Cognitive and psychosocial functioning in genetic generalised epilepsy

Amy Loughman

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Melbourne School of Psychological Sciences
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne

Abstract

Genetic generalised epilepsies (GGE) are a common, but under-studied cluster of epileptic syndromes of predominantly child and adolescent onset. The primary syndromes of GGE are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and genetic generalised epilepsy with generalised tonic-clonic seizures only (GTSCO). Important questions remain regarding: the degree of cognitive and psychopathological comorbidity, particularly in adults and in syndromes other than JME; effects of the disease on cognitive function; and psychopathology and psychosocial wellbeing in these patient groups.

This thesis aimed to provide a detailed and quantitative description of cognitive function and psychopathology in GGE, assess the impact of contributing factors including subclinical epileptiform discharges on cognitive and psychopathology outcomes, and to evaluate the relationship between psychopathology and cognition.

Methods employed include narrative systematic review, quantitative meta-analysis, and prospective assessment of cognitive and psychosocial functioning of a relatively large sample of people with GGE.

Results indicated mild to moderately large reductions across most cognitive factors relative to that of healthy control participants and age-based normative data, with a relative weakness in long-term retrieval and memory function. Short-term memory function was not reduced relative to age-based normative data. Overall cognitive ability and memory function was negatively associated with total duration of epileptiform discharges during a 24-hour period. Approximately 50% of the sample reported elevated symptoms on a measure of psychopathology spanning six symptom types, with depression and anxiety the most common amongst these. Collectively, these findings highlight the need for increased awareness, screening and the provision of services for psychological comorbidities for people with GGE.

Declaration

I hereby certify that this thesis comprises only my original work except where indicated below, that due acknowledgement has been made in the text to all other material used and is fewer than 100 000 words in length, exclusive of tables, references and appendices.

The following list of peer-reviewed publications are included in the thesis as they appear in their respective journals. For each, I am the primary author and contributed at least 50% of the writing. Detailed descriptions of contributions by all authors appears below and bears signatures verifying these.

Chapter 2

Loughman, A., Bowden, S.C. and D'Souza, W.J. (2014). Cognitive functioning in idiopathic generalised epilepsies: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 43, 20-34*.

Amy Loughman (AL), Stephen Bowden (SB) and Wendyl D'Souza (WD) conceived of and designed the study. AL determined the eligibility criteria and undertook the database search for eligible articles. AL and SB assessed the retrieved articles for eligibility. AL extracted data from eligible studies, conducted the meta-analyses and drafted the manuscript. AL, SB and WD edited the manuscript. All authors discussed the results and implications, edited and commented on the manuscript at all stages.

Overall contributions: AL 75%, SB 15%, WD 10%.

Chapter 3

Loughman, A., Bendrups, N., and D'Souza, W.J. (2016). A systematic review of psychiatric and psychosocial comorbidities of genetic generalised epilepsies (GGE). *Neuropsychology Review,* 26(4), 364-375.

AL conceived and designed the study. AL determined the eligibility criteria and undertook the database search for eligible articles. AL and Nicholas Bendrups (NB) assessed the retrieved articles for eligibility and extracted data from eligible studies. AL drafted the manuscript. All authors discussed the results and implications, edited and commented on the manuscript at all stages.

Overall contributions: AL 75%, NB 15%, WD 10%, with interpretive assistance from SB.

Chapter 7

Loughman, A., Bowden, S,C. and D'Souza, W.J. (2016). A comprehensive assessment of cognitive function in the common genetic generalised epilepsy syndromes. *European Journal of Neurology. (Published online 27th December 2016). doi:10.1111/ene.13232*

WD and SB conceived and designed the study. SB and AL selected the tests of cognitive function and the data analysis strategy. AL conducted the data analysis and drafted the manuscript. All authors discussed the results and implications, edited and commented on the manuscript at all stages.

Overall contributions: AL 70%, SB 20%, WD 10%.

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WD conceived and designed the study. Udaya Seneviratne (US) designed and conducted EEG analyses. SB and AL selected the tests of cognitive function and the data analysis strategy. AL conducted the data analysis. AL and US drafted the manuscript. All authors discussed the results and implications, edited and commented on the manuscript at all stages.

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Chapter 9

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WD and SB conceived and designed the study. SB selected the measure of psychosocial functioning. AL and SB designed the data analysis strategy. AL conducted the data analysis and drafted the manuscript. All authors discussed the results and implications, edited and commented on the manuscript at all stages.

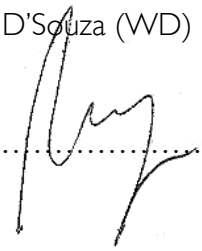
Overall contributions: AL 70%, SB 20%, WD 10% with acknowledgment of EEG analysis by US.

Co-author signatures

Stephen Bowden (SB)

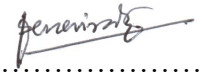
…… Date: …28/1/2017……

Wendyl D'Souza (WD)



…… Date: 19/1/2017

Udaya Seneviratne (US)



…… Date: 12/01/2017

Nicholas Bendrups (NB)

…… Date: 20/01/2017

Publications, Presentations & Awards during Candidature

Publications

Loughman, A., Bowden, S.C. and D'Souza, W.J. (2014). Cognitive functioning in idiopathic generalised epilepsies: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 43, 20-34.*

Loughman, A., Seneviratne. U., and D'Souza, W.J. (2016). Epilepsy beyond seizures: Predicting enduring cognitive dysfunction in genetic generalized epilepsies. *Epilepsy & Behavior, 62, 297-303.*

Loughman, A., Bendrups, N., and D'Souza, W.J. (2016). A systematic review of psychiatric and psychosocial comorbidities of genetic generalised epilepsies (GGE). *Neuropsychology Review,* 26(4), 364-375.

Loughman, A., Bowden, S.C. and D'Souza, W.J. (2017). Self and informant report ratings of psychopathology in genetic generalised epilepsy. *Epilepsy & Behavior, 37, 13-19.*

Loughman, A., Bowden, S.C. and D'Souza, W.J. (2016). A comprehensive assessment of cognitive function in the common genetic generalised epilepsy syndromes. *European Journal of Neurology. (Published online 27th December 2016). doi:10.1111/ene.13232*

International Conference Presentations

National Academy of Neuropsychology Annual Meeting, Austin, TX. (2015). Platform presentation entitled *Cognitive functioning in GGE: the role of epileptiform discharges*

International Epilepsy Congress, Istanbul, Turkey. (2015). Poster presentation entitled *Epileptiform discharges and cognitive ability in genetic generalised epilepsy (GGE)*

American Epilepsy Society Annual Meeting, Seattle, W.A. (2014). Poster presentation entitled *Psychopathology in idiopathic generalised epilepsies*

American Epilepsy Society Annual Meeting, Washington D.C. (2013). Poster presentation entitled *Cognitive Function in Idiopathic Generalized Epilepsies: a Meta-Analysis*

Domestic Conference Presentations

College of Clinical Neuropsychologists Annual Conference, Adelaide. (2014). Platform presentation entitled *Neuropsychological issues in understanding idiopathic generalised epilepsies (IGE)*

Epilepsy Melbourne Annual Meeting, Melbourne. (2014). Invited platform presentation entitled *Psychopathological comorbidity in genetic generalised epilepsies*

Clinical College of Neuropsychologists Annual Conference, Brisbane. (2013). Platform presentation entitled *Cognition in Idiopathic Generalised Epilepsy: Systematic Review and Meta-Analysis*

Other Presentations

Yale Comprehensive Epilepsy Program, New Haven, CT. Invited presentation. (2015)

RRR 'Einstein A Go Go' radio program guest. (2014)

3 Minute Thesis Competition Grand Final, University of Melbourne. (2014)

Awards, Scholarships and Grants

Melbourne School of Psychological Sciences Special Career Development Grant (2015)

Adam J Berry Memorial Scholarship, Australian Academy of Science & National Institutes of Health (2014)

Melbourne Abroad Traveling Scholarship (2014)

Grand Finalist 3 Minute Thesis Competition, University of Melbourne (2014) American

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Abbreviations

AED	Anti-epileptic drug/s
ASEBA	Achenbach System of Empirically Based Assessment
CAE	Childhood Absence Epilepsy
CHC	Cattell-Horn-Carroll
ED	Epileptiform discharge/s
EEG	Electroencephalogram
EF	Executive function
G	General ability
Gc	Crystallised intelligence/Acquired knowledge
Gf	Fluid intelligence
GGE	Genetic generalised epilepsy
Glr	Long-term memory
Gs	Speed of information processing
Gsm	Short-term memory
GTCS	Generalised tonic-clonic seizure
GTCSO	GGE with generalised tonic-clonic seizure only
IED	Interictal epileptiform discharge/s
IGE	Idiopathic generalised epilepsy
JAE	Juvenile Absence Epilepsy
JME	Juvenile Myoclonic Epilepsy
MRI	Magnetic resonance imaging
WJ-III	Woodcock Johnson III Tests of Cognitive Ability

'All medical conditions that are chronic impact, to a greater or lesser degree, on the life quality of those affected by them. Epilepsy is a chronic condition characterised by clinical uncertainty'.

Baker, 2001

A note about terminology

The terminology associated with seizure types and epilepsy syndromes is reviewed regularly by the International League Against Epilepsy's Commission on Classification and Terminology. This Commission published its first report in 1960, and by its own description is based on concepts that 'predate modern neuroimaging, genomic technologies and concepts in molecular biology' (Berg et al., 2010). Revisions since then have sought to enlist the expertise of leaders in the fields of genetics, neuroimaging, statistics and research design and to reflect current evidence-based knowledge. As epilepsy research progresses and knowledge evolves, the official classification and terminology of epilepsy syndromes and concepts is accordingly updated.

The Commission's 1989 report and its proposed revision in 2001 use the term 'idiopathic generalised epilepsies' to describe forms of primary generalised epilepsies with an 'EEG expression' that is generalised, bilateral, synchronous and symmetrical (ILAE, 1989). The ILAE Proposal for Revised Terminology for Organisation of Seizures and Epilepsies in 2010 suggested the new term 'genetic' to replace 'idiopathic', since idiopathic epilepsies were now presumed to be directly due to genetic defects. This revised Commission report was published in the same year as the initial approval of the larger project in which this study belongs, thus the term 'idiopathic' had already been nominated for its title: *Long-term Prognosis of Idiopathic Generalised Epilepsy: A Prospective Study*. Since this Proposal, the term *genetic generalised epilepsy* has gradually replaced *idiopathic generalised epilepsy*. *Genetic generalised epilepsy (GGE)* will be used throughout the current document in acknowledgment of the adoption of this term in the epilepsy research community (e.g. Gallentine & Mikati, 2012).

The systematic review and meta-analysis published in 2014 (Loughman, Bowden & D'Souza; see Chapter 3) uses *idiopathic*, as this term was used by all of the included studies.

Overview and purpose

This thesis, and the larger project in which it is housed, the *Long-Term Prognosis Study*, seeks to form part of the scientific pavement towards an evidence-based practice in epilepsy management and care. The research was conducted in order to contribute to the understanding of genetic generalised epilepsies using reproducible, reliable and valid methods with strong theoretical underpinnings.

The goal of improving evidence-based practice was front-of-mind during this study and informed the process throughout. Evidence-based practice refers to the integration of best research evidence, clinical expertise and patient values into clinical practice (Sackett, Straus, Richardson, Rosenberg, & Haynes, 2000). For example, it informed methodological decisions such as the use of cognitive tests that reflect underlying latent variables of cognitive functioning such that the results can be interpreted without test-specific knowledge or belief, and can be compared with other studies despite variations in test choice. I employed this principle of interpreting findings through a theoretical lens when conducting the systematic review and meta-analysis in Chapter 3. This method is the most effective way to cohesively and meaningfully integrate findings from the twenty six methodologically diverse studies, and represents the highest level of evidence in evidence-based medicine (Burns, Rohrich, & Chung, 2011). To communicate the output, I worked to write and publish work as analyses were completed, in order to expose the research to peer review and critical appraisal early, and make it available to the scientific community in the manner that all research should be - as soon as possible. The thesis chapters and journal articles have been written in accordance with the STROBE Statement of items that should be included in reports of observational studies (Strengthening the Reporting of Observational Studies in Epidemiology; Von Elm et al., 2007).

Structure of the thesis

Chapters 1 and 2 are the Introduction to this thesis, providing an overview of the topics relevant to the thesis, and more detailed 'mini-reviews' of pertinent issues. Two systematic reviews and meta-analyses of the primary questions regarding cognitive and psychosocial function respectively, complement the literature review and are presented in Chapters 3 and 4. Chapters 5 and 6 outline the methods and results respectively, while Chapters 7, 8 and 9 provide empirical papers addressing each research question and the findings from the three key themes of the thesis: cognitive function, the potential role of epileptiform discharges and psychosocial function. Chapter 10 contains the General Discussion, in which conclusions from all preceding sections of the thesis are embedded into current research literature, clinical guidelines and suggestions for future applications of this work.

Chapter 1: An Introduction to Epilepsy

Epilepsy is a chronic, non-communicable disease of the brain in which there is a tendency to have recurrent, unprovoked seizures (Blumenfeld, 2010; World Health Organization, 2016). Although epilepsy has been referred to as a 'disorder' in the past, in 2014 the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy agreed that this term implied a temporary failure which could minimise the seriousness of the condition. These international associations recommended that it be instead referred to as a 'disease' (Fisher, Acevedo, Arzimanoglou, Bogacz, Cross, Elger, Engel, Forsgren, French, Glynn, Hesdorffer, Lee, Mathern, Moshé, et al., 2014). The 'practical clinical definition' outlined in this report by the ILAE states that the diagnosis of epilepsy is suitable given any one of the following conditions:

1) At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;

2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;

3) Diagnosis of an epilepsy syndrome.

This working definition of epilepsy as defined by the ILAE 1993 and 2005 was primarily an 'enduring predisposition' to generate seizures, and could simply entail two unprovoked epileptic seizures more than 24 hours apart (Fisher, Acevedo, Arzimanoglou, Bogacz, Cross, Elger, Engel, Forsgren, French, Glynn, Hesdorffer, Lee, Mathern, Moshé, et al., 2014; Fisher et al., 2005; International League Against Epilepsy & Prognosis, 1993). Following revision of ILAE definitions in 2006, there has been some debate about whether the definition should include provisions for cases where a single epileptic seizure, in the presence of other conditions, may also be considered a suitable conceptual, if not operational, definition of epilepsy (Fisher & Leppik, 2008). As Fisher and colleagues state, the other necessary conditions for diagnosis include 'surrogate markers' such as clinical, EEG, neuroimaging or genetic factors indicating a high likelihood of future seizures. However this conceptual definition is considered separate from criteria that inform clinical decisions which are made on the basis of the

consideration of patient-centred risks and benefits rather than diagnostic criteria per se (Fisher & Leppik, 2008).

Clearly then, epilepsy is not synonymous with seizure. A seizure is an episode of 'abnormally synchronised and high-frequency firing of neurons in the brain' that is accompanied by a subjective experience or behavioural abnormality (Blumenfeld, 2010). Seizures have a lifetime prevalence of 10-15% and can occur in people who do not have epilepsy (Blumenfeld, 2010). Causes can include exposure to neurotoxins, traumatic brain injury, alcohol withdrawal and low blood sugar. Seizures under these conditions are considered to be provoked, and are therefore not considered indicative of epilepsy in their own right. Conversely, just as seizures are not necessarily indicative of epilepsy, some epilepsy conditions do not bear seizures as their primary feature. One example is Landau-Kleffner Syndrome, which is characterised by progressive cognitive impairment and aphasia related to paroxysmal EEG abnormalities, with or without seizures (Pearl, Carrazana, & Holmes, 2001).

Epilepsy is far from being a unitary construct; there are a large variety of causes, treatments and prognostic outcomes. Some of the aetiologies of epilepsy syndromes are attributable to genetic, structural (e.g. brain tumour) and metabolic causes, whilst others remain unknown. The time-course of epilepsy syndromes also varies, with some resolving spontaneously and others expected to persist throughout life. Epilepsy is considered 'resolved' (as opposed to being 'in remission' or 'cured') when a patient is seizure free for 10 years and off AED for 5 years (Fisher, Acevedo, Arzimanoglou, Bogacz, Cross, Elger, Engel, Forsgren, French, Glynn, Hesdorffer, Lee, Mathern, Moshe, et al., 2014).

There are over forty different epilepsy syndromes which vary widely with respect to onset, aetiology, treatment, psychosocial sequelae and long-term prognosis (Berg et al., 2010). It is the appreciation of this variability and a need for precise, syndrome specific knowledge that drives syndrome-based rather than mixed group studies in epilepsy. This thesis will examine a cluster of epilepsy syndromes, namely genetic generalised epilepsies (GGE).

1.1 A Brief History of Epilepsy

'The history of epilepsy can be summarised as 4000 years of ignorance, superstition and stigma, followed by 100 years of knowledge, superstition and stigma.'

Kale, 1997

Epilepsy has long been misunderstood and wrongly attributed to a number of mystical and spiritual causes, adding insult to the illness in the form of discrimination and stigma. Early Greek mythology considered epilepsy to be an act of God, due to the powerful and inexplicable nature of seizures and their spontaneous recovery (Temkin, 1994). A number of cultures similarly attributed seizures to spiritual means such as demonic possession (The History and Stigma of Epilepsy, 2003), or punishment of sins (Jelik, 1979). These superstitious attributions were challenged by Hippocrates as early as 400BC, who stated ahead of his time and in the absence of medical evidence, that the cause of epilepsy lies surely in the brain (The History and Stigma of Epilepsy, 2003). Although speculating that aberrations of 'sun, cold and wind' were to blame, he correctly identified biological heredity rather than supernatural origins as a likely aetiology of the condition.

Despite this early wisdom, myths and misunderstanding have plagued the field of epilepsy, with fears of contagion from the disease present in European society even in the 18th century (The History and Stigma of Epilepsy, 2003). Hughlings Jackson's 1873 writings on seizures and epileptiform discharges as sudden electrochemical discharges of energy in the brain laid the foundations for current understanding of the neurological underpinnings of epilepsy (York & Steinberg, 2011).

Historical treatments for epilepsy in Western culture have mirrored the development of understanding regarding its cause, and have included the consumption of foods with 'drying' properties (bread and acrid herbs) or lifestyle (living in a dry climate) due to the Hippocratic belief that epilepsy was caused by an excess of phlegm (Gross, 1992). Religious rituals have also been practiced to treat epilepsy. Even in the 19th century when the physiological mechanisms were increasingly becoming understood, primitive treatments persisted, including mistletoe, turpentine, circumcision and castration (Gowers, 1901). At this time, potassium bromide, a sedative medication began to be

used, the efficacy of which was marred by side effects. This first drug treatment paved the way for the use of the pharmacologically-related substance, phenobarbital, from 1912. Phenobarbital also harboured a balance of benefit and harm and remained a relatively common anti-epileptic prescription until reports of negative behavioural and cognitive side-effects in children made its use controversial (Farwell et al., 1990). Surgical procedures for epilepsy began in the 19th century, hemispherectomy in the early 20th century and surgery targeted to an epileptogenic focus performed for the first time in 1938 by Gibbs and Lennox (Hermann & Stone, 1989). Contemporary treatment for epilepsy includes 1) surgery, with ever-evolving diagnostic, imaging and surgical technology and techniques); 2) anti-epileptic drugs (AED), with significant improvement in side-effect profiles since potassium bromide); 3) the ketogenic diet; 4) vagus nerve stimulation; 5) psychological therapies; 6) medical marijuana and alternative and complementary therapies such as herbal medicine, Ayurvedic medicine, and traditional Chinese medicine (Hermann & Stone, 1989).

The stigmatisation of people with epilepsy as suffering gross behavioural abnormalities and psychiatric conditions was another longstanding feature of misunderstanding about the disease by the medical and general community. According to Masia and Devinsky (2000), the notion of an 'epileptic personality' evolved slowly, and can be attributed to a combination of factors. These factors include stigma about a disease of apparently mystical origins, misunderstanding and the fact that a significant proportion of people with epilepsy are likely to have experienced concurrent central nervous system disorders or psychogenic non-epileptic seizures and would therefore have suffered a higher incidence of comorbid psychiatric disturbance than in the healthy population. The 'epileptic personality' was popularised in the early 20th century and was defined by a disparate and atheoretical set of characteristics such as or including aggression, circumstantiality, emotional lability, guilt, hypo- or hyper-moralism, paranoia and 'viscosity', a tendency for repetition, tenacity (Masia & Devinsky, 2000). Although the 'epileptic personality' has since fallen out of favour, similar trait-based characterisations of some epilepsy syndromes continue to be discussed in the clinical research literature (Devinsky & Najjar, 1998). Of course in many cases these descriptions of behavioural features may stem from at least a kernel of physiological truth. The immediate ictal and postictal period can include psychosis and may be accompanied by significant

behavioural change. Additionally, as will be discussed in Chapters 2, 4 and 9, mood disorders are strongly associated with epilepsy (Barry, 2003).

Myths and misconceptions about epilepsy have been at the root of both institutionalisation and institutionalised discrimination throughout history. A range of discriminatory, unfortunate and occasionally bizarre conditions have been imposed on people with epilepsy. For example, marriage was alternately recommended for its favourable influence on the disease (for women), and discouraged due to the 'creation of a diseased progeny generally lower in mental, moral, and physical stamina than their antecedents' (Spratling, 1904, p302–303). Eugenic laws were first enacted against people with epilepsy in Connecticut, USA in 1895, and these were repealed in Connecticut only in 1953. The last state to repeal such laws did so in 1980 (Minagar, 2010). Supernatural attributions to seizures persist in many parts of South-East Asia, where misconceptions about contagion, madness and infertility are particularly powerful in maintaining strong stigma against people with epilepsy and their families (Jacoby, Snape, & Baker, 2005; World Health Organisation).

Discrimination remains prevalent in modern times. A study of British and European health practitioners in the 1990s revealed the belief in an 'epileptic personality' was held by approximately 15% of those surveyed, whilst over a third believed that epilepsy is accompanied by intellectual deficits (de Boer et al., 1994). A number of relatively recent global campaigns have aimed to destigmatise epilepsy, and to legislate against discrimination in the workplace and other domains, such as when applying for insurance and for a driving license (de Boer, Mula, & Sander, 2008; Schneider & Conrad, 1980). Stigma has been defined as the 'relation between the differentness of an individual and the devaluation society places on that particular differentness', and is particularly powerful when the recipient of stigma holds the same devalued view of themselves as does the society (Dell, 1986). The personal experiences of people with epilepsy can commonly include low self-esteem and internalisation of societal stigma (Jacoby, 2002) (de Souza & Salgado, 2006). In a survey by the World Health Organisation in Nepal, nearly a quarter of Nepali people with epilepsy personally endorsed the society's belief of their own low social value and stated that they were unable to work due to their condition (World Health Organization, 2011).

In addition to societal perception, discrimination and stigma, it remains an unfortunate reality that epilepsy can result in a restriction of vocational and lifestyle outcomes. Safety considerations require limitations on driving licenses (six month restrictions on driving following a seizure in Australia), and patients are advised by healthcare providers on lifestyle modifications to reduce the risk of seizures (SIGN, 2015). These lifestyle recommendations can be a source of frustration to adolescent and young adult patients in particular, since suggestions often include maintaining regular routines, and avoiding sleep deprivation, excessive alcohol and stress (Collins, 2011; Eatock, 2007).

1.2 Current challenges

There are a number of challenges to the progress of research and evidence-based practice in epilepsy care and management. A significant presence in the research and clinical landscape of epilepsy is the constantly evolving diagnostic criteria and classification system updated regularly by the International League Against Epilepsy (ILAE). These updates respond to the ongoing evolution of research findings and reflect the changing practice and expertise of clinicians in the field. However the changing nature of diagnostic criteria can provide a challenge to those seeking to interpret contemporary findings with respect to previous studies and the historical context in which such studies were conducted.

An issue to be discussed in further detail in Chapter 2.4.3 (page 37), is the difficulty procuring and providing clear advice about the risk and side-effect profiles of AED. The development of new AED agents continues, and is accompanied by uncertainty about the longer-term side effects produced by these as well as any combined or interactive effects (Chung, Wang, & Hank, 2007; Tomson, 2004). The individual nature of treatment protocols that are designed to balance seizure control, tolerability, and side-effect profile within an individual patient makes research into interaction effects particularly difficult (Bromfield, 2003; Tomson, 2004). There is a well-documented discrepancy between patient reported side-effects of AED and objectively measured and documented side effects, particularly those concerning cognitive function - a common report of patients (Kwan & Brodie, 2001; Piazzini, Canevini, Maggiori, & Canger, 2001). There are several possible reasons for this discrepancy, including individual responses to AED, differences in the language used to describe cognition, and the ecological validity of neuropsychological tests (Perucca & Gilliam, 2012; Piazzini et al., 2001; Postal &

Armstrong, 2013). There remains no clear explanation of the mechanisms underlying side-effects in the majority of cases (Arif et al., 2009; Kwan & Brodie, 2001).

A further challenge to the care of people with epilepsy is an inherent tension between the twin goals of raising awareness about difficulties experienced by people with epilepsy, and reducing the societal stigma that has been associated with the disease throughout history. This is a problem that has emerged in public campaigns regarding mental illness (Kvaale, Haslam, & Gottdiener, 2013), and a nuanced and sensitive approach is required to achieve the goal of raising awareness without stigma.

1.3 Genetic Generalised Epilepsy (GGE)

1.3.1 Features of GGE

GGE is a cluster of primary generalised epilepsy syndromes, defined as such due to the generalised nature of the onset of the resulting types of seizures: absence, clonic, tonic, atonic, myoclonic (myoclonic, myoclonic-tonic or myoclonic-atonic), and generalised tonic-clonic (ILAE, 1989). Generalised seizures originate within or rapidly spread to 'bilaterally distributed' networks or systems (Berg et al., 2010), and are distinguished from focal seizures or those with unknown origins (see Figure 1 below). Electrophysiologically, the overall hallmark of GGE, is bilateral, synchronous and symmetrical generalised spike-wave activity on EEG (spikes, polyspike, spike wave and polyspike waves) with a frequency greater than 2-3Hz, typically occurring on a normal EEG background, whereas symptomatic generalised epilepsies in contrast typically have disorganised and slow backgrounds (Seneviratne, Cook, & D'Souza, 2012).

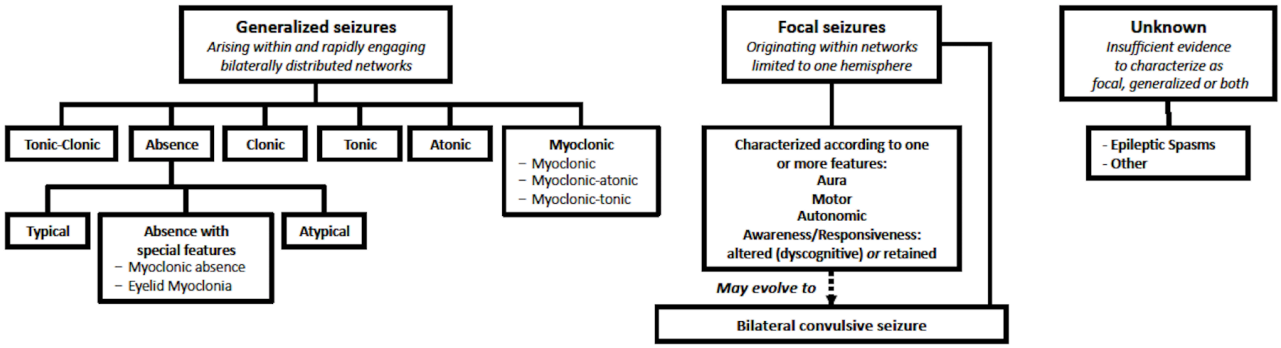


Figure 1. Classification of Seizures.
Adapted from (Berg et al., 2010).

