					

Reasons for discarding: duplicated, Algerian Conference paper, Turkish conference publication not available in English, USA conference paper unavailable, not LGI1, paediatric cases, other syndromes, other antibodies, unavailable, poster abstracts only

PSYCHINFO 2009-2019	ALL	2.3.19	AUTOIMMUNE ENCEPHALITIS.mp.		43	33	10	10

Reasons for discarding: duplicated, Portuguese conference paper - unavailable in English, not LGI1, paediatric cases, other syndromes, other antibodies, unavailable

OVID MEDLINE 2009-2019	ALL	2.3.19	AUTOIMMUNE LIMBIC ENCEPHALITIS.mp.		121	112	25	9

Reasons for discarding: duplicated, Case studies in Dutch only, Korean only, Japanese only, feline model, mice model, rabbit model, South Korean only available to purchase, not LGI1, paediatric cases, other syndromes, other antibodies, unavailable

PUBMED 2009-2019	ALL	2.3.19	AUTOIMMUNE LIMBIC ENCEPHALITIS	AND	9	9	9	0
			NEUROPSYCHOLOGICAL.					

Reasons for discarding: duplicated, other antibodies

SCOPUS 2009-2019	ALL	2.3.19	AUTOIMMUNE LIMBIC ENCEPHALITIS		88	81	7	4

Reasons for discarding: duplicated, surgical case, dementia, feline model, literature reviews from China on papers already included, not LGI1, paediatric cases, other syndromes, other antibodies, unavailable, book chapters only

COCHRANE LIBRARY 2009-2019	ALL	2.3.19	AUTOIMMUNE LIMBIC ENCEPHALITIS		2	2	2	0

Reasons for discarding: RCTs – N/A

OXFORD UNI. SOLO LIBRARY SEARCH 2009-2019	ALL	3.3.19	AUTOIMMUNE LIMBIC ENCEPHALITIS	ANY	35	24	1	1
			NEUROPSYCHOLOGICAL	ANY				
			INTERVIEWS	ANY				

Reasons for discarding: duplicated, other antibodies, paedriatric, posters unavailable, other syndromes

OXFORD UNI. SOLO LIBRARY SEARCH	ALL	3.3.19	AUTOIMMUNE LIMBIC ENCEPHALITIS	CONTAINS	11	10	1	1

2009- 2019								
			CARER	ANY				
			INTERVIEWS	EXACT PHRASE				

Reasons for discarding: duplicated, other antibodies, paedriatric, other syndromes

PSYCHINFO, **PUBMED,** **CINAHL,** **MEDLINE,** **EMBASE** 2009-2019	ALL	3.3.19	NEUROLOGY	CONTAINS	5	5	5	1
			INTERPRETATIVE	AND	0	N/A	N/A	

			PHENOMENOLOGICAL ANALYSIS					

Reasons for discarding: Swedish article on dementia, not available, Parkinsons, duplicate

Appendix 4: Database search flow diagram (until April 2019)
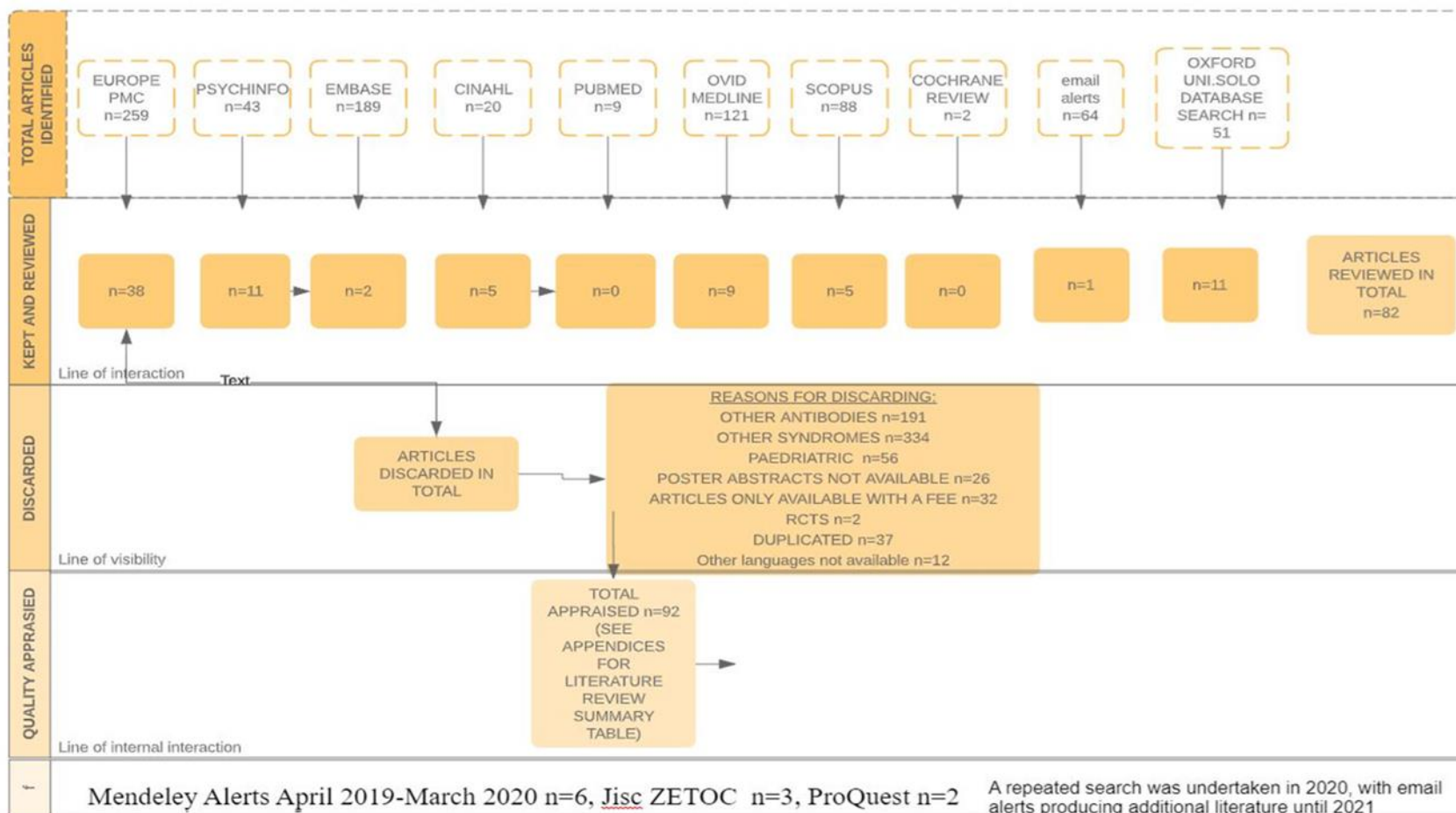
Appendix 5: Literature review summary table