Electrophysiology and Neurobiology

Whilst generalised epileptiform activity and seizures are the hallmarks of GGE, focal EEG features can also be found (Seneviratne et al., 2012). A recent paper co-authored by researchers leading the *Long-Term Prognosis Study* within which this thesis is contained (see Section 5.1, page 76 for details) concluded that 'atypical EEG abnormalities' not currently included in the ILAE definition of GGE were relatively common in a prospectively recruited sample of adult GGE patients (Seneviratne, Hepworth, Cook, & D'Souza, 2015). These included amplitude asymmetry, focal onset and offset of paroxysm, focal discharges, atypical morphology and generalised paroxysmal fast rhythm. These findings serve as a reminder of the evolving understanding of epilepsy syndromes, and the 'grey areas' between diagnostic boundaries into which a not insignificant proportion of cases may fall.

Other ongoing debates relevant to GGE include the minimum duration of generalised spike-wave or polyspike wave activity that constitutes an absence seizure (two to three seconds are currently the most endorsed views; Seneviratne et al., 2012). Similarly, whilst the distinction between 'ictal' and 'interictal' epileptiform activity is nominally that which occurs during a seizure and lasts at least a few seconds, as opposed to occurring outside of a seizure and lasting 'at most a few seconds', this is not necessarily a clear distinction in practice (Fisher, Scharfman, & deCurtis, 2014; Seneviratne et al., 2012). According to this definition, ictal activity should be accompanied by clinical and behavioural features of a seizure; if not, these are considered 'subclinical seizure activity'. The accuracy of

these descriptors may be contingent on the presence of an informed observer who can attest to the individual's inability to interact with their environment in some way. In order to avoid ambiguous or controversial use of terminology, I have used the term 'epileptiform discharge' to denote abnormal epileptiform activity of any duration and regardless of accompanying behavioural signs and symptoms (Chapters 8 and 9 provide in-depth analysis and discussion of these issues).

GGE is a 'non-lesional' epilepsy, meaning the brain is macroscopically normal, although subtle histological and spectroscopic abnormalities have been reported (Dickson, Wilkinson, Howell, Griffiths, & Grunewald, 2006). The observation of larger mesial frontal cortical grey matter in 40% of JME patients using voxel-based analysis suggests that at a more fine-grained neuroanatomic level than is typically investigated, structural cerebral abnormalities may be present (Woermann & Woermann, 1999).

The thalamocortical network is implicated in generalised seizures and in the spike-wave complex that occurs in GGE, and the thalamus is known to be specifically involved in absence seizures (Seneviratne et al., 2012; Snead, 1995; Tyvaert et al., 2009). Abnormal thalamocortical structural connectivity is related to disease severity in JME, as measured by diffusion tensor imaging (O'Muircheartaigh et al., 2012). Resting state functional connectivity studies have shown decreased connectivity between frontal and parietal regions within the default mode network, areas which are thought to be implicated in 'mentalising' i.e understanding one's own and others' mental states (Luo et al., 2011; McGill et al., 2012). Although the functional consequences of these neurobiological changes have not been definitively demonstrated, the authors of these studies postulate that they contribute to cognitive deficits seen in GGE.

White matter abnormalities have also been reported in JME, specifically in the crura of the fornix, body of the corpus callosum, uncinate fasciculi, superior longitudinal fasciculi, anterior limb of internal capsule, and corticospinal tracts (Liu, Concha, Beaulieu, & Gross, 2011). A meta-analysis of studies of JME found cumulative evidence for increased grey matter volume in the bilateral medial frontal gyri and anterior cingulate, and decreased grey matter volume in the bilateral thalamus, providing further support for thalamocortical circuitry involvement in JME (Cao et al., 2013).

Syndromes

The GGE syndromes differ primarily in their age of onset, and in the predominant seizure type that occurs. The most common GGE syndromes are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and GGE with generalised tonic-clonic seizures only (GTCSO). The attributes of each of these syndromes is summarised in Table 1 below. In addition to these syndromes benign familial neonatal seizures and benign myoclonic epilepsy in infancy are rare GGE syndromes, each representing less than 1% of all childhood epilepsies (Jallon & Latour, 2005). Epilepsy with myoclonic absences, epilepsy with myoclonic-astatic seizures (Doose syndrome) are other less common subtypes of GGE included in the ILAE Classification report of 2001 (Engel, 2001). Other conditions with characteristics broadly consistent with GGE have been reported and may comprise subtypes that are not currently recognised by the ILAE, including perioral myoclonia with absences and adult-onset GGE (Seneviratne et al., 2012). Due to their rarity or occurrence in early infancy, these syndromes are not included in the young adult and adult sample of GGE in this study.

Table 1

Summary of GGE syndrome attributes.

	Childhood Absence Epilepsy	Juvenile Absence Epilepsy	Juvenile Myoclonic Epilepsy	GGE with Generalised Tonic-Clonic Seizures Only
Age of onset	<10 years, peak at 5-6 years	7-16 years, peak at 10-12 years	8-26 years, peak at 12-18 years	12-18 years
Nature of seizures	Very frequent typical absences of 4-30 seconds in duration, associated with severe impairment of consciousness.	Less frequent absences than in CAE. GTCS can be frequent, often on awakening. Also myoclonic seizures occur infrequently. Absence status epilepticus in 1/5.	Commonly early morning seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. May cause sudden falls. No disturbance of consciousness. Often GTCS, less often, infrequent absences	GTCS only, not limited to seizures occurring on awakening (as per previous GTCS on awakening).
Electrophysiology	Bilateral, synchronous symmetrical spike-waves, usually 3 Hz on normal background activity	Spike waves often >3Hz, normal background	bilateral symmetrical 4–6 Hz polyspike-and-wave, often photosensitivity present	Normal background, 3–5-Hz generalized spike and wave
Seizure epilepsy prognosis	GTCS often develop during adolescence, otherwise absences remit or persist as the only seizure type. Can be self-limited	15-20% of children with CAE/JAE progress on to JME	85-90% achieve control with appropriate medication; remission following discontinuation of AED is rare (approx. 10%).	As for JME.
Incidence	0.7-8 per 100,000 person; 10-12% of children with epilepsy under 12 years; more common in girls (2-5 fold predominance)	20% of GGE cases. *May be underdiagnosed due to absence being overlooked.	1 per 100,000 persons; 17-18% of GGE cases; 4-10% of all epilepsies.	1.8 per 100,000 persons *Few data available and recent change to classification and terminology.

Compiled from: Camfield, Striano, & Camfield (2013); Jallon & Latour (2005); Wirrell, Camfield, Camfield, Gordon & Dooley (1996).

GGE: One or many syndromes

Among broader discussions about terminology and diagnostic criteria in epilepsy, GGE has been the topic of another specific debate. This debate concerns the distinctiveness of the GGE syndromes, and whether they should be considered to exist on a 'biologic spectrum' rather than as separate entities (Berkovic, Andermann, Andermann, & Gloor, 1987). Since EEG is the only well-established biologic marker of GGE syndromes, the characteristics of epileptiform abnormalities seen on EEG readouts are a critical aspect of classification and diagnosis. An in-depth review of a number of features including the morphology of the spike-wave complex, how seizures are provoked and factors impacting on the EEG in GGE concluded that differences between the syndromes are present (Panayiotopoulos, Obeid, & Waheed, 1989). Further specific EEG features have been reported more recently in each of the electroclinical syndromes of GGE (Seneviratne et al., 2012). Differences in white matter abnormalities between JME and GGE-GTCSO have also been reported (Liu et al., 2011). In contrast, a Melbourne-based group found no differences between adolescent and adult onset groups, supporting the idea of a 'life-long age spectrum' of the classic GGE syndromes (Yenjun et al., 2003). Those authors retrospectively examined the EEG of 177 GGE patients with varying diagnoses and corresponding ages of onset treated during the period 1975-2000 (Reutens & Berkovic, 1995; Yenjun et al., 2003). Blinded to age of onset and diagnosis, two investigators reviewed the background rhythm (posterior dominant rhythm, amplitude and frequency) and occurrence, amplitude, frequency and duration of generalised spike-wave and generalised polyspike-waves, as well as paroxysmal slow and fast activity. Part of the evidence and rationale for the conceptualisation of a continuum is that not all patients fit within the described syndromes, and that accounting for these 'border' cases within a GGE diagnosis remains possible within a continuum model (Berkovic et al., 1987).

There is no specific evidence with respect to cognitive and psychosocial outcomes of GGE syndromes to support conceptualisation of GGE as a spectrum or separate entity at this time. This question will be addressed in systematic reviews in Chapters 2 and 3, and in the primary research study in Chapter 7.

1.3.2 Idiopathic becomes genetic

As mentioned in *A note about terminology* (page xvii) a proposed revision of a number of terms related to epilepsy by the ILAE was published in 2010 (Berg et al., 2010). The terminology related to the aetiology of syndromes was one focus of this revision, and the term 'genetic' was favoured over 'idiopathic' to refer to the cluster of generalised syndromes described in this thesis as well as others such as benign familial neonatal-infantile seizures. This reflected the accumulation of research made possible by advances in genetic methods that has collectively suggested an underlying genetic basis to GGE and other previously termed 'idiopathic' epilepsy syndromes. Historical family studies have long supported the notion of the genetic contribution and heritability of GGE, though the extent and modes of inheritance were not clear (Gardiner, 2005). For this reason, the term 'idiopathic' in this context was previously understood to reflect this 'possible hereditary predisposition', however the replacement of this with 'genetic' is considered a more accurate acknowledgement of definitive genetic origins of the condition as the mechanisms began to be elucidated.

Still, we are far from a comprehensive account of the genetic underpinnings of GGE. A number of mutually inclusive hypotheses continue to be investigated, such as mutations on genes encoding voltage or ligand-gated ion channels thought to underlie these so called 'channelopathies' (George, 2004). It should be noted that despite the proposed change in terminology, the ILAE report also maintains the possibility of additional non-genetic environmental causes to GGE.

The genetic inheritance of GGE is generally considered non-Mendelian, with the exception of an autosomal dominant form of JME. Autosomal recessive, two locus and multifactorial models are all considered possible (Gardiner, 2005). A study of 126 family members with GGE revealed a complex pattern of non-parametric linkage signals in their samples with numerous chromosomal regions reaching the threshold of 'suggestive evidence' for causal contribution to disease (Hempelmann et al., 2006). The authors of that study found that specific loci conferred risk of individual seizure types, including absence and myoclonic seizures (susceptibility loci: 11q13, 1322-q31) or GTCS on awakening (5q34, 6p12, 19q13). In addition to being complex, the genetic contribution in GGE may be relatively modest, particularly in the context of the non-specialist understanding of genetic transmission. No common variants have been identified,

instead some multiple, rare variants such as the calcium channel subunit gene CACNA1H have been implicated in contributing to GGE (Scheffer & Berkovic, 2010). The copy number variant 15q13.3 microdeletion has also been found in a higher rate in GGE than healthy controls (occurring in 1% cf. 0.1% of the respective populations) (Stone, 2008; Helbig 2009). This copy number variant microdeletion also occurs at a higher rate in those with other neurological conditions including schizophrenia, autism and intellectual disability, which suggests the possibility of shared genetic risk between these and epilepsy (Helbig et al., 2009). In addition to these relatively small genetic contributions that have been identified to date, gene mapping studies also remain largely unreplicated in GGE samples (Ottman & Risch, 2012).

The non-Mendelian nature of GGE heritability has brought rise to some disagreement about the change in terminology from 'idiopathic' to 'genetic', with some arguing that it is misleading when only few culprit genes have been identified, and there are no clinical distinctions between 'genetic' and 'non-genetic' epilepsies (Ottman & Risch, 2012). The rates of GGE in sibling and twin studies are illustrative of this complex genetic contribution: risk of epilepsy by age 40 in siblings of those with GGE was 7.8 % (cf. 4.6% in other epilepsy syndromes; Flex et al., 2005). Factors known to increase the risk of heritability of genetic epilepsies include younger parent age at onset, mother affected with epilepsy, and greater number of affected relatives (Winawer, 2005).

In spite of ongoing debate about the propriety and accuracy of this term, the term *genetic generalised epilepsy* has gradually replaced *idiopathic generalised epilepsy* since the revision was published (see Figure 2).

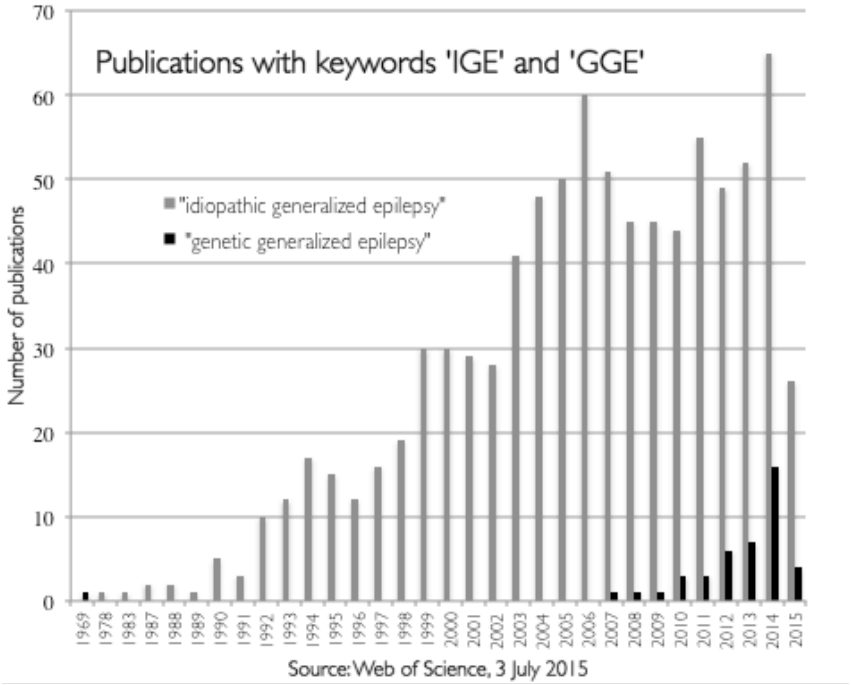


Figure 2. Change in publication keywords from idiopathic to genetic generalised epilepsy

1.3.3 Conclusion

This first chapter provides an introduction to aspects of the historical context and concepts relevant to epilepsy, and also to genetic generalised epilepsy more specifically. On this foundation, the following chapter introduces the scientific literature regarding cognitive and psychosocial functioning in epilepsy, defines the scope of this thesis, and culminates in the rationale, aims and hypotheses for the thesis.

Chapter 2: Cognitive and Psychosocial Function in GGE: Current Issues

The long-term prognosis of GGE beyond seizure outcomes remains an under-studied area. Key issues related to the study of cognitive and psychosocial functioning in epilepsy are developed in depth in this second introductory chapter. There is at least one long-term prognosis study that has assessed long-term educational, vocational and psychosocial outcomes such as long-term relationships and financial stability in GGE (the Nova Scotia study; Camfield & Camfield, 2009; Camfield & Camfield, 2010; Wirrell, Camfield, Camfield, Gordon, & Dooley, 1996). This and other work related specifically to GGE are described in detail in the systematic reviews in Chapters 3 and 4. The rationale, aims and hypotheses for all studies in this thesis are outlined in Section 2.5 (page 44).

2.1 Cognitive Functioning

2.1.1 Relevance in epilepsy

As outlined in Chapter 1, the term 'epilepsy' includes a large number of distinct conditions, and a correspondingly wide range of prognostic outcomes. Despite this variability cognitive dysfunction occurs frequently and is considered one of the 'essential comorbidities' of epilepsy (Berg, 2011).

The pathophysiology of epilepsy is attributable to aspects of brain structure and function from causes that can be 'small scale', such as excitatory and inhibitory electrophysiological impulses at a cellular level. Also, the pathophysiology can culminate in structural changes to brain tissue such as hippocampal sclerosis, or occur in response to traumatic brain injury and brain tumours (Ferguson et al., 2010; Hildebrand et al., 2005). In the case of GGE, where epilepsy is neither the cause nor the result of gross structural abnormality, cognitive dysfunction is considered to occur as a result of multifactorial changes to brain function including ictal and interictal states, channelopathies and receptor dysfunction, and thinning of grey matter (Badawy, Johnson, Cook, & Harvey, 2012; Helbig, Scheffer, Mulley, & Berkovic, 2008). Neuroanatomical abnormalities in GGE are not readily visible via neuroimaging modalities such as computerised tomography (CT) or magnetic resonance imaging (MRI;

Duncan, 2005). However other contributing factors are also considered likely, including the underlying cause of these epilepsies (increasingly considered to be genetically based), the seizures themselves, subclinical electrophysiological abnormalities, side-effects of AED, comorbid mood disorder and psychosocial factors such as adjustment and educational disruption (Hommet et al., 2006). These will be considered in more detail in Section 2.4 (page 32), and in Chapters 3 and 7.

The recognition of cognitive dysfunction in GGE has received less attention than in some focal epilepsy syndromes such as temporal lobe epilepsy (TLE) which have well-studied cognitive deficits that accompany well-localised anatomical areas (Zhao et al., 2014). Findings of memory and language dysfunction in TLE were previously considered consistent with the discrete localisation of function view of the 18th century, whereby in continuity of phrenology, discrete parts of the brain were thought to house separate mental functions (Darby & Walsh, 2005). Flourens (1794 - 1867) was one of the first to dispute this idea, and his claim was followed by a rapid evolution of knowledge about the interconnectedness of brain areas and the involvement of networks in focal as well as generalised epilepsies. Since Flourens' time, the cognitive and associated difficulties experienced in 'non-lesional' epilepsy syndromes and those in which the neurobiology was not well understood continue to be an area of scientific and clinical interest.

2.1.2 'Dysexecutive syndrome' of juvenile myoclonic epilepsy

One particular hypothesis of a specific cognitive and behavioural profile in GGE was the 'dysexecutive syndrome' in JME. In the context of the history of epilepsy this notion is analogous to the so-called 'temporal lobe epilepsy personality disorder' or 'Gastaut-Geschwind Syndrome', comprising of deepened emotions, hypergraphia, altered religiosity and circumstantiality (Torta & Keller, 1999; Trimble & Freeman, 2006). More recently Bear and Fedio's inventory designed to evaluate interictal dysphoric disorder, a similar left-TLE 'syndrome' outlined by Gerschwind, has added to the description for a total of 18 hallmark features including hypermoralism, dependency and paranoia (Bear & Fedio, 1977). Although popular, this hypothesis has no support on objective assessment (Foran, Bowden, Bardenhagen, Cook, & Meade, 2013).

Janz and Christian described particular personality characteristics of their JME patients (Janz & Christian, 1957; Trimble & Schmitz, 2002). Specifically, the authors describe a

contradictory and inconsistent set of cognitive and behavioural traits that include being 'quick to learn and judge, flexible and adaptable' but lacking discipline, being hedonistic and 'frequently failing to appear at follow up visits or to take their medications regularly' (Janz, 2002, p54). They further describe labile mood states, shyness, fear, inhibition and both mistrust and gullibility. These features, particularly that of 'limited rational self-control' were interpreted as evidence for involvement of frontal brain regions, and compatible with bilateral frontal or frontal-central spike-wave activity apparent on EEG (Janz, 2002, p55).

> *'…frequently characterised by unsteadiness, lack of discipline, hedonism and indifference towards their disease…all quick to learn and judge, flexible and adaptable, school and professional or occupational training were easy for them. But they promise more than they deliver…frequently fail to appear at follow up visits or to take their medications regularly…Many handle themselves with great assurance and demanding but they may also be decidedly mistrustful, and shy, fearful and inhibited. Their labile feeling of self worth also leads them to be both eager to help, to invite, to give on the one hand and to be able to react in an exaggeratedly sensitive way on the other. Their mood changes rapidly and frequently…They are easy to encourage and discourage, they are gullible and unreliable.'*
>
> **Janz, 1957 as presented in Janz, 2002, p54**

At certain points in his description, Janz describes frustration in treating his JME patients, since he finds that they are unmotivated to commit to the lifestyle changes that he believes would benefit their health.

> *'Some of the causes are so extreme that one is tempted to say that it is no wonder that seizures occur. However, the patients describe the events as unavoidable, and one tends to pardon theses excesses at first. One becomes suspicious when seizures continue to occur after repetitions of the same or similar events. It is surprising that the patients often do not avoid the situations which provoke seizures, and it is not clear why the patients are unable to learn from experience. One gets the impression that the patients*

are unable to draw conclusions from their own negative experiences and to change their lifestyles…'

Janz, 2002, p48

In the modern context of respect and autonomy of people who are consumers of health-care (e.g. Australian Psychological Society, 2013), it is uncomfortable to read and recount these generalisations about a group of people who bear only a neurological condition in common, and a condition that is not unanimously understood to disrupt behaviour (such as behavioural-variant frontotemporal dementia does, for example). An alternative way in which to interpret Janz' descriptions may be as broad features of the stereotypical adolescent. The typical age of diagnosis of JME is during adolescence, and so it is possible that Janz' sample is biased to this age group. Alternatively, the societal perception or stigma of epilepsy in the cultural and historical context may have prompted the onset of such behaviours in response to this stigma, and have been interpreted by Janz in the above way. Since JME and other GGEs are not accompanied by a visible and resectable lesion they may be particularly susceptible to psychological rather than medical attributions of behavioural or personality characteristics.

The 'dysexecutive syndrome' hypothesis has continued even in contemporary research into JME. In more recent studies, the hypothesis is demonstrated by an emphasis on measuring cognitive executive functions in this GGE subgroup. There is relatively less emphasis on the personality and behavioural components of 'dysexecutive syndrome', likely due to early null findings with objective measurement. This issue will be further discussed in Chapter 3 and Chapter 7, where tests of so called 'executive functions' are analysed separately from cognitive domains within the Cattell-Horn-Carroll (CHC) model in order to test the hypothesis of selective deficits in this area.

2.1.3 Cognition, psychosocial functioning and quality of life

Cognitive function does not occur in a vacuum, independent of other human states of body and mind. As one of the higher human abilities, cognitive function relies on a base of a number of other prerequisite abilities and states of homeostasis. Even basic cognition is easily disrupted by common threats such as sleep deprivation, sensory distractions, stress, anxiety and medical illness (Lewis et al., 2011; Moriarty, McGuire, & Finn, 2011; Pilcher & Huffcutt, 1996). Higher cognitive functions such as divided

attention and problem solving are, as suggested by the hierarchy displayed in Figure 3 below, susceptible to disruption by any of these factors and the more basic cognitive functions such as attention and speed of information processing. Although this basic hierarchy applies as much in epilepsy and other neurological conditions as it does in the general population, this fact is often overlooked. A person's primary medical or neurological condition can often come to be understood as the defining, and sole, influence on their abilities, their health and their wellbeing. That is, a deficit in memory, for example, may be misinterpreted to occur solely as a function of a known diagnosis, rather than due to the possible impairment of lower level cognitive abilities that are required for intact memory function.

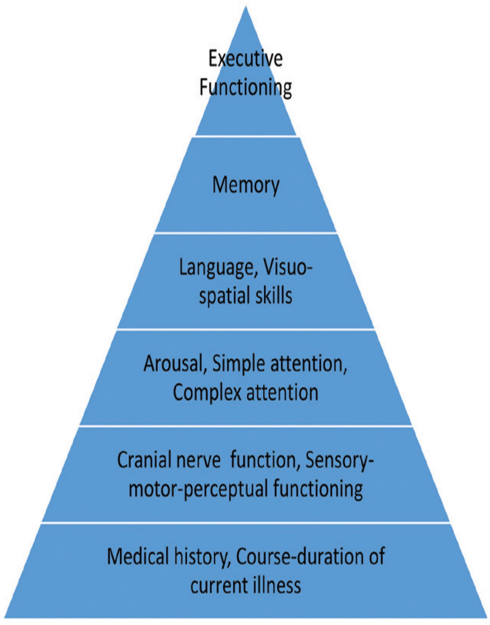


Figure 3. Hierarchy of cognitive functions.
Adapted from Schoenberg & Scott, 2011.

In quantitative medical research the goal is often to isolate the contribution of a condition of interest to a given outcome, such as cognition - as is the focus of this thesis. The separation of samples into clearly defined groups, and the limitations of the number of covariates that can be entered into quantitative analyses are statistical realities. Nevertheless, it bears remembering that functional outcomes in general, and cognitive outcomes in particular are multi-determined. A particularly obvious yet often overlooked

influence on cognitive functioning is that of mood state and disorder. Both acute distress and chronic mood disturbance have known impacts on cognition: attention, memory encoding and retrieval functions in particular (Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000). In depression, cognitive functioning is impaired, although effect sizes are relatively small (McDermott & Ebmeier, 2009). In anxiety also, multiple aspects of cognition are known to be affected, including perception, working memory, speed of information processing and learning (Robinson, Vytal, Cornwell, & Grillon, 2013; Vytal, Cornwell, Arkin, Letkiewicz, & Grillon, 2013). More severe and long-lasting deficits that can accompany schizophrenia are considered a particularly important contributor to the functional deficits that can make this condition debilitating (Green, 2006; Rund, 1998). In addition to these demonstrated impacts of mood on cognitive and daily functioning, the presence of mood disorder is a more accurate predictor of objective cognitive ability than is subjective estimation (Hall, Isaac, & Harris, 2009; Liik, Vahter, Gross Paju, & Haldre, 2009). For this reason memory complaints in chronic neurological conditions for example, may be as likely to reflect mood disorders as a memory problem that can be ascertained by objective cognitive assessment (Liik et al., 2009).

To foreshadow the following section of this chapter regarding psychosocial function (Section 2.2, page 24), mood disorder and psychosocial dysfunction is significant in epilepsy. For neurobiological as well as psychological, adaptive and social reasons to be discussed in further detail, mood disorders are more prevalent in all epilepsies relative to healthy control groups, other chronic illness groups and even most other neurological conditions (Hanssen-Bauer, Heyerdahl, & Eriksson, 2007; Rai et al., 2012).

Psychosocial functioning, a multifaceted concept broadly encompassing the extent to which an individual can meet expected societal milestones and participate in their community, is also heavily impacted by mood and by cognitive ability (Ro & Clark, 2009). Mood state, cognitive ability and psychosocial functioning together are in-turn intimately linked to the concept of quality of life and broader wellbeing (Ro & Clark, 2009; Suurmeijer, Reuvekamp, & Aldenkamp, 2001).

The great heterogeneity in psychosocial outcomes, just as in health and seizure outcomes in people with epilepsy bears remembering here. As documented in a large qualitative sociological study personal experiences of epilepsy can vary widely (Schneider & Conrad, 1981). Schneider and Conrad (1981) described personal experiences of epilepsy as

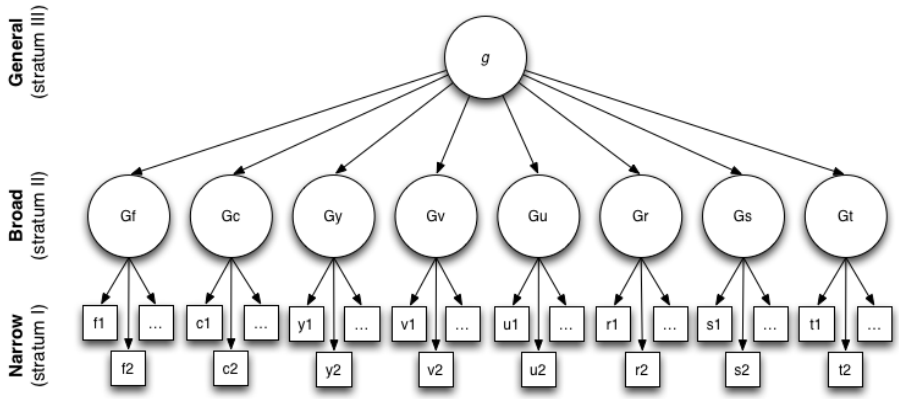
ranging from the disease being 'no big thing', to being a positive life experience that motivated the individual to overcome it - or that enabled greater empathy for the struggles of others, to representing a 'curse' or 'defect' on the person's life. This variability in outcomes was attributed at least as much to individual and family adaptive styles as to the metrics of medical and seizure severity (Schneider & Conrad, 1981). This is the broader context in which resides the study of the clinical epilepsy factors related to cognitive and psychosocial outcomes in GGE.