(in electronic version of Thesis, please click on Table to open it)**.**

Source	Authors	Year	Title	Country	Study Aims and Objectives	Research Design	Sample	Data Collection Methods	Key Findings and Relevance	NOTES
PMC 1	Wandinger KP, Leypoldt F, Junker R.	2018	Autoantibody-Mediated Encephalitis	Germany	Review of literature on autoantibody mediated diagnoses	Literature review	72 articles reviewed	Medline	Therefore, all patients with high clinical suspicion of autoimmune encephalitis	Key messages for neurologists and treatment
2	Thomas Christian, Lehrich Christoph, Gross Catharina C., Wiendl Heinz, Meuth Sven G., Melzer Nico	2018	Primary B Cell Lymphoma of the CNS Mimicking Anti-LGI1 Limbic Encephalitis	Germany	we show that incipient primary central nervous system lymphoma can closely resem	Patient case	1	Case study of male patient	we show that incipient primary central nervous system lymphoma can closely	Not relevant for my research
3	Macher S, Zimprich F De Simoni D, Höftberger R, Rommer P.	2018	Management of Autoimmune Encephalitis: An Observational	Austria	compare demographics, diagnostics, treatment options and outcomes with knowled	Observational Monocentric Study	38 patients	Diagnostic and treatment algorithms will be compared	Diagnostic and treatment algorithms will be compared : their data from one si	Recommendations for neurologists and lab scientists
4	Liu Yanjun, Tang Xiangqi	2018	Depressive Syndromes in Autoimmune Disorders of the Nerv	China	systematically reviewed the current literature to highlight the prevalence, etiology and	Systematic review	Not stated	Not stated	shed light on depressive syndromes associated with autoimmune disorders	Challenges for neurologists in this treatment, not LGI1 specific
5	Ibrahim I, Abdulelah N, Al jasser MD and Kalthoum G	2017	A rare case of autoimmune limbic encephalitis: an uncharted	Saudi Arabia	describe a case of autoimmune limbic encephalitis associated with positive voltage g	case report	1	Case report of one female patient	Symtoms, and treatment	Useful
6	Körtvelyessy P, Prüss H, Thurner L, Maetzler W, Vittore-Wellonig D, Schultze-Amberger J, Heinze H, Reinhold D, Leypoldt F, Schreiber S, Bittner D	2017	Biomarkers of Neurodegeneration in Autoimmune-Mediated E	Germany	to investigate whether these parameters represent also biomarkers in autoimmune-m	Retrospective examination of CSF, with follow up data including	38 patients with AE, 10 with LGI1	Biomarkers measured in CSF	show for the first time that biomarkers of neurodegeneration originating from	The pathologically elevated biomarkers correlated with the mRS, the clinical course and the antibody titre-useful
7	Ho C, Ho R, and Quek A	2015	Chronic Manganese Toxicity Associated with Voltage-Gated	International Journal	describe the case of a man who presented with recurrent episodes of confusion, psy	Case study	1 man	EEG, bloods tests, ultrasound of hepatobiliary system	This is the first report to examine an association between Mn and VGKC ant	Interesting, but not my research
8	Taneja S, Suri V, Ahuja A, Jena A.	2018	Neuropsychological and FDG-PET profiles in VGKC autoimm	Italy	aimed to go beyond the limitations of previous cognitive studies in LE by (1) explorin	Case study	3 cases	Blood and cerebrospinal fluid (CSF) analyses, whole-body CT	Not clear, but further reading indicates a case study	interesting
9	Miller T , Chong T, Davies A , Ng T, Johnson M , Irani S, Vincent A, Husain M, Jacob S, Maddison	2017	Focal CA3 hippocampal subfield atrophy following LGI1 VGK	UK	LGI1 VGKC-complex antibody-mediated limbic encephalitis were investigated using a	Case control study	18 patients, 17 with LGI1	Clinical records were retrospectively interrogated for time-to-treatment from first symptom, first-line treatments, then MRI sequencing	T cell-mediated inflammatory responses that enable specific antibodies to enter the CNS and initiate irreversible tissue damage in CA3.
10	Finke C, Prüss H, Heine J, et al.	2017	Evaluation of Cognitive Deficits and Structural Hippocampal	Germany, but JAMA Neurology	What are the neuroimaging characteristics and the cognitive long-term outcome in p	Cross sectional study	30patients	Observe atrophy of hippocampus and correlate with verbal and visuospatial deficits: MRI and cognitive outcome	Anti-LGI1 encephalitis is associated with cognitive deficits and disability as a	For neurologists distinguishing conditions and treatments
11	Patira R, Khatri V, Gutierrez C, Zubkov S	2016	LGI1-negative faciobrachial dystonic seizures originating	USA	report the distinct characteristics of insular faciobrachial dystonic-like seizures that w	Case report	1 female patient	Observation, EEG, blood test, MRI	useful-they also reported on a Dutch study incidence of RP 0.83/million for anti LGI1 encephalitis
12	Simabukuro M, Nóbrega P, Pitombeira M, Cavalcante W, Grativvol R, Pinto L, Castro L, and Nitrini	2016	The importance of recognizing faciobrachial dystonic seizure	Brazil	to improve clinical recognition	Case study, but not stated	2 patients, 1 male, 1 female	CSF, blood test, MRI, mini mental state examination,	Unawareness of FDBS may induce to misdiagnosing a treatable cause of RP	Both patients in acute/subacute disease phase showed increased glucose metabolism . metabolic profile may improve the diagnostic accuracy yet in the early dise
13	Griess R, Davis J and Querforth H	2016	Cognitive Impairments Preceding and Outlasting Autoimmun	USA	Once recognized, ALE typically responds to treatment with immune therapies, but lon	Case study	1 female, 1 male	FDG PET, EEG, MMSE, CSF, VEEG video 48 hours	These cases underscore the difficulty associated with diagnosing LGI1 LE a	Very useful
14	Schröder O, Schriewer E, Golombeck K, Kürten J, Lohmann H, Schwindt W, Wiendl H, Bruchmann M, Melzer N, Straube T	2015	Impaired Autonomic Responses to Emotional Stimuli in Aut	Germany	This study investigates behavioral and autonomic responses to discrete emotion evo	Case control study	1 male, 19 healthy control (5 femael, 14 male)	FDG PET, MRI, controls watched film clips to elicit emotional	patient absence of emotional change compared to healthy controls due to pronounced amydala- impaired in judging basic emotions of happiness and disgust	Very useful
15	van Sonderen A, Thijs R, Coenders E, Jiskoot I, Sanchez E, de Bruijn M, van Coevorden-Hameete	2016	Anti-LGI1 encephalitis: Clinical syndrome and long-term follo	Netherlands	gives a detailed description of the clinical features and long-term outcome of anti-leuc	collected patients prospectively from October 2013, and retrospectively from samples sent to our lab	Medical notes, interviews, relatives, MRIs	Better recognition will lead to earlier diagnosis, essential for prompt start of t	Very useful
16	Adeline S, Kramr J, Geschwind M	2015	Clinico-pathological correlation in adenylate kinase 5 autoim	USA	present the complete clinical picture for one of these patients and the first reported ne	Case study, 1 male	1 male	MRI, CT body,	This was reflected in our patient with AK5-autoimmunity who had histopathol	Recommendations to neurologists of this syndrome
17	D'Angelo R, Rinaldi R, Parchi P,	2014	Wait and see: a 5 year history of 'recurrent dementia'	Italy	describe a case of a man in whom the clinical and laboratory presentation suggested	Case study	1 male	MR Y, blood flow single-photon emmision CT, EEG, CSF	VGKC antibodies may be found in sera of patients with Creutzfeldt-Jakob disease. The utility of therapy in autoimmune encephalitis should be validated.	Interesting other conditions misdiagnosed
18	Rocamora R, Becerra J, Fossas P, Gomez M, Vivanco-Hidalgo R, Mauri J, Molins A.	2014	Pilomotor seizures: an autonomic semiology of limbic enceph	Spain	describes a so far not well-recognized autoimmune association of pilomotor seizures	Retrospective study	766 patients	clinical records of patients who underwent video EEG monitoring between 2007-13	Our series describes a so far not well-recognized possible autoimmune assoc	Not relevant to my research unless patient complains of
19	Lascano M, Korff C, Picard F	2016	Seizures and Epilepsies due to Channelopathies and Neurot	Switzerland	to focus on 2 proteins involved LGI1 and NMDS	Review	not clear	These mechanisms include gene defects as well as immune-mediated	interesting, use Tabel for LGI1 For thesis	Not useful for my thesis
20	Wagner J, Witt J, Helmstaedter C, et al	2015	Automated volumetry of the mesiotemporal structures in anti	Germany	to evaluate and quantify these volume changes by applying a fully automated volume	Retrospective observational study, with healthy controls	28 patients	MRI, antibody, exploratory analyses	regarding seizure, mnestic and psychiatric disturbances in VGKC-LE, which	Not useful for my thesis
21	Naasan G, Irani S, Bettcher B, Geschwind M, Gelfand J	2014	Episodic bradycardia as neurocardiac prodrome to voltage-g	USA	We describe a novel neurocardiac prodrome of voltage-gated potassium channel (VGKC)-Ab/LGI1-encephalitis.	Case studies	14 patients	antibody testing and cardiac tests	Episodic bradycardia is a distinctive prodrome of VGKCc/LGI1-Ab encephalitis	Not for my thesis, but interesting as recognition of episodic bradycardia may prompt early consideratio of LGI1
22	Radja G, Cavanna A	2013	Treatment of VGKC Complex Antibody-Associated Limbic En	UK	to identify all published studies on VGKC complex associated limbic encephalitis	systematic literature review	19 identified and reviewed	database search	no randomized, controlled trials currently exist to show which of these treatm	Really useful for my lit review and tables for thesis
23	Henson R, Greve A, Cooper E et al	2016	The effects of hippocampal lesions on MRI measures of struc	UK	study examined a human sample of six amnesic individuals with focal, adult-acquired	case study description	6 patients	MRI, neurpsychological testing,	This study revealed clear effects of acquired hippocampal lesions on structur	Really useful neuropsychological stats and how to present them
24	Piepgras J, Holtje M, Ruprecht K	2015	Intrathecal immunoglobulin A and G antibodies to synapsin i	Germany	To report on the identification of intrathecally synthesized immunoglobulin (IgA) an	case study	1 patient	clinical characterization, indirect immunofluorescence, immunoprecipitation, mass spectrometry, immunoblots of wild-type and synapsin I/II/III knockout mice, and cell-based assays	Limbic encephalitis is characterized by memory dysfunction, seizures, behav	Scientific paper, ,lab based findings
25	Gastaldi M, Thouin A, Vincent A	2016	Antibody-Mediated Autoimmune Encephalopathies and Immu	UK	review focuses mainly on N-methyl D-aspartate receptor- and voltage-gated potassiu	Review based on retrospective studies	?	Treatments include first-line steroids, intravenous immunoglo	Despite the interest in identifying the autoimmune forms of encephalitis desc	Useful for general information on LGI1 and incidence etc
26	Krastinova E, Vigneron M, Le Bras P, Gasnault J and Goujard C	2011	Treatment of limbic encephalitis with anti-glioma-inactivated	France	report a 72-year-old patient who developed acute limbic encephalitis initially consider	case report	1 patient	Detailed information on clinical presentation, MRI appearance,	Although no consensus treatment standard exists, immunotherapy, including	Useful as captures everything simply
27	Aupy J, Collongues N, Blanc F, Tranchant C, Hirsch E De Seze J	2013	[Autoimmune encephalitis, clinical, radiological and immunol	France	aim of our study was to describe a clinical, radiological and immunological characteristic of	retrospective study	16 patients, 8 men, 8 women	clinical evaluations were recorded	The frequency of extra-temporal lobe impairment suggests that the term of lim	Interesting
28	Leypoldt F, Armangue T, Dalmau J	2015	Autoimmune encephalopathies	Spain/Germany	We review here the process of discovery, the symptoms, and the target antigens of	review	12 disorders reviewed	clinical treatment, MRI, antibody testing	The discovery of autoimmune encephalitis has changed paradigms in the dia	Interesting
29	Butter B, Gelfand J, Irani S, Neuhaus J, Forner S, Hess C, Geschwind M	2014	More than memory impairment in voltage-gated potassium ch	USA	More than memory impairment in voltage-gated potassium channel complex antibody	case studies	12	More than memory impairment in voltage-gated potassium ch	by identifying not only memory and executive function deficits but also langu	Interesting
30	Pertzov M, Miller T,Gorgoraptis N, Caine D, Schott J, Butler C, Husain M	2013	Binding deficits in memory following medial temporal lobe da	UK	Binding deficits in memory following medial temporal lobe damage	case reports	7	MRI scans from the acute stage of six patients	Our novel behavioural measures also have the potential to assist in monitorin	Interesting-We found that memory performance of VGKC-Ab limbic encephalitis patients is comparable with control subjects when one item has to be retained over
31	Derry C, Wilkie M, Davenport R	2011	Autoimmune limbic encephalitis	UK	to correctly diagnose	case history	1	CT, MRI, antibody testing	Treatment summary	veru useful as clear, understandable langauge
32	Nahum L, Ptak P, Leemann B, Lalive P	2010	Behaviorally spontaneous confabulation in limbic enc	Switzerland	describe one lady from HSV LE. They suggest different processew may generate false memories and verbal expression	case study	1	MRI, antibody testing, CSF, brain biopsy, neurorehab 2 months, then worsened, neuropsychological tests,	patient presented all features of behaviorally spontaneous confabulation: she spoke 'untruthfully'	really interesting and useful as relatives often say they
33	Kayser M and Dalmau J	2011	The Emerging Link Between Autoimmune Disorders and Neu	USA	we review autoimmune encephalitides caused by antineuronal antibodies that attack	review of encephalitides	review of current knowledge	description of all conditions	Although a link between behavior and immune function has been hypothesize	useful, as summarises everything
34	Samarasekera S, Vincent A, Welch J, Jackson M, Nichols P, Griffiths T	2006	Course and outcome of acute limbic encephalitis with negati	UK	to describe 4 cases with typical presentation, during a follow up of 18 months	case reports	4	antibody testing, CSF, clinical features, cognitive and memory test	All patients had negative testing for VGKC-Ab measured during their acute presentation. All patients made some recovery, although they were left with marked cognitive deficits and persistent seizures.	useful Table 1, I must use This combination of cognitive and affective or behavioural features represents a major obstacle to the ret
35	Antozzi C et al	2006	Immunotherapy responsive startle with antibodies to volt	Italy	to describe a patient with startle syndrome with VGKC-ab but not LE		1	MRI, CSF, EEG, EMG,	association of startle and throid antibodies	not relevant as not LE
36	Vincent A, Buckley C et al	2004	Potassium channel antibody-associated encephalopathy: a	UK	Here we review the clinical, immunological and neuropsychological features	restrospective study	10 pts, 9 male, 1 female		Our patients presented with a neuropsychological profile characterized by me	useful as earlier research : First, there was a striking temporal relationship between clinical improvement and reduction in antibody titre in several patients
37	Parthasarathi U et al	2006	Psychiatric presentation of voltage-gated potassium channel	UK	we describe a 58-year-old man who presented with panic attacks and psychogenic n	case report	1 male	antibody tests, EEG, cognitive scores, CSF	This case illustrates how easy it is to mistake frontal lobe seizures for psychoti	very precise memory review -maybe to heavy for my
38	Dickerson B and Eichenbaum H	2010	The Episodic Memory System: Neurocircuitry and Disorders		A brief historical survey will outline several of the early observations regarding amne	review			Additional work on the detailed anatomy and connectivity of MTL regions, bot	
CINAHL 1	Badruddin A, Menon R, Reder, A	2009	4-AMINOPYRIDINE TOXICITY MIMICS AUTOIMMUNE-MEDIAT	USA	We document that severe 4-AP overdose causes significant abulia, cognitive impairm	case report	1 male	MRI, CSF, EMG, muscle biopsy, EEG	Clinical improvement as 4-AP was metabolized was fairly rapid and nearly full removal of the drug, does not mention 'experience'	Interesting, does not mention 'experience'
2	Kuroda T et al	2015	Autobiographical age awareness disturbance syndrome in a	Japan		case presentation	2 female	MRI, antibody testing, memory score,	This syndrome is characterized by three elements: 1) failure to subjectively r	Fascinating, but my patinets remember their ages, but use Table 1 useful text on memory
3	Morrow J	2016	Autoimmune limbic encephalitis due to VGKC-Ab. Thanks for	UK	Self-case report, informative description og the illness	case self reported	1 male	MRI, EEG, antibody testing,	Limbic encephalitis is not always linked to an underlying tumour. Autoimmune limbic encephalitis is treatable and can have a good prognosis. Listen to your partner.	Use Figure 1
4	DUPLICATE DERRY ET AL									
5	Dodich	2016	Neuropsychological and FDG-PET profiles in VGKC autoimm	Italy	Cognitive abilities are evaluated with an in-depth neuropsychological battery focus	case report	2 males, 1 female	CSF, FDG-PET, neuropsychological battery, antibody tests	Episodic memory and fear recognition deficits characterize the cognitive profile of LE. Commonalities and differences may occur in the brain metabolic patterns. Single-subject voxel-based analysis of FDG-PET imaging could be useful in the early detection of the metabolic correlates of cognitive and non-cognitive deficits	use Table 1- used empathy test, which we do not- In this study, we aimed at going beyond previous cognitive studies in LE reporting for the first time (1) an in-depth neuropsychological evaluation, not only assessing basic cognitive functions, but also exploring different facets of social cognition abilities (i.e., emotion recognition and processing, cognitive and affective theory of mind) and (2) the FDG-PET patterns i
EMBASE 1	Lee W-J et al	2016	Rituximab treatment for autoimmune limbic encephalitis in an	Korea	To determine efficacy and safety of rituximab treatment as a second-line immunother	case control study	80 patinets	CT, MRI, antibody testing, CSF, modified Rankin Scale	The effect of rituximab was the same regardless of autoantibody status. Additi	The most remarkable finding of the current study was that the effects of rituximab in the antibody-negative group and the paraneoplastic autoantibody group were
2	Nascimento A, Maruta C, Albuquerque L, Martins I	2017	Dissociation findings between short-term and long-term memory in autoimmune limbic encephalitis		We reviewed the cognitive profile of six cases of limbic encephalitis observed in our c	Letter to Editor	6 cases	review cases	We propose that the 'sentence''subacute onset (rapid progression of less than 3months) of working memory deficits (short-term memory loss)''should be completed with''or of episodic memory impairment (long-termmemory)'	interesting
3	Gerace C, Corsi F, Blundo C	2013	Rotigotine for Apathy in Limbic Autoimmune Encephalitis	Italy	Reviewed one patient	Letter to Editor	1 male	CT, PET, autoantibodies, anti-thyroid, CSF	his behavior markedly improved, with an Apathy Scale score of 15. He contin	Interesting about apathy and how this medication works
	duplicates 4 within same search									
	4 articles reviewed as included neuropsychological testing									
	Hansen N, Widman G, Stuff S et al	2018	Cancer frequency detected by positron emission tomograp	Germany	Cancer frequency in limbic encephalitis detected via FDG-PET/CT is low.	observational, reptrospective stydt	93patients, 39 women, 54 men	patients underwent magnetic resonance imaging (MRI) of the	These patients underwent neuropsychological testing to detect any memory	rated memory function as defined by lying above or below the standard deviation
	Paucer M, Bergendal A, Gustavsson P, Nordenskjold M et al	2018	Novel Features and Abnormal Pattern of Cerebral Glucose M	Sweden	we describe a Swedish SCA19/22 family spanning five generations and harboring the	case study	4 patients same family	clinical investigation, psychometric testing, neuroimaging studies, electroneurography (ENeG) and genetic analyses.		Used different scores, not relevant, bute study is genetic based
	Norrman C, Frase L, Berger M, Nissen C	2013	Steroid-responsive depression	Germany	we describe the case of a 48-year-old man who initially, and for a long period of time,	case study	1 man		Antidepressive treatment, including medication and psychoth	Hashimoto's encephalopathy (HE) is a rare but possibly underdiagnosed dis	Neuropsychological symptoms mentioned, but not details on the test battery
	Flanagan E, Drubach D, Boeve B	2016	Autoimmune dementia and encephalopathy.	USA	Repeat cognitive testing after immunotherapy helps document objective improvements. Aim to shown, as summed up full access	unknown			presence of a personal/family history of autoimmunity, inflamm	Bedside cognitive assessment and/or detailed neuropsychological testing are i	Access not obtained
PsychInfo 1	Petit-Pedrol et al	2018	LGI1 antibodies alter Kv1.1 and AMPA receptors changing sy	Spain/Switzerland	LGI1 antibodies alter Kv1.1 and AMPA receptors changing synaptic excitability, plasticity and memory					too scientific
2	Dubey et al	2018	Predictors of neural-specific autoantibodies and immunotherapy response in patients with cognitive		Our aim to assess the utility of these models for patients with cognitive dysfunction.	Review current knowledge and findings				too scientific
3	Vollmer L and McCarthy M	2016	Autoimmune encephalitis-A more treatable tragedy if diagno	Canada		reviews other research-editiorial			reviews current research and findings	not useful,
4	Wang S-J et al	2016			Discussion of one case report	case report	1 woman	confirms other findings only:	not useful,
5	Kuroda et al, Doch, Lee, DUPLICATE		Limbic encephalitis associated with positive anti-LGI1 and antithyroid antibodies							
6	de Witte L et al	2015	Auto-immune encephalitis in psychiatric practice	Holland	To propose practical guidelines for the recognition and diagnosis of an underlying auto-immune limbic encephalitis in patients with acute psychiatric symptoms.	report		review with discussions with psychiatrists, neurologist, neuroimmunologist	important diagnostic consideration in patients with acute psy	not useful, too general
7	Quartuccio et al	2015	The role of PET/CT in the evaluation of patients affected by li	Italy	The paper is a practical guide to the clinical Neurologist in order to program an effect	reviews other research-edThis Review presents the state-of-the art of PET/CT evaluation in the management of patients affected by Limbic Encephalitis.itiorial		evaluation of the role of PET and PET/CT in patients	important diagnostic consideration in patients with acute psychiatric sympt	practical guide to the clinical Neurologist in order to program an effective diagt known already.-PET/CT should be integrated with other clinical and imaging investigations, such as MRI.
8	Sarkis R et al	2014	Neuropsychiatric and seizure outcomes in nonparaneoplasti	USA	A retrospective chart review of autoimmune limbic encephalitis is performed focusing	A retrospective chart review of autoimmune limbic encephalitis is performed focusing	16 patients ; 4 with LGI1 /CASPR2 not specific	review of clinical data	Nonparaneoplastic autoimmune limbic encephalitis, the	not useful, not LGI1 specific
9	Najjar S et al	2011	Spontaneously Resolving Seronegative Autoimmune Limbic	USA	e describe a patient with seronegative autoimmune limbic encephalitis (SNALE) ca	case rprt	1 woman	review of MRI and blood tests	SNALE may masquerade as glioma.	not useful, not LGI1 specific
10	Honnorat J	2011	Is autoimmune limbic encephalitis a channelopathy?	France	a reflective article in the Lancet	reflection			In summary, the identifi cation of LGI1 as the main target in patients with limb	confirmation - not useful
11	Khan N et al	2009	HISTOPATHOLOGY OF VGKC ANTIBODY-ASSOCIATED LIMBIC	USA	We describe histopathology from whole brain in a patient with autoimmune limbic enc	case report- post mortem	1 male	MRI, blood tests, EEG,		
OVID MEDLINE 1	Benhamou O-M et al	2018	Gastaut-Geschwind Syndrome, Faciobrachial Dystonic Seizu	USA	we report a case of a 55-year-old male who had presented with recent falls and behav	case report	1 male	MRI, EEG, blood tests	Taken together, the GG syndromal pattern may contribute to the suspicion of	useful as taken from psychiatrist view
2	Serarogllu E	2018	Autoimmune Epilepsy and/or Limbic Encephalitis Can Lead t	Turkey	We studied the sleep and number of sleep spindles in the continuous electroencepha	case-control	5 patinets	MRI, Video EEG,	The sleep abnormalities in LE can result from the disruption of thalamo-limbic	interesting-Our findings related to decreased frequency of sleep spindles in patients with autoimmune epilepsy and/or LE can be related to acute-subacute lesions in the thalamo-limbic circuits.
3	Schroder O et al	2015	Impaired Autonomic Responses to Emotional Stimuli in Auto	Germany	This study investigates behavioral and autonomic responses to discrete emotion evoking and neutral film clips in a patient suffering from LE associated with contactin-associated protein-2 (CASPR2)					n/a CASPR2
4	DUPLICATE Wilkey, Salman and Davenport									
5	Wingfield et al	2012	Autoimmune limbic encephalitis	UK	There are important additional issues leading on from this succinct article that may b	Editors review	1 article	review of database	It is clear that the earlier AE or LE is diagnosed and therapy started, the better	not useful
6	Kinsella J et al	2018	Use of intravenous immunoglobulin for the treatment of auto	UK	To date, however, randomized trials supporting its use in this context have been lack	retrospective audit	625 patient records	review of database	Whilst there was no statistically significant improvement in many cases of patient	interesting - useful