2.1.4 Cognition: Terminology and methods of measurement

This section aims to orient the reader to a significant theoretical approach to the measurement of cognitive function used in this thesis. The Cattell-Horn-Carroll (CHC) Model of cognitive ability is a factor-analytically derived framework of human cognition. It comprises a taxonomy as well as theoretical explanations regarding the measurement of cognitive abilities. The CHC Model evolved from Spearman's general cognitive ability *G,* and constitutes the integration of the Horn-Cattell Gf-Gc theory and Carroll's three-stratum theory (McGrew, 2009). By way of brief history, Raymond B. Cattell was a graduate student of Charles Spearman, who posited that general cognitive ability *G* could be better understood as a combination of fluid (Gf) and crystallised (Gc) intelligence. This theory was built upon by John Horn, a student of Cattell's, who used factor analytic research to confirm the validity of separate factors Gf and Gc and to demonstrate improvement of the model with an additional 8 factors (Schneider & McGrew, 2012). Carroll's three stratum theory provided the structure of the CHC Model, which retains the general factor *G* (Stratum III), the eight broad abilities beneath *G* (Stratum II) and over seventy narrow abilities (Stratum I) that are subsumed under the broad abilities (see Figure 4; McGrew, 1997; McGrew, 2005).

The CHC Model is now the consensus psychometric model of the structure of human cognitive abilities in the intelligence theory and assessment literature (Lichtenberger & Kaufman, 2009; McGrew, 2009). It is now the basis of the contemporary comprehensive intelligence test batteries including the Kaufman Assessment Battery (2nd Edition), Stanford-Binet Intelligence Scale (5th Edition), Woodcock Johnson III Tests of Cognitive Ability (3rd Edition) and the adult and child Weschler Batteries (4th and 3rd Editions respectively; DiStefano & Dombrowski, 2006; Reynolds, Keith, Fine, Fisher, & Low, 2007; Wechsler, 1997; Wechsler, Coalson, & Raiford, 2008; Woodcock, 2001). Validity

evidence comes from developmental, neurocognitive as well as confirmatory factor analytic studies (DiStefano & Dombrowski, 2006; Reynolds et al., 2007). In the standardisation sample of the Woodcock Johnson III Tests in 2001, the CHC Model was found to be the most plausible representation of the data obtained from normative sample scores on these tests (Woodcock, McGrew, & Mather, 2001).



CHC Broad (Stratum II) Ability Domains

Gf	Fluid reasoning	*Gkn*	General (domain-specific) knowledge
Gc	Comprehension-knowledge	*Gh*	Tactile abilities
Gsm	Short-term memory	*Gk*	Kinesthetic abilities
Gv	Visual processing	*Go*	Olfactory abilities
Ga	Auditory processing	*Gp*	Psychomotor abilities
Glr	Long-term storage and retrieval	*Gps*	Psychomotor speed
Gs	Cognitive processing speed		
Gt	Decision and reaction speed	(see Table 1 for definitions)	
Grw	Reading and writing		
Gq	Quantitative knowledge		

Figure 4. Three stratum model and its components,
Adapted from (Bates, 2013) & (McGrew, 2009)

Descriptions of CHC Factors and cognitive ability terminology that will be used in this thesis can be found in Table 2 below. Of the 10 confirmed Broad Ability Domains included in the CHC Model, five were selected for measurement in the study described in Chapters 5-9. This is because not all Broad Ability Domains can be measured using the Woodcock Johnson III Tests of Cognitive Ability since they do not relate strictly to cognitive function (e.g. Sensory Functioning domains, Gh Tactile Abilities, Gk

Kinesthetic Abilities, Go Olfactory Abilities). Domains relating primarily to academic or educational achievement (e.g. Grw Reading and Writing; Gq Quantitative Knowledge) were considered of secondary relevance to core cognitive ability and could not be justified in the time-limited adult testing setting in which this study was embedded.

Table 2

Description of broad stratum abilities in the Cattell-Horn-Carroll model of cognitive ability.

Cattell-Horn-Carroll factor	Description
General cognitive ability (G)	Aggregate of all thinking abilities
Crystallised intelligence (Gc)	Acquired verbal knowledge such as vocabulary and factual information. Also verbal comprehension and communication ability
Fluid intelligence (Gf)	Novel problem solving and reasoning ability
Long-term storage and retrieval (Glr)	Ability to store information and fluently retrieve it after a delay
Speed of cognitive processing (Gs)	Speed of information processing; the ability to maintain focused attention and perform automatic cognitive tasks under pressure.
Short-term memory (Gsm)	The ability to hold and manipulate information in mind; memory span; working memory.
Visuo-spatial Thinking (Gv)	Ability to perceive, analyse and think with visual patterns.

Adapted from Woodcock, R., McGrew, K., & Mather, N. (2001).

2.2 Psychosocial Functioning

2.2.1 Scope and definitions

Psychosocial functioning can be defined as psychological development and functioning in the context of a social environment (Ro & Clark, 2009). Psychosocial functioning encompasses the mental health, personality and social function required to enable participation in daily life, including educational, vocational and social activities (Ro & Clark, 2009). 'Psychosocial dysfunction' is used throughout this thesis synonymously with 'psychopathology' in recognition of the implications of poor mental health on broader aspects of life, and to destigmatise psychopathology. In epilepsy psychosocial outcomes may be determined by social and lifestyle consequences of the chronic illness experience

as well as by the epilepsy per se. Indeed, the greatest predictors of quality of life in epilepsy were found to be the following aspects of psychosocial function: psychological distress, loneliness, adjustment and coping and stigma perception (Suurmeijer et al., 2001).

The attainment of sound psychosocial function is not simply a matter of achieving a certain or fixed type of psychological status or social circumstance. It can be achieved through a process of adaptation and requires acknowledging and acting on the adjustment of lifestyle, expectations and activities to reflect the limits of a given situation, albeit medical, psychological, social, geographic or financial (Ro & Clark, 2009). Lazarus and Folkman's 1984 theory of psychological adjustment attributed appraisal and coping as the mediating factors that intervened between common stressors and an individual's psychosocial adjustment to it (Lazarus & Folkman, 1984). Kendall and colleagues' expanded model was designed to explain injured people's psychosocial adjustment to closed head injury. In their model additional factors such as cognitive impairment, neurological factors and personal and environmental resources were cited as further determinants of psychosocial outcome (Kendall, 1996). The social environment can also facilitate or hinder positive psychosocial function, for example by means of stigma about epilepsy and the impact of the disease, as well as how an individual's functioning affects their family relationships and their own interactions with the community. Further details regarding determinants of psychosocial functioning are presented in Kendall's model in Figure 5. The present study will focus on cognitive and neurological factors, however the author of this thesis acknowledges the importance of the broader context outlined above.

In contrast to psychosocial function, quality of life refers to overall personal satisfaction with various aspects of life such as physical mobility, vocational participation and personal relationships. Formally, quality of life is defined by the WHO Quality of Life Group as 'the individual's' perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns' (World Health Organisation, 1995, p1405). Quality of life is measured in the larger *Long-Term Prognosis Study* but is not examined within this thesis.

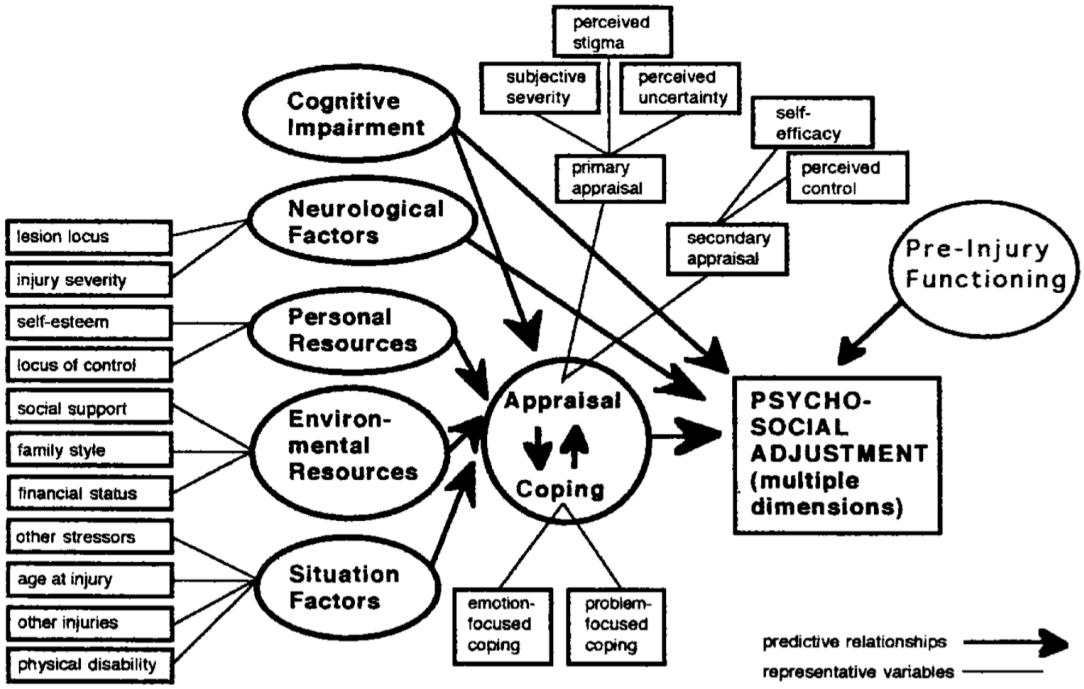


Figure 5. Factors impacting psychosocial functioning following head injury. From (Kendall, 1996).

2.2.2 Psychosocial functioning and mental health in epilepsy

Psychosocial function is reduced in epilepsy due to a combination of previously mentioned factors: cognitive dysfunction, comorbid mood disorder, reduced participation and opportunity, limitations on lifestyle such as driving independence and societal stigma. Given the flow-on effects to quality of life, community participation and the corresponding economic burden of the disease, there are ample reasons for measuring and improving psychosocial function. This is one of the current challenges in the management of epilepsy.

Mood disorders are prevalent and particularly debilitating comorbidities of epilepsy, and comprise an important component of psychosocial function. Mood disorders are also considered the largest contributor to quality of life in chronic conditions such as epilepsy, accounting for more variance than epilepsy factors such as seizure frequency (Boylan et al., 2004; Gilliam, Hecimovic, & Sheline, 2003; Hoppe & Elger, 2011). The prevalence rates of depression in people with epilepsy varies from 13% in large community samples, to 25% in smaller community-based samples and up to 50% in

high-risk tertiary care samples such as pre-surgical patients (Gilliam et al., 2003). Overall, the risk of depression in epilepsy has been described as being up to 10 fold greater than in the non-epilepsy population (Bell & Sander, 2009; Meador, 2008). Depression doubles the costs of medical care in chronic conditions such as epilepsy (Peña, Sancho, Rufo, Martínez, & Rejas, 2009). In contrast, bipolar disorder has been shown to occur no more frequently in epilepsy than in the general population (Mula, Marotta, & Monaco, 2010).

There is a dearth of longitudinal research examining the relationship between psychosocial functioning and long-term prognosis. It remains unclear the degree to which psychosocial functioning predicts both epilepsy and quality of life outcomes. Nonetheless, the importance of early identification and treatment of symptoms of mood disorder and other psychopathology symptoms is being recognised as fundamental to the care of people with epilepsy (de Araujo Filho & Yacubian, 2013). A brief summary of putative causes of psychopathology, to be discussed in further detail in this Chapter, and Chapters 4 and 9, appears in Table 3.

Table 3
Causes of psychiatric problems in epilepsy.

Patient-related
Gender
Pre-morbid personality
Temperament and character features
Epilepsy-related
Psychological
Role of the disease
Ongoing societal stress and stigma
Low expectancy of achievement by family or friends
Neurophysiological
Low inhibition levels
Channels dysfunctions
Anatomical
Hippocampal shrinking
Amygdala hypertrophy
Head injury
Brain damage (stroke, head injury, infections)
Anti-Epileptic Drug related

Adapted from (Mula & Monaco, 2009).

2.3 Clinical Practice

2.3.1 Guidelines and common practice

There are no evidence-based clinical guidelines regarding the prevention or treatment of the psychological sequelae of epilepsy available from American Epilepsy Society (AES) or American Academy of Neurology (as at January 2015), although the AES has the *Practice Tool for Cognitive and Behavioural Effects of Epilepsy* for adults and children (Society, 2012a, 2012b). These resources have documents with 'non-required actions' for discussion. Regarding cognition, functioning is said to be 'normal or nearly normal' in adults, however the documents recommend neuropsychological assessment for adults with specific risk factors for decline, which include pharmaco-resistant seizures, focal seizure onset, frequent or recurrent seizures, history of multiple episodes of status epilepticus and longer duration of epilepsy. According to the AES documents cognitive and behavioural well-being is considered at greater risk in children with epilepsy, with risk factors including absence seizures, abnormality apparent on MRI, any developmental regression, use of AED, pharmaco-resistant seizures, and epileptiform activity on EEG. They further recommend screening for attention problems and review of possible AED side effects in children. In adults, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E; Gilliam et al., 2006) and the GAD-7 (Spitzer, Kroenke, Williams, & Löwe, 2006) screening tools are listed for depression and anxiety respectively, whilst no specific tools are recommended for children.

With respect to other components of psychosocial functioning, the AES suggests referral to vocational rehabilitation programs for people whose ability to work is negatively impacted by seizures, AED or comorbid cognitive and psychological problems (Society, 2012b). Clinicians are also recommended to ask their patients about sleep and quality of life, in case the provision of further resources might address other needs.

The International League Against Epilepsy makes no mention of cognitive or behavioural sequelae in their published guidelines on epilepsy management. The UK's National Institute for Health and Care Excellence (NICE) published Epilepsy diagnosis and management guidelines (CG137; January 2012). These management guidelines are endorsed and listed by the ILAE. The Epilepsy Society of Australia, a much smaller professional organisation for epilepsy in Australia, has developed guidelines on particular issues at the request of members, or where some controversy is thought to occur. Topics

include generic AED, marijuana in the treatment of epilepsy and suicidality with AED, however to date the guidelines do not cover recommendations for management of cognitive or behavioural issues. Instead, the Epilepsy Society of Australia refers to the NICE and Scottish Intercollegiate Network Guidelines (SIGN) for any topics not covered in the Australian guidelines. According to the NICE guidelines, access to information about all of the potential issues in epilepsy is an important component to providing empowerment for 'children, young people and adults with epilepsy and their families and/or carers should be empowered to manage their condition as well as possible' to encourage coping with epilepsies (NICE guideline 1.2.1, p13). This includes access to sources of information about all of the potential issues, including (pertinent to this thesis), psychological issues, education and healthcare at school, prognosis, lifestyle, leisure and social issues.

In contrast to relatively limited clinical guidelines or recommendations published by the professional associations in epilepsy and neurology care, there is no shortage of mention of such recommendations in the scientific literature. A recent report of the ILAE Neuropsychology Task Force (Diagnostic Methods Commission) recommended routine neuropsychological assessment at epilepsy onset for cognition, mood and behaviour, as well as at any subsequent point when signs or symptoms of a focal cognitive impairment are apparent, when a neurodevelopment delay or decline is suspected, and at any other point in order to consider the effects of the disorder and its treatment (Wilson et al., 2015). Wilson and colleagues' recommendation echoed a previous consensus statement from 2011 regarding the management of neuropsychiatric conditions in epilepsy (Kerr et al., 2011). Other authors have also advocated for a multidisciplinary approach, with each patient's mental state evaluated at every point throughout their care (Devinsky, 2003). However in spite of what appears to be heightened recognition of the importance of early detection, screening and intervention of psychopathology and cognitive dysfunction in epilepsy, some estimates reveal that as few as 23-33% of children with comorbid disorders receive mental health services (Caplan et al., 2005; Caplan et al., 2008). There are however some indications that these empirical recommendations will be translated to policy and practice. For example, recommendation of an audit by Western Australian's Department of Health Epilepsy Review Committee identified a significant lack of availability of psychological and psychiatric care, and the importance of early intervention to avoid the considerable financial and human costs of delayed diagnosis

and treatment (Epilepsy Review Committee, 2008). The uptake of these recommendations into international guidelines and standard practice will hopefully become a reality in the near future.

2.3.2 Self- and informant-reports of psychopathology symptoms

With universal agreement that screening of psychopathology and psychosocial function should be standard practice, the remaining questions relate to how to do so, for example what tools to use and from whom to obtain a report. Self-report symptom questionnaire or interview is a common screening method however there may be reasons to also consider an informant report from a close friend or relative. Informant reports are most often used when the person being assessed is incapable of providing a reliable report due to mental state, cognitive impairment, being a young child or when a forensic situation precludes self-report (Caplan et al., 2005), however research suggests that informant reports may provide more than just a proxy for when self-report is unavailable (Achenbach, Achenbach, Krukowski, Dumenci, & Ivanova, 2005). This is not simply because one type of report is necessarily superior in accuracy, but because they each provide unique perspectives on the person being assessed. Depending on the context, reports from different informants may highlight otherwise overlooked issues such as degree of insight or willingness to disclose problems, and reveal relationship issues which may be at the heart of some of the problems. Also, multiple reports may add value in comparison to self-report alone, which has demonstrated disadvantages and measurement artefacts in clinical evaluation (Paulhus & Vazire, 2007). The limitations of self-report include consistency seeking, self-enhancement and self-presentation, self-deception, memory features and accuracy of self-perception (Paulhus & Vazire, 2007).

When assessing children, it is common to obtain two informant reports (such as from a teacher and a parent), however the inter-rater correlation between two independent informants tends to be lower than between that of self report and informant report, regardless of the chosen informant (Achenbach, 2006). Overall, cross-informant correlations are only modest, although they do vary by symptom type (Achenbach et al., 2005). In adults, concordance was greater for reports of substance abuse and externalising problems (Pearson's r=0.44) than problems of any other kind (Achenbach et al., 2005), with internalising problems bearing similar concordance (Pearson's r=0.43) for instruments with parallel forms for informants. Where the items differed between the

self- and informant report measures, correlations were unsurprisingly lower, around 0.30. For personality disorders, concordance can range vastly, between .18 to 0.80, likely depending on degree to which characteristics are publicly apparent (Klonsky & Oltmanns, 2002). In children also, the detection of certain symptom types appears to be more or less effective depending on the source of the report. For example, there was a low level of parental recognition of recent-onset internalising symptoms in children, relative to externalising and other symptom types (Caplan et al., 2005). These limitations are seen as a point in favour of collecting information from both self- and informant reports, since they may each be providing complementary information.

Both self and informant reports of psychopathology have predictive utility, with one study showing that either report type was indicative of depressive symptoms and global functioning after 7 year follow up, with informant reports particularly useful for predicting social adjustment - adding unique value over self-report alone (Klein, 2003). As the authors of the study point out, small cross-informant correlations do not necessarily imply inaccuracy, and instead could be providing information about different aspects of a person's functioning (Klein, 2003). The consistencies and disagreements between self and informant report alike can be useful in understanding problem areas which may not be adequately recognised by the subject, or possible relationship difficulties with the informant - which may also be of potential clinical relevance.

Another important question relevant to the attainment of symptom report is which of the questionnaire or clinical interview modalities offers the best balance of reliability and efficiency for identifying psychopathology in people with epilepsy. Research suggests that informant-report is useful regardless of the screening method, with cross informant correlations similar in magnitude when in-depth interviews were used instead of questionnaires (Achenbach et al., 2005). An average agreement of only 29% is found between diagnoses made on the basis of DSM structured interview (basically self-report, yet considered 'gold standard') and clinical evaluations (Rettew, Lynch, Achenbach, Dumenci, & Ivanova, 2009). This raises questions about the gold standard status of the diagnostic interview, and whether indeed a self-report interview is sufficient data from which to ascertain an accurate DSM diagnosis (Achenbach, 2006). This is difficult to evaluate, given that informant report is obtained infrequently in either clinical or research settings. A study by Achenbach and colleagues found that only 0.2% of 51,000 adult psychopathology studies measured cross-informant correlations (Achenbach et al., 2005).

In addition to the time required to obtain informant reports, one barrier may be the perception of difficulty in obtaining such a report. However a large US study, the National Survey of Children, Youths and Adults obtained a rate of 81% completion of an informant questionnaire from the over 2000 who participated, suggesting that obtaining a friend or family member report is unlikely to be a practical constraint (Achenbach, 2006). Indeed, family and friends of people with chronic illness often feel helpless to contribute to their loved one's wellbeing, and could welcome the opportunity to help (Eckes, Radunovich, & Brumbaugh, 2009).

There is therefore no consensus regarding the type of assessment of psychopathology in current practice, in general or within epilepsy contexts specifically. An understanding of the information that self and informant report may provide in screening and assessment of psychopathology in epilepsy could assist with decision-making regarding optimal methods of assessment.

2.4 Prognostic Factors

The burden of epilepsy can be broad and includes seizures, postictal and interictal fatigue, insomnia, seizure related injuries, cognitive impairment and the reduced psychosocial outcomes that can result from these physical symptoms (Hoppe & Elger, 2011). As documented in previous sections of Chapters 1 and 2 (the current chapter), a moderately large literature has demonstrated a range of psychological comorbidities specifically in people with genetic generalised epilepsies. Identifying the physiological processes in epilepsy that contribute to cognitive and other psychological functions is considered one of the important questions in understanding common neurobehavioral comorbidities in epilepsy (Hermann, Jones, Jackson, & Seidenberg, 2012). However, determinants of cognitive and psychosocial functioning in epilepsy are considered multifactorial (Binnie, 2003). The extent to which comorbidities are due to epilepsy characteristics (such as the frequency of seizures, use of AED and the effects of interictal or ictal discharges), psychological factors (such as mood disorders) and structural or functional neuroanatomical differences continues to be debated. The literature on each of these areas and possible causes of psychosocial dysfunction will be discussed here in turn. Further in-depth analysis will be presented in systematic reviews in Chapter 3 and Chapter 4.

2.4.1 Epilepsy factors and psychosocial function - the case of depression

Depression is now understood to be one of the most common and significant comorbidities of epilepsy (Hermann, Seidenberg, & Bell, 2000). Some researchers consider it to be on the 'epilepsy spectrum', a term designed to reflect the common comorbidities of the disease and the lack of clarity about their origins (Jensen, 2011). The diathesis-stress model is one way in which the occurrence of depression in epilepsy can be understood (Hoppe & Elger, 2011). According to this model, chronic stress results from the subjective experience of living with epilepsy, and learned helplessness can occur due to the uncertainty of seizures, developing into a psychological risk factor for depression. The diathesis or inherent vulnerability, for example, the neurobiology of epilepsy, determines the relative resilience or vulnerability of an individual to depression in response to this stressor. In contrast to the implication inherent in this model that depression is a reaction to the stress of epilepsy however, epidemiological studies show that depression may predate epilepsy (Ferguson et al., 2010; Petrovski et al., 2010). Preexisting depression also has a negative effect on seizure outcomes following epilepsy resection surgery (Kanner, Byrne, Chicharro, Wuu, & Frey, 2009; Metternich et al., 2009), however these studies refer to temporal and frontal lobe epilepsies respectively - not generalised epilepsies such as GGE. Reciprocal causal relationships have been found for a number of neurological and more general medical conditions including stroke, cardiovascular disease, diabetes and dementia (Dickens et al., 2008; Hoppe & Elger, 2011; Pan et al., 2010).

Indeed, some research suggests that epilepsy factors themselves may play only a small role in psychosocial sequelae. People who do not have epilepsy themselves but who are negatively affected by seizures, such as those with psychogenic non-epileptic seizures (PNES) and parents of children with epilepsy, have similar levels of depression to people with epilepsy (Chiou & Hsieh, 2008; Marchetti et al., 2008). A critical review published in 2011 found that no epilepsy-related factors were convincingly predictive of depression - at least in TLE (Hoppe & Elger, 2011). The factors considered included seizure type (focal or generalised), lateralisation or syndrome. Acute epilepsy factors such as seizures, epileptiform discharges and some anti-epileptic drugs can cause depressed mood states. Postictal depression can even last for hours to days, and postictal manic episodes can also occur (Nishida et al., 2006). However, whether these events lead to more prolonged mood disorders is not clear and remains to be investigated

Similar to the aforementioned idea of the 'epilepsy spectrum' of co-occurring disorders such as depression, there is also the idea of 'essential comorbidity' of epilepsy, whereby epilepsy and its comorbidites co-occur due to shared mechanisms (Berg, 2011). This is relatively difficult to test, and begs the question of what are the shared mechanisms? In epilepsy with genetic origins, genetic factors would appear highly relevant. The genetic considerations for psychological functioning in GGE will be discussed in the following section.

2.4.2 Genetics, environment and psychosocial factors

Given the demonstrated and presumed genetic basis of GGE, research in the area has begun to consider the role of inheritance to explain the neuropsychological profiles observed in patients. There is evidence from family studies that relatives of GGE probands are at increased risk of developing seizure disorders (Levav et al., 2002). Siblings of probands can exhibit some of signs and symptoms of epilepsy without exhibiting clinical manifestations consistent with a full diagnosis of the condition (Jain et al., 1996). Studies have typically involved examining first-degree family members unaffected by epilepsy, in particular siblings, with the obvious benefit of controlling for two of the largest factors known to influence cognitive function, namely, genes and developmental environment (Berg et al., 2008).

There also appear to be differential genetic underpinnings of the GGE syndromes, with higher correlations of cognitive assessment scores between patients and relatives in JME than CAE and TLE (Levav et al., 2002). Perhaps for this reason the study of JME appears to be more popular than other GGE syndromes. Three studies examining neuropsychology in people with GGE (two of which pertain to JME) and healthy family members are summarized here. One other study included participants with both IGE and cryptogenic epilepsy ('uncomplicated epilepsies') and is included in the summary below, despite the differences in the nature of its sample given the thoroughness of its methods and the limited existing research.

In 2002, Levav and colleagues published the culmination of a series of investigations into JME, CAE and TLE probands and family members (parents or siblings) of 65 families and healthy community controls in Israel and Canada. With a sample spanning a large age range (5-70 years), the authors used an extensive battery of tests comprising the Weschler Scales of intelligence, list learning tasks, visuo-spatial tasks, several attention

measures including Continuous Performance Tasks, and tests of so called executive functions including the Trail Making Test, Stroop task and Wisconsin Card Sorting Test. Overall, scores in the group of patient relatives fell between those of probands (with JME, CAE or TLE) and the healthy control groups – this comparison was not reported separately for the three syndrome groups. They found that JME relatives scored significantly lower on tests of visual and auditory sustained attention, with greater variability in response time although it is unclear whether this is lower than their relatives or healthy controls. No differences in other neuropsychological domains or between relatives of other subjects with epilepsy syndromes (i.e. CAE or TLE) were detected. This group also found a gender effect of poorer attentional function in female relatives of people with GGE and attributed this to the 'maternal effect' hypothesis that IGE is passed with maternal genes (Levav et al., 2002).

Using a smaller sample, Iqbal and colleagues (2009) assessed differences between eight patients with JME, eight of these patients' healthy siblings and 16 socio-demographically matched hospital staff and community volunteers, on a battery of neuropsychological measures. Tests were selected with an emphasis on the tests of so-called executive functions (Stroop, Brixton Spatial Anticipation Test, verbal fluency, and the Cognitive Estimates Test), the depression (Hospital Anxiety and Depression Scale) and behavioural dysexecutive syndrome (Dysexecutive Questionnaire, self- and informant-report). Selected tests were undertaken concurrently with EEG and video recording, however only two patients demonstrated spike and wave activity during recording (none of the sibling or controls did). The authors made comment on the possible effect of this activity during testing however given the infrequen occurrence of any kind of activity, the relationship is highly speculative. The only statistically significant group difference was reduced phonemic fluency scores in the patient group (Iqbal et al., 2009). There were non-significant differences in reduced scores in verbal measures, suggesting the need for larger studies. Qualitatively, the pattern of results in the sibling group resembled that of patients more than controls (although no significant differences were apparent here either). With regards to psychosocial functioning, JME patients had higher self-reported dysexecutive behavioural symptoms than either the sibling or healthy control group. The size of this effect was deemed to be large.

Considering the common symptom of 'memory problems' in patients with epilepsy, Wandschneider and colleagues (2010) examined prospective memory. Drawing on the

theoretical framework that executive functions underlie prospective memory, the authors measured both executive function and prospective memory in order to evaluate the extent to which the functions are linked in this population. Their sample comprised 21 patients with JME, 21 healthy siblings and 21 healthy controls. This study used a multi-step prospective memory task in which participants are required to plan, and execute a set of six subtasks after a delay (Kliegel, McDaniel, & Einstein, 2000). The results indicated that people with JME were impaired, that siblings of people with JME showed some, but not all deficits in prospective memory, and none of the executive functions deficits were demonstrated by those with JME. These findings do suggest some common genetic vulnerability to some of the cognitive features observed with higher incidence in people with JME, namely prospective memory. Wandschneider and colleagues' study did not measure neurophysiological events in their sample; it remains possible that the underlying cause to a shared vulnerability could be related to epileptiform discharges, or another kind of heredity unrelated to the epilepsy phenotype.

In a large study of children with epilepsy and their siblings eight to nine years following epilepsy diagnosis, a large proportion of psychosocial function variance was predicted by the ongoing use of AED and lack of epilepsy remission (Berg et al., 2007). However even in children who were in remission and off AED, significant case-sibling differences were observed in a number of areas of psychopathology including internalising disorders. Epilepsy itself was therefore considered to confer an independent risk for psychosocial dysfunction.

In summary, whilst studies investigating familial heredity of cognitive and psychosocial deficits in GGE have focussed on JME, they do provide tentative evidence for the genetic contribution to some deficits seen in GGE, with siblings of people with GGE falling somewhere between probands and healthy controls on psychological measures. This conclusion is observed with the caveats that sample sizes have typically been small, or have not established findings specific to GGE syndromes.

Opportunities for further research exist in including siblings alongside healthy controls in GGE samples of syndromes other than JME, and with the measurement of comprehensive psychosocial functioning. Including an assessment of epileptiform discharges may further assist in determining whether any observed shared familial vulnerability is attributable to subclinical electrophysiological activity. The role of

psychosocial factors that may confer risk or protection could also be integrated in future investigations. For example, general factors such as social support, family resources, higher income also have demonstrated impacts in epilepsy (Austin et al., 2010; Reisinger & DiIorio, 2009).

2.4.3 Anti-Epileptic Drugs

Anti-epileptic drugs, also known as 'anti-convulsants', are intended to reduce the seizure threshold of the brain. They achieve this by different modes of action including decreasing neural membrane excitability, increasing postsynaptic inhibition or altering the synchronisation of neural networks. There are two broad classes of AED: 1) those with gamma aminobutyric acid (GABA)-mediated synaptic inhibition with sedating effects, and 2) those that attenuate glutaminergic synaptic excitation with stimulatory effects on the central nervous system (Hoppe & Elger, 2011). There are a small number of AED that employ both modes of action (e.g. Topiramate). Specific classes of AED within these two broad categories include sodium channel blockers, calcium channel blockers, gamma-aminobutyric acid enhancers, glutamate blockers, carbonic anhydrase inhibitors, hormonally acting drugs and drugs with unknown mechanisms (Macdonald & Kelly, 1995). Some medications used in epilepsy were developed or first used to treat other conditions, with fortuitous or secondary anti-epileptic actions (e.g. levetiracetam, which is also prescribed for diabetes; clonazepam, a benzodiazepine for anxiety disorders).

AED are prescribed on the basis of particular seizure types, rather than epilepsy syndromes per se and need to be trialled in each patient to establish suitability due to occasional idiosyncratic effects (Zaccara, Franciotta, & Perucca, 2007). In some cases, an incompatible AED can exacerbate seizures. In GGE, unsuitable AED have included carbemazepine, phenytoin, oxcarbazepine, tiagabine, and gabapentin (Benbadis, Tatum, & Gieron, 2003). Benbadis and colleagues (2003) reviewed AED prescribed to GGE patients and found that when they modified the 'ill-advised' prescriptions identified in as many as 85% of the study sample (41/58), 78% of these patients achieved full seizure control. Their conclusion was that appropriate choice of AED can improve apparent intractability of seizures in GGE.

While seizure reduction is the primary goal of AED, tolerability and side-effect profile are also important considerations with respect to choice of agent. For example, sodium valproate is the 'first line' treatment for JME and other GGE syndromes, effective across

many seizure types, however has some known teratogenic effects so is not suitable for all patients (Karceski, Morrell, & Carpenter, 2001). There has been a trend away from prescribing of older classes of AED in favour of newer agents due to improvements in the adverse effects (Brunbech & Sabers, 2002).

Cognitive side-effects of AED are commonly reported by patients and are important for tolerability (Carpay, Aldenkamp, & van Donselaar, 2005; Uijl et al., 2006). Cognitive side effects can include: reduced psychomotor speed and attention due to the actions of AED that decrease membrane excitability, increased postsynaptic inhibition, and alteration of synchronization of neural networks (Loring, Marino, & Meador, 2007). Other central nervous system (CNS) side-effects of AED can include fatigue, drowsiness, lethargy, insomnia, and dizziness (Ortinski & Meador, 2004). Motor, gastrointestinal, sleep and mood problems are also commonly reported (Carpay et al., 2005).

In a retrospective study of over 1000 patient medical files, in the approximately 20% with GGE, 18.9% of patients reports experiencing cognitive difficulties with AED treatment (Arif et al., 2009). Topiramate had the highest rate of intolerance (21.5%) relative to other AED whether prescribed in monotherapy or polytherapy. Rates of intolerable subjective cognitive experiences was higher in polytherapy than monotherapy. In monotherapy, carbamazepine and sodium valproate were associated with significantly fewer complaints than lamotrigine, phenytoin and oxcarbazepine. A prospective Dutch study of 399 people with epilepsy also found greater self-reported adverse experiences with polytherapy compared to monotherapy, and increased concentration difficulties with phenytoin than sodium valproate (Carpay et al., 2005). Memory problems were the most commonly reported type of cognitive side-effect (21% of all cognitive complaints).

The literature has been mixed with respect to the exact nature of cognitive side-effects measured objectively with validated measures, and these have not been well-replicated. A review of prior research regarding cognitive side-effects of the AED prescribed to the GGE patients in this study is provided in Table 4 below. However, nonspecific effects of AED can impact cognitive processes both directly and indirectly. For example, disruption to homeostasis with respect to pain, arousal, sensation or emotion can threaten the overall physical and mental status that underlies normal cognitive function (Brunbech &

Sabers, 2002). For this reason, these general AED side-effects and their impact on quality of life can secondarily result in cognitive dysfunction.

Table 4
Summary of common AED side effects from studies of objectively measured cognitive function.

Generic name	Cognitive side-effect profile
Valproate	Some inattention problems (errors of omission) in children with CAE when compared with lamotrigine and ethosuximide.
Lamotrigine	No adverse cognitive effects commonly reported; favourable to carbemazepine in healthy adults. Slightly better QoL than patients taking phenytoin (side effects and life satisfaction). Use in patients with mental retardation has indicated improved behaviour and alertness. Can be useful in relieving affective symptoms.
Levetiracetam	Possible nootropic action. Few formal data exist. Short term studies show no cognitive effects and some cognitive enhancement.
Topiramate	Associated with poor concentration, dizziness and emotional lability, verbal memory deficits. WFDs reported in up to 1/3 patients. Some small studies showing cognitive decline after 4 weeks of use. Larger studies across longer periods show that verbal functions (particularly verbal fluency) was the most common area of decline. This improved after discontinuation or dose reduction.
Zonisamide	Some studies report sedation, mild sleepiness, speech abnormalities.
Phenytoin	Reduced performance reported on tests of motor speed, problem solving and attention.
Carbemazepine	Reduced performance on motor tasks.

Compiled from: Masur et al., 2013; Brunbech et al., 2002; Koo et al., 2013 & Ortinski & Meador, 2004.

Whilst it is difficult to predict the cognitive consequences of one or more AED in a given patient, polytherapy and higher AED blood concentration are understood to be is associated with a greater risk of adverse effects (Aldenkamp, Krom, & Reijs, 2003; Ortinski & Meador, 2004). Of course, polytherapy is also an indicator of more intractable epilepsy, so it is difficult to quantify the contribution of the additive or synergetic effect on reported symptoms. There are a number of other challenges to reviewing the unintended (positive or negative) effects of AED on cognition (Brunbech & Sabers, 2002). The specific mechanisms of drug action are often not well defined, making it difficult to infer possible adverse cognitive effects (the mechanisms of which

are also poorly understood) and then to assess these. The most ecologically valid studies evaluating AED are in clinical samples of people with epilepsy, which means that systematic, randomised, placebo or blinded trials are seldom possible. For practical and ethical reasons different plasma concentrations or dosages will be based on clinical need rather than following a standardised protocol. Further, the AED of interest is commonly provided as an addition to an AED regimen which brings into question general effects of polytherapy and epilepsy severity requiring polytherapy, as well as possible interaction effects, together making the findings of those studies unlikely to be generalisable to patients with other AED combinations.

Short study duration also precludes the assessment of chronic side effects, which could be quite different to short-term side effects. As a result, the available evidence compares large, short-term differences between the AED, and remains uncontrolled for possible contributions of epilepsy type, severity, and the interaction between AED used in polytherapy. Indeed, the authors of a critical review of AED side-effects concluded with the question of whether the methodological challenges are too great to meet the challenges of measuring small or medium cognitive effects of these drugs (Brunbech & Sabers, 2002). If one is to be cognisant of these limitations within the relatively small body of literature on the topic, the task of counselling patients about what to expect with respect to possible side effects of their AED regimen is a challenge.

2.4.4 Transient and cumulative effects of interictal epileptiform discharges

Interictal epileptiform discharges (IED) are brief, isolated spike and sharp wave electrophysiological abnormalities thought to be generated by epileptogenic cells (Holmes & Lenck-Santini, 2006). These events are visible on EEG, and not accompanied by a behavioural change (i.e. IED do not meet the clinical definition of a seizure). They have also been described as paroxysmal hyper-synchronous neural discharges (Hoppe & Elger, 2011). IED have been reported to occur frequently in people with epilepsy, and in some people who do not have epilepsy: 0.2-0.5% of adults and up to 6.5% of children (Helmstaedter, Hermann, Lassonde, Kahane, & Arzimanoglou, 2011). IED are increasingly considered to have a negative impact on cerebral function, either due to direct transient disruption of behaviour or interference with more enduring processes relating to brain plasticity (Holmes & Lenck-Santini, 2006).

The clinical relevance of determining the impact of IED on cognition relates to the notion of treating the subclinical EEG abnormalities as well as the seizures. The epileptic encephalopathies, such as Dravet syndrome and Lennox-Gastaut syndrome provide a demonstration of the negative impact of IED on cognition. In these conditions, regression or delay of cognitive development is attributed to seizures and abnormal interictal activity, and the treatment of these neurophysiological abnormalities results in improvement in cognition (Holmes & Lenck-Santini, 2006). However, the neurophysiological processes underlying epileptic encephalopathy may not be limited to those syndromes (Berg, 2011). It is not currently routine practice to treat EEG abnormalities in other epilepsy syndromes. However some argue that the occurrence of EEG abnormality accompanied by cognitive change meets contemporary criteria for a seizure and therefore AED treatment should be considered in these cases (Aldenkamp, 1997; Aldenkamp, Overweg, et al., 1996; Binnie, 2003).

A small literature documents relationships between cognitive test performance and IED in non-encephalopathic epilepsies, beginning with Gibbs' early work in 1936 and gaining momentum since the late 1980s. The notion of cognitive effects of IED was originally described as the acute disruption of cognitive processes, so called 'transitory cognitive impairment' or 'transient cognitive impairment (TCI; Aarts, Binnie, Smit, & Wilkins, 1984; Gibbs, Lennox, & Gibbs, 1936). The TCI effect of reduced cognitive performance during periods of epileptiform discharges has been measured in a small number of studies of children with epilepsy (e.g. Aldenkamp & Arends, 2004; Binnie, Kasteleijn-Nolst Trenité, Smit, & Wilkins, 1987). By definition, TCI is distinct from prolonged post-ictal effects such as post-ictal slowing, the enduring impact of the syndrome or underlying aetiology, and from 'stable cognitive impairment' occurring due to any cause in people with epilepsy (Aldenkamp, 1997).

Experimental TCI paradigms typically involve two to five hours of concurrent video-EEG monitoring and cognitive assessment. This simultaneous monitoring paradigm enables the exclusion of subtle behavioural features that may indicate the presence of a seizure rather than an IED, and some evidence suggests that the improved detection of seizures using this method has in fact decreased findings of TCI (Aldenkamp, 1997). Simultaneous testing has the advantage of enabling the synchronisation of responses to cognitive tests with EEG activity, however the degree to which this is reflected in study methodology varies. For example, one approach is to examine response accuracy during a

specified window of time (e.g. 2 seconds) proceeding a discharge that was observed on EEG, and then define TCI as an association between errors and post-discharge time window (Binnie et al., 1987). More commonly reported approaches to coding IED burden is to distinguish between either 1) those with or without IED observed, 2) those with or without IED occurring less than or greater than 1% of the time during cognitive testing, or 3) those with 'mild burden' defined as fewer than three discharges of less than three seconds' duration each or those with a 'heavy burden' with greater than three discharges of longer duration (Aldenkamp, Overweg, et al., 1996; Aldenkamp & Johan Arends, 2004; Tromp et al., 2003; Siebelink, Siebelink, Bakker, Binnie, & Kasteleijn-Nolst, 1988). These methodologies do not therefore quantify the exact frequency or duration of IED or measure their direct and acute effect on cognitive processes.

Early reports of TCI found that the effect was most readily detected during generalised spike and wave discharges of at least three seconds' duration, which, it has been noted, may simply reflect the known cognitive effects of an absence seizure (Binnie, 2003; Delgado-Escueta, 1979). The TCI notion is therefore controversial because it could represent an artefact of a subtle seizure that was missed due to inadequate monitoring of behavioural signs (Aldenkamp & Arends, 2004). The use of concurrent video-EEG technology in TCI research was an advancement aimed at improved delineation between IED and seizures. However it remains the case that this distinction also rests on the details of definition of seizure terminology such as how long an abnormal event needs to be, and how subtle the behavioural features can be, to be considered TCI. The term 'epileptiform discharge' (ED) will be used now in this report, since the distinction between ictal and interictal is somewhat controversial and dependent on the presence of an informed observer able to detect often subtle behavioural signs.

The only three known studies of ED in relation to cognitive or behavioural features, with samples comprised solely of people with GGE reported mixed results. An early study found no significant differences in the cognitive function of a group of patients with ED compared to a group without (Needham, Bray, Wiser, & Beck, 1969), but a more contemporary study reported that the duration of discharges and absence seizures occurring during cognitive assessment was correlated with performance on a visual memory task in a pre-treatment group of children with CAE (Siren et al., 2007). An additional study of children with CAE using a non-simultaneous paradigm measured the

impact of EEG abnormalities and found an adverse effect of longer epileptiform events and errors of omission on an attentional task (Dlugos et al., 2013).

The findings from these studies of heterogeneous epilepsy syndromes indicates that a greater burden of epileptiform discharges is associated with a degree of reduction in some cognitive functions, including reaction time and processing speed, memory short-term memory and overall IQ (Tromp et al., 2003; Aldenkamp & Arends, 2004; Koop, Koop, Fastenau, Dunn, & Austin, 2005; Lv et al., 2013; Siebelink et al., 1988). Negative findings are also common (Aldenkamp, Aldenkamp, et al., 1996; Aldenkamp et al., 2001; Needham et al., 1969). In two studies measuring EEG in both wakefulness and sleep, findings are mixed with regards to the differing importance of discharges in these states (Lv et al., 2013; Scott, 2013). The majority of studies examining ED and cognition have been conducted in children; the situation in adults remains largely unexplored. Although of less relevance to GGE, there is also some evidence for lateralisation of transitory cognitive effects in people with focal discharges. Right-sided discharges impact visuospatial abilities while left-sided discharges affect verbal abilities (Binnie, Channon, & Marston, 1990; Binnie et al., 1987).

The use of simultaneous recording methods and measurement of acute disruption to cognition lend themselves well to assessing speed of information processing or reaction time tasks, more so than measures of new learning, memory retrieval, crystallised intelligence or fluid intelligence where the time taken to cogitate or respond to each item may be longer than a few seconds. It is presumably for this reason that fewer studies conduct comprehensive cognitive assessment of enduring functions rather than 'mechanistic' or transient abilities such as attention span (Aldenkamp & Arends, 2004). While TCI refers to acute disruption of cognition, some demonstrations of temporally non-specific deficits increasing with cumulative or longer-term ED burden have prompted the call for early recognition of ED (Binnie, 2003; van Rijckevorsel, 2006). For example, in the following studies using non-simultaneous EEG-cognition paradigms, the presence of IED at baseline was one of the predictors of stable processing speed deficits in children with new onset epilepsy after 3 years (odds ratio: 1.90; Fastenau et al., 2009), and non-dominant IED in a group of children with focal epilepsy were associated with worse visuo-spatial function and memory of visual information in a rare 24-hour EEG monitoring study (Ebus et al., 2012). Cumulative or enduring cognitive deficits as a result of ED has been considered a tenable extension of the concept of TCI, with a reasonable

likelihood that frequent or sustained ED would result in adverse effects - particularly for memory encoding and consolidation (Badawy et al., 2012).

The potential impact of ED on cognition remains under-studied in GGE, with a literature search yielding only the three previously described studies considering the acute effects of ED. In the aforementioned study by Dlugos and colleagues (2013), the EEG and cognitive tests were not conducted concurrently. However it is possible that their results still did reflect real-time disruptions to the attention tasks (TCI) rather than a chronic or cumulative detriment. The relationship between enduring cognitive functions and ED have not been investigated in GGE. Indeed, the burden of ED in GGE remains unquantified. In other syndromes, EEG monitoring periods are typically short, occur only during wakefulness and have categorical rather continuous appraisal of ED burden. Further, the impacts of ED on cognition have not been examined in the context of other potential contributing factors such as AED use and seizure burden.

Several questions therefore remain. Firstly, what is the precise burden of ED in wakefulness and sleep in GGE? Secondly, are ED associated with enduring cognitive dysfunction in these epilepsy syndromes? Finally, what is the relative contribution of ED and other clinical variables to the prediction of cognitive and psychosocial function in GGE?

2.5 Aims, rationale and hypotheses of the current study

It is long recognised that epilepsy is accompanied by 'essential comorbidities' including cognitive, behavioural and psychosocial difficulties. These comorbidities comprise an important predictor of quality of life in epilepsy.

The emphasis on focal epilepsies has meant a relative paucity of evidence regarding prognostic outcomes in GGE, a common group of epilepsy syndromes. Specifically, the nature of the published literature comprises a small group of studies that has identified a potential reduction in functioning using varied and at times limited methodologies, and does not examine risk or protective factors in a quantified way. Also, cognition and psychosocial functioning have been studied in isolation, ignoring the interactions between them that is well recognised in psychology more generally. There is therefore no conclusive evidence base from which clinicians can consider prognostic advice for GGE patients.

This relative paucity of research is accompanied by, and reflected in a lack of clear clinical guidelines about the screening and intervention of cognitive and psychosocial problems in this patient group. The result is that there is no consensus regarding whose responsibility it is to address these issues along the clinical pathway, and how they might best do so. Therefore, an improved understanding of the nature of cognitive and psychosocial difficulties in GGE has the potential to improve clinical practice and patient outcomes.

Through the use of several methodological improvements this study will extend upon existing knowledge to help inform an evidence-base for clinical practice. Specifically, a large, well-defined and prospectively recruited sample from all GGE syndromes will enable greater contextualisation of our findings to other representative cohorts. Comparisons with other research will be assisted by the use of validated cognitive assessment measures with a strong theoretical underpinning, which are both detailed and comprehensive (not limited, for example to memory or executive functioning). Finally, detailed, manual EEG reading of 24 hours of recording will provide reliable data about both diurnal and nocturnal subclinical epileptiform activity, shedding light on the potential clinical relevance of previously unmeasured electrophysiological events.

This PhD study aims to:

1. Synthesise the literature regarding cognitive and psychosocial comorbidities of GGE using detailed quantitative and qualitative methods;

And in a large, prospectively recruited sample of people with GGE, examine:

2. Cognitive functioning in GGE syndromes,

3. The relationship between epileptiform discharges and other clinical characteristics and cognitive outcomes, and

4. The nature of psychosocial functioning in GGE, and risk factors for poorer psychosocial outcomes.

It is hypothesised that:

1. A small literature will document cognitive and psychosocial deficits in GGE syndromes, and that the particular focus on JME will not reveal quantifiably different or worse outcomes in this syndrome relative to other GGEs.

2. Participants with GGE will demonstrate reduced cognitive functioning across all latent variables reported.

3. Epileptiform discharges will be associated with poorer cognitive functioning.

4. Participants with GGE will demonstrate reduced psychosocial functioning when this is measured by self- and informant-report.

Chapter 3: A Systematic Review and Meta-Analysis of Cognitive function in GGE

In the previous chapter the current psychological issues were outlined, with regard to both mood functioning and cognition, that are relevant to the research and clinical management of GGE syndromes. The aims, rationale and hypotheses for this thesis were also provided (page 44). The following publication constitutes the first piece of work towards these aims, and seeks specifically to document the existing knowledge and knowledge gaps, providing a foundation on which to build subsequent components of this research. It is a systematic review and meta-analysis of cognitive functioning in GGE syndromes, a qualitative and quantitative synthesis of the 26 eligible studies. It employs the well-established Cattell-Horn-Carroll theory of cognitive abilities to provide a theoretical framework by which to interpret and synthesise methodological diverse findings. To date, this paper, published in *Neuroscience & Biobehavioral Reviews* has been cited 16 times.

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Review

Cognitive functioning in idiopathic generalised epilepsies: A systematic review and meta-analysis

A. Loughman [a,*], S.C. Bowden [a,b], W. D'Souza [c]

[a] Melbourne School of Psychological Sciences, University of Melbourne, Parkville VIC 3010, Australia
[b] Department of Clinical Neurosciences, St. Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy VIC 3065, Australia
[c] Department of Medicine, St, Vincent's Hospital, The University of Melbourne, 41 Victoria Parade, Fitzroy VIC 3065, Australia

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ABSTRACT

Cognitive function in idiopathic generalised epilepsies (IGE) is of increasing research attention. Current research seeks to understand phenotypic traits associated with this most common group of inherited epilepsies and evaluate educational and occupational trajectories. A specific deficit in executive function in a subgroup of IGE, juvenile myoclonic epilepsy (JME) has been a particular focus of recent research. This systematic review provides a quantitative synthesis of cognitive function outcomes in 26 peer-reviewed, case–control studies published since 1989. Univariate random-effects meta-analyses were conducted on seven cognitive factor-domains and separately on executive function. Patients with IGE demonstrated significantly lower scores on tests across all cognitive factor-domains except visual–spatial abilities. Effect sizes ranged from 0.42 to 0.88 pooled standard deviation units. The average reduction of scores on tests of executive function in IGE compared to controls was 0.72 standard deviation units. Contrary to current thinking, there was no specific deficit in executive function in JME samples, nor in other IGE syndromes. Of more concern, people with IGE are at risk of pervasive cognitive impairment.

Contents

* Corresponding author. Tel.: 61 3 8344 6377; fax: +61 3 9347 6618.
E-mail address: amy.loughman@unimelb.edu.au (A. Loughman).

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1. Introduction

The idiopathic generalised epilepsies (IGE) are a cluster of syndromes presumed to be of genetic origin. IGE syndromes are characterised electroencephalographically by bilaterally, synchronous activity with symmetrical spike-and-waves or polyspike-and-waves originating at some point within, and rapidly engaging bilateral networks of the brain (Berg et al., 2010). As a group, IGE constitute approximately 15–20% of all epilepsies (Jallon and Latour, 2005). The four most common forms of IGE recognised by the current ILAE classification are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and IGE with generalised tonic–clonic seizures only (IGE-GTCS; Berg et al., 2010). Although classified as distinct syndromes by the ILAE (Berg et al., 2010), some authors suggest that these subtypes may represent a 'neurobiologic continuum' (e.g. Berkovic et al., 1987; Nordli, 2005). A recent revision of the ILAE classification in 2010 recommended that the term 'idiopathic' be replaced by 'genetic', however there remains disagreement about the need for this change (Shorvon, 2011). The core syndromes remain essentially unchanged with the exception of GTCS on awakening now encompassed by IGE with generalised tonic clonic seizures only. Therefore, the term 'IGE' will be retained here to reflect its continued use in clinical and research practice, and in the diagnostic and classification systems used within studies included in this review.

In contrast to focal syndromes such as temporal lobe epilepsy (TLE), relatively little is known about cognitive function in IGE or in the hypothesised sub-syndromes. IGE effects on cognition are often considered relatively benign, *within normal range but lower than the general population* is a common description (e.g. Cutting et al., 2001; Hommet et al., 2006; Jeong et al., 2011). Studies of cognition in patients with IGE have typically been limited by small sample sizes, and lack of control groups. Inconsistent neuropsychological test selection and inadequate description of factors such as use of anti-epileptic drugs (AED) and co-morbid mood disturbance complicate interpretation of many of the available studies. Methodological factors relating to cohort selection (i.e. incident versus prevalent cases) and recruitment setting (i.e. community versus tertiary or specialised epilepsy centres) also complicate interpretation of prognosis (Seneviratne et al., 2012). Investigation of cognitive impairment across IGE syndromes, to date, does not provide a clear picture of the nature or extent of cognitive impairment in people with these syndromes.

The most frequently studied of the IGE syndromes has been JME, the most common form of IGE (Hommet et al., 2006). Specific deficits have been reported in so-called 'executive' or 'frontal lobe' functions such as planning, abstract reasoning, concept formation and verbal fluency (Devinsky et al., 1997; Roebling et al., 2009) although, as is well known, deficits in these functions may arise from dysfunction in a wide variety brain regions (Goldstein and Scheerer, 1941; Dodrill, 1997). Findings of aberrant frontal lobe structure and function including an increase of grey matter in the mesiofrontal regions (Woermann and Woermann, 1999) and reduction in glucose metabolism in a variety of brain regions including the dorsolateral prefrontal cortex have been reported (Swartz et al., 1996). These findings have encouraged the investigations of Janz's original hypothesis of a dysexecutive syndrome in JME (Janz, 1985). If supported, this hypothesis has important implications for the educational, occupational and psychosocial prognosis of patients and for the types of interventions most likely to benefit patients with JME.

No systematic review or quantitative synthesis of the literature has been conducted to date. The primary aim of this review is to evaluate cognitive dysfunction in the four primary syndromes of IGE: CAE, JAE, JME and IGE-GTCS. Specifically we seek to answer the following questions: (a) Is there evidence of cognitive dysfunction in people with IGE? (b) Which cognitive abilities are affected and to what extent? (c) Are there differences in the nature and extent of cognitive impairment between the four IGE syndromes?