Appendix 6 PRISMA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary 2 criteria, participants, and findings; systematic review		Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	

DISCUSSION

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	

FUNDING

| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | |

Appendix 7: Participant Information Sheet

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PARTICIPANT INFORMATION SHEET FOR PATIENTS

Memory and motivation in health and disease

IRAS ID: 248379. Ethics Approval Reference: 18/SC/0448

Limbic Encephalitis: A Sub-Study

We'd like to invite you to take part in this research investigating limbic encephalitis. This is a Sub-Study of the Memory and Motivation Study, to which you have already consented. Participation in this Sub-Study is completely optional. It is part of a Doctorate in Health programme conducted by Rhea Zambellas. Before you decide whether you would like to give consent to take part in this Sub-Study, please take the time to consider the following information, which has been written to help you understand what the research involves.

What is the purpose of the study? Patients with limbic encephalitis can have difficulties with their memory or their motivation to do things. The purpose of this research is to investigate the severity of difficulties with memory or motivation, and their relationship to experiences of the impact of the illness. Someone who knows you well, will also be invited to share their experiences and views. There will be a particular focus on your experiences from your initial symptoms, through diagnosis to now.

This research uses the already obtained neuropsychological assessment, together with interviews and digital diaries, to improve our understanding of the burden and experience of limbic encephalitis from a patient's perspective. It also allows you to take an active role in research into the illness you are experiencing. We hope that this approach will add value to the current research, which focuses on symptoms and treatment, by adding in-depth patient accounts. It is important to us that patient-rated outcomes (symptoms directly reported by yourself) are also a priority for future research.

We hope that this work will enhance healthcare professionals' understanding, and thereby contribute to improving the ongoing support they can provide.

Participant Information Sheet for Patients
Memory & Motivation in Health & Disease: Limbic Encephalitis Sub-Study (LESS)
Prof Masud Husain/Rhea Zambellas

LESS Version 1.1 10.10. 19
Ethics Ref: 18/SC/0448
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Appendix 8: Participant Information Sheet (Informant/carer)

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PARTICIPANT INFORMATION SHEET FOR INFORMANTS

Memory and motivation in health and disease

IRAS ID: 248379. Ethics Approval Reference: 18/SC/0448

Limbic Encephalitis: A Sub-Study

We'd like to invite you to take part in this research investigating limbic encephalitis. This is a Sub-Study of the Memory and Motivation Study, to which you have already consented. Participation in this Sub-Study is completely optional. It is part of a Doctorate in Health programme conducted by Rhea Zambellas. Before you decide whether you would like to give consent to take part in this Sub-Study, please take the time to consider the following information, which has been written to help you understand what the research involves.

What is the purpose of the study?

Patients with limbic encephalitis can have difficulties with their memory or their motivation to do things. The purpose of this research is to investigate the severity of difficulties with their memory or motivation, and to relate it to experiences of the impact of the illness. We would like to understand your experiences from the patient's initial symptoms through to diagnosis to now.

This research uses the already obtained neuropsychological assessment, together with interviews and digital diaries, to improve our understanding of the burden and experience of limbic encephalitis. This also allows you to take an active role in the research into the illness of the person you share experiences with. This approach is expected to add value to the current research, which focuses on symptoms and treatment, by adding an in-depth, valuable personal account. It is important to us to add your perspectives to the research.

We hope this work will enhance healthcare professionals' understanding, and thereby contribute to improving the ongoing support they can provide.

Participant Information Sheet for Informants
Memory & Motivation in Health & Disease: Limbic Encephalitis Sub-Study (LESS)
Prof Masud Husain/Rhea Zambellas

LESS Version 1.1 10.10. 19
Ethics Ref: 18/SC/0448

Appendix 9: Informed Consent Form

NUFFIELD DEPARTMENT OF
CLINICAL NEUROSCIENCES

UNIVERSITY OF OXFORD

Professor Masud Husain
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Study Code:

PARTICIPANT CONSENT FORM

IRAS ID: 248379. Ethics Approval Reference: 18/SC/0448
Memory and motivation in health and disease

Limbic Encephalitis: A Sub-Study

Please initial each box

1. I confirm that I have read and understand the information sheet version_____dated _____ for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

3. **ALL PARTICIPANTS :**I understand that data collected during the study may be looked at by individuals from University of Oxford, from regulatory authorities [and from the NHS Trust(s)], where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records

    PATIENT PARTICIPANTS: In addition to the above, I understand that relevant sections of my medical notes may be looked at by individuals from University of Oxford, from regulatory authorities [and from the NHS Trust(s)], where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records

4. I agree to give permission to share my neuropsychological data with Rhea Zambellas, Doctorate in Health student.

5. I give consent to the audiotaping and transcription of the interview and digital diary which will be deleted after transcriptions.

6. I give consent to use unidentified quotes in research reports and publications.

7. I agree to take part in the study

_____   _____   _____
Name of Participant   **Date**   **Signature**

_____   _____   _____
Name of person taking consent   **Date**   **Signature**

1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes (if participant is a patient).

LESS Version 1.1 10.10.19
Memory & Motivation in Health & Disease: Limbic Encephalitis Sub-Study (LESS)   Ethics Ref: 18/SC/0448

Appendix 10: Digital Diary Dictaphone Information Sheet

Memory and Motivation in health and disease
Limbic Encephalitis: A Sub-Study
Dictaphone instructions For Patients and Informants

Thank for taking this dictaphone home for 2 weeks. It is also referred to as a digital diary. Please contact the researcher if you have any queries, on the telephone number below.

Please share the dictaphone between you both.

Before recording, please state your name. This will be de-identified in the transcriptions.

Please record any thoughts/feelings/concerns (positive or negative) that you want to relay, concerning the autoimmune limbic encephalitis.

As a patient, you may want to record aspects to do with your mood, temperament, level of tiredness, coping strategies in daily activities, relationship with your spouse, or work issues.

As a patient, you may want to talk about your qualities and character before and after diagnosis, and whether you feel differently now.

As an informant, you may want to talk about how your spouse has changed, concerning their character, qualities or behaviour, and how this makes you feel now.

You may both talk about what it is like living with autoimmune limbic encephalitis, so we can get a better understanding.

No entry is right or wrong. You may want to speak daily or maybe not. It depends on you.

LESS Version 1.1 10.10.19
Memory & Motivation in Health & Disease: Limbic Encephalitis Sub-Study (LESS)   Ethics Ref: 18/SC/0448

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Appendix 11: Screening Log

STUDY NUMBER-N	INFORMATION SHEET SENT	THESIS STUDY NO.	ICFs	DIGITAL DIARY SENT	INTERVIEW DATE	TRANSCRIPTIONS DONE FOR INTERVIEW	TRANSCRIPTIONS DONE FOR DIGITAL DIARIES	CHECKED TRANSCRIPTS	CODED TRANSCRIPTS	THEMES AND QUOTES	SENT TO BC	COPY TO PARTICIPANT	DELETED TRANSCIPTS ON COMPUTER AND DEVICES
p427													
P428													
P429	sent 18.10.19	LESS 7	6.12.19	27.1.20	30.11.19	YES	YES	YES	YES	YES	YES	YES	
P430													
P431													
P432			REFUSED										
P433													
P281	15.12.19	LESS 9	13.1.20	5.2.20	16.1.20	YES	YES	YES	YES	YES		YES	YES
P434													
P445	sent 18.10.19	LESS 3	31.10.19	22.11.19 given in clinic	19.12.19	YES	YES	YES	YES	YES		YES	YES
P446													
P481													
P482													
P483													
P511	sent 18.10.19	LESS 2	24.10.19	31.10.19	4.11.19	YES	YES	YES	YES	YES	YES	YES	YES
P517													
P518			REFUSED										
P519													
P520													
P521													
P522													
P526													
P523													
P634	sent 18.10.19	LESS 1	24.10.19	31.10.19	1.11.19	YES	YES plus a 'snapshot' extra s	YES	YES	YES	YES	YES	YES
P525													
P567		LESS 6	14.11.19	12.12.19	25.11.19	YES	YES	YES	YES	YES		YES	YES
P571													
P569	sent 29.11.19	LESS 8		22.11.19	10.12.19	YES	said nothing for digital diari	YES	YES	YES		YES	YES
P625													
P627													
P633													
P628													
P630													
P629													
P680													
P681	RIP 31.10.19												
P685													
P686	emailed 17.12.19												
P687													
P684	sent 18.10.19	LESS 5	5.11.19	12.12.19	4.11.19	YES	YES	YES	YES	YES		YES	YES
P678													
P626													
P733													
P734	sent 18.10.19	LESS 4	24.10.19	22.11.19 given in clinic	27.11.19	YES	said nothing to add to digital di	YES	YES	YES		YES	YES
P737													
P735													
P828													
P570	12.12.19	LESS 10	27.1.20	2.2.20	15.1.20	YES	YES	YES	YES	YES		YES	YES

Appendix 12: Neuropsychological test battery for the patient and carer

Patient	Domain	Carer	Domain
Addenbrooke's Cognitive Examination-Revised (ACE-R)	Attention, memory, fluency, language, visuo-spacial	Neuropsychiatric Inventory (NPI)[8]	Behavioural functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, night-time behavioural disturbances, appetite and eating abnormalities, and aberrant motor behaviour
WMS-III Digit Span[1]	Short term memory	The Lille Apathy Rating Scale (LARS-Caregiver)[9]	Apathy
Apathy Motivation Index (AMI)[2]	Apathy-motivation	AMI_Caregiver[10]	Apathy-motivation

Snaith-Hamilton Pleasure Scale (SHAPS)[3]	Pleasure	The Bayer-Activities of Daily Living Scale (B-ADL)[11]	Carer's evaluation of the patient doing specific tasks/activities of daily living
Mood Scale	Mood	Zarit Burden Interview (ZBI)[12]	Carer self-report measure of burden
Beck Depression Inventory-II (BDI-II)[4]	Depression	IQCODE [13]	Carer comparing patient's performance in certain areas, with 10 years ago
Fatigue Severity Scale (FSS)[5]	Fatigue		
Pittsburgh Sleep Quality Index (PSQI)[6]	Sleep		
The World Health Organisation- Five Well-Being Index (WHO-5)[7]	Wellbeing		
Cantrill Ladder	Wellbeing		

Neuropsychological testing battery: a structured approach to the assessment of cognitive function and behavioural.

1.Wechsler, 1997. 2 Ang et al., 2017, 3 Snaith-Hamilton 1995, 4 Beck 1996, 5 Krupp et al 1988, 6 The Pittsburgh Sleep Quality Index (PSQI) is copyrighted by Daniel J. Buysse, 7 WHO 1995, 8 Zigmond and 1983, 9 Cummings, 2020, 10 Dujardin et al 2008, 11 Bayer 1998, 12 Zarit 1996, 13 Jorm 1994.