2. Methods

2.1. Protocol registration

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: registration number CRD42013004177). The review was conducted according to PRISMA guidelines (Moher et al., 2009).

2.2. Search strategies

Medline and Scopus databases were used to identify eligible studies. A keyword (Medline and Scopus) and MeSh term (Medline only) search was conducted on 2nd April 2013 for IGE and cognition terms (see Appendix A for list of search terms used). To limit the impact of changes in diagnostic criteria, publication date was specified from 1989 (the year of publication of a major ILAE revision to classification of epileptic syndromes) to 2013. Screening of title and abstract was used to identify relevance. The reference lists of eligible articles were also searched for additional studies. A final list of full-text articles was completed on 10th April 2013, and updated on 21st August 2013.

2.3. Selection criteria

Studies meeting the following criteria were included: (a) original research published in a peer-reviewed journal, (b) case–control studies with both a sample of participants with a diagnosis of IGE (either consisting of mixed syndromes or one of the ILAE-recognised syndromes of IGE), and a matched healthy control group, (c) outcomes included any domain of cognitive functioning measured by published neuropsychological tests.

Studies were excluded if (a) the control group was a non-epilepsy diagnosis-positive sample (rather than healthy controls); (b) full-text article was not available; (c) sample included IGE patients but separate analyses were not presented for an IGE group (e.g. Idiopathic partial and generalised epileptic syndromes grouped together); (d) only the significance values of statistical tests were presented, without descriptive statistics on cognitive test scores.

Table 1
Descriptions of Cattell-Horn-Carroll broad stratum abilities (Woodcock et al., 2001).

Cattell-Horn-Carroll factor	Description
General cognitive ability (G)	Aggregate of all thinking abilities
Crystallised intelligence (Gc)	Acquired verbal knowledge such as vocabulary and factual information. Also verbal comprehension and communication ability
Fluid intelligence (Gf)	Novel problem solving and reasoning ability
Long-term storage and retrieval (Glr)	Ability to store information and fluently retrieve it after a delay
Speed of cognitive processing (Gs)	Speed of information processing; the ability to maintain focused attention and perform automatic cognitive tasks under pressure.
Short-term memory (Gsm)	The ability to hold and manipulate information in mind; memory span; working memory.
Visuo-spatial Thinking (Gv)	Ability to perceive, analyse and think with visual patterns.

Adapted from Woodcock, McGrew, & Mather, N. (2001). Examiner's manual. Woodcock-Johnson III Tests of Cognitive Ability. Itasca, IL: Riverside Publishing.

2.4. Data items and summary measures

For each eligible study, data were extracted for descriptive and diagnostic variables (IGE syndrome, sample size, age, medication status, age of onset) and information relating to outcome (cognitive test scores).

A wide variety of cognitive tests were employed in the studies reviewed. To enable theoretically meaningful comparisons and collation of results across studies, all cognitive tests used were classified into a single Cattell-Horn-Carroll (CHC) cognitive factor-domain that best represented the respective test. The CHC model provides a comprehensive and exhaustive account of cognitive abilities for diagnostic assessment (Carroll, 1993; McGrew, 2009). Factor-analytic studies of cognitive tests such as the Weschler Intelligence Scales and many other tests have demonstrated that the CHC model provides a parsimonious factor structure (Carroll, 1993; McGrew, 2009; Phelps et al., 2005; Reynolds et al., 2013). Seven of the nine broad stratum abilities described in CHC theory represented the majority of tests used in eligible studies: general cognitive ability (G), crystallised intelligence (Gc), fluid intelligence (Gf), long-term storage and retrieval (Glr), speed of cognitive processing (Gs), short-term memory (Gsm) and visual-spatial thinking (Gv). (see Table 1 for specific descriptions.) Of note, Gc, also known as *acquired knowledge* incorporates clinical assessment of language and semantic memory tests. Short-term memory is commonly termed 'working memory', and we will refer to Gsm as 'short-term/working memory' to highlight the equivalence of these terms in CHC theory. Assignment to CHC factor was based on the latent variable or factor structure of tests as presented in prior literature and the judgement of two independent raters (AL and SB). Where a combination of factors was represented in a test, the single factor with the greatest loading was selected. For a complete list of primary CHC factor classification by test, see Appendix B.

Given the diversity of eligible studies, the range of coverage of the seven CHC factors varied. In addition, it was common for studies to employ several tests of the same factor. When a study included several tests of the same factor, or more than one subtest for a single test (e.g. Trail Making Tests A & B) each was counted as a separate instance of the respective factor. Conversely, where scores from a single test with only one set of stimuli were presented in the form of several scores, only a single representative score was included (e.g. for the Wisconsin Card Sorting Test, the number of categories was the score included).

To address recent research questions, an additional classification was made for author-reported tests of "executive functions" to enable separate analyses of this cluster of abilities, although all these tests are readily classified under several CHC factors. The executive function cluster included tests such as the Tower of London, Stroop and word-generation fluency. A full list of these tests can be found in Appendix C.

The summary effect measure used was the difference between IGE and control group means. For most test scores, a higher score indicates better performance, however for those tests where the opposite was true (e.g. reaction time), group mean scores were multiplied by −1 (see Higgins and Green, 2005). To enable comparability across measures on different scales, scores were standardised, with control group scores used as the estimated population parameters. Where a study employed more than one test from a single factor, an average standardised score of that factor was derived. Thus, an average standardised score was generated for each factor tested for each study for the quantitative synthesis using univariate meta-analyses.

2.5. Assessment of quality

No ideal standard exists for the assessment of quality or risk of bias in observational studies (Sanderson et al., 2007). The following aspects were considered for the assessment of risk of study-level bias in this review: (i) representative sampling; (ii) appropriateness of measurement of variables; and (iii) comprehensiveness of reporting. Evaluation of study-level bias was not incorporated into quantitative syntheses of results.

The following criteria were used to assess risk of bias in these three areas.

(i) Representative sampling covers the reporting of (a) patient ascertainment; use of ILAE diagnostic criteria, incident disease, disease duration, AED use, etc.; (b) recruitment methods; (c) control group age and socio-demographic matching.
(ii) Measurement of variables relates to (a) epilepsy diagnosis; (b) cognitive function outcomes; (c) reporting of factors that may have an impact on cognitive function; neurological illness, age of seizure onset, duration of illness, seizure type, seizure frequency, AED use.
(iii) Comprehensiveness of reporting relates to the reporting of study-outcomes for all planned analyses, regardless of significance.

2.6. Meta-analyses

A random effects univariate meta-analysis of aggregate standardised scores (with DerSimonian-Laird estimator for heterogeneity of variance across studies) was conducted on each cognitive factor, and also executive function. For each analysis, a forest plot displays the estimated effects for all studies, and subgroup effects where applicable. The *I squared* statistic describes the percentage of variation between studies that is due to sample mean heterogeneity (Higgins et al., 2003).Effects are reported as Cohen's where 0.2 is small, 0.5 medium, 0.8 large (Cohen, 1988).

3. Results

3.1. Study selection and characteristics

Twenty-six studies met selection criteria and were included (Fig. 1). Eleven studies reported patients with JME, four with CAE, two with IGE-GTCS, none with JAE and eight with mixed IGE syndrome diagnoses. One additional study (Levav et al., 2002)

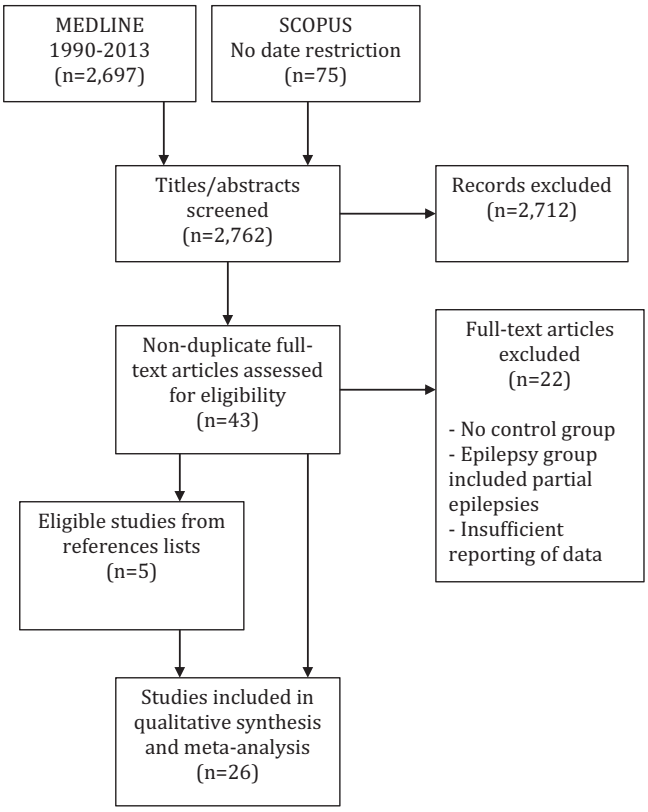

Fig. 1. Flow diagram of eligibility screening of studies.

conducted separate analyses of JME and CAE patient samples. Table 2 displays characteristics of included studies.

Studies varied with respect to demographic and epilepsy variables. CAE groups had mean age from 8 to10 years; participants in JME samples were adult, except for one study which reported a mean age of 15 years; samples of IGE-GTCS patients had mean age of 10 years. The IGE heterogeneous studies reported adolescent samples (aged 10–15 years) except for two studies using adult samples.

As shown in Table 2, the mean disease duration varied, with the shortest duration in samples of CAE and IGE-GTCS patients, and an overall longer duration reported in samples of JME and IGE heterogeneous diagnoses. Mean age at diagnosis varied correspondingly, being lower for CAE and IGE-GTCS, higher for JME and highly variable for heterogeneous samples.

With the exception of four studies, with largely medication naïve participants, most reported AED medication status of monotherapy or polytherapy. Thirteen out of twenty six studies reported that a majority of patients were treated with sodium valproate monotherapy. Dosage was not routinely reported.

3.2. Meta-analyses

Figs. 2.0–2.7 show forest plots from univariate meta-analyses conducted on each CHC factor.

As shown in Fig. 2.0, eight studies reported measures of general cognitive ability, (usually Full-Scale IQ) with 38% showing significant differences between patient and control groups. On average, IGE patient scores were reduced by 0.64 SD units (95% CI: 0.34–0.94), a medium to large effect (Cohen, 1988). For the significant studies, two involved patients with CAE and one a heterogeneous group.

The majority of studies ($n = 12$) reporting crystallised intelligence were JME, reflective of the large proportion of JME studies compared to other IGE syndromes. Half of these were statistically significant across all diagnostic categories (Fig. 2.1). On average, IGE patient estimates of crystallised intelligence were 0.61 SD units, a medium effect size (95% CI: 0.46–0.75) below those of controls.

Fifteen studies reported IGE fluid intelligence measures with significant reductions only in 40% albeit a large observed effect, at 0.72 (95% CI: 0.46–0.97) SD units below controls (Fig. 2.2). Of the significant studies, two were CAE, three JME and one IGE-GTCS.

Sixteen studies reported measures of long-term memory retrieval and storage with 38% reaching statistical significance. IGE group scores were 0.42 (95% CI: 0.20–0.63) SD units lower compared to controls (Fig. 2.3), representing a small to medium effect. Of the statistically significant studies, three each were JME and mixed diagnosis. While JME patients showed worse performance than CAE for long-term memory retrieval the differences were equivocal.

Nineteen studies reported measures of cognitive processing speed, showing significantly lower scores for IGE than control groups in 84% of studies (Fig. 2.4) with a large effect (0.88 SD units; 95% CI: 0.66–1.10). The relatively large number of tests per study (up to eight) measuring this factor supports the robustness of this observation.

Fig. 2.5 shows eighteen studies reported measures of short-term/working memory with 61% of studies reaching statistical significance. A medium to large reduction in short-term/working memory was seen in IGE compared to control groups (0.69 SD units; 95% CI: 0.48–0.90).

Three studies reported differences between IGE and control groups in visual–spatial thinking ability, revealing a small, non-significant effect (0.28 SD units; 95% CI: −0.17–0.73; Fig. 2.6). The two significant studies included younger patients with mean age 9–10 years, whilst the non-significant JME studies reported mean age ranges of 21–28 years (Conant et al., 2010; Singhi, 1992). The remaining non-significant study of mixed IGE syndromes reported a mean age of 14 (Henkin et al., 2005). Age of onset of epilepsy was also different, being below the age of 10 for significant versus above 10 or during later adolescence for non-significant studies, respectively.

Nineteen studies reported author-classified tests of executive function with more than half significant at the study level. On average, performance on tests thought to assess inhibition, strategy use and cognitive flexibility, showed a medium to large reduction in IGE patients compared to healthy controls; 0.72 SD units (95% CI: 0.51–0.94; Fig. 2.7).

3.3. Synthesis of results

On average, IGE samples performed significantly below control samples in all cognitive factors except visual–spatial thinking ability, which showed a non-significant effect. Effects ranged from 0.42 to 0.88 standard deviation units, with long-term memory retrieval showing a significant small effect, and speed of cognitive processing the largest effect. As illustrated by the *I squared* statistic on each forest plot, there was considerable heterogeneity between studies for all cognitive factors except crystallised intelligence. Apart from the trend towards a difference between syndromes in long-term memory described above, there were no significant differences between CAE, JME or IGE-GTCS in cognitive ability.

3.4. Risk of bias

Representativeness of sampling is a potential source of bias in this systematic review. Variability in diagnostic criteria may affect representativeness and was evident in the varied use of

Table 2
Characteristics of included studies.

Study	Syndrome	*n* (pt)	Age (mean or range)	AED use	AED type	Seizure	Years since diagnosis (mean)	Age at diagnosis (mean or range)	ILAE criteria year
Caplan, R., Siddarth, P., Stahl, L., Lanphier, E., Vona, P., Gurbani, S., Shields, W.D., 2008. Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. Epilepsia 49 (11), 1838–1846. doi: 10.1111/j1.1528-1167.2008.01680.x	CAE	69	9.6	Mix: monotherapy, polytherapy, naïve	Valproate, ethosuximide or other	Absence only	3.5	6.0	1989
Conant, L.L., Wilfong, A., Inglese, C., Schwarte, A., 2010. Dysfunction of executive and related processes in childhood absence epilepsy. Epilepsy Behav. 18 (4), 414–423.	CAE	16	8.0	Mix: monotherapy, polytherapy, naïve	Most valproate	Absence only	Not reported	4.5-8yrs (no mean avail)	1989
D'Agati, E., Cerminara, C., Casarelli, L., Pitzianti, M., Curatolo, P., 2012. Attention and executive functions profile in childhood absence epilepsy. Brain Dev. 34 (10), 812–817. doi: 10.1016/j.braindev.2012.03.001	CAE	15	11.4	All monotherapy	Valproate only	Absence only	2.6	8.8	1989
Pavone, P., Bianchini, R., Trifiletti, R. R., Incorpora, G., Pavone, A., Parano, E., 2001. Neuropsychological assessment in children with absence epilepsy. Neurology 56 (8), 1047–1051	CAE	6	9.2	Mix: monotherapy or polytherapy	Most valproate	absence only	not reported	3-8yrs (no mean avail)	1989
Iqbal, N., Caswell, H.L., Hare, D.J., Pilkington, O., Mercer, S., Duncan, S., 2009. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: a preliminary controlled experimental video-EEG case series. Epilepsy Behav.	JME	8	28.0	Most monotherapy	Most valproate	none within 24 hrs	not reported	n/a	1989
Kim, S.-Y., Hwang, Y.-H., Lee, H.-W., Suh, C.-K., Kwon, S.-H., Park, S.-P., 2007. Cognitive impairment in juvenile myoclonic epilepsy. J. Clin. Neurol. (Seoul, Korea) 3 (2), 86–92.	JME	27	19.0	None for 6 mths prior	n/a	no gtcs within week or myoclonic jerks within 24 hrs	2.9 years	16–20	1989
Kim, J.H., Suh, S.-I., Park, S.-Y., Seo, W.-K., Koh, I., Koh, S.-B., Seol, H.Y., 2012. Microstructural white matter abnormality and frontal cognitive dysfunctions in juvenile myoclonic epilepsy. Epilepsia 53 (8), 1371–1378.	JME	25	25.3	Mix: monotherapy or polytherapy	Most valproate	myoclonic, GTCS and absence	10.6	14.7	not specified

Table 2 (*Continued*)

Study	Syndrome	*n* (pt)	Age (mean or range)	AED use	AED type	Seizure	Years since diagnosis (mean)	Age at diagnosis (mean or range)	ILAE criteria year
Moschetta, S.P., Valente, K.D., Juvenile myoclonic epilepsy: the impact of clinical variables and psychiatric disorders on executive profile assessed with a comprehensive neuropsychological battery. Epilepsy Behav. 2012.	JME	42	16–48	All monotherapy	Valproate	45% seizure free	17.0	14.0	1989
O'Muircheartaigh, J., Vollmar, C., Barker, G.J., Kumari, V., Symms, M.R., Thompson, P., Richardson, M.P., 2011. Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy. Neurology 76 (1), 34–40. doi: 10.1212/WNL.0b013e31	JME	28	33.0	Mix: monotherapy, polytherapy, naïve	Not reported	57% seizure free	20.0	14.0	1989
Pascalicchio, T.F., de Araujo Filho, G.M., da Silva Noffs, M.H., Lin, K., Caboclo, L.O.S.F., Vidal-Dourado, M., Yacubian, E.M.T., 2007. Neuropsychological profile of patients with juvenile myoclonic epilepsy: a controlled study of 50 patient	JME	50	26.2	All monotherapy	Valproate	most had myoclonic and other seizure types (absence and GTCS)	not reported	not reported	1989
Piazzini, A., Turner, K., Vignoli, A., Canger, R., Canevini, M.P., 2008. Frontal cognitive dysfunction in juvenile myoclonic epilepsy. Epilepsia 49 (4), 657–662. doi: 10.1111/j.1528-1167.2007.01482.x	JME	50	37.0	Mix: monotherapy or polytherapy	Most valproate	most had myoclonic and other seizure types (absence and GTCS)	18.0	19.0	1989
Pulsipher, D.T., Seidenberg, M., Guidotti, L., Tuchscherer, V.N., Morton, J., Sheth, R.D., Hermann, B., 2009. Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. Epilepsia 50 (5), 1210–1219.	JME	20	15.5	All monotherapy	Most valproate	not reported	0.8	14.0	-
Roebling, R., Scheerer, N., Uttner, I., Gruber, O., Kraft, E., Lerche, H., 2009. Evaluation of cognition, structural, and functional MRI in juvenile myoclonic epilepsy. Epilepsia 50 (11), 2456–2465.	JME	18	24.2	None in week preceeding testing; mix: montherapy, polytherapy, naïve	Most valproate	myoclonic or GTCS	not reported	not reported	-
Sonmez, F., Atakli, D., Sari, H., Atay, T., Arpaci, B., 2004. Cognitive function in juvenile myoclonic epilepsy. Epilepsy Behav. 5 (3), 329–336. doi: 10.1016/j.yebeh.2004.01.007	JME	35	21.7	All monotherapy	Valproate	initial seizure type myoclonic, absence or GTCS	not reported	10–15 years	-

Table 2 (*Continued*)

Study	Syndrome	*n* (pt)	Age (mean or range)	AED use	AED type	Seizure	Years since diagnosis (mean)	Age at diagnosis (mean or range)	ILAE criteria year
Wandschneider, B., Kopp, U.A., Kliegel, M., Stephani, U., Kurlemann, G., Janz, D., Schmitz, B., 2010. Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. Neurology 75 (24), 2161–2167.	JME	21	25.5	Mix: monotherapy, polytherapy, naïve	Most valproate	myoclonic, absence and GTCS only	11.0	14.5	-
Singhi, P. D. (1992). Determinants of IQ profile in children with idiopathic generalized epilepsy. Epilepsia, 33(6), 1106–1114.	IGE - GTCS	50	10.0	Mix: monotherapy or polytherapy	Mix: phenobarbital, phenytoin, or both	seizure free 7 days - 3 years	2.9 years	7.0	1981
Tian, Y., Dong, B., Ma, J., Zhou, S., Zhou, N., Wang, K., 2010. Attention networks in children with idiopathic generalized epilepsy. Epilepsy Behav. 19 (3), 513–517. doi: 10.1016/j.yebeh.2010.07.003	IGE - GTCS	37	10.9	All naïve	n/a	GTCS	0.5	10.0	1981
Davidson, M., Dorris, L., O'Regan, M., Zuberi, S.M., 2007. Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. Epilepsy Behav. 11 (3), 394–400. doi: 10.1016/j.yebeh.2007.05.004	IGE heterogenous	21	11.5	Mix: monotherapy, polytherapy, naïve	Most valproate	not reported	not reported	not reported	2004
Dickson, J.M., Wilkinson, I.D., Howell, S.J.L., Griffiths, P.D., Grunewald, R.A., 2006. Idiopathic generalised epilepsy: a pilot study of memory and neuronal dysfunction in the temporal lobes, assessed by magnetic resonance spectroscopy. Journal	IGE heterogenous	29	30.0	Mix: monotherapy, polytherapy, naïve	Valproate, lamotrigine, levetir and others		20.0	not reported	1989
Gascoigne, M.B., Barton, B., Webster, R., Gill, D., Antony, J., Lah, S.S., 2012. Accelerated long-term forgetting in children with idiopathic generalized epilepsy. Epilepsia 53 (12), 2135–2140. doi: 10.1111/j.1528-1167.2012.03719.x	IGE heterogenous	20	10.8	Mix: monotherapy or polytherapy	n/a	not reported	4.5	6.0	1989
Gelziniene, G., Jurkeviciene, G., Marmiene, V., Adomaitiene, V., Endziniene, M., 2011. Executive functions in adolescents with idiopathic generalised epilepsy. Medicina (Kaunas, Lithuania) 47 (6), 313–319.	IGE heterogenous	59	15.5	Mix: most medication naïve, others monotherapy or polytherapy	Most valproate	no absence only; none had gtcs in prior 24 hrs	1.2	13.0	1989

Table 2 (*Continued*)

Study	Syndrome	*n* (pt)	Age (mean or range)	AED use	AED type	Seizure	Years since diagnosis (mean)	Age at diagnosis (mean or range)	ILAE criteria year
Henkin, Y., Sadeh, M., Kivity, S., Shabtai, E., Kishon-Rabin, L., Gadoth, N., 2005. Cognitive function in idiopathic generalized epilepsy of childhood. Dev. Med. Child Neurol. 47 (2), 126–132. doi: 10.1017/s0012162205000228	IGE heterogenous	24	14.0	All monotherapy	Valproate only	absence only OR gtcs only	not reported	not reported	-
Levav, M., Mirsky, A.F., Herault, J., Xiong, L., Amir, N., Andermann, E., 2002. Familial association of neuropsychological traits in patients with generalized and partial seizure disorders. J. Clin. Exp. Neuropsychol. 24 (3), 311–326. doi: 10.1076/jcen.24.3.311.985	IGE heterogenous	28	14.0	Mix: most no AED, others monotherapy or polytherapy	Most valproate or carbamazepine	not reported	n/a	5.0	-
Levav, M., Mirsky, A.F., Herault, J., Xiong, L., Amir, N., Andermann, E., 2002. Familial association of neuropsychological traits in patients with generalized and partial seizure disorders. J. Clin. Exp. Neuropsychol. 24 (3), 311–326. doi: 10.1076/jcen.24.3.311.985	IGE heterogenous	11	36.8	Mix: monotherapy or polytherapy	Most valproate or carbamazepine	not reported	n/a	15.0	-
Maganti, R., Sheth, R.D., Hermann, B.P., Weber, S., Gidal, B.E., Fine, J., 2005. Sleep architecture in children with idiopathic generalized epilepsy. Epilepsia 46 (1), 104–109. doi: 10.1111/j.0013-9580.2005.06804.x	IGE heterogenous	11	13.0	Mix: monotherapy or polytherapy	valproate, ethosuximidfe, topiramate	had to be currently seizure free	5.0	8.0	-
Muhlert, N., Grunewald, R.A., Hunkin, N.M., Reuber, M., Howell, S., Reynders, H., Isaac, C.L., 2011. Accelerated long-term forgetting in temporal lobe but not idiopathic generalised epilepsy. [Comparative Study]. Neuropsychologia 49 (9), 2417–2426. doi: 10.1016/j.neuropsychologia.2011.04.018	IGE heterogenous	14	31.0	Mix: monotherapy, polytherapy, naïve	Mix	GTCS with or without absence	16.0	14.0	-
Shehata, G.A., Bateh, A.E.-a.M., 2009. Cognitive function, mood, behavioral aspects, and personality traits of adult males with idiopathic epilepsy. Epilepsy Behav. 14 (1), 121–124. doi: 10.1016/j.yebeh.2008.08.014	IGE heterogenous	71	28.9	All monotherapy	Carbamazepine or valproate	n/a	8.0	20.0	1981

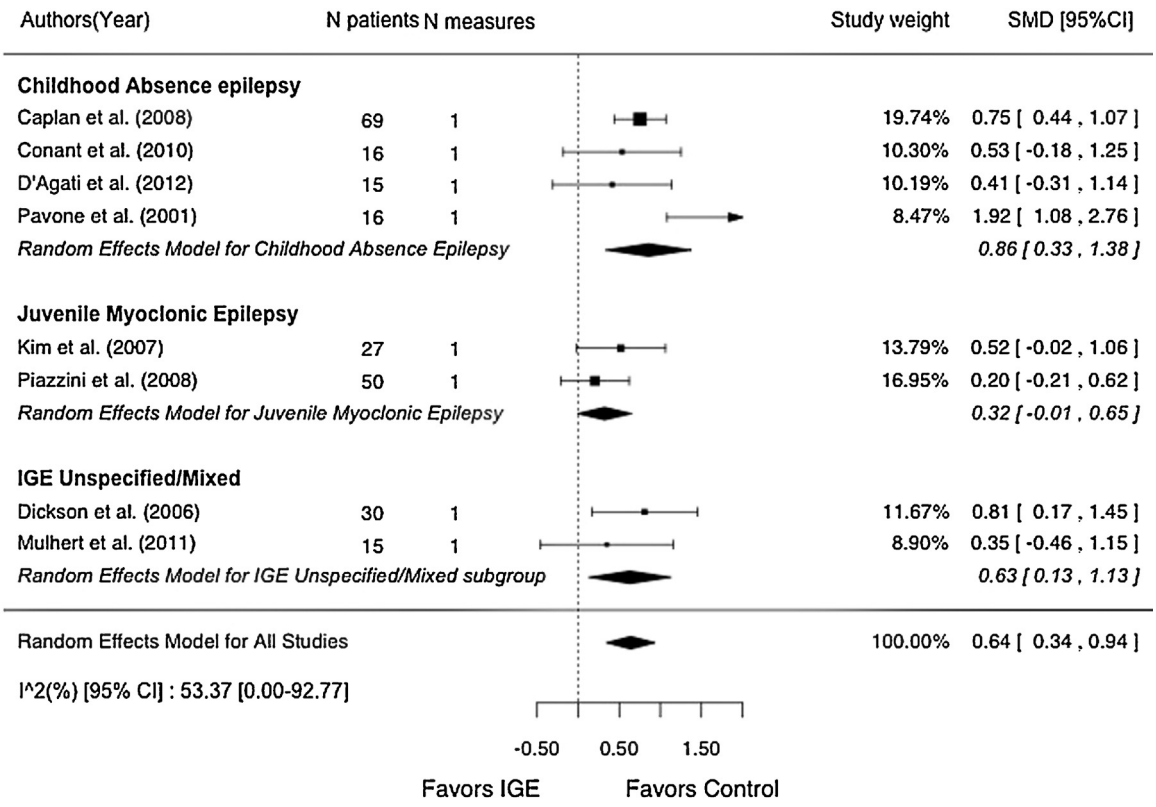

Fig. 2.0. Difference scores of general cognitive ability (G) between IGE and healthy control groups. Effect sizes are in standard deviation (SD) units, with 95% confidence intervals (CI). Positive effect values indicate higher control means. Subgroup effects are reported where results from more than one IGE syndrome were available. Note that in some comparisons, the sample size in the "N patient" column in the forest plots represents an average of sample size across tests, where the number of patients assessed was not consistent across tests of the respective ability.

ILAE Commission diagnostic criteria, or equivalent, published in 1981 (reported by three studies), 1989 (thirteen studies), 2004 (one study) or no stated criteria (nine studies). However numbers were too small for any formal comparison of the effects of different diagnostic criteria.

Other potential sources of bias include the reliability of measures. The neuropsychological tests reported vary in reliability from 0.3 to 0.9, approximately (Franzen, 2000; Strauss et al., 2006). The large number of different measures makes evaluation of the impact of test reliability impractical. However, the meta-analytic strategy of aggregating scores for averaged effects should provide more accurate estimates of cognitive effects than is available from any one study. Bias due to referral source was not assessed because most studies did not report the referral source or population characteristics.

Sample characteristics including age, incident or prevalent cohort, AED treatment and illness duration were also considered for their potential impact on the variability of results between studies. However, the small number of studies providing details of these variables precluded detailed quantitative comparisons.

4. Discussion

4.1. Summary of findings

To our knowledge, this is the first systematic review and meta-analysis of cognitive function in IGE. To date, studies have focussed on JME, with relatively few studies of CAE and IGE-GTCS and no studies of JAE meeting inclusion criteria. The paucity of research on IGE-GTCS and JAE may be due to the relatively recent reclassification of the IGE-GTCS syndrome (incorporating epilepsy with GTCS on awakening) and the likely under-diagnosis of JAE (Engel, 2001; Jallon and Latour, 2005).

Although the heterogeneity of observed effects prompts cautious interpretation, meta-analytic summary effects showed significantly lower scores in IGE patients than in healthy controls in all cognitive factors except visual-spatial thinking ability. Overall, the greatest degree of reduction in patient scores was seen in cognitive processing speed (large effect), crystallised and fluid intelligence and short-term/working memory (medium to large effects) and long-term memory retrieval (small to medium effect). A medium to large effect was observed in the measures of overarching generalised cognitive ability. The relatively smaller reduction in memory function is at odds with reports of poor memory being the most common cognitive symptom in patients with epilepsy (Fisher et al., 2000). The frequency of self-report memory symptoms may reflect the fact that working memory impairments are less well tolerated than reductions in other cognitive domains and that subjective memory symptoms, often expressed in response to reductions in short-term or working memory, may be more closely associated with mood disturbances such as depression and anxiety than with objective cognitive function (David et al., 2012; Hall et al., 2009; Marino et al., 2009). It is possible that reports of subjective memory difficulties reflect misestimation of cognitive deficits (Hall et al., 2009; Marino et al., 2009) and 'memory problems' may be the most accessible descriptor patients have for broader, cognitive difficulties. These alternative interpretations require further study. Importantly, there was insufficient data to assess the impact of mood disorder on cognition in the studies reviewed here.

Overall, no distinctive cognitive profiles, in terms of relative strengths and weaknesses, emerged for either CAE or JME, the only two syndromes for which sufficient data were available. Although data are limited, the results of the systematic review fail to support

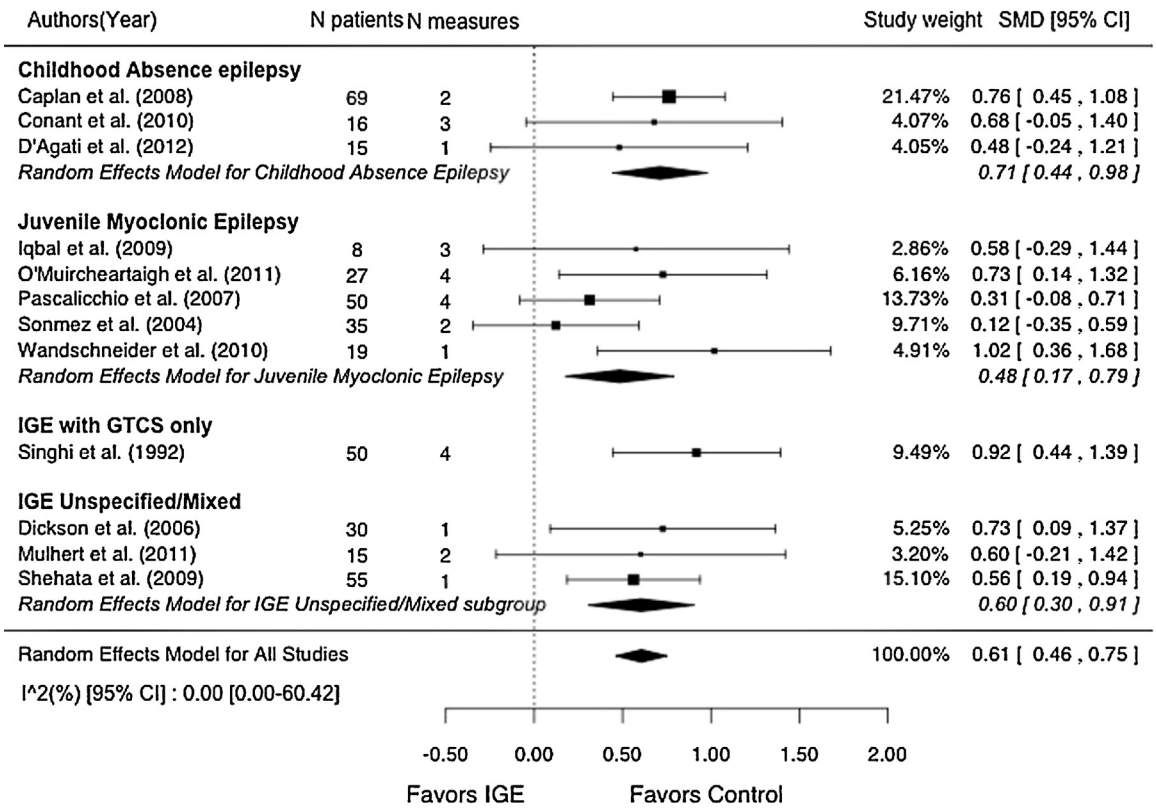

Fig. 2.1. Difference scores of crystallised intelligence (Gc) between IGE and healthy control groups. Effect sizes are in standard deviation (SD) units, with 95% confidence intervals (CI). Positive effect values indicate higher control means. Subgroup effects are reported where results from more than one IGE syndrome were available. Note that in some comparisons, the sample size in the "N patient" column in the forest plots represents an average of sample size across tests, where the number of patients assessed was not consistent across tests of the respective ability.

the hypothesis of differential cognitive effects in any subsyndrome of IGE (Berg et al., 2010).

4.1.1. CAE

CAE samples showed large deficits across all cognitive abilities except long-term memory retrieval, where there was no significant difference between CAE and control groups. This finding corroborates increasing evidence that CAE is not the cognitively benign syndrome it was once considered to be (Wirrell et al., 1997). However in the absence of longitudinal research, the prognosis for cognitive function into adulthood is uncertain, particularly for patients in remission. It is possible that the observed deficits are caused by the acute or chronic effects of frequent daily absences, general or specific AED treatment, or by underlying functional changes to brain networks.

4.1.2. JME

Studies of JME samples reported large deficits in the factors of fluid intelligence, cognitive processing speed, short-term/working memory and author-classified tests of executive function. Small–medium deficits were observed in crystallised intelligence and long-term memory retrieval, as well as the overarching measures of generalised cognitive ability. Contrary to the hypothesis of selective executive deficits, JME samples did not perform more poorly on tests of executive function compared to tests of other abilities, and an executive function deficit at the study-level was present in less than half. These five studies did not differ in any obvious way to the remaining seven, in terms of sample or study design and a substantial degree of overlap was observed in the confidence intervals of all included studies (see Fig. 2.7).

It should be noted that all tests of so-called executive functions are categorised under the well-defined CHC factors of fluid intelligence, processing speed and working memory (Carroll, 1993; McGrew, 2009). So it is not surprising that a systematic review of these abilities reveals widespread impairments in JME (and IGE) samples. However it is notable that tests of all broad CHC abilities also revealed deficits in IGE and JME, with the exception of visual–spatial thinking. The two studies that reported significant reductions in this ability in IGE included samples of children, whereas the remaining non-significant studies included young adult samples. It is therefore possible that a visual processing deficit is present in pre-adolescent, elementary school aged children (or those diagnosed in childhood) but not in older children and adults with IGE. This hypothesis requires further investigation.

A focus on the hypothesis of selective executive deficits may have distracted attention from the pervasive nature of cognitive impairment in patients with IGE and JME, in particular. Since these impairments are likely to have significant educational, vocational and management impact for a proportion of patients, future studies of cognition in IGE and JME should ensure that cognitive abilities are sampled in a broadly representative fashion, so as not to underestimate the potential impact of these seizure syndromes.

4.1.3. Contribution of disease factors

A post hoc examination of the direction and size of effects in all cognitive factors failed to reveal any difference based on patient age at assessment, age at onset of epilepsy or medication use. These results may be due to the fact that many studies restricted study participants to those on monotherapy or on a particular AED. The issue of cognitive side-effects of AEDs has been of great interest, although several reviews have reported equivocal

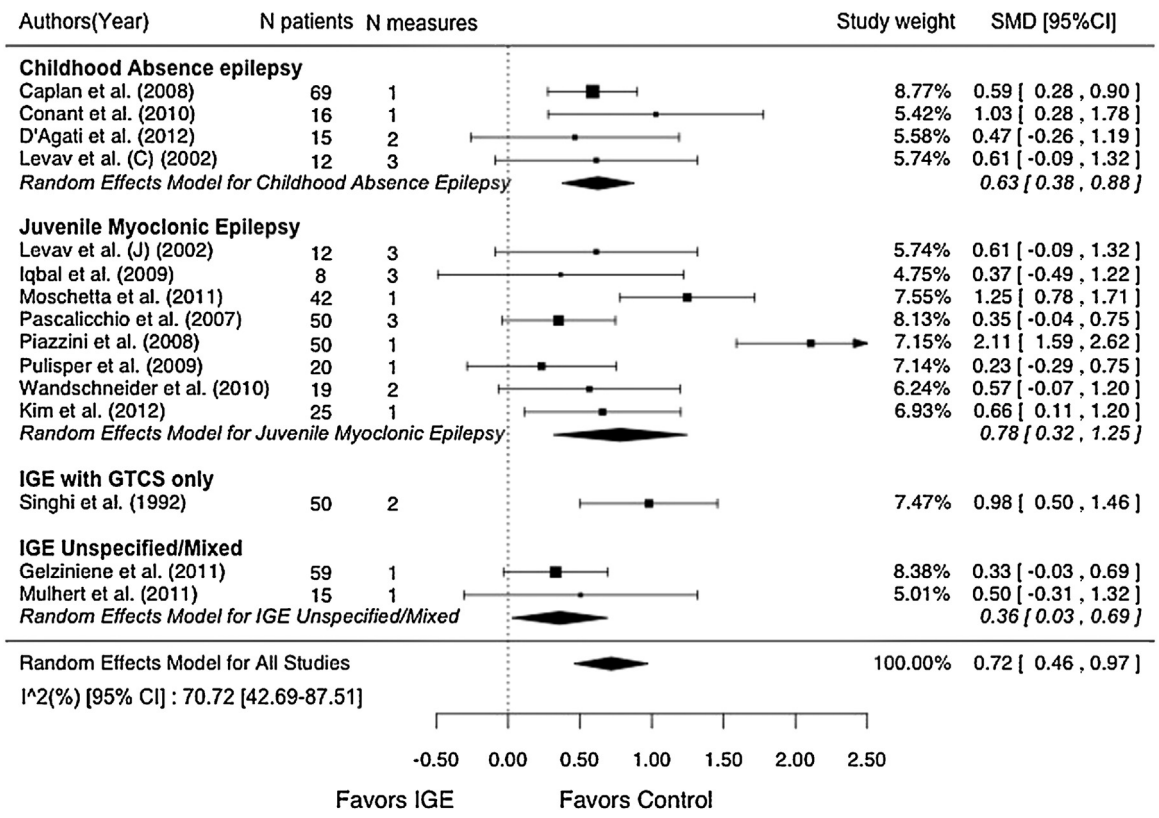

Fig. 2.2. Difference scores of fluid intelligence (Gf) between IGE and healthy control groups. Effect sizes are in standard deviation (SD) units, with 95% confidence intervals (CI). Positive effect values indicate higher control means. Subgroup effects are reported where results from more than one IGE syndrome were available. Note that in some comparisons, the sample size in the "N patient" column in the forest plots represents an average of sample size across tests, where the number of patients assessed was not consistent across tests of the respective ability.

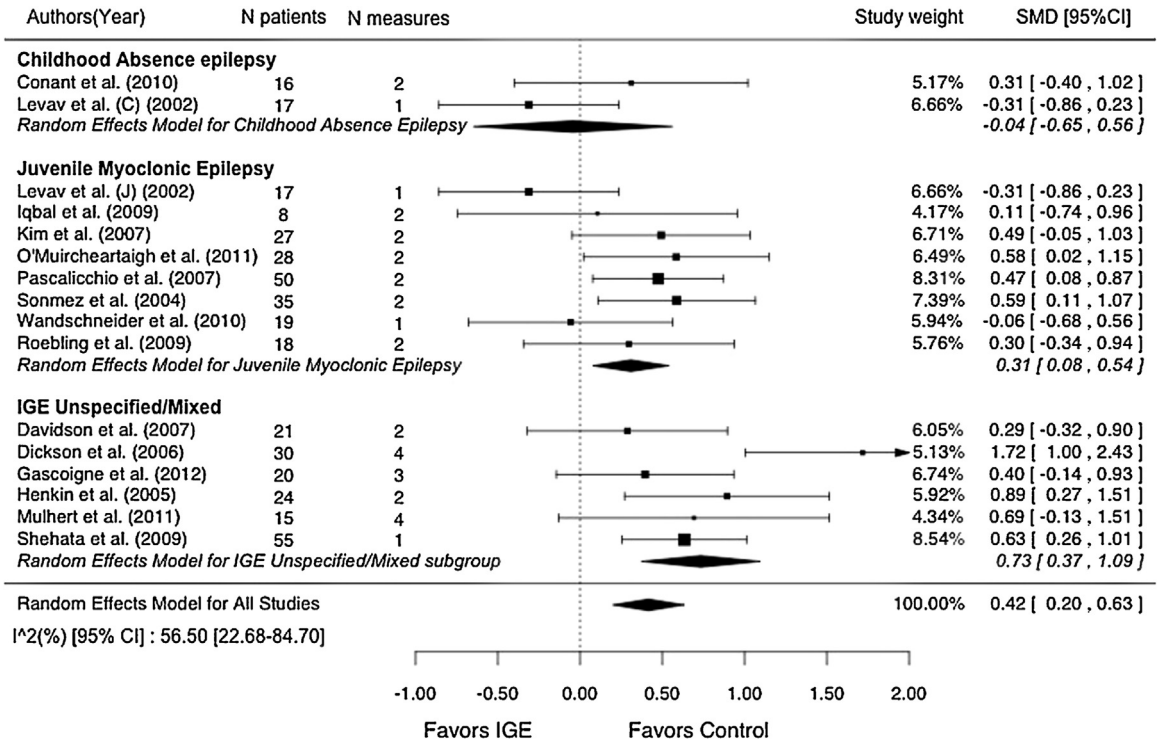

Fig. 2.3. Difference scores of long-term storage and retrieval (Glr) between IGE and healthy control groups. Effect sizes are in standard deviation (SD) units, with 95% confidence intervals (CI). Positive effect values indicate higher control means. Subgroup effects are reported where results from more than one IGE syndrome were available. Note that in some comparisons, the sample size in the "N patient" column in the forest plots represents an average of sample size across tests, where the number of patients assessed was not consistent across tests of the respective ability.

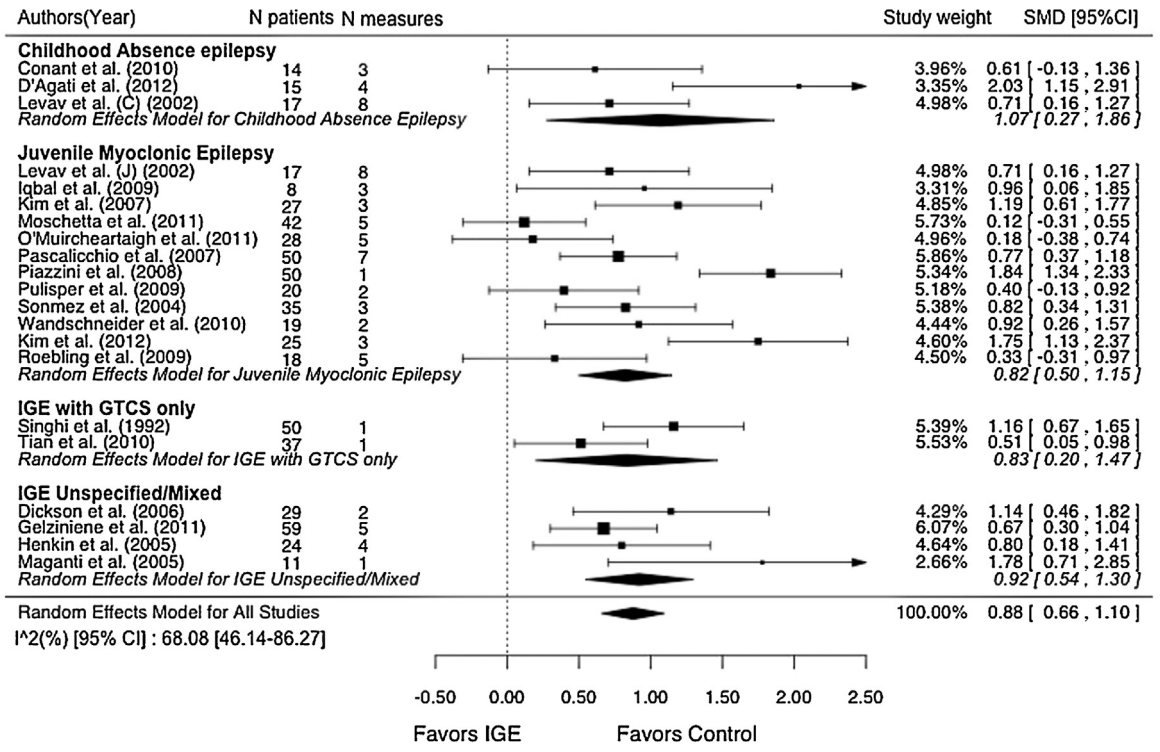

Fig. 2.4. Difference scores of speed of cognitive processing (Gs) between IGE and healthy control groups. Effect sizes are in standard deviation (SD) units, with 95% confidence intervals (CI). Positive effect values indicate higher control means. Subgroup effects are reported where results from more than one IGE syndrome were available. Note that in some comparisons, the sample size in the "N patient" column in the forest plots represents an average of sample size across tests, where the number of patients assessed was not consistent across tests of the respective ability.

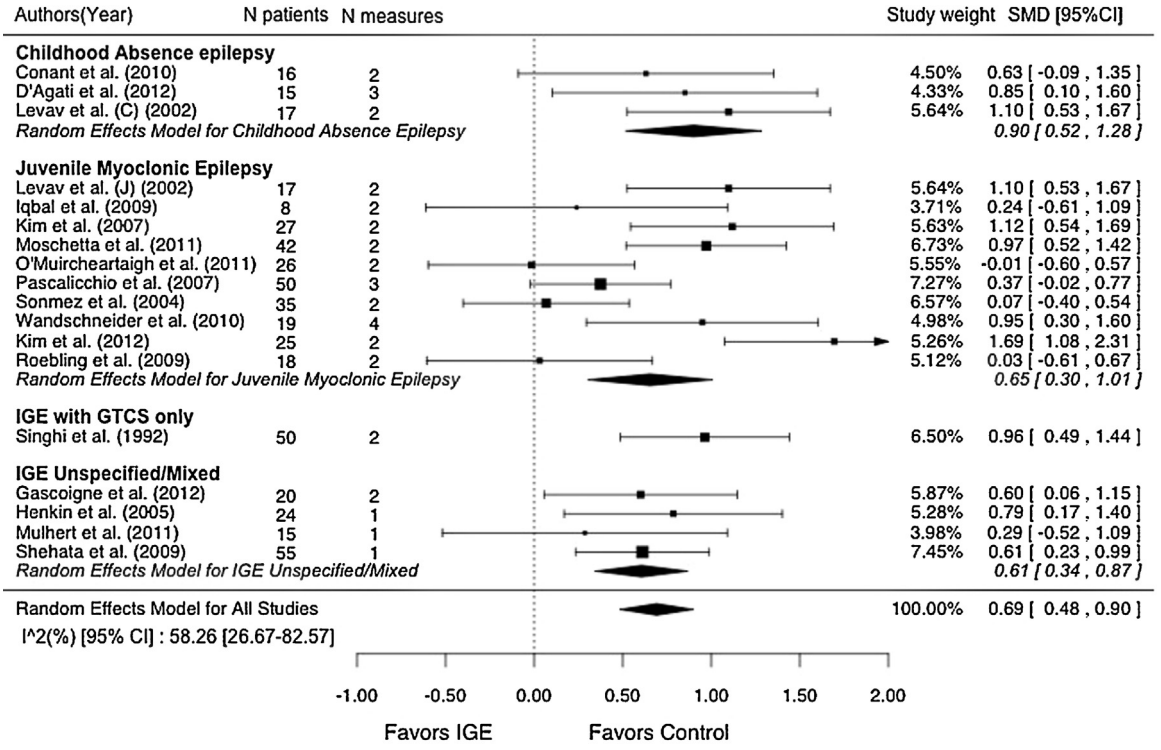

Fig. 2.5. Difference scores of short-term memory ability (Gsm) between IGE and healthy control groups. Effect sizes are in standard deviation (SD) units, with 95% confidence intervals (CI). Positive effect values indicate higher control means. Subgroup effects are reported where results from more than one IGE syndrome were available. Note that in some comparisons, the sample size in the "N patient" column in the forest plots represents an average of sample size across tests, where the number of patients assessed was not consistent across tests of the respective ability.

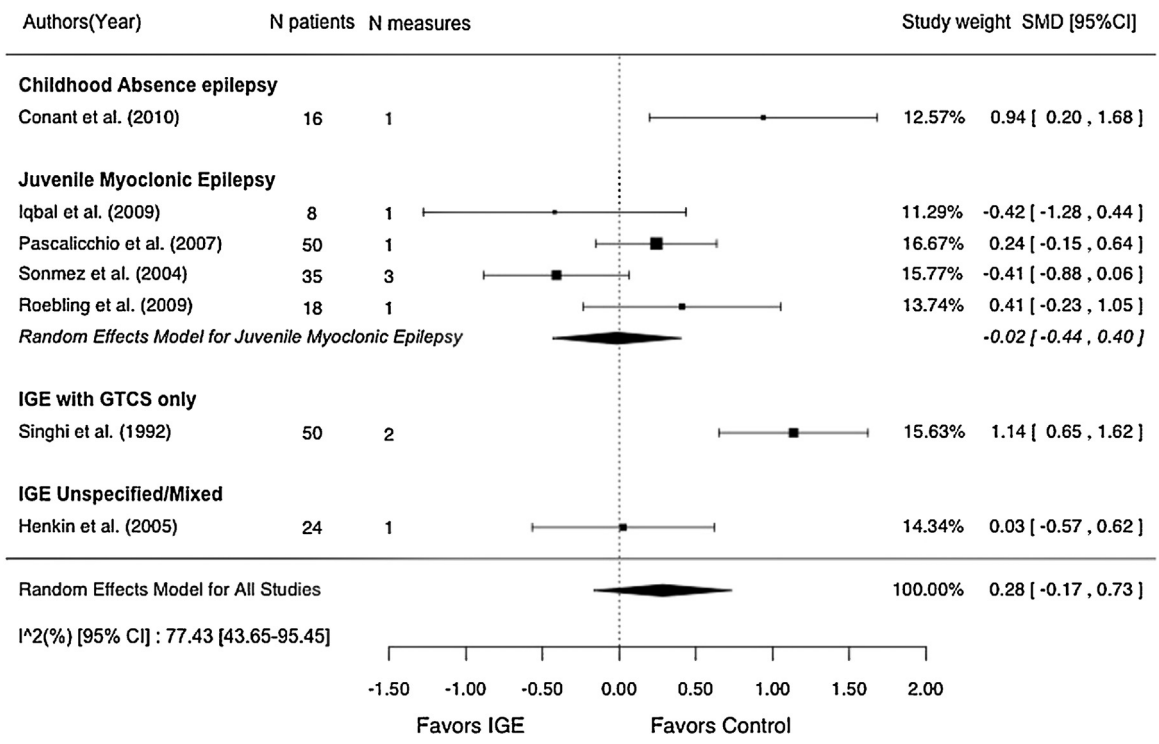

Fig. 2.6. Difference scores of visual-spatial thinking ability (Gv) between IGE and healthy control groups. Effect sizes are in standard deviation (SD) units, with 95% confidence intervals (CI). Positive effect values indicate higher control means. Subgroup effects are reported where results from more than one IGE syndrome were available. Note that in some comparisons, the sample size in the "N patient" column in the forest plots represents an average of sample size across tests, where the number of patients assessed was not consistent across tests of the respective ability.

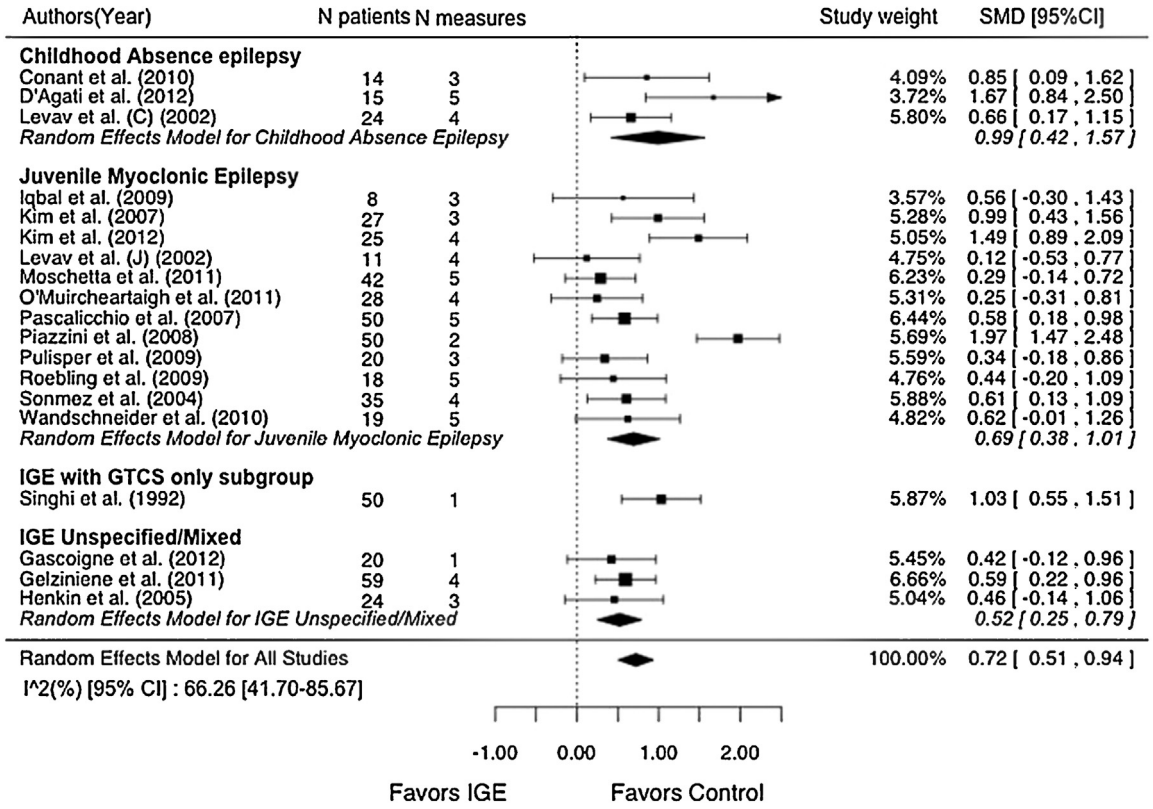

Fig. 2.7. Difference scores of executive function ability (EF) between IGE and healthy control groups. Effect sizes are in standard deviation (SD) units, with 95% confidence intervals (CI). Positive effect values indicate higher control means. Subgroup effects are reported where results from more than one IGE syndrome were available. Note that in some comparisons, the sample size in the "N patient" column in the forest plots represents an average of sample size across tests, where the number of patients assessed was not consistent across tests of the respective ability.

results (e.g. Brunbech and Sabers, 2002; Ortinski and Meador, 2004; Vermeulen and Aldenkamp, 1995). Although not well documented in the reviewed studies, the current systematic review failed to reveal evidence of any differential cognitive deficits attributable to medication use or other disease variables. However, a prospective study of representative incident cases prior to AED treatment with power to test effects of specific AED initiation and withdrawal may clarify this issue.