Appendix 13: ACE-R

Appendix 13_ACE-R
Cognitive Assessmen

ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III
English Version A (2012)

Name:	Date of testing: ___/___/___
Date of Birth:	Tester's name:_____
Hospital No. or Address:	Age at leaving full-time education:_____
	Occupation: _____
	Handedness: _____

A T T E N T I O N

➢ Ask: What is the	Day	Date	Month	Year	Season	**Attention** [Score 0-5]
	_____	_____	_____	_____	_____	
➢ Ask: Which	No./Floor	Street/Hospital	Town	County	Country	**Attention** [Score 0-5]
	_____	_____	_____	_____	_____	

A T T E N T I O N

	Attention [Score 0-3]
➢ Tell: "I'm going to give you three words and I'd like you to repeat them after me: lemon, key and ball." After subject repeats, say "Try to remember them because I'm going to ask you later". ➢ Score *only* the first trial (repeat 3 times if necessary). ➢ Register number of trials: _____	

A T T E N T I O N

	Attention [Score 0-5]
➢ Ask the subject: "Could you take 7 away from 100? I'd like you to keep taking 7 away from each new number until I tell you to stop." ➢ If subject makes a mistake, do not stop them. Let the subject carry on and check subsequent answers (e.g., 93, 84, 77, 70, 63 – score 4). ➢ Stop after five subtractions (93, 86, 79, 72, 65): ____ ____ ____ ____ ____	

M E M O R Y

	Memory [Score 0-3]
➢ Ask: 'Which 3 words did I ask you to repeat and remember?' _____ _____ _____	

F L U E N C Y

➢ **Letters**
Say: "I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, if I give you the letter "C", you could give me words like "cat, cry, clock" and so on. But, you can't give me words like Catherine or Canada. Do you understand? Are you ready? You have one minute. The letter I want you to use is the letter "P".

Fluency [Score 0 – 7]

				≥ 18	7
				14-17	6
				11-13	5
				8-10	4
				6-7	3
				4-5	2
				2-3	1
				0-1	0
				total	correct

➢ **Animals**
Say: "Now can you name as many animals as possible. It can begin with any letter."

Fluency [Score 0 – 7]

				≥ 22	7
				17-21	6
				14-16	5
				11-13	4
				9-10	3
				7-8	2
				5-6	1
				<5	0
				total	correct

MEMORY

⊘ Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me.
So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."

Score only the third trial.

	1ˢᵗ Trial	*2ⁿᵈ Trial*	*3ʳᵈ Trial*
Harry Barnes 73 Orchard Close Kingsbridge Devon	_____ _____ ___ _____ _____ _____ _____	_____ _____ ___ _____ _____ _____ _____	_____ _____ ___ ____ _____ _____ _____

MEMORY

⊘ Name of the current Prime Minister... ⊘
Name of the woman who was Prime Minister .... ⊘
Name of the USA president..
⊘ Name of the USA president who was assassinated in the 1960s...

LANGUAGE

⊘ Place a pencil and a piece of paper in front of the subject. As a practice trial, ask the subject to "**Pick up the pencil and then the paper**." If incorrect, score 0 and do not continue further.

⊘ If the subject is correct on the practice trial, continue with the following three commands below. x   Ask the subject to "**Place the paper on top of the pencil**" x   Ask the subject to "**Pick up the pencil but not the paper**" x   Ask the subject to "**Pass me the pencil after touching the paper**"
Note: Place the pencil and paper in front of the subject before each command.

LANGUAGE

⊘ Ask the subject to write two (or more) complete sentences about his/her last holiday/weekend/Christmas. Write in complete sentences and do not use abbreviations.
Give 1 point if there are two (or more) complete sentences about the one topic; and give another 1 point if grammar and spelling are correct.

⏱ Ask the subject to name the following pictures:

LANGUAGE

⏱ Ask the subject to repeat: **'All that glitters is not gold'**

Language
[Score 0-1]

⏱ Ask the subject to repeat: **'A stitch in time saves nine'**

Language
[Score 0-1]

LANGUAGE

🕐 Ask the subject to name the following pictures:

L A N G U A G E

265
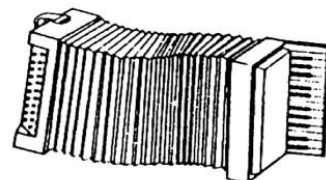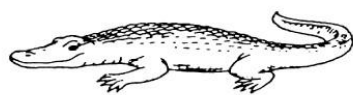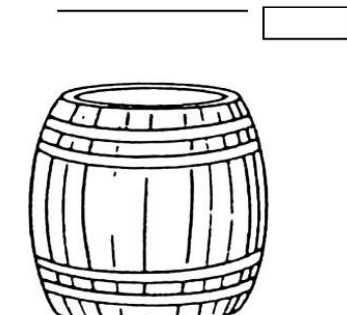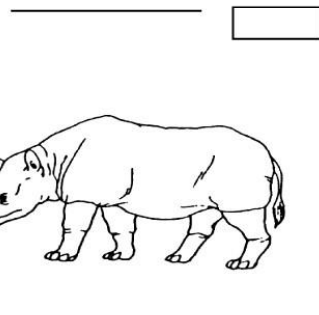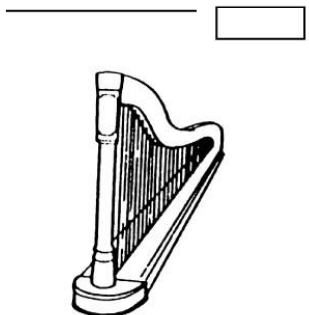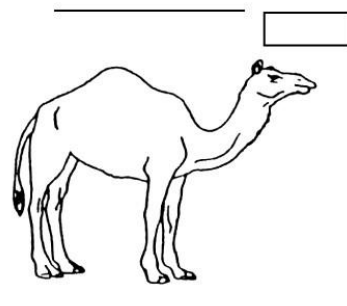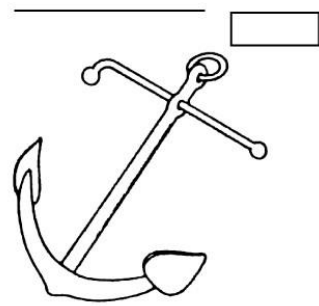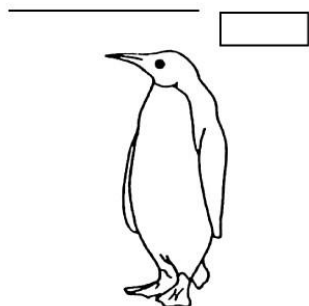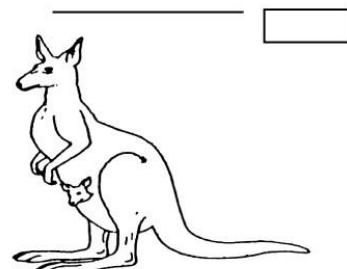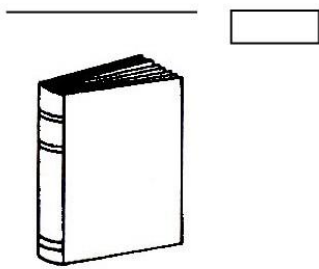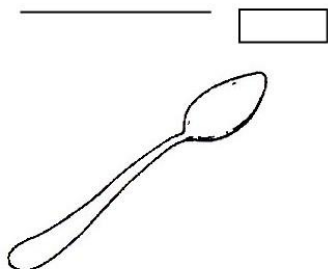
🕐   Using the pictures above, ask the subject to:

     x Point to the one which is associated with the monarchy   …………………………………………….. x
Point to the one which is a marsupial   …………………………………………….. x
Point to the one which is found in the Antarctic   ………………………………………….

     x Point to the one which has a nautical connection   ………………………………………….
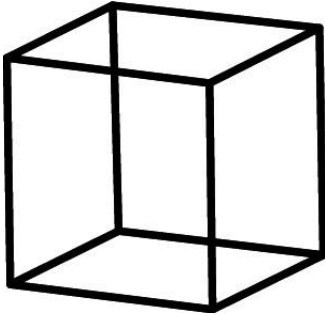
L A N G U A G E

🕐   Ask the subject to read the following words: (Score 1 only if all correct)

sew pint

soot

dough

height

V I S U O S P A T I A L   A B I L I T I E S

🕐   Infinity Diagram: Ask the subject to copy this diagram
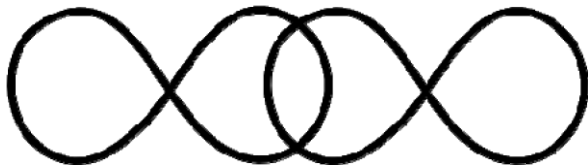
		Visuospatial
⊕	Wire cube: Ask the subject to copy this drawing (for scoring, see instructions guide).	[Score 0-2]

		Visuospatial
⊕	Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (For scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct).	[Score 0-5]

Ask the subject to count the dots without pointing to them

Visuospatial
[Score 0-4]
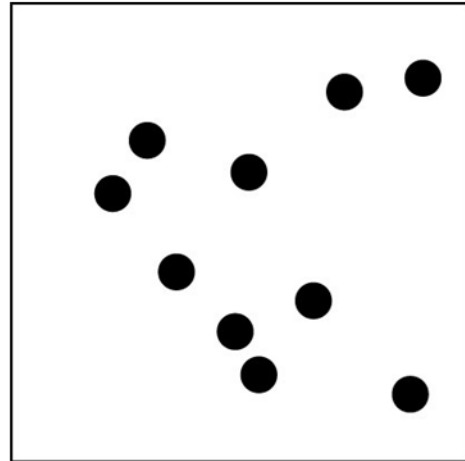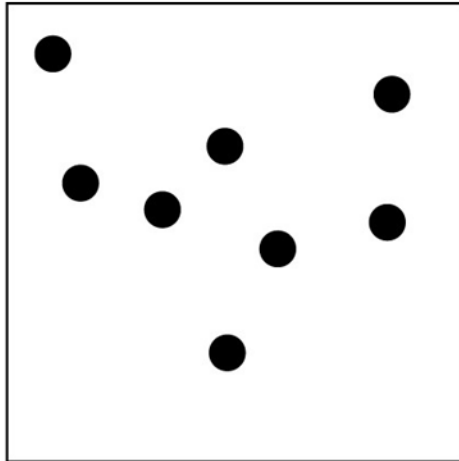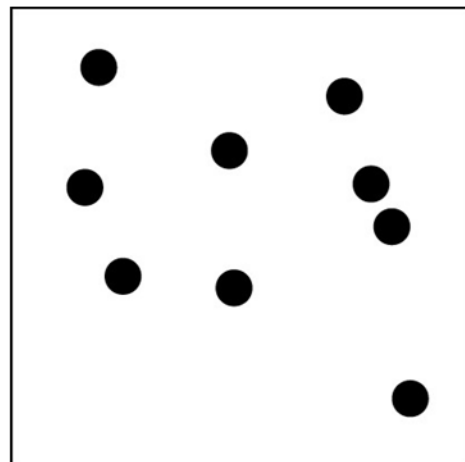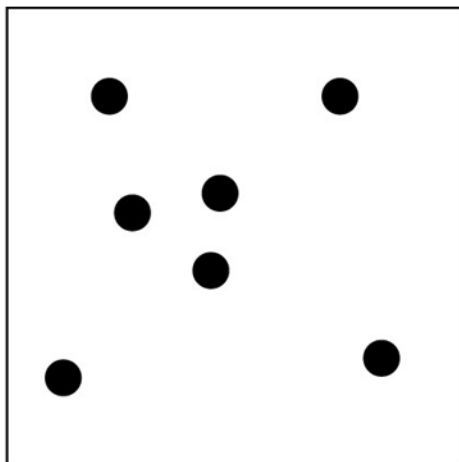
V I S U O S P A T I A L   A B I L I T I E S

	Visuospatial
⏱ Ask the subject to identify the letters	[Score 0-4]
	☐

M E M O R Y

⏱ Ask "Now tell me what you remember about that name and address we were repeating at the beginning"

Harry Barnes	…………………. ………………………………… ……	**Memory**
	………………………. ……………………….	
73 Orchard Close		[Score 0-7]
	………………………………………………………	☐

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Kingsbridge Devon	………………………………………………………	

M E M O R Y

	Memory
☺ This test should be done if the subject failed to recall one or more items above. It all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right hand side; and then test not recalled items by telling the subject "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point, which is added to the point gained by recalling.	[Score 0-5]

Jerry Barnes		Harry Barnes		Harry Bradford		recalled	
37		73		76		recalled	
Orchard Place		Oak Close		Orchard Close		recalled	
Oakhampton		Kingsbridge		Dartington		recalled	
Devon		Dorset		Somerset		recalled	

S C O R E S

TOTAL ACE-III SCORE	/100
Attention	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

Appendix 14: WMS-III Digit span

Digits Forward

Item/Trial		Response	Score 0 or 1
1.	Trial 1	1 – 7	
	Trial 2	6 – 3	
2.	Trial 1	5 – 8 – 2	
	Trial 2	6 – 9 – 4	
3.	Trial 1	6 – 4 – 3 – 9	
	Trial 2	7 – 2 – 8 – 6	
4.	Trial 1	4 – 2 – 7 – 3 – 1	
	Trial 2	7 – 5 – 8 – 3 – 6	
5.	Trial 1	6 – 1 – 9 – 4 – 7 – 3	
	Trial 2	3 – 9 – 2 – 4 – 8 – 7	
6.	Trial 1	5 – 9 – 1 – 7 – 4 – 2 – 8	
	Trial 2	4 – 1 – 7 – 9 – 3 – 8 – 6	
7.	Trial 1	5 – 8 – 1 – 9 – 2 – 6 – 4 – 7	
	Trial 2	3 – 8 – 2 – 9 – 5 – 1 – 7 – 4	
8.	Trial 1	2 – 7 – 5 – 8 – 6 – 2 – 5 – 8 – 4	
	Trial 2	7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8	

Forward Total Score Range = 0 to 16 [ ]

Digits Backward

Item/Trial		(Correct Response)/Response	Score 0 or 1
1.	Trial 1	2 – 4 (4 – 2)	
	Trial 2	5 – 7 (7 – 5)	
2.	Trial 1	6 – 2 – 9 (9 – 2 – 6)	
	Trial 2	4 – 1 – 5 (5 – 1 – 4)	
3.	Trial 1	3 – 2 – 7 – 9 (9 – 7 – 2 – 3)	
	Trial 2	4 – 9 – 6 – 8 (8 – 6 – 9 – 4)	
4.	Trial 1	1 – 5 – 2 – 8 – 6 (6 – 8 – 2 – 5 – 1)	
	Trial 2	6 – 1 – 8 – 4 – 3 (3 – 4 – 8 – 1 – 6)	
5.	Trial 1	5 – 3 – 9 – 4 – 1 – 8 (8 – 1 – 4 – 9 – 3 – 5)	
	Trial 2	7 – 2 – 4 – 8 – 5 – 6 (6 – 5 – 8 – 4 – 2 – 7)	
6.	Trial 1	8 – 1 – 2 – 9 – 3 – 6 – 5 (5 – 6 – 3 – 9 – 2 – 1 – 8)	
	Trial 2	4 – 7 – 3 – 9 – 1 – 2 – 8 (8 – 2 – 1 – 9 – 3 – 7 – 4)	
7.	Trial 1	9 – 4 – 3 – 7 – 6 – 2 – 5 – 8 (8 – 5 – 2 – 6 – 7 – 3 – 4 – 9)	
	Trial 2	7 – 2 – 8 – 1 – 9 – 6 – 5 – 3 (3 – 5 – 6 – 9 – 1 – 8 – 2 – 7)	

Backward Total Score Range = 0 to 14 [ ]

Total Score Range = 0 to 30 [ ]

(Sum Forward Total Score & Backward Total Score)

Appendix 15: Norms tables for the Digit Span

PDF

wms3_norms.pdf

Appendix 16: Apathy-Motivation-Index (Patient)

Below are a number of statements. Each statement asks you to think about your life over the last 2 weeks.

For each statement, select how appropriately it describes your life right now. Select "Completely true" if the statement describes you perfectly, "Completely untrue" if the statement does not describe you at all over the last 2 weeks, and use the answers in between accordingly.

		Completely UNTRUE	Mostly untrue	Neither true nor untrue	Quite true	Completely TRUE
1	I feel sad or upset when I hear bad news.	☐	☐	☐	☐	☐
2	I start conversations with random people.	☐	☐	☐	☐	☐
3	I enjoy doing things with people I have just met.	☐	☐	☐	☐	☐
4	I suggest activities for me and my friends to do.	☐	☐	☐	☐	☐
5	I make decisions firmly and without hesitation.	☐	☐	☐	☐	☐
6	After making a decision, I will wonder if I have made the wrong choice.	☐	☐	☐	☐	☐
7	Based on the last two weeks, I will say I care deeply about how my loved ones think of me.	☐	☐	☐	☐	☐
8	I go out with friends on a weekly basis.	☐	☐	☐	☐	☐
9	When I decide to do something, I am able to make an effort easily.	☐	☐	☐	☐	☐
10	I don't like to laze around.	☐	☐	☐	☐	☐
11	I get things done when they need to be done, without requiring reminders from others.	☐	☐	☐	☐	☐
12	When I decide to do something, I am motivated to see it through to the end.	☐	☐	☐	☐	☐
13	I feel awful if I say something insensitive.	☐	☐	☐	☐	☐
14	I start conversations without being prompted.	☐	☐	☐	☐	☐
15	When I have something I need to do, I do it straightaway so it is out of the way.	☐	☐	☐	☐	☐
16	I feel bad when I hear an acquaintance has an accident or illness	☐	☐	☐	☐	☐
17	I enjoy choosing what to do from a range of activities.	☐	☐	☐	☐	☐
18	If I realise I have been unpleasant to someone, I will feel terribly guilty afterwards.	☐	☐	☐	☐	☐

Appendix 17: Apathy-Motivation-Index (Informant/carer)

AMI version 1.0

Below are a number of statements. Each statement asks you to think about the person you are answering for on the basis of the last 2 weeks. For each statement, select how appropriately it describes the persons thoughts and behaviours. Select "Completely true" if the statement describes them perfectly, "Completely untrue" if the statement does not describe them at all, and use the answers in between accordingly.

Name of person you are answering for _____

Relationship _____

Length of time you have known one another _____

		Completely UNTRUE	Mostly untrue	Neither true nor untrue	Quite true	Completely TRUE
1	Feels sad or upset when they hear bad news.	☐	☐	☐	☐	☐
2	Starts conversations with random people.	☐	☐	☐	☐	☐
3	Seems to enjoy doing things with people he/she has just met.	☐	☐	☐	☐	☐
4	Suggests activities to do.	☐	☐	☐	☐	☐
5	Makes decisions firmly and without hesitation.	☐	☐	☐	☐	☐
6	After making a decision, will wonder if they made the wrong choice.	☐	☐	☐	☐	☐
7	Seems to care deeply about what their loved ones think of them.	☐	☐	☐	☐	☐
8	Goes out with friends on a weekly basis.	☐	☐	☐	☐	☐
9	When he/she decides to do something, he/she is able to make an effort easily.	☐	☐	☐	☐	☐
10	Doesn't like to laze around.	☐	☐	☐	☐	☐
11	Gets things done when they need to be done, without requiring reminders from others.	☐	☐	☐	☐	☐

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Scoring Instructions

Each item is negatively scored i.e., you will need to REVERSE ALL ITEMS:

Completely TRUE = 0

Quite true = 1

Neither true nor untrue = 2

Mostly untrue = 3

Completely UNTRUE = 4

Three domains of apathy-motivation are assessed with the mean score, which ranges from 0-4 (with 0 being motivated and 4 being apathetic).

    (1)   Behavioural: Q5, 9, 10, 11, 12, 15
    (2)   Social: Q2, 3, 4, 8, 14, 17
    (3)   Emotional: Q1, 6, 7, 13, 16, 18

Appendix 18: Snaith Hamilton Pleasure Scale

	Strongly Agree	Agree	Disagree	Strongly Disagree
1. I would enjoy my favourite television or radio program.	☐	☐	☐	☐
2. I would enjoy being with my family or close friends.	☐	☐	☐	☐
3. I would find pleasure in my hobbies and pastimes.	☐	☐	☐	☐
4. I would be able to enjoy my favourite meal.	☐	☐	☐	☐
5. I would enjoy a warm bath or refreshing shower.	☐	☐	☐	☐
6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread.	☐	☐	☐	☐
7. I would enjoy seeing other people's smiling faces.	☐	☐	☐	☐
8. I would enjoy looking smart when I have made an effort with my appearance.	☐	☐	☐	☐
9. I would enjoy reading a book, magazine or newspaper.	☐	☐	☐	☐
10. I would enjoy a cup of tea or coffee or my favourite drink.	☐	☐	☐	☐
11. I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend.	☐	☐	☐	☐
12. I would be able to enjoy a beautiful landscape or view.	☐	☐	☐	☐
13. I would get pleasure from helping others.	☐	☐	☐	☐
14. I would feel pleasure when I receive praise from other people.	☐	☐	☐	☐

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Appendix 19: Becks Depression Inventory

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

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. Pessimism

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. Past Failure

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. Loss of Pleasure

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. Guilty Feelings

0   I don't feel particularly guilty.
1   I feel guilty over many things I have done or should have done.
2   I feel quite guilty most of the time.
3   I feel guilty all of the time.

6. Punishment Feelings

0   I don't feel I am being punished.
1   I feel I may be punished.
2   I expect to be punished.
3   I feel I am being punished.

7. Self-Dislike

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.

8. Self-Criticalness

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.

9. Suicidal Thoughts or Wishes

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.

10. Crying

0   I don't cry anymore than I used to.
1   I cry more than I used to.
2   I cry over every little thing.
3   I feel like crying, but I can't.

11. Agitation

0   I am no more restless or wound up than usual.

1   I feel more restless or wound up than usual.

2   I am so restless or agitated that it's hard to stay still.

3   I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0   I have not lost interest in other people or activities.

1   I am less interested in other people or things than before.

2   I have lost most of my interest in other people or things.

3   It's hard to get interested in anything.

13. Indecisiveness

0   I make decisions about as well as ever.

1   I find it more difficult to make decisions than usual.

2   I have much greater difficulty in making decisions than I used to.

3   I have trouble making any decisions.

14. Worthlessness

0   I do not feel I am worthless.

1   I don't consider myself as worthwhile and useful as I used to.

2   I feel more worthless as compared to other people.

3   I feel utterly worthless.

15. Loss of Energy

0   I have as much energy as ever.

1   I have less energy than I used to have.

2   I don't have enough energy to do very much.

3   I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0   I have not experienced any change in my sleeping pattern.

1a   I sleep somewhat more than usual.

1b   I sleep somewhat less than usual.

2a   I sleep a lot more than usual.

2b   I sleep a lot less than usual.

3a   I sleep most of the day.

3b   I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0   I am no more irritable than usual.

1   I am more irritable than usual.

2   I am much more irritable than usual.

3   I am irritable all the time.

18. Changes in Appetite

0   I have not experienced any change in my appetite.

1a   My appetite is somewhat less than usual.

1b   My appetite is somewhat greater than usual.

2a   My appetite is much less than before.

2b   My appetite is much greater than usual.

3a   I have no appetite at all.

3b   I crave food all the time.

19. Concentration Difficulty

0   I can concentrate as well as ever.

1   I can't concentrate as well as usual.

2   It's hard to keep my mind on anything for very long.

3   I find I can't concentrate on anything.

20. Tiredness or Fatigue

0   I am no more tired or fatigued than usual.

1   I get more tired or fatigued more easily than usual.

2   I am too tired or fatigued to do a lot of the things I used to do.

3   I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0   I have not noticed any recent change in my interest in sex.

1   I am less interested in sex than I used to be.

2   I am much less interested in sex now.

3   I have lost interest in sex completely.

Scoring the Beck Depression Inventory: After you have completed the questionnaire, add up the score for each of the 21 questions. The following table indicates the relationship between total score and level of depression according to the Beck Depression Inventory.

Classification	Total Score	Level of Depression
Low	**1-10**	**Normal ups and downs**
	11-16	**Mild mood disturbance**
Moderate	**17-20**	**Borderline clinical depression**
	21-30	**Moderate depression**
Significant	**31-40**	**Severe depression**
	Over 40	**Extreme depression**

Appendix 20: Fatigue Severity Scale

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week.
1 indicates that you strongly disagree with the statement and 7 indicates that you strongly agree with it.

	Strongly Disagree --------- Strongly Agree						
1. My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2. Exercise brings on my fatigue	1	2	3	4	5	6	7
3. I am easily fatigued	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Visual Analogue Fatigue Scale (VAFS)

Please mark an 'X' on the number line which describes your global (general/total) fatigue with 0 being worst and 10 being normal.

Worst   Normal

0   1   2   3   4   5   6   7   8   9   10

Appendix 21: Pittsburg Sleep Quality Index

Pittsburgh Sleep Quality Index

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you...	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes	☐	☐	☐	☐
B. Wake up in the middle of the night or early morning	☐	☐	☐	☐
C. Have to get up to use the bathroom	☐	☐	☐	☐
D. Cannot breathe comfortably	☐	☐	☐	☐
E. Cough or snore loudly	☐	☐	☐	☐
F. Feel too cold	☐	☐	☐	☐
G. Feel to hot	☐	☐	☐	☐
H. Have bad dreams	☐	☐	☐	☐
I. Have pain	☐	☐	☐	☐
J. Other reason(s), please describe and rate how often you have had trouble sleeping because of this reason(s):	☐	☐	☐	☐
6. During the past month, how often have you taken medicine (prescribed or 'over the counter') to help you sleep?	☐	☐	☐	☐
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?	☐	☐	☐	☐

	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

Appendix 22: WHO5

WHO (Five) Well-Being Index (1998 version)

Please indicate for each of the five statements which is closest to how you have been feeling over the last two weeks. Notice that higher numbers mean better well-being.

Example: If you have felt cheerful and in good spirits more than half of the time during the last two weeks, put a tick in the box with the number 3 in the upper right corner.

	Over the last two weeks	All of the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1	I have felt cheerful and in good spirits	5	4	3	2	1	0
2	I have felt calm and relaxed	5	4	3	2	1	0
3	I have felt active and vigorous	5	4	3	2	1	0
4	I woke up feeling fresh and re-sted	5	4	3	2	1	0
5	My daily life has been filled with things that interest me	5	4	3	2	1	0

Scoring:

The raw score is calculated by totalling the figures of the five answers. The raw score ranges from 0 to 25, 0 representing worst possible and 25 representing best possible quality of life.

To obtain a percentage score ranging from 0 to 100, the raw score is multiplied by 4. A percentage score of 0 represents worst possible, whereas a score of 100 represents best possible quality of life.

Appendix 23: Neuropsychiatric Inventory

Please answer the following questions based on <u>changes</u> that have occurred since the patient first began to experience memory problems.

Circle "Yes" <u>only</u> if the symptom(s) has been present <u>in the last month</u>. Otherwise, circle "No". For each item marked "Yes":

a) Rate the SEVERITY of the symptom (how it affects <u>the patient)</u>:
      1 = Mild (noticeable, but not a significant change)
      2 = Moderate (significant, but not a dramatic change)
      3 = Severe (very marked or prominent, a dramatic change)

b) Rate the DISTRESS you experience due to that symptom (how it affects <u>you</u>):
      0 = Not distressing at all
      1 = Minimal (slightly distressing, not a problem to cope with)
      2 = Mild (not very distressing, generally easy to cope with)
      3 = Moderate (fairly distressing, not always easy to cope with)
      4 = Severe (very distressing, difficult to cope with)
      5 = Extreme or Very Severe (extremely distressing, unable to cope with)

Please answer each question carefully. Ask for assistance if you have any questions.

Delusions	Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?

Yes   No   SEVERITY: 1 2 3   DISTRESS: 0 1 2 3 4 5

Hallucinations	Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear or see things that are not present?

Yes   No   SEVERITY: 1 2 3   DISTRESS: 0 1 2 3 4 5

Agitation/Aggression	Is the patient resistive to help from others at times, or hard to handle?

Yes   No   SEVERITY: 1 2 3   DISTRESS: 0 1 2 3 4 5

| Yes | No | SEVERITY: 1 2 3 | DISTRESS: 0 1 2 3 4 5 |

Irritability/Lability Is the patient impatient and cranky? Does he/she have difficulty coping with delays or waiting for planned activities?

| Yes | No | SEVERITY: 1 2 3 | DISTRESS: 0 1 2 3 4 5 |

Motor Disturbance Does the patient engage in repetitive activities such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?

| Yes | No | SEVERITY: 1 2 3 | DISTRESS: 0 1 2 3 4 5 |

Nightime Behaviors Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?

| Yes | No | SEVERITY: 1 2 3 | DISTRESS: 0 1 2 3 4 5 |

Appetite/Eating Has the patient lost or gained weight, or had a change in the type of food he/she likes?