4.2. Findings in context

The purpose of this review was to make best sense of a disparate body of literature reflecting heterogeneous methods in a poorly understood population. Taken one study at a time, currently there is no cohesive picture regarding cognitive function in IGE. In contrast, at the meta-analytic level a clearer picture is evident. The results show that many areas of cognitive functioning appear to be affected in patients with IGE. In the studies reviewed, most cognitive abilities examined, representative of a comprehensive model of abilities, displayed medium to large disease effects. These effects will impact everyday function to a moderate degree in many patients with a diagnosis of IGE and to a larger degree in a subset of patients. To take one example, the average disease effect observed across general cognitive ability (Full Scale IQ) reported above (Fig. 2.0) was .64 standard deviation units. Therefore, under normal distribution assumptions, it can be estimated that in the IGE cohort, the incidence of learning difficulties or intellectual disability, using the criterion of an intelligence test score less than or equal to 70, is 9% approximately, compared to the general population incidence of 2% approximately. In addition the incidence of people with cognitive abilities in the 'borderline' range (intelligence scores in the range 70–80) will be an additional 16% approximately, compared to the population incidence of 7%.

While these figures are approximate, the meta-analysis above reveals an estimated 25% cumulative incidence of intellectual disability or 'borderline' cognitive abilities in patients with IGE and illustrates the potential for a dramatically increased frequency of educational intervention needs in this population, more than double the incidence in the general population. Inadequate provision of educational interventions are likely to lead to increased risk of secondary psychological adjustment disorders with concatenating social and vocational effects. The results of this meta-analysis highlight the importance of providing better intervention services for people with IGE. These educational needs have not been clearly articulated in previous research with people with IGE.

Considerable methodological heterogeneity was apparent at the study-level in this meta-analysis. Some of the heterogeneity may be attributable to sampling differences noted previously, conflated diagnoses or less than representative sampling together with mixtures of incident and prevalent cases. Future studies should aim to more carefully control sampling to better estimate the impact of IGE.

Any synthesis of cognitive deficits in IGE will necessarily acknowledge the apparent heterogeneity of the diagnosis and subtypes. While this systematic review provides no evidence for focal deficits, focal or selective deficits are of course possible within individuals. The consistently large deficit seen in speed of information processing (Fig. 2.4) supports the inference of diffuse cognitive 'dampening' that might be expected from these epilepsies, in view of the likely diffuse expression of the, as yet poorly understood, pathophysiology. As well, individual developmental profiles, personality style, co-morbid mood or anxiety disorders (Rai et al., 2012) or AED therapy together with educational and social opportunities will all interact with cognitive disability.

The possibility of unmeasured explanatory factors also warrants consideration. There is emerging, albeit inconsistent, evidence of brain changes associated with JME. The most consistent finding is a reduction in thalamic volumes seen across the majority of studies (Cao et al., 2013). In addition, both increased, and decreased frontal cortical grey matter volumes have been reported, with one study failing to find any difference between JME patients and controls (Roebling et al., 2009). The voxel-based morphometry (VBM) used in these studies is an automated technique of quantitative MRI analysis and is particularly affected by total intracranial volume, age, gender, scanner used and the size of control group comparison (Pell et al., 2008; Yasuda et al., 2010). Therefore, although it is possible that these observed neuroanatomical abnormalities could be linked with cognitive function they remain of uncertain functional significance, at present.

4.3. Limitations

For the purpose of this meta-analysis, it was necessary to classify cognitive tests by single cognitive factors, which may involve some simplification of the cognitive abilities assayed by some tests. In addition, an average score of multiple tests of each factor was required to undertake univariate meta-analyses. The simplification of data in this way was preferable to the more detailed multivariate meta-analysis, the methodology for which is under-developed and exploratory (Wei and Higgins, 2013).

4.4. Future directions

While the literature on cognitive deficits in IGE in general is rapidly expanding, this review revealed a paucity of published research regarding cognitive outcomes in patients with JAE and IGE-GTCS. In view of the similarity of clinical features of these syndromes, comparison of cognition in patients with JAE versus patients with CAE could facilitate better understanding of the impact of age of onset and seizure frequency. Also, the possible differences between CAE and JME observed in long-term memory retrieval in this review requires further investigation of, for example, age of onset or other diagnostic features.

Future studies of IGE should carefully control and describe sample features such as the inclusion of incident cohorts, prospective samples drawn from community-based settings, untreated patients and larger samples spanning the spectrum of syndromes, particularly JAE and IGE-GTCS. Consecutive recruitment would also improve representativeness of sampling (Loring and Bowden, 2013). Together with consistent reporting of potentially confounding variables such as seizure frequency and diurnal and nocturnal interictal epileptiform discharges, future studies should improve our understanding of cognition in IGE and sub-syndromes.

Finally, many seizure disorders are accompanied by a high prevalence of psychopathology (Beyenburg et al., 2005; Kimiskidis et al., 2007). Concurrent psychopathology can have significant impacts on cognitive function (Elixhauser et al., 1999). However, as few studies to date have considered the impact of co-morbid psychopathology on cognitive function in patients with IGE, this question remains unanswered. Future research with comprehensive measurement of both cognitive function and psychopathology is critical to properly understand the developmental and cognitive trajectories in patients with IGE.

5. Conclusions

Medium to large deficits in cognitive function (up to 0.88 standard deviation units) were observed in patients with IGE, with the greatest reduction in scores observed on measures of cognitive processing speed. These deficits were observed despite a large degree of heterogeneity across results of individual studies. The heterogeneity of results may be due to the inherent heterogeneity of

the clinical expression of these conditions or due to the variable methodologies used to study IGE. Consistent with the observation of a general reduction in cognitive function, all broad CHC cognitive factors except visual–spatial thinking ability showed significant impairment. There was no evidence for specific cognitive profiles in IGE syndromes and scores on measures of executive functioning showed no greater impairments relative to other cognitive abilities, both in JME and in other IGE syndromes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2014.02.012.

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Chapter 4: A Systematic Review of Psychosocial Function in GGE

The previous chapter presented a systematic review and meta-analysis of cognitive functioning in GGE that was published in 2014. In acknowledgement of the high standard of evidence and clarity that the systematic review form affords, this chapter provides the second such document in this thesis, a systematic review of psychosocial function in GGE. As will be demonstrated, the overall data quality of the available literature precluded the inclusion of meta-analysis - a quantified synthesis of previous findings. Nonetheless, the undertaking of this review proved to be a useful exercise and the work was published in *Neuropsychology Review,* providing systematic compilation of the data.

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REVIEW

A Systematic Review of Psychiatric and Psychosocial Comorbidities of Genetic Generalised Epilepsies (GGE)

A. Loughman[1,2] · **N. A. Bendrups**[1] · **W. J. D'Souza**[3]

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Abstract Psychiatric disorders and associated poor psychosocial outcomes are recognised to be a common sequelae of epilepsy. The extent to which this is true of genetic generalised epilepsies (GGE), particularly syndromes other than juvenile myoclonic epilepsy (JME) is unclear. This systematic review synthesises findings regarding psychiatric and associated comorbidities in adults and children with GGE. Systematic review yielded 34 peer-reviewed studies of psychiatric and psychosocial outcomes in adults and children with GGE. Clinically significant psychiatric comorbidity was reported in over half of all children and up to a third of all adults with GGE. There was no evidence to support the presence of personality traits specific to JME or other syndromes; rather rates mirrored community samples. A small number of studies report poor psychosocial outcomes in GGE, however the interpretation of these findings is limited by paucity of healthy comparison groups. Some evidence suggests that anti-epileptic drug polytherapy in children and seizure burden at all ages may constitute risk factors for psychopathology. Findings highlight the importance of early screening so as not to overlook early or developing symptoms of psychopathology.

Keywords Idiopathic/genetic generalised epilepsy · Psychiatric comorbidity · Psychopathology · Psychosocial

Introduction

Genetic generalised epilepsies (GGE), a cluster of epilepsy syndromes, account for 15–20 % of all epilepsy and comprise subtypes of childhood absence, juvenile absence, juvenile myoclonic, and epilepsy with generalised tonic-clonic seizures (Jallon and Latour 2005). As interest in GGE has burgeoned, a small literature describes elevated risk of psychiatric disorders and poor psychosocial outcomes. In adults with GGE, increased prevalence of depression, anxiety and personality disorders are reported (Akanuma et al. 2008; Cutting et al. 2001; Moschetta et al. 2011) whilst depression, anxiety and non-specific attentional, emotional and conduct problems are described in children (Vega et al. 2011; Dafoulis and Kalyva 2012; Piccinelli et al. 2010). These findings – alongside evidence of cognitive dysfunction in GGE – suggest that despite relatively high rates of seizure remission, it is no longer appropriate to consider these syndromes as 'benign' (Hommet et al. 2006; Wirrell et al. 1997; Loughman et al. 2014; Seneviratne et al. 2012).

However further synthesising the limited literature regarding psychopathology in GGE is impeded by variability in sample characteristics with regards to syndrome, age, recruitment source and by methodologies used to report psychopathological outcomes. In considering this variability between studies, this

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✉ A. Loughman
amy.loughman@unimelb.edu.au

N. A. Bendrups
nbendrups@gmail.com

W. J. D'Souza
wendyl1@icloud.com

[1] Melbourne School of Psychological Sciences, University of Melbourne, Parkville, VIC 3010, Australia

[2] School of Health & Biomedical Sciences, College of Science, Engineering & Health, RMIT University, PO Box 71, Bundoora, VIC 3083, Australia

[3] Department of Clinical Neurosciences, Department of Medicine, St Vincent's Hospital, The University of Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia

systematic review aims to: (1) summarise the literature on psychiatric and psychosocial functioning in GGE; (2) consider risk factors for psychiatric and associated outcomes in GGE; and (3) compare comorbidities in GGE with other chronic illness.

Methods

Search Strategies and Selection Criteria

Medline and Scopus databases were searched for primary research articles reporting psychiatric comorbidity or psychosocial functioning in people with GGE. Search terms included *idiopathic generalised epilepsy* (IGE; the previously used term for GGE), *genetic generalised epilepsy* and the subsyndromes of GGE, combined with common psychiatric disorders. A complete list of search terms is provided in Appendix A. The reference lists of eligible studies were also searched for additional articles. A final list of included studies was completed on 20 November 2015. This review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO Registration Number CRD42014013395). The review was conducted and reported in accordance with the MOOSE guidelines (Stroup et al. 2000).

Study eligibility criteria comprised: (a) original research published in a peer-reviewed journal with full-text in English; (b) sample or subsample with a diagnosis of GGE (either consisting of mixed, unspecified syndromes or one of the ILAE-recognised syndromes of IGE/GGE from 1989 ILAE Classification guidelines onwards: Childhood absence epilepsy [CAE], juvenile absence epilepsy [JAE], juvenile myoclonic epilepsy [JME], GGE with generalised tonic-clonic seizures only (previously known as IGE with generalised tonic-clonic seizures on awakening) [GGE-GTCS]); (c) outcomes including rates of psychiatric comorbidity, rates of psychopathological symptoms on a validated measure, mean scores on a validated measure of psychopathological symptoms or study-designed questionnaire. Studies were ineligible if results were not presented separately for at least one GGE patient group.

Data items included descriptive variables (e.g. GGE syndrome, age, study size, cohort ascertainment, diagnosis, classification and methodology), psychopathological and psychosocial outcomes, and risk factors such as epilepsy disease characteristics.

Assessment of Quality

The STROBE statement provides guidelines on the quality of reporting of observational studies (Vandenbroucke et al. 2007). One component of the STROBE checklist of particular relevance to this review concerns patient ascertainment, diagnostic criteria and methods of measurement. To enable comparisons between studies and the interpretation of findings, details of the abovementioned methodological characteristics are included in Table 1 and Online Resource 1. Table 2 expands on acronyms used in Table 1. The diagnostic criteria for GGE syndromes was omitted from some studies, problematic in an era of evolving opinion regarding diagnosis of epilepsy (Andermann and Berkovic 2001). However, in the interests of comprehensiveness, studies were not excluded for reasons of inadequate reporting of methodology.

Results

Study Selection and Characteristics

Figure 1 illustrates the selection process. Four-hundred and sixty eight articles were retrieved, of which 28 were eligible for detailed review. An additional six articles were eligible from reference lists of these studies. No unpublished studies or abstracts were obtained using the search strategy. See Table 1 for details of all 34 included studies, including the number used to refer to each study hereafter.

In the obtained studies, the ILAE 1989 classification of GGE (or equivalent) was the most commonly cited method of diagnosis. Sampling methods are best characterised as 'convenience samples' from tertiary referral centres, or public and private clinics. Some studies conducted retrospective reviews of medical files, which may have resulted in more comprehensive sampling than studies relying on prospective recruitment. However, the methodological quality of these studies was reduced by the use of existing psychiatric diagnoses as an estimate of prevalence (rather than measurement of current symptoms in the entire sample).

Sample size in the included studies ranged from 11 to 157 GGE patients, with a cumulative total of as many as 1266 participants across the studies. (Some information about potentially overlapping samples was not available). The largest samples were derived from retrospective review of hospital records. The majority of studies, however, reported prevalent samples, recruited prospectively from community or tertiary hospital clinics. Incidence samples, or those restricted to clearly defined GGE syndrome, seizure type or AED type, were rare. The reliance on prevalence sampling results in heterogeneous, and often rather small GGE samples. This sampling strategy precludes subgroup or covariate analyses of clinical variables that may be relevant to psychosocial outcomes.

Aim 1: Psychiatric and Psychosocial Functioning Outcomes

Psychiatric Comorbidity in Children with GGE

Eleven studies included children with GGE. Six samples comprised mixed syndromes (#1, 2, 8–11); four included CAE

Table 1 Summary of included studies

ID #	Authors	Syndrome/s	Age (years) M (SD)	Age range (years)	N (GGE)	Interpretation and main findings
1	Almane, Jones, Jackson, Seidenberg & Hermann (2014)	GGE heterogenous; localisation-related epilepsy, healthy first degree cousins	13.3 (3.4)	8–18	61	Both epilepsy groups had higher problem scores and lower competence scores than controls.
2~	Caplan, Arbelle, Magharious, Guthrie, Komo, Shields, Chayasirisobhon & Hansen (1998)	GGE heterogeneous; partial epilepsies	10 (2.6)	5–16	40	Epilepsy diagnosis before age 5 associated with psychiatric diagnosis.
3~	Caplan, Siddarth, Gurbani, Hanson, Sankar & Shields (2005)	CAE; Complex partial seizure disorder	9.8 (2.2)	5–16	71	Higher rate of anxiety in CAE compared to CPS, and the inverse for depression. No seizure variables differentiated patients with and without psychiatric comorbidity.
4~	Caplan, Siddarth, Stahl, Lanphier, Vona, Gurbani, Koh, Sankar & Shields (2008)	CAE	9.6 (2.5)	6–11	69	CBCL elevations most common for attention and somatic complaints, followed by social and thought problems. Predictors of psychopathology: duration of illness, seizure frequency, and AED monotherapy compared with no drug treatment.
5	Conant, Wilfong, Inglese & Schwarte (2010)	CAE	8.0 (1.3)	6–11	16	CAE group showed greater levels of social dysfunction
6	Hermann, Black & Chhabria (1981)	GGE heterogeneous	10.3 (3.5)	6–16	21	No differences were found between TLE and GGE patients on the compared measures.
7	Holtkamp, Senf, Kirschbaum & Janz (2014)	JME, CAE, JAE	60.9 (13)	30–85	82	Favourable psychosocial long-term outcomes in JME, similar to outcomes of absence epilepsy group. No apparent correlation between 5 year seizure freedom and psychosocial outcomes.
8	Jones, Watson, Sheth, Caplan, Koehn, Seidenberg & Hermann (2007)	GGE heterogeneous; partial epilepsies	12.7 (3.3)	8–18	23	Higher rates of comorbidity in new onset epilepsy than controls. No significant differences were found between generalised and localisation-related idiopathic epilepsies (except higher rate of conduct diosrders in GGE).
9	Maganti, Sheth, Hermann, Weber, Gidal & Fine (2005)	GGE heterogeneous	13.36	5–18	11	3/11 patients had discharges during sleep. Trend observed between total behaviour problems scale and REM percentage. Authors postulate that discharges could disrupt quality of sleep, cause chronic poor sleep and sleep deprivation itself facilitates more discharges and seizures.
10~	Ott, Siddarth, Gurbani, Koh, Tournay, Shields & Caplan (2003)	GGE heterogeneous; partial epilepsies	9.9 (2.8)	5–16	52	Less than half of those with a psychiatric diagnosis received treatment. Despite the high rate of diagnosis, CBCL group means well below clinically significant cut-off points. GGE children with a single psychiatric diagnosis less likely to be treated than CPS children with >1 comorbidity. AED polytherapy associated with mental health treatment.
11	Plattner, Pahs, Kindler, Williams, Hall, Mayer, Steiner & Feucht (2007)	JME	18.7 (2.9)	13–20	25	JME patients showed double the rate of psychiatric symptoms of the normative sample. No specific personality type of JME found, however higher levels of

Table 1 (continued)

ID #	Authors	Syndrome/s	Age (years) M (SD)	Age range (years)	N (GGE)	Interpretation and main findings
						'repressive defensiveness' than age-matched norm and 'trend towards' less restraint (i.e. higher impulsivity) in JME patients.
12	Vega et al. (2011)	CAE	10.4 (3.4)	6–16	45	No relationship was found between disease duration, active seizures, or medication use with anxiety or depression scores.
13	Akanuma et al. (2008)	GGE heterogeneous	35	18–72	157	26 % comorbidity in this adult-onset GGE sample and was associated with poor seizure control.
14^	Camfield & Camfield (2009)	JME	36 (4.8)	20–30	23	There is some evidence of poor long term psychosocial outcome in JME. No association reported between seizure and social outcomes.
15^	Camfield & Camfield (2010)	GTSCO	31.9 (6.2)	21.7–47	30	75 % GTCSO had 'serious social problems'. These were similar to patients with JME from our cohort except that those with GGE-GTC had greater school problems.
16	Cutting et al. (2001)	GGE heterogeneous (50 % JME)	n/a	n/a	42	Rates of psychiatric disorders similar to general epilepsy population, most common were depression and anxiety. Rates lower than hospital samples which typically include more intractable cases. Psychotropic medications not found to directly affect seizure control, but a trend towards poor seizure control and multiple psychotropic use. Authors thought this could be attributable to a more refractory condition or other reasons.
17	de Araujo Filho, Pascalicchio, Lin, Sousa, Yacubian (2006)	JME	n/a	14–39	42	GAD associated with lack of seizure control and >20 lifetime GTCS. No difference found between Valproate/ Topiramate groups.
18*	de Araujo Filho, Pascalicchio, da Silva Sousa, Lin, Guilhoto & Yacubian, (2007)	JME	19.5 (2.1)	18–54	100	Psychiatric disorder significantly more prevalent in JME than HC. Higher seizure frequency and >20 lifetime GTCS associated with psychiatric disorder. Treatment with AED >2 years protective of psychiatric disorder. No association between psychiatric outcomes and duration of epilepsy, type of medication or time since medication use.
19*	de Araujo Filho, Rosa, Lin, Caboclo, Sakamoto & Yacubian (2008)	JME; TLE	24.5 (12.1)	n/a	100	No differences found in rates of psychiatric diagnoses between JME and TLE. JME was associated with anxiety disorders, while TLE was associated with psychotic disorders.
20	Ertekin, Kulaksizoglu, Ertekin, Gurses, Bebek, Gokyigit & Baykan (2009)	GGE; TLE	32.9 (10.4)	19–54	27	Psychiatric comorbidity rates were significantly higher in TLE than GGE and HC.
21	Gelisse, Genton, Thomas, Rey, Samuelian & Dravet (2001)	JME	33 (10.3)	15–70	155	Drug resistance was found in 15.5 % of this sample, and was associated with much poorer psychiatric outcomes. The authors assert that the existence of psychiatric problems are a risk factor

Table 1 (continued)

ID #	Authors	Syndrome/s	Age (years) M (SD)	Age range (years)	N (GGE)	Interpretation and main findings
						for poor seizure control, however, their analyses were not appropriate for the attribution of causality.
22*	Guaranha, de Araujo Filho, Lin, Guilhoto, Caboclo & Yacubian (2011)	JME	24.4 (7.28)	n/a	65	Patients were divided into good vs poor seizure control, and then seizure free vs ongoing from 3 year follow up results. The 'Persistent seizure' group had higher incidence of Cluster B personality disorders. Higher severity of anxiety scores associated with persistent seizures.
23	Karachristianou, Katsarou, Bostantjopoulou, Economou, Garyfallos & Delinikopoulou (2008)	JME	17.6 (2.19)	15–24	25	No irregularities in personality were found at onset or before treatment of JME. Those with higher 'psychotic tendencies' pre-treatment had more normal post-treatment EEG.
24*	Martins, Alonso, Vidal-Dourado, Carbonel, De Araujo Filho, Caboclo, Yacubia & Guilhoto (2011)	GGE; symptomatic focal epilepsy	29.7 (11.6)	n/a	39	Lower adverse events scores from AED for GGE relative to the symptomatic focal epilepsy group.
25	Mino, Kugoh, Hosokawa, Akada, Suwaki & Hosokawa (1995)	GGE; symptomatic focal epilepsy	27.0 (9.6)	n/a	25	Depressive symptomalogy significantly lower in GGE than the 3 symptomatic focal epilepsy groups and 'normal standard score'. No associations were found between depression and age, illness duration or seizure severity.
26	Moschetta et al. (2011)	JME	26.57 (8.38)	16–48	42	Novelty seeking interpreted as lower impulse control. Early epilepsy onset and frequency of myoclonic seizures were correlated with novelty seeking scores.
27	Olsson & Campenhausen (1993)	GGE heterogeneous	22.5	18–27	58	Authors reported that social isolation was occasionally due to practical issues such as lack of drivers' license, or fatigue. Even these 'benign' epilepsies such as GGE have a profound effect on patients' lives.
28	Pung & Schmitz (2006)	JME; TLE	34	15–60	20	No significant differences were found between JME and TLE on any psychopathological or psychosocial measures. Authors hypothesised circadian rhythm differences, with JME patients as 'evening types'.
29	Perini, Tosin, Carraro, Bernasconi, Canevini, Canger, Pellegrini & Testa (1996)	JME; TLE	27 (7.6)	n/a	18	TLE patients have a higher incidence of psychiatric disorder than JME, T1D, and HC. Authors suggest that TLE patients show interictal depression while JME/primary generalised patients do not. They propose that having temporal epileptogenic foci is a risk factor for the development of affective symptoms, but having generalised seizures is not.
30	Sarkis, Pietra, Cheung, Baslet & Dworetzkyl (2013)	GGE; TLE	36.9 (15.7)	n/a	19	Patients with GGE had lower depression scores on the BDI-II than patients with TLE. In the group with GGE, the BDI-II scores were inversely correlated with epilepsy duration.

Table 1 (continued)

ID #	Authors	Syndrome/s	Age (years) M (SD)	Age range (years)	N (GGE)	Interpretation and main findings
31	Schneider-von Podewils, Gasse, Geithner, Wang, Bombach, Berneiser, Herzer, Kessler & Runge (2014)	JME	52.3 (12.34)	33–77	33	BDI scores above 14 predicted unemployment. Long term seizure freedom (>15 years) reduces the risk of depression. Seizure freedom and management is integrally linked to psychosocial functioning.
32	Shehata & Bateh (2009)	GGE heterogenous; idiopathic partial epilepsy	29.2 (8.6)	n/a	55	GGE status associated with depression, aggression, neuroticism, extroversion, psychotic personality and lying. Severity of epilepsy factors were correlated with psychotic personality scores.
33	Trinka, Kienpointner, Unterberger, Luef, Bauer, Doering & Doering (2006)	JME	32.4 (13.0)	15–63	43	Axis 1 rates only slightly above representative community-based samples in German-speaking countries. However personality disorders were double that of the known rates. No significant differences were found between with/without psychiatric diagnoses groups with respect to duration epilepsy, seizure freedom, seizure type, and compliance.
34^	Wirrell et al. (1997)	CAE; JAE	23.1	18–31	56	Worse outcomes were found in absence epilepsies than in juvenile rheumatoid arthritis (specifically in the academic-personal, and behavioral categories). Only weak relationships between some epilepsy variables and psychosocial outcome.

Symbols ~^* indicate overlapping samples

Numbers have been rounded to 1 decimal place and to the nearest whole percentage

only (#3–5, 12); one included JME only (#11). Several studies were co-authored by the same team, and correspondence with the lead author confirms overlapping sampling (#2–4, 10).

Using the psychiatric interview method to assess psychopathology, five studies reported prevalence of a psychiatric disorder at 55–61 % in children with GGE syndromes (#2–3, 4, 8, 10). This prevalence contrasts with 15–23 % prevalence of healthy comparison groups (#2, 4, 8). In all samples, attention deficit and oppositional defiance problems (or 'externalising' problems) were the most common, followed by affective and anxiety disorders ('internalising' problems), and less frequently, the presence of both.

As shown in detailed the table in Online Resource 1, four of the five studies reporting mean scores on psychopathology symptom checklists reported mean scores for GGE patients within the normal range - albeit higher than healthy control means in some cases (#1, 5, 9, 12). However, rates of clinically significant symptom endorsement in broad band (that is, internalising or externalising problem domains), or narrow band problem areas (such as attention deficit and oppositional defiance problems) were reported to occur in a quarter to one third of GGE samples, more frequently than in the normative sample of the relevant measure (e.g. for the commonly used *Child Behavior Checklist,* 6 % by definition, representing scores 1.5 or more standard deviation units above the mean).

In contrast to studies reporting high rates of affective disturbance, Conant and colleagues (#5) reported no differences between children with CAE and a healthy comparison group or children with diabetes mellitus Type 1 on somatic or anxious-depressed symptoms. These authors did, however, find significant differences on items measuring withdrawal, social problems and thought problems. The null results regarding rates of anxiety or depressive symptoms may be attributable to the relatively mild epilepsy in the sample of 16 children, many of whom were newly diagnosed (n = 6; 37.5 %) or experiencing seizure freedom (n = 8; 50 %).

There is insufficient evidence from the included studies to comment on the onset or progression of psychopathological symptoms in children, although two studies reported higher rates of behaviour problems event at onset of GGE (#1, 8).