NPI-Q Summary

	No	Severity			Caregiver Distress					
Delusions	0	1	2	3	0	1	2	3	4	5
Hallucinations	0	1	2	3	0	1	2	3	4	5
Agitation/Aggression	0	1	2	3	0	1	2	3	4	5
Dysphoria/Depression0	0	1	2	3	0	1	2	3	4	5
Anxiety	0	1	2	3	0	1	2	3	4	5
Euphoria/Elation	0	1	2	3	0	1	2	3	4	5

Apathy/Indifference 0	0	1 2 3	0 1 2 3 4 5		
Disinhibition	0	1 2 3	0 1 2 3 4 5		
Irritability/Lability	0	1 2 3	0 1 2 3 4 5		
Aberrant Motor	0	1 2 3	0 1 2 3 4 5		
Nighttime Behavior 0	0	1 2 3	0 1 2 3 4 5		
Appetite/Eating	0	1 2 3	0 1 2 3 4 5		
TOTAL					

Appendix 24: Lille Apathy Rates Scale (Informant/carer)

i-LARS

1. Everyday productivity

a. What does your spouse do during the day? Tell me about your day-to-day life.

i. Number and variety of activities mentioned: ___

ii. Periods when completely inactive ___

2. Interests

a. What is your spouse interested in? What do they like doing to keep themselves occupied?

i. Number of activities mentioned: ___

ii. How many times a week? ___

iii. Is interested in this activity as before?

3. Taking the initiative

a. In general, does he/she decide to do things or does someone have to push him/her a little? ___

b. When he/she has to go to an appointment, a meeting or a formal occasion, does he/she get ready? When he/she has to make an appointment (for example with the doctor or dentist),

does he/she do it him/herself or wait for you to do it ? ___

d. Do he/she take part spontaneously in daily living activities or does he/she needto be asked? ___

4. Novelty seeking

a. Does he/she like finding out about something new (a new TV programme or a new book)? ___

b. Does he/she like trying out new products, tools or recipes that he/she is not familiar with? ___

c. Does he/she like visiting places he/she has never been to before? ___

d. When he/she goes out for a drive or when he/she is travelling by train or bus, does he/she enjoy looking at the countryside, the houses? ___

5. Motivation – Voluntary actions

a. When he/she decides to do something, is he/she easily able to make an effort or is it difficult? ___

b. When he/she doesn't manage to do something, does he/she try to find other solutions? ___

c. When he/she decides to do something, does he/she see it through to the end or does he/shetend to give up? ___

d. When he/she can't find something (for example a document or an object), does he/she go to a lot of trouble looking for it? ___

6. Emotional responses

a. When he/she watches a film, does he/she easily become emotional or moved? ___

b. When someone tells him/her a joke or when he/she watches a comedy sketch on TV, does he/she laugh easily? ___

c. Does he/she feel happy when he/she hears some good news? ___

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d. Does he/she feel sad when he/she hears some bad news? ___

7. Concern

a. When you have a problem (for example when your TV set breaks down),

does it worry him/her? ___

b. When something's not working or when something unexpected happens,

does he/she think about finding a solution? ___

c. When your partner or children have a minor problem (when they're ill,

for example), does that concern him/her, does he/she worry about them? ___

d. Does he/she like to ask how your family and friends are on a regular basis? ___

8. Social life

a. Does he/she have friends? ___

b. When he/she meets friends, does he/she enjoy spending time with them or is it a chore?
___

c. In conversation, does he/she start talking or do the others tend to speak to him/her first?
___

d. During a discussion, does he/she give his/her own opinion spontaneously or does he/she
fall into line with someone else's opinion? ___

9. Self-awareness

a. Is he/she able to criticise own decisions and change opinions ___

b. After having taken a decision, does he/she sometimes think that he/she has made the wrong choice? ___

c. When he/she has been unpleasant to someone, does he/she sometimes feel guilty afterwards? ___

d. If, during a discussion, he/she realises that he/she is in the wrong, is he/she able to admit it – at least to himself/herself??

Appendix 25: Bayer Activities of Daily Living Scale

Bayer Activities of Daily Living Scale

The following questions are about everyday activities with which the person you are being asked about might have difficulty.

Please indicate how often difficulties occur by marking the appropriate number. The higher the number the more difficulty the person has with the activity in question. If difficulties never occur please mark 1, if difficulties always occur please mark 10.

If a question does not apply to the person for any reason please put a cross in the 'not applicable' box.

If you cannot decide on the difficulty the person has please put a cross in the 'unknown' box.

	Does the person have difficulty...	never ... always	Not applicable	Unknown	Score
1	...managing his/her everyday activities?	1 2 3 4 5 6 7 8 9 10	☐	☐	
2	...taking care of him/herself?	1 2 3 4 5 6 7 8 9 10	☐	☐	
3	...taking medication without supervision?	1 2 3 4 5 6 7 8 9 10	☐	☐	
4	...with personal hygiene?	1 2 3 4 5 6 7 8 9 10	☐	☐	
5	...observing important dates or events?	1 2 3 4 5 6 7 8 9 10	☐	☐	
6	...concentrating on reading?	1 2 3 4 5 6 7 8 9 10	☐	☐	
7	...describing what he/she has just seen or heard?	1 2 3 4 5 6 7 8 9 10	☐	☐	
8	...taking part in a conversation?	1 2 3 4 5 6 7 8 9 10	☐	☐	
9	...using the telephone?	1 2 3 4 5 6 7 8 9 10	☐	☐	
10	...taking a message for someone else?	1 2 3 4 5 6 7 8 9 10	☐	☐	
11	...going for a walk without getting lost?	1 2 3 4 5 6 7 8 9 10	☐	☐	
12	...shopping?	1 2 3 4 5 6 7 8 9 10	☐	☐	
13	...preparing food?	1 2 3 4 5 6 7 8 9 10	☐	☐	
14	...correctly counting out money?	1 2 3 4 5 6 7 8 9 10	☐	☐	

Does the person have difficulty...	never									always	Not applicable	Unknown	
15	...understanding his/her personal financial affairs?	1 2 3 4 5 6 7 8 9 10									☐	☐	
16	...giving direction if asked the way?	1 2 3 4 5 6 7 8 9 10									☐	☐	
17	...using domestic applicances?	1 2 3 4 5 6 7 8 9 10									☐	☐	
18	...finding his/her way in an unfamiliar place?	1 2 3 4 5 6 7 8 9 10									☐	☐	
19	...using transportation?	1 2 3 4 5 6 7 8 9 10									☐	☐	
20	...participating his/her leisure activities?	1 2 3 4 5 6 7 8 9 10									☐	☐	
21	...continuing with the same task after a brief interruption?	1 2 3 4 5 6 7 8 9 10									☐	☐	
22	...doing two things at the same time?	1 2 3 4 5 6 7 8 9 10									☐	☐	
23	...coping with unfamiliar situations?	1 2 3 4 5 6 7 8 9 10									☐	☐	
24	...doing things safely?	1 2 3 4 5 6 7 8 9 10									☐	☐	
25	...performing a task when under pressure?	1 2 3 4 5 6 7 8 9 10									☐	☐	

Appendix 26: Zarit Burden Interview

The Zarit Burden Interview

0 : NEVER
1 : RARELY
2 : SOMETIMES
3 : QUITE FREQUENTLY
4 : NEARLY ALWAYS

Please circle the response the best describes how you feel.

Question	Score
1 Do you feel that your relative asks for more help than he/she needs?	0 1 2 3 4
2 Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	0 1 2 3 4
3 Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	0 1 2 3 4
4 Do you feel embarrassed over your relative's behaviour?	0 1 2 3 4
5 Do you feel angry when you are around your relative?	0 1 2 3 4
6 Do you feel that your relative currently affects our relationships with other family members or friends in a negative way?	0 1 2 3 4
7 Are you afraid what the future holds for your relative?	0 1 2 3 4
8 Do you feel your relative is dependent on you?	0 1 2 3 4
9 Do you feel strained when you are around your relative?	0 1 2 3 4
10 Do you feel your health has suffered because of your involvement with your relative?	0 1 2 3 4
11 Do you feel that you don't have as much privacy as you would like because of your relative?	0 1 2 3 4
12 Do you feel that your social life has suffered because you are caring for your relative?	0 1 2 3 4

	Question	Score
13	Do you feel uncomfortable about having friends over because of your relative?	0 1 2 3 4
14	Do you feel that your relative seems to expect you to take care of him/her as if you were the only one he/she could depend on?	0 1 2 3 4
15	Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses?	0 1 2 3 4
16	Do you feel that you will be unable to take care of your relative much longer?	0 1 2 3 4
17	Do you feel you have lost control of your life since your relative's illness?	0 1 2 3 4
18	Do you wish you could leave the care of your relative to someone else?	0 1 2 3 4
19	Do you feel uncertain about what to do about your relative?	0 1 2 3 4
20	Do you feel you should be doing more for your relative?	0 1 2 3 4
21	Do you feel you could do a better job in caring for your relative?	0 1 2 3 4
22	Overall, how burdened do you feel in caring for your relative?	0 1 2 3 4

Interpretation of Score:

0 - 21 little or no burden
21 - 40 mild to moderate burden
41 - 60 moderate to severe burden
61 - 88 severe burden

Appendix 27: Informant Questionnaire Code Short Form

Informant Questionnaire Code Short Form

Now we want you to remember what your partner/friend/relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 2007. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much".

	Compared with 10 years ago how is this person at:	Much improved	A bit improved	Not much change	A bit worse	Much worse
1	Remembering things about family and friends e.g. occupations, birthdays, addresses	☐	☐	☐	☐	☐
2	Remembering things that have happened recently	☐	☐	☐	☐	☐
3	Recalling conversations a few days later	☐	☐	☐	☐	☐
4	Remembering his/her address and telephone number	☐	☐	☐	☐	☐
5	Remembering what day and month it is	☐	☐	☐	☐	☐
6	Remembering where things are usually kept	☐	☐	☐	☐	☐
7	Remembering where to find things which have been put in a different place from usual	☐	☐	☐	☐	☐
8	Knowing how to work familiar machines around the house	☐	☐	☐	☐	☐
9	Learning to use a new gadget or machine around the house	☐	☐	☐	☐	☐
10	Learning new things in general	☐	☐	☐	☐	☐
11	Following a story in a book or on TV	☐	☐	☐	☐	☐
12	Making decisions on everyday matters	☐	☐	☐	☐	☐
13	Handling money for shopping	☐	☐	☐	☐	☐
14	Handling financial matters e.g. the pension, dealing with the bank	☐	☐	☐	☐	☐
15	Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends	☐	☐	☐	☐	☐
16	Using his/her intelligene to understand what's going on and to reason things through	☐	☐	☐	☐	☐

Appendix 28: Interview Schedules for Patient and carer

<u>Memory and Motivation in health and disease</u>

<u>Limbic Encephalitis: A Sub-Study</u>

<u>TOPIC GUIDE/INTERVIEW SCHEDULE FOR THE PATIENT</u>

PI:

Date and time:

Location:

Interviewer:

Interviewee Participant Number:

Test recorder first with interviewee:

- Introduce myself

- Confirm consent

- Confirm that I will provide them with a dictaphone for two weeks, and explain instructions and recorded delivery

- Explain purpose of the research- to get your experience of living with autoimmune limbic encephalitis, and how it has impacted on your life

- Explain what it will not make a direct difference to their care, but will help us understand how we can improve ways to support you

- Explain that the interview will be recorded – recorded data will be transcribed into text, reviewed by researchers and stored on a password protected university computer, in an anonymised form only using your research participant number. Once transcribed, the audio recording will be deleted.

- If you feel uncomfortable with any question, you can stop the interview without explanation.

- Explain it will take approximately 30 minutes in total

- Please let me know if you need a break at all

1.   Healthcare provision: I would like you to describe the period awaiting a diagnosis, as far as you can remember, please.

- what was it like when you are awaiting a diagnosis?

- What are your feelings towards the health care services provided at that time

- perhaps you do not recall this period but have heard other people's accounts

2.   Treatment: I would like you to describe what improvements you have experienced since your treatment started, please

3.   Professional support/ongoing support? I would like you to explain if you were given or offered any ongoing support

- perhaps through a Neuropsychologist, cognitive behavioural therapist, or from a local or national charity?

- could you tell me more about this?

4.   Identity: Could you describe to me how you saw yourself before the condition developed?

- (prompts) your qualities, your character, self-image.

- You may want to tell me how you see yourself now

- (Does this mean the condition has made you feel differently about yourself?)

- Can you also tell me how those closest to you understand how you have changed?

5.   Impact: Kindly explain to me what it feels like to have autoimmune limbic encephalitis?

• Please describe whether your current symptoms affect your everyday activities?

6.   Coping/resilience strategies: Can you tell me about a particularly difficult situation or scenario for you, and what are your own coping mechanisms to deal with this

7.   Character changes: I am interested in hearing about your experiences in any changes in your character that you would like to describe to me, please?

• This maybe a sensitive area, but it is important to ask you, due to the nature of this condition

8.   Relationships with partner, family and friends: Could you kindly describe any changes you have experienced within the relationships you share with your closest family and friends?

• Perhaps you would like to express any concerns about your intimate relationship with your spouse/partner and how this may have affected you.

9.   Work situation: Please could you tell me how the autoimmune encephalitis may have changed your future work plans?

• perhaps, if you are retired, other plans you have made.

10.   Uncertainty about the future with the condition: I would like you to describe any aspects of the condition that cause you concern for the future?

- Perhaps this involves your loved ones?

Conclusion

- Check basic understanding of points -Reflection

- Is there anything else you would like to talk about?

- Thank you for taking part today

Interview Notes:

Write down my reflection of the interview.

Consider: how engaged they were, whether hesitant, forgetful, frustrated, irritable, tired, the rapport I had with them, my response to their experiences, their reaction to questions, the fluency of the interview.

I WILL NOW STOP THE RECORDING NOW

Memory and Motivation in health and disease

Limbic Encephalitis: A Sub-Study

TOPIC GUIDE/INTERVIEW SCHEDULE FOR THE CARER

PI:

Date and time:

Location:

Interviewer:

Interviewee Participant Number:

Test recorder first with interviewee

- Introduce myself

- Confirm consent

- Confirm that I will provide them with a dictaphone for two weeks, and explain instructions and recorded delivery

- Explain purpose of the research- to get your experience of living with someone who has autoimmune limbic encephalitis, and how it has impacted on

your life

- Explain what it will not make a direct difference to the person who has the condition's care, but will help us understand how we can improve ways to support you both

- Explain that the interview will be recorded – recorded data will be transcribed into text, reviewed by researchers and stored on a password protected university computer, in an anonymised form only using your research participant number. Once transcribed, the audio recording will be deleted.

- If you feel uncomfortable with any question, you can stop the interview without explanation.

- Explain it will take approximately 30 minutes in total

- Please let me know if you need a break at all

1. Healthcare provision: I would like you to describe the period awaiting a diagnosis, as far as you can remember, please.

- what was it like when you were both waiting for a diagnosis?

- What are your feelings towards the health care services provided at that time

2. Treatment: I would like you to describe what improvements you have seen since their treatment started, please.

3. Professional support/ongoing support? I would like you to explain if you were given or offered any ongoing support

• perhaps through a Neuropsychologist, cognitive behavioural therapist, or from a local or national charity?

• could you tell me more about this?

4.   Identity: Could you describe to me how you saw them before the condition developed?

• (prompts) their qualities, their character, their self-image.

• You may want to tell me how you see them now.

• (Does this mean the condition has made you feel differently about them?)

5.   Impact: Kindly explain to me what it feels like to live with someone with autoimmune limbic encephalitis?

6.   Coping/resilience strategies: Can you tell me about a particularly difficult situation or scenario for you, and what are your own coping mechanisms to deal with

this

7.   Character changes: I am interested in hearing about your experiences in any changes in their character that you would like to describe to me, please.

• This maybe a sensitive area, but it is important to ask you, due to the nature of this condition

8.   Relationships with partner, family and friends: Could you kindly describe any changes you have experienced within the relationships you share with your closest family and friends, due to you living with a person with the condition?

• Perhaps you would like to express any concerns about your intimate relationship with your spouse/partner and how this may have affected you.

9.   Work situation: Please could you tell me how the autoimmune encephalitis may have changed your future work plans?

• perhaps, if you are retired, other plans you have made.

10.   Uncertainty about the future with the condition: I would like you to describe any aspects of the condition that cause you concern for the future?

Conclusion

- Check basic understanding of points -Reflection

- Is there anything else you would like to talk about?

- Thank you for taking part today

Interview Notes:

Write down my reflection of the interview.

Consider: how engaged they were, whether hesitant, forgetful, frustrated, irritable, tired, the rapport I had with them, my response to their experiences, their reaction to questions, the fluency of the interview.

I WILL NOW STOP THE RECORDING NOW

Appendix 29: All Patient Data for MAXQDA

Study.Subj	ACE_Attention	ACE_Memory	ACE_Fluency	ACE_Language	ACE_Visuospatial	ACE_Total	DS_Forward	DS_Backward	DS_total	AMI_BehaviouralS	AMI_SocialScore	AMI_Emotional	AMI_TotalScore	SHAPS_4Sc	SHAPS_2S	BDI_Affec	BDI_Dysph	BDI_LossIr	FSS_Score	PSQI_Tota	WHO5_Pe	CantrilLadder
LESS 1	16	16	10	23	15	80	12	7	19	2	3	1.3333	2.1111	26	1	1	2	2	3.667	4	60	7
LESS 2	18	19	12	26	16	91	12	10	22	1	2.8333	0.6667	1.5	19	0	4	5	1	5	9	52	5
LESS 3	18	26	10	25	15	94	12	8	20	0.1667	1	1.1667	0.7778	20	0	0	2	0	3.667	3	84	9
LESS 4	18	22	8	26	16	90	12	7	19	1.8333	1.5	1.1667	1.5	24	1	3	3	1	3.556	6	92	9
LESS 5	18	25	13	26	16	98	12	12	24	0.5	1	0.3333	0.6111	17	0	0	0	0	1	10	80	8
LESS 6	18	26	11	26	16	97	10	6	16	1	0.6667	1.6667	1.1111	17	0	1	1	0	1.667	2	80	8
LESS 7	18	21	12	26	16	93	10	3	13	1.6667	2	1.3333	1.6667	29	4	0	2	3	3.889	5	60	7
LESS 8	18	23	8	26	16	91	10	6	16	0.8333	0.8333	1.1667	0.9444	25	0	3	4	0	1.333	5	84	9
LESS 9	14	19	8	26	15	82	11	3	14	1.3333	3.3333	1.8333	2.1667	25	1	8	9	1	5.111	3	56	8
LESS 10	12	22	8	26	16	84	13	6	19	1.8333	1.6667	1	1.5	29	1	5	7	5	6	5	40	5

PDF

Appendix 29 All
Patient Data for Ma

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Appendix 30: All Carer Data for MAXQDA

Study.Subj	NPI_Total	NPI Carer Distress Sco	LARS carer intellectural Curiosity	LARS Carer Emotion	LARS Carer Action Initiation	LARS Carer Self-Awareness	LARS Carer Total	ZaritBurdenInterview_Total	BADL_TotalScore	IQCODE_Score
LESS 1	12	9	-1.25	-1	0	-1	-8	22	3.76	4.125
LESS 2	0	6	-1.5	-2	-2	-3	-17	22	1	3.188
LESS 3	32	25	-0.25	2	-1	2	3	54	6.1304	4.125
LESS 4	4	2	-2.25	-2	-4	-4	-25	7	3.12	3.69
LESS 5	26	4	-3.25	-3	-3.5	-4	-30	23	4.125	4.438
LESS 6	12	10	-3.75	-3	-4	-4	-33	11	1.44	3.438
LESS 7	15	12	-2.5	-4	-3.5	-4	-29	47	1.72	3.5
LESS 8	16	14	-2.75	-3.5	-3	1	-23	34	2.04	3.25
LESS 9	28	30	1.5	-2	2	-1	5	39	6.3478	4.125
LESS 10	39	13	-1.25	0.5	3.5	-2	1	62	8.84	5

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Appendix 30 All
Carer Data for MAXC

Appendix 31: All data from Open Clinica used for analysis

Too large as an Excel spreadsheet, but available to open on the electronic version of Thesis.

Appendix 31 All
Data from Open Clir

Appendix 32: Shapiro-Wilk Normality Tests for the NPTB using GraphPad Prism

	ACE_Total	AMI_Total	SHAPS_To	FSS_Score	PSQI_Total	Cantril Lac	BDI_Total	NPI_Total	NPI_Carer [	LARS_Care	ZBI_Total	BADL_Total	IQCODE_To	AMI_Carer_Total
Test for normal distribution														
Shapiro-Wilk test														
W	0.95	0.94	0.66	0.93	0.9	0.85	0.94	0.95	0.86	0.88	0.94	0.89	0.9	0.9
P value	0.61	0.59	<0.01	0.42	0.23	0.05	0.51	0.7	0.07	0.15	0.52	0.16	0.2	0.36
Passed normality	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
P value summary	ns	ns		ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Number of values	10	10	10	10	10	10	10	10	10	10	10	10	10	6

Appendix 33: MAXQDA Themes, Codes and Screenshots

Coding:

In order to capture the coding involved during one transcript (LESS7 wife), the screenshot below demonstrates how this was presented using MAXQDA, in the margin of the text. To the left is the Code Favourites. These codes were based on the five themes mentioned above, and are colour coded in the Overview of Codes.
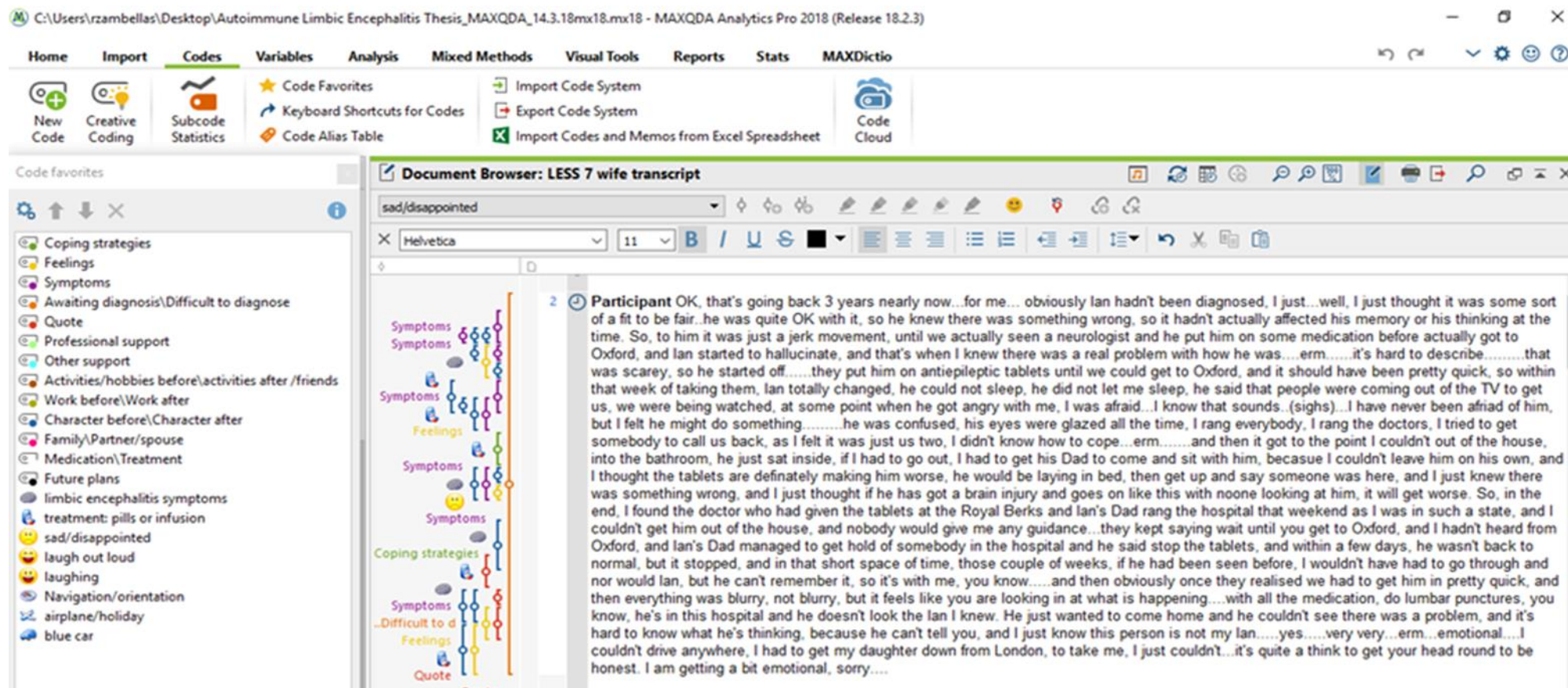
Coding becomes more and more compressed, as the text is re-read and coding revised.

On the live MAXQDA version of Coded Segments, just by clicking on the code, automatically opened to highlighted text (screenshot, below). This way, the researcher organised the themes, and can refer back to them easily.

Showing the frequencies of codes for each participant, can be viewed in the Code Matrix Browser's results, as shown below in screenshot. It allowed the researcher to visualise code frequencies at a glance. Furthermore, it was the ideal tool to illustrate and analyse the distribution of coded segments in different transcripts.

Coded Matrix.

Memo text:

Document name	Title	Memo text
LESS1_wife_1.11.19	Additional document	Word document provided by wife; very useful diary entries of events
LESS 8 wife and patient transcripts (same call	Additional information	Powerpoint presentation also available to view
LESS 6 patient transcript	Additional information	Powerpoint presentation also available to view
LESS1-patient_1.11.19	Bracketing	I tried not to be assuming that he can or cannot remember this period, so left it open for him to tell me, yet I repeated myself as if I was assuming he didn't understand the question.
LESS1-patient_1.11.19	Reflections	Started to say something, then I redirected it, into a close-question. I didn't intend to do that.
LESS1-patient_1.11.19	Reflection	Too many questions in one.
LESS1-patient_1.11.19	Researcher's feelings	Really felt humbled that he felt this way.
LESS1-patient_1.11.19	Additional documentation	He received additioanal support by social workers, home care, and occupational therapists when he was discharged. Information provided in the additional document.

Document portrait:

A visual glance of how each transcript was composed using the codes was viewed in the Document Portrait, which displays coloured dots to show the occurrence of codes visually. The screenshot below demonstrates the largest proportion of codes for LESS1 without measuring them, was 'feelings' (in yellow).
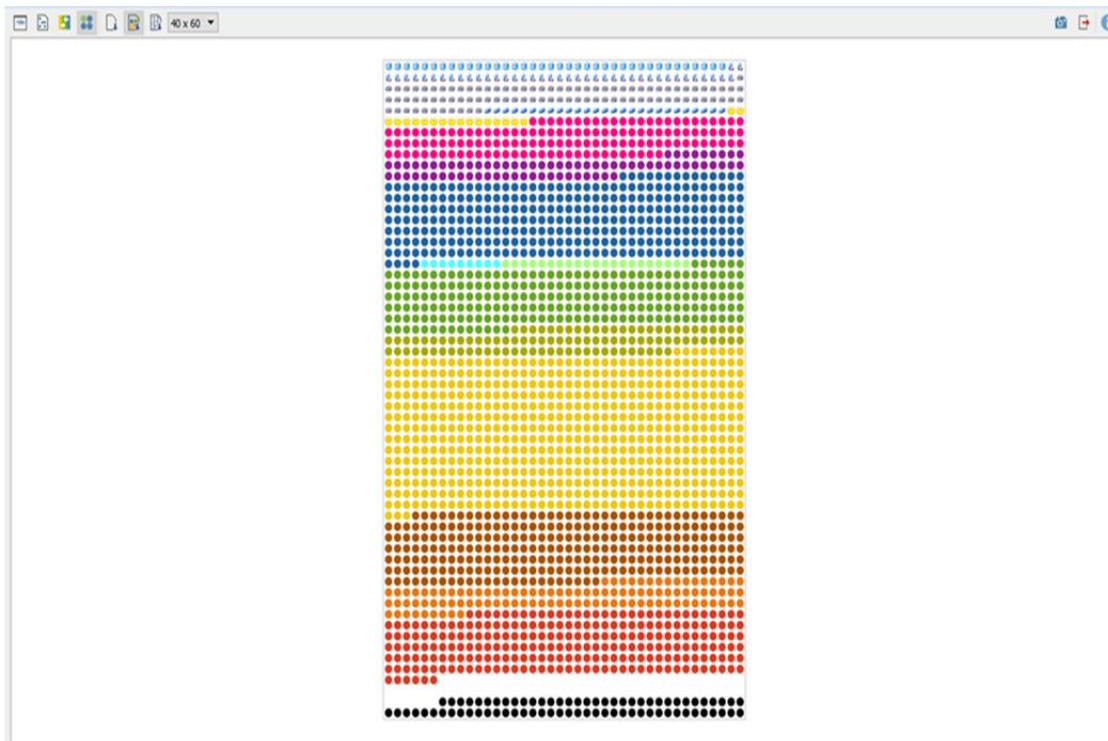
Smart coding tool:

In addition, the researcher clicked on the code in the Smart Coding Tool, to automatically take her to the relevant transcript entries, needed to analyse, and find patterns or differences. Screenshot 6 below shows how the notepad code is associated with different participants' code segments. They related to coping strategies to prompt or aid their memory loss.