Table 2 Expansion of acronyms used in Table 1

Acronym	Full term
BASC	Behavior Assessment System for Children
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory-II
CAE	Childhood Absence Epilepsy
CBCL	Child Behaviour Checklist
CPS	Complex Partial Seizures
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GAF	Global Assessment of Functioning scale
GTCS	Generalised Tonic Clonic Seizure
GTCSO	Genetic Generalised Epilepsy with Generalised Tonic Clonic Seizures Only
HADS	Hospital Anxiety and Depression Scale
HC	Healthy control
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
GGE	Genetic generalised epilepsy
ILAE	International Leage Against Epilepsy
JAE	Juvenile Rheumatoid Arthritis
JME	Juvenile Myoclonic Epilepsy
K-SADS	Schedule for Affective Disorders and Schizophrenia for School-Aged Children
LAEP	Liverpool Adverse Events Profile
MMPI	Minnesota Multiphasic Personality Inventory
QoLIE-31	Quality of Life in Epilepsy-31
QoLIE-31-P	Quality of Life in Epilepsy-31 - Problems
SADS	Schedule for Affective Disorders and Schizophrenia
SCID 1	Structured Clinical Interview for the DSM-IV Axis I Disorders
SCID 2	Structured Clinical Interview for the DSM-IV Axis II Disorders
SDS	Self-rating Depressive Scale
STAI	State-Trait Anxiety Inventory
STAIX1	State and Trait Anxiety Inventory (State X1)
STAIX2	State and Trait Anxiety Inventory (State X2)
T1D	Type 1 Diabetes
TCI	Temperament and Character Inventory
TLE	Temporal Lobe Epilepsy
WAI	Weinberger Adjustment Inventory
WPSI	Washington Psychosocial Seizure Inventory
Y-BOCS	Yale–Brown Obsessive Compulsive Scale
YSR	Youth Self-Report

Psychiatric Comorbidity in Adults with GGE

23 studies reported psychopathology in adult GGE samples, six studies including adolescents. The prevalence of clinically significant psychopathology in adults with GGE (either established via DSM or ICD-10 criteria, or by study-specific questionnaire) was estimated at 20–35 % in five independent studies (#13, 16, 18, 29, 33). Depression and anxiety were the most prevalent disorders. Other diagnoses such as addiction, impulse control or psychotic disorders were relatively rare (1–5 % prevalence).

Five studies from two research teams in Brazil and Turkey reported substantially higher rates of psychiatric comorbidity: 47–62 % (#17–20, 22). An examination of the recruitment and eligibility criteria in these tertiary referral samples did not reveal any obvious reason to explain the higher prevalence. It is possible that the reported rates may refer to lifetime rather than current symptom prevalence.

Personality Disorder and Traits

Personality disorders and traits were reported only in samples of late adolescents and adults. Eight studies used validated measures of personality disorders or personality traits with JME patients only. Rates of personality disorders ranged from 5 % to 25 % (#18, 19, 21, 22, 33), one study reporting higher rates in refractory compared to non-refractory patients (#21). One study observed a higher rate

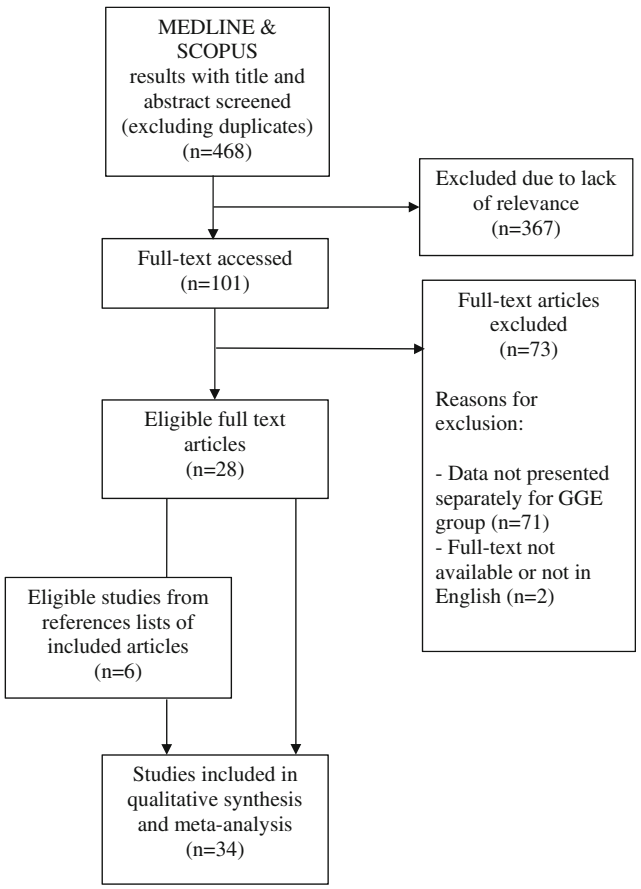

Fig. 1 Flow diagram of study selection

of personality disorders (23 %) than mood disorders (19 %: #33). A study of Egyptian males with JME (#32) reported levels of aggression, neurosis, extroversion, psychosis and 'lying', of between 0.44 and 1.37 standard deviation units above that of a healthy comparison group. Limitations of this study include unclear definition of the significance of the elevated scores and an atypical sample that excluded females.

Moschetta et al. (2011, #26) reported a range of elevated temperament scores on Cloninger's Temperament and Character Inventory including 'exploratory excitability vs stoic rigidity' and 'impulsiveness vs reflection,' amongst others. However, the clinical significance of these findings in relation to the broader literature is unclear. For example, elevated 'harm avoidance' was interpreted as evidence of lower frustration tolerance, confirming anecdotal descriptions of JME patients as 'irresponsible and neglectful of duties'. Citing neurobiological research on the mediation of novelty seeking traits by dopamine neurotransmitters, Moschetta and colleagues suggested that patients with JME may experience alterations of the dopaminergic system.

A study by Karachristianou and colleagues (#23) found no significant differences on personality or psychopathology scales of the MMPI-2 between young adult JME and their healthy comparison group. The MMPI-2 is a sensitive and validated measure of psychopathology and personality traits (Graham 2006). This was the only study to report a null finding despite the proliferation of studies regarding personality abnormalities in JME following Janz' oft cited anecdote describing careless and impulsive patients (Janz 1985).

In sum, there is a dearth of literature using validated measures of personality and psychopathology (McCrae and Costa 1999). In the absence of strong empirical evidence or theoretically plausible explanations for the JME personality type, this hypothesis remains speculative and is reminiscent of Geschwind's controversial 'interictal personality disorder' of TLE (Benson 1991; Foran et al. 2013). Janz' original descriptions were written on the basis of his clinical observation rather than standardised measurement so it is possible that the assessment tools used by contemporary research may not be well suited to measuring these so-called personality traits. The descriptions given for JME personality type are also non-specific and bear more resemblance to stereotypical adolescent behaviour than enduring character traits.

Psychosocial Outcomes

A small series of studies have reported adverse psychosocial outcomes in GGE samples. In Nova Scotia, Camfield and colleagues reported higher rates of unemployment, poorer quality of life, reduced educational attainment and increased rates of unplanned pregnancy in GGE patients (#14, 15).

In a German sample Schneider von Podewils and colleagues observed 'major unfavourable social outcomes', such as unemployment, withdrawal from school and criminal conviction in 87.9 % of those surveyed (#31). In addition, 36.2 % of their sample reported unplanned pregnancies, although the 19.2 % rate of induced abortions was considered comparable to the cited rate in the general population (13.7 %). The rate of unemployment in GGE was considered to be well above the population average. Another sample also from Germany was followed an average of over 40 years following diagnosis was reported to have favourable educational, occupational and social outcomes in JME, CAE and JAE groups, although healthy control comparison rates were not provided (#7).

A higher rate of single relationship status (52 %) and unemployment (10 %) was described by Cutting and colleagues in an American adult-onset GGE sample (#16). Whilst no control group comparisons were reported, these findings, together with rates of depression and anxiety of 23.8 % and 16.6 %, respectively, were interpreted as evidence of good outcomes in adult-onset GGE by the authors. It should be noted that child and adolescent onset is more typical in GGE (Cutting et al. 2001; Andermann and Berkovic 2001) therefore an age-standardised comparison for particular psychosocial outcomes such as employment and relationship status is the most accurate comparison standard.

Aim 2: Factors Impacting on Outcome

The Impact of GGE Syndromes

There was no clear evidence of differences between the GGE syndromes with respect to psychiatric and associated comorbidities in the reviewed studies. JME was studied by a number of authors however other GGE syndromes were not studied separately, precluding ease of comparison between them.

The proliferation of JME research may be due to greater patient availability or researcher interest, rather than clinically important differences between JME and other GGE syndromes. Increasing evidence regarding the cognitive and psychosocial outcomes points to the similarity of JME and other GGE syndromes rather than JME being a distinct syndrome with different cognitive outcomes (Loughman et al. 2014). In the case of personality style, comparison with other syndromes is precluded by lack of studies with sufficient methodological rigour. Long-term psychosocial outcome findings also seem to support similarity across GGE syndromes (#7).

The comparison of psychosocial outcomes in different GGE syndromes is also possible in the Nova Scotia population-based study of epilepsy (studies #14, 15 and 34). This study is unique in its detailed reporting of very long-term outcomes in people with JME, GGE-GTCS and absence epilepsies (CAE and JAE), all drawn from a common population recruited at the same time – a significant strength. However in

addition to a relatively small sample size (n = 23, 30 and 56 in each of those studies), an important caveat on this comparative approach is that outcomes in Study #34 were published 8 years prior to the others, reflecting a shorter follow-up period (and younger sample). Nonetheless, the three studies report similar psychosocial outcomes for all subtypes of GGE patients 10–25 years following their initial diagnosis. The presence of a psychiatric disorder during the follow up period, unemployment and pregnancies 'outside of a stable relationship' occurred equally frequently across the three GGE syndromes. An exception was the rate of high school graduation, which was significantly higher in JME (87 %) than in CAE/JAE (64 %) and GGE-GTCS (60 %), mirroring educational findings from Almane and colleagues (#7).

Relevance of Epilepsy Disease Characteristics

Epilepsy disease variables known to impact prognostic outcomes include (i) clinical history (e.g. duration of epilepsy; age at diagnosis), (ii) seizure burden (e.g. current seizure frequency; seizure burden; seizure type) and (iii) drug treatment (e.g. anti-epileptic drug [AED] treatment; monotherapy versus polytherapy; type of AED). Of these, seizure burden was the most commonly reported to be associated with psychopathology (studies #4, 13, 17, 18, 21, 22, 26, 31, 32, 34). For example, increased seizure frequency predicted the presence of psychopathology in children with CAE (#4) and poor seizure control was associated with psychiatric diagnosis (#13). In a Brazilian JME sample, lifetime occurrence of 20 or more GTCS seizures was associated with increased likelihood of generalised anxiety disorder (#17, 18). Five studies reported no association between seizure variables and psychiatric outcome (#3, 7, 12, 25, 33).

AED treatment, particularly polytherapy – which can be interpreted as a marker of seizure severity - was associated with psychopathology in children with CAE (#4, 8). However, other studies have reported no association (#12), and that psychopathology predates first diagnosis (#8). Study #17 found that AED treatment of longer than 2 years was *protective* of psychiatric comorbidity, and there was no difference in these outcomes between groups taking valproate or topiramate.

The association between epilepsy history and psychiatric outcome was similarly equivocal, with some studies reporting poorer outcomes in early epilepsy diagnosis before age 5 and longer epilepsy duration (#2, 4, 26, 30), other studies reporting null findings (#12, 25, 33). Epileptiform discharges in sleep were reported, however there was insufficient power to evaluate their impact on psychopathology (#9). It is likely that psychosocial factors such as parent-child relationship quality moderate mental health outcomes (Rodenburg et al. 2005), however such factors were not considered in any of the included studies. Additionally, the relationship between epilepsy disease characteristics and psychosocial functioning was not reported.

Aim 3: Comparisons with other Chronic Health Conditions

Other than healthy controls, comparison groups consisted of people with juvenile rheumatoid arthritis (#34), diabetes mellitus Type 1 (#7, 29), temporal lobe epilepsy (#8, 19–20, 28–30) and other focal epilepsy syndromes (#1, 8, 24–25, 32). These studies report poorer psychosocial outcomes in GGE than the non-neurological groups, but the worst outcomes in TLE or focal epilepsies. An exception was the study by Pung and Schmitz (#28) who reported no differences between 20 adults with JME and 20 with TLE on measures of depression, five-factor personality traits and psychosocial outcomes. This study excluded participants with any 'significant psychiatric comorbidity', which may limit the extent to which the sample can be considered representative of these two syndromes. Hermann and colleagues' authored two other studies reporting equivalent outcomes in parent-report psychosocial function in GGE, TLE and other localization-related epilepsies (#1, 8).

Discussion

This review summarises the literature regarding psychiatric and psychosocial comorbidities in GGE. The results of this review suggest clinically significant psychiatric comorbidity in more than half the children and a third of all adults with GGE. This prevalence is higher than in the general population (Baumeister and Harter 2007). Higher rates of psychopathology in children compared to adults, together with the equivocal relationship between increased psychopathology and duration of epilepsy, suggest that the risk of psychopathology in GGE may decrease across the lifespan. However the use of different instruments to measure risk across different studies is a caveat, and longitudinal research is required to further examine this possibility. The limited available evidence relating to predictors of poor outcome suggests a detrimental impact of seizure burden on psychological well-being. One possible interpretation of the findings is that initial neurobiological disruption and psychosocial adjustment to epilepsy in childhood and adolescence results in increased risk of psychological distress (manifesting as externalising or internalising disorders). Clinical expression of distress may resolve in up to half of those affected and may be linked to seizure control or spontaneous remission. A portion of the population with persisting GGE may develop psychopathology in adulthood, most commonly mood spectrum disorder.

Regarding personality style or dysfunction, there is little evidence to suggest a particular profile or predisposition in

JME or other GGE syndromes. In view of the controversial history of 'TLE' personality style (Reilly et al. 2006) and the risk of undue stigmatisation and missed diagnosis of bona fide conditions, such as depression, extreme caution should be exercised when inferring syndrome-specific variants of psychopathology, variants which may prove implausible when measurement invariance of the underlying latent structure is examined (Reilly et al. 2006; Devinsky et al. 1999; Foran et al. 2013). Indeed, our results indicate that the relative frequency of psychiatric disorders within GGE is similar to the frequency reported from larger, epidemiological studies; anxiety and affective disorders are the most prevalent, followed by personality disorders, then schizophrenia and other psychotic disorders (Kessler et al. 2009; Torgersen et al. 2001; Jablensky 1997; Reich et al. 1989).

Limitations of the Current Study

At the review level, the data presented by the eligible studies were too heterogeneous to enable quantitative meta-analysis. This variability proved another challenge to the synthesis of findings. Some studies reported rates of elevated symptoms, others studies reported scores sometimes without interpretive guidelines. Therefore the reported elevations on diagnostic or screening measures across different studies do not necessarily represent the same degree of adverse outcome. The reporting of common endpoints would enable more consistent understanding of psychopathology in these populations. Small sample sizes and cross-sectional study also limits the conclusions that can be made from the available evidence.

Also, given the relatively small number of relevant studies retrieved in initial literature searching, we did not exclude studies on the basis of methodological characteristics, consequently studies included are heterogeneous in methods quality.

Implications for Clinical Practice and Future Research

The results of this review provide a representative overview of the growing literature on psychological sequelae of GGE. Mirroring results of a recent meta-analysis on cognitive outcomes in GGE (Loughman et al. 2014), the current findings suggest that whilst the majority of people with GGE will experience good psychological adjustment, a proportion will be vulnerable to increased risk of psychiatric comorbidity and poor psychosocial outcome.

Rates of psychiatric comorbidity are high in both children and adults with GGE. Further, psychosocial dysfunction several years following diagnosis of GGE also occurs more frequently than the estimated prevalence in the healthy population. Presuming that the risk of these problems accumulates over time, data suggest that there may be a window of opportunity for intervention for these treatable conditions. These findings highlight the importance of careful, early screening so as not to overlook incipient psychopathology.

Whether the source of this vulnerability to psychopathology is neurobiological, psychosocial or both remains to be determined. The ambiguous findings regarding direction of association between seizure control and psychopathology, and mechanisms that underlie any possible association, are not yet well understood. Therefore, in light of the possibility that psychopathology may be a risk factor for poor seizure control as well as the reverse, screening for psychopathology should be considered a routine component of seizure management and remission.

Future studies should consider the use of self and informant-report screening questionnaires in adult as well as child samples as a compliment to time-intensive 'gold standard' structured psychiatric interviews. Other considerations for future research include: 1) targeted investigation of syndromes other than JME, and ongoing evaluation of the concept of a 'neurobiologic continuum' of GGE (Berkovic et al. 1987; Nordli 2005), 2) routine inclusion of an appropriate control group, 3) reporting of both categorical outcomes and descriptive statistics summarising psychopathology endpoints, and 4) the comprehensive, objective assessment of psychological function. In addition, larger community-based incident samples studied longitudinally may enhance understanding of risk and protective factors of outcomes across the course of the disease. Comprehensive, longitudinal studies may be facilitated by the initiation of privacy protecting linkage projects tracking patient outcomes (e.g. Australia's National Assessment Program – Literacy and Numeracy, NAPLAN).

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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Chapter 5: Methodology

Having reviewed the current state of the published scientific knowledge regarding the two main questions pertaining to this thesis in the previous Chapters 3 and 4, the following Chapter outlines the methodology that was used to answer the research questions outlined in Section 2.5 (page 44). Detailed descriptions and psychometric properties of the measures used can also be found in this methodology Chapter.

5.1 Design

As previously noted, the present study comprised one component of a larger study entitled *Long-term Prognosis of Idiopathic Generalised Epilepsy: A Prospective Study* conducted at St Vincent's Hospital Melbourne (Protocol No.: HREC-A 132/09), Monash Medical Centre (Protocol HREC-B 10290) and North West Regional Hospital, Tasmania (Southern Tasmania Health and Medical Human Research Ethics Committee Protocol H6377). This study began in 2010 and is ongoing. The broad aim of this larger study is to examine the long-term prognosis of these common presumed genetic epilepsies with respect to seizure remission, cognition, psychosocial comorbidity and quality of life. Additionally, the study sought to identify seizure phenotype, electrophysiological and treatment characteristics that were predictive of these outcomes. Other components of this larger project include genetic studies entitled *Pharmacogenetic Study of The Influence of Genetic Factors on the Outcome of Medication Treatment For Epilepsy* (SVHM Protocol HREC-A 103/03) and *Mapping Genes for Epilepsy* (SVHM Protocol HREC-A 110/01).

The work described in this thesis comprises the neuropsychology component of the *Long-Term Prognosis Study*. The *Long-Term Prognosis Study* commenced in 2011 and aimed to investigate the cognitive and psychosocial functioning in GGE patients, with the broader goal of understanding long-term functioning and behavioural aspects of prognosis. As explained in detail in relevant sections below, a subset of GGE patients from the *Long-Term Prognosis Study* cohort was recruited for assessment of their cognitive and psychosocial functioning between 2011 and 2015. Cognitive and psychosocial functioning were the primary outcomes of interest in this observational study, with epilepsy and electrophysiological characteristics used as predictive variables.

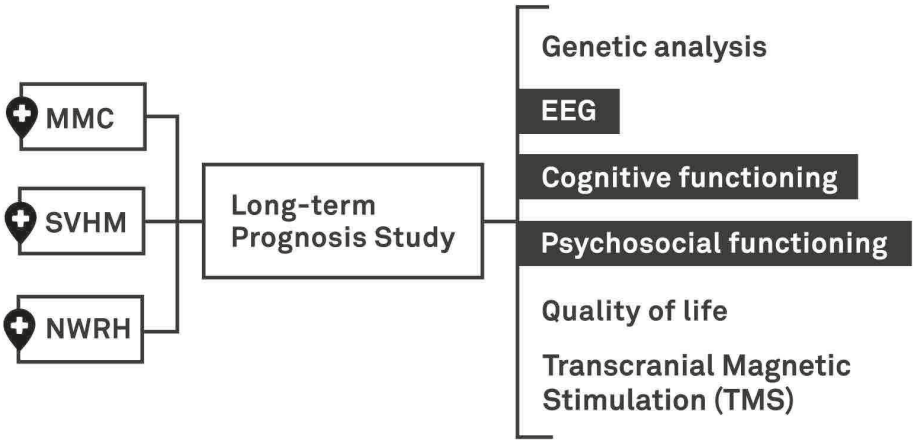

Figure 6. Design of the Long-Term Prognosis Study.
Dark shading denotes areas of focus in this thesis. MMC: Monash Medical Centre. SVHM: St Vincent's Hospital Melbourne. NWRH: North West Regional Hospital (Tasmania).

5.2 Participants

Participants were current patients of neurologists at St Vincent's Hospital Melbourne, Monash Medical Centre and North-West Region of Tasmania, who had a confirmed diagnosis of GGE based on the combination of consistent clinical features and a positive EEG showing generalized ED on at least one occasion, and consented to take part in the study. Diagnosis of GGE was based on diagnostic criteria of the International League Against Epilepsy (ILAE) which include the following clinical features: age of onset, seizures types and EEG characteristics (Berg et al., 2010; ILAE, 1989; Seneviratne et al., 2012). All patients underwent brain magnetic resonance imaging (MRI) as part of routine practice of the neurologists.

Exclusion criteria were:

1) the presence of potentially epileptogenic structural abnormalities (such as hippocampal sclerosis) detected via brain MRI scan,

2) coexistent focal and generalized epilepsies,

3) secondary bilateral synchrony as defined by Blume and Pillay (Blume & Pillay, 1985), and

4) single seizure with generalized epileptiform abnormalities on EEG. The presence of a significant neurological condition that was known to cause functional impairment such as traumatic brain injury or dementia was also an exclusionary condition. Participants were not excluded on the basis of comorbid medical, psychiatric, or non-specific intellectual disorder.

All medical records including EEG and neuroimaging were reviewed independently by two epilepsy specialists (Wendyl D'Souza, Udaya Seneviratne) with any discordance on syndromic diagnosis resolved by consensus based on ILAE criteria. On this basis, patients were classified into the following syndromes of GGE: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalised epilepsy with generalised tonic-clonic seizures only (GTCSO; ILAE, 1989; Berg et al., 2010). Those who did not meet the criteria of these major syndromes were grouped together as a fifth subgroup, genetic generalised epilepsy unspecified (GGEU). The relative frequency of each syndrome can be found in Table 8, Chapter 6, on page 95).

5.2.1 A priori sample size calculation

The factors limiting recruitment of participants included patient availability from referring neurologists, patient interest in participating, and investigator availability. The maximum number of participants was recruited within the time constraints of this thesis. Nonetheless, below is a calculation of the required sample size for the estimated effect sizes.

A priori power analyses for the primary comparisons of interest were conducted. While several statistical tests were anticipated, the two tests that best represented this study are independent groups t-test comparing GGE and normative control group scores, and subtype comparisons within the GGE group (CAE, JAE, JME, GTCSO). On the basis of previous research, the effect size of subtype differences was estimated to be 0.62 standard deviation units, or 9.3 standard score points below the normative mean (the

average reduction in cognitive function scores across cognitive domains in the meta-analysis presented in Chapter 3; Loughman et al., 2014). The normative standard deviation of cognitive test standard score points is 15 by definition.

For the comparison between the GGE sample and normative group mean, sample size calculation for the two-tailed one-sample t-test in G*Power 5 on the basis of a moderately large estimated effect size of 0.62 standard deviations, 0.95 power and alpha of 0.05 yielded an estimated sample size of approximately 36 (Faul, Erdfelder, Lang, & Buchner, 2007).

There was insufficient previous primary research comparing cognitive function between GGE subtypes to estimate the effect size of these comparisons. Similarly, statistical comparisons between subgroups were not conducted in the aforementioned meta-analysis, however the forest plot Figure 7 below graphically displays diamonds denoting the 95% confidence interval of general intelligence *G* in three GGE subtypes, and in GGE heterogeneous groups. All of these overlap, suggesting that if differences between GGE subtypes do exist in the population, they are likely to be small. However, given methodological limitations of previous studies including varied measurement quality and sampling issues, it is possible that larger effects are present but have not been documented. Effect sizes of approximately d=0.5 and larger are most likely to be of clinical interest (Wolf, 1986). On the basis of a medium effect size (f^2: 0.01), a total sample size across the four groups was estimated at 156 to provide 0.95 power and 108 to provide 0.80 ('adequate') power to detect a global difference between the four GGE subtypes on the five cognitive factors using MANOVA (Cohen, 1988; Faul et al., 2007).

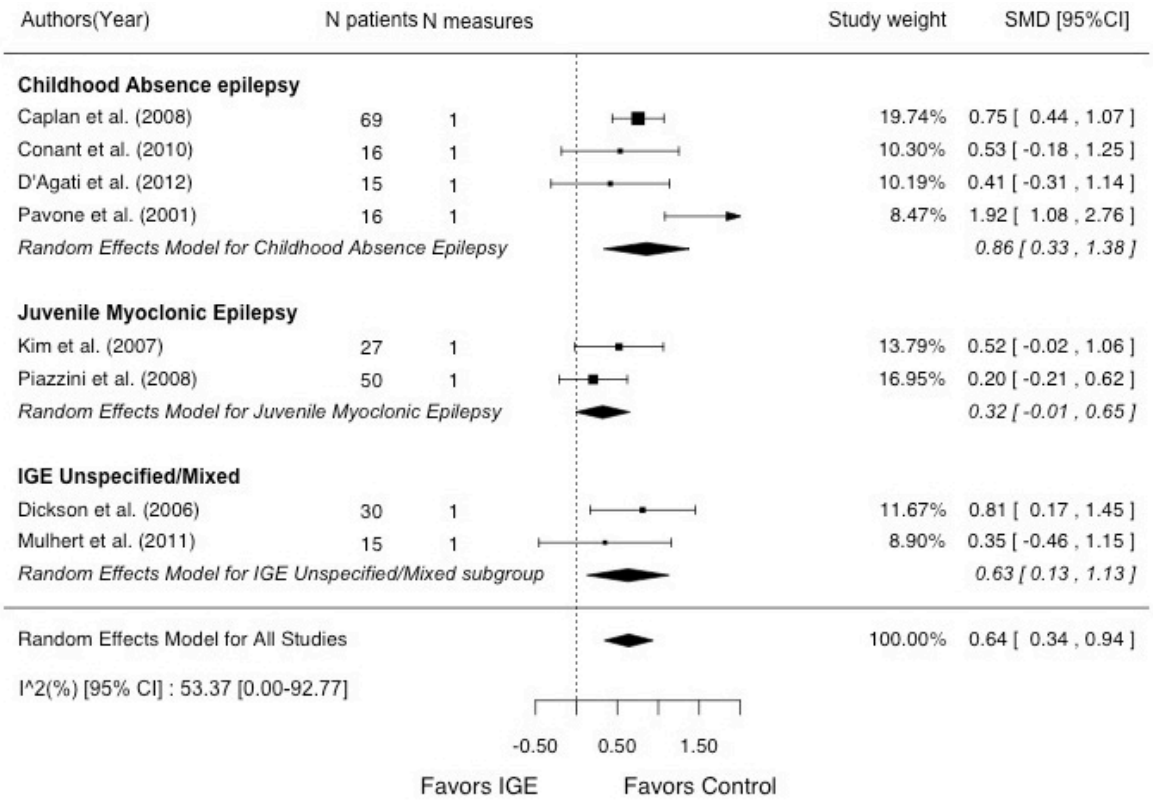

Figure 7. Meta-analysis forest plot of generalised intelligence G (Loughman et al., 2014).

5.3 Procedure

5.3.1 Recruitment and selection

Eligible patients