Summaries with Coded Segments. By using MAXQDA's Overview of Coded Segments, the researcher was able to click on each code for each participant, to retrieve the relevant text

Code	Coded segments	Summary
note pad	I am having to look at diaries and ask the family have we done this before LESS 7 transcript : 22 - 22 (0) I have a white chalkboard in the kitchen/dining room, so I write things down that are important…..I do I write things down to jog the memory so when I see it in the morning, I deal with it straight away then…….that's how I remember things…but Linda has been terrific, giving me a nudge, don't forget this, don't forget that, so we still work as a team, but , yeh, it is a struggle still LESS 7 transcript : 24 - 24 (0)	
	.I've written down LESS 3 wife transcript: 6 - 6 (0)	
	she can remember things if she thinks we've got a photograph and she keeps the photograph, she'll remember it and remember things to do with that photograph or she'll remember things she's written in the daily diary but you know after a couple of weeks if you were to say you know " Can you remember what our hotel was like" she wouldn't have a clue, couldn't describe it at all. LESS 4 husband transcript: 54 - 54 (0)	

MAXQDA Overview of Codes, showing number of coded segments and % of all documents is shown below.

Color	Parent code	Code
●	Activities/hobbies before	activities after /friends
●		Activities/hobbies before
		airplane/holiday
		astonished
●		Awaiting diagnosis
●	Character before	Character after
●		Character before
●		Coping strategies
		crying
●	Awaiting diagnosis	Difficult to diagnose
		driving
●		Family
●		Feelings
●	Activities/hobbies before	Friends
●		Future plans
		hospital
		laugh out loud
		laughing
		limbic encephalitis symptoms
●		Medication
		Navigation/orientation
		note pad
●		Other support
●	Family	Partner/spouse
●		Professional support
●		Quote
		sad/disappointed
●	Character after	Self-image
		smiling
	Medication	Treatment
		treatment: pills or infusion
●	Work before	Work after
●		Work before

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Color	Parent code	Code	Coded segments of all documents	% Coded segments
	Activities/hobbies before	activities after /friends	159	6.27
		Activities/hobbies before	4	0.16
		airplane/holiday	19	0.75
		astonished	5	0.20
		Awaiting diagnosis	15	0.59
	Character before	Character after	231	9.12
		Character before	3	0.12
		Coping strategies	187	7.38
		crying	8	0.32
	Awaiting diagnosis	Difficult to diagnose	115	4.54
		driving	16	0.63
		Family	4	0.16
		Feelings	530	20.92
	Activities/hobbies before	Friends	9	0.36
		Future plans	42	1.66
		hospital	16	0.63
		laugh out loud	37	1.46
		laughing	14	0.55
		limbic encephalitis symptoms	360	14.21
		Medication	26	1.03
		Navigation/orientation	4	0.16
		note pad	8	0.32
		Other support	16	0.63
	Family	Partner/spouse	176	6.95
		Professional support	16	0.63
		Quote	345	13.61
		sad/disappointed	30	1.18
	Character after	Self-image	5	0.20
		smiling	2	0.08
	Medication	Treatment	10	0.39
		treatment: pills or infusion	34	1.34
	Work before	Work after	81	3.20
		Work before	7	0.28

	Frequency	Percentage
Feelings	525	20.49
Quote	320	12.49
Symptoms	232	9.06
Character before\Character after	223	8.70
limbic encephalitis symptoms	222	8.67
Coping strategies	177	6.91
Family\Partner/spouse	173	6.75
Activities/hobbies before\activities after /friends	153	5.97
Awaiting diagnosis\Difficult to diagnose	114	4.45
Work before\Work after	81	3.16
Future plans	41	1.60
Laugh out loud	37	1.44
Treatment: tablets/infusion	34	1.33
Sad/disappointed	28	1.09
Medication	26	1.01
Airplane/holiday	19	0.74
Other support	16	0.62
Professional support	15	0.59
Driving licence	15	0.59
Hospital treatment	15	0.59
Awaiting diagnosis	15	0.59
Laughing	14	0.55
Activities/hobbies before\Friends	9	0.35
Medication\Treatment	9	0.35
Crying	8	0.31
Note pad/post-it notes/diaries	7	0.27
Work before	7	0.27
Astonished/shocked	5	0.20
Character after\Self-image	5	0.20
Activities/hobbies before	4	0.16
Family	4	0.16
Navigation/orientation	4	0.16
Character before	3	0.12
Smiling	2	0.08
TOTAL (valid)	2562	100.00

Theme One: Acute symptoms and a correct diagnosis of aLE.

Integrated/not sub-themes	Codes used in MAXQDA	To achieve
Acute phase	Awaiting diagnosis	Acute symptoms and feelings associated with waiting for correct diagnosis
Hospitalisation	hospital	Feelings, experiences
Professional support	Professional support	Feelings

Theme Two: Chronic symptoms and personal impact

Sub-theme	Codes used in MAXQDA	To achieve
Ongoing impact on patient	Feelings Symptoms treatment: pills or infusion	Ongoing symptoms and feelings /experiences associated with these.

Ongoing impact on carer	limbic encephalitis symptoms treatment: pills or infusion sad/disappointed laugh out loud laughing Navigation/orientation crying astonished Feelings Symptoms	As above, for the carer.
Coping strategies and support	Coping strategies note pad Other support	Methods of adaptation, coping strategies for patient and carer; self-initiated/devised by others. Family/friends/Church.

Theme Three: Relationships

Sub-theme	Codes used in MAXQDA	To achieve
Spouse/partner	Family Partner/spouse	Feelings/experiences Changes since aLE Role reversal
Family and friends	Family Friends	Feelings

Theme Four: Work and activities

Sub-theme	Codes used in MAXQDA	To achieve
Work	Work before Work after	Adaptation to new work Role reversal Feelings Financial aspect

Activities	Activities/hobbies before Friends activities after /friends	Ongoing symptoms/feelings

Theme Five: Future plans

Sub-theme	Codes used in MAXQDA	To achieve
Impact of aLE	Future plans	Feelings
	Feelings	Adjustment/adaptation
With other health issues		

Transcripts are available on request. Quotes for each theme are available also.

Appendix 34: Overview of researcher's memos, reflections, bracketing, additional information

PDF

Overview of Memos
(1).pdf   Long document available as electronic PDF

Appendix 35: PowerPointPresentation_LESSS6 patient

PDF

Appendix 35
Powerpoint Present

Appendix 36: PowerPoint Presentation LESS8 wife

PDF

Appendix 36
Powerpoint Present

Additional information from LESS1

(Available to read on request, as data referring to patient, hospital name and doctor, would need redaction).

Appendix 37: REC Approval -substantial amendment

IRAS project ID:	248379
REC reference:	18/SC/0448
Short Study title:	Memory and motivation v1.0
Date complete amendment submission received:	30 August 2019
Amendment No./ Sponsor Ref:	Substantial amendment 1
Amendment Date:	29 August 2019
Amendment Type:	**Substantial**
Outcome of HRA Assessment	**This email also constitutes HRA and HCRW Approval for the amendment, and you should not expect anything further.**

I am pleased to confirm that this amendment has been reviewed by the Research Ethics Committee and has received a Favourable Opinion. Please find attached a copy of the Favourable Opinion letter.

HRA and HCRW Approval Status

As detailed above, **this email also constitutes HRA and HCRW Approval for the amendment**. No separate notice of HRA and HCRW Approval will be issued. You should implement this amendment at NHS organisations in England and/or Wales, in line with the conditions outlined in your categorisation email.

- If this study has HRA and HCRW Approval, this amendment may be implemented at participating NHS organisations in England and/or Wales once the conditions detailed in the categorisation section above have been met
- If this study is a pre-HRA Approval study, this amendment may be implemented at participating NHS organisations in England and/or Wales that have NHS Permission, once the conditions detailed in the categorisation section above have been met. For participating NHS organisations in England and/or Wales that do not have NHS Permission, these sites should be covered by HRA and HCRW Approval before the amendment is implemented at them, please see below;
- If this study is awaiting HRA and HCRW Approval, I have passed your amendment to my colleague and you should receive separate notification that the study has received HRA and HCRW Approval, incorporating approval for this amendment.

User Feedback

The Health Research Authority is continually striving to provide a high-quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

If you require further information, please contact hra.amendments@nhs.net

18/SC/0448/AM02 Please quote this number on all correspondence

Kind regards,

Mark

Mark Thompson
Approvals Officer
Health Research Authority
Bristol Research Ethics Committee Centre | Whitefriars | BS1 2NT
E. nrescommittee.southcentral-oxforda@nhs.net
W. www.hra.nhs.uk

Appendix 38: -HRA Favourable Opinion

NHS
Health Research Authority

South Central - Oxford A Research Ethics Committee

Bristol Research Ethics Committee Centre
Whitefriars
Level 3 Block B
Lewins Mead
Bristol
BS1 2NT

> **Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.**

14 October 2019

Professor Masud Husain
Professor of Neurology & Cognitive Neuroscience, Wellcome Trust Principal Research Fellow
University of Oxford
Nuffield Dept Clinical Neurosciences
John Radcliffe Hospital
Oxford
OX39DU

Dear Professor Husain

Study title:	**Memory and motivation in health and disease**
REC reference:	**18/SC/0448**
Amendment number:	**Substantial amendment 1**
Amendment date:	**29 August 2019**
IRAS project ID:	**248379**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Interview schedules or topic guides for participants [Interview schedules]	1.1	10 October 2019
Notice of Substantial Amendment (non-CTIMP)	Substantial amendment 1	29 August 2019
Participant consent form [Consent form]	1.1	10 October 2019
Participant information sheet (PIS) [PIS Patients]	1.1	10 October 2019
Participant information sheet (PIS) [Dictaphone PIS]	1.1	10 October 2019
Participant information sheet (PIS) [PIS Informants]	1.1	10 October 2019
Research protocol or project proposal [Clean]	1.6	18 August 2019
Research protocol or project proposal [TC]	1.6	18 August 2019

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

18/SC/0448:	Please quote this number on all correspondence

Yours sincerely
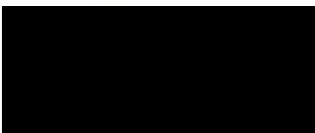
On behalf of Dr. Hugh Davies
Chair

E-mail: nrescommittee.southcentral-oxforda@nhs.net

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Appendix 39-ACE Scoring

[PDF icon]
Appendix 39
ACE-III_Scoring_(UK)

Appendix 40: Psychometric conversion table

[PDF icon]
Psychometric_Conv
ersion_Table. for WI

Appendix 41: Electronic Patient Records (EPR) on referrals and MRI

Appendix 41 EPR notes on referrals ar

STUDY ID	JR	P	Referral Notes	MRI details	Patient /carer sent us personal notes
LESS 1	JR930	P634	Referral from Salford Royal. Steroids, TPE, Rituximab 2013.	No MRI on EPR	Could not do MRI dues to pacemaker Nov 2011
			Confused after having pacemaker for bradycardia.		Full brain CT-reduced swelling Dec 2011
			Temporal lobe seizures, left upper arm automatism with eyes turning to left		EEG no seizures Jan 2012
					Seizure Feb 2012
					CT brain clear Mar 2012
					Apply for funding for IVIG and Rituximab Mar 2012
					Confabulation and confusion throughout, hallucinations, missing feeding himself, emotional, didn't know where household items went when he returned home May 2012, speech a little slurred, took him back in hospital 5 months, but home at weekends only, Neuro rehab ward (clinical psychologist, keyworker, OT) Jun 2012,
					Home Jul 2012, assisted technology offered for epilepsy sensor incase Paul leaves house, an alram will go off.
					Social worker rings, Home Care Team help with kitchen tasks, needs prompting about road safety,
					Community neuro rehab Jul 2012 go with Paul on bus to assess
					Seizures continue, butterflies in stomach, feels wobbly
					Rituximab May 2013, maybe again in 12-18 months
					Rituximab Jun 2015
					Readmitted Jul 2018 they said anxiety attack, but wife mentioned his encephalitis- relapse-confused, slurred speech, wobbly, TPE, agitated, discharged end Jul 2018
					PID document for his 'tour' of hositpal admisions, home visits etc
LESS 2	JR911	PS11	Referral from Salford Royal 2017	No MRI on EPR	
			Right arm shaking, FBDS, sudden fall, broke hip		
LESS 3	JR982	P734	Seizures including surges of emotion and parasthesia, pallor without piloerectile thermal sensations, increase in spending on motorbikes,		
			Premorbid history-calm and loving	MRI-slightly high signal in left hippocampus Dec 2017	
			Psychiatrist 2018		
LESS 4			Referral from Gloucester Royal 2019	MRI-right MTL expansion Aug 2019	
			Memory loss 2016, focal seizures, includin ggoosebumps rising sensations, TPE Jul 2019		
LESS 5			Referral Brighton, Sussex.	MRI-NAD	
			2016 Memory loss		
			No seizures		
LESS 6			Referral from Kettering Hospital 2015	MRI-bilateral cerebral atrophy including bilateral hippocampal atrophy	
			Parkinsons too 2017		
LESS 7			LGI1 2016		
			Episodes of brief extension right arm and right leg	MRI-Feb 2020- no convincing factors of autoimmune encephalitis	
			Vacant 3-4 times a day		
			2017 relapse FBDS		
LESS 8			Referral from Southampton	MRI- nothing on EPR	
LESS 9			Referral from Essex	No MRI on EPR	
			Was being seen at Cognitive Disorders Clinc (MH)		
LESS 10				MRI Feb 2016 Right hippocampus amygdala remains slightly increased T2 signal constant with daignosis. Left amygdala borderline atrophic.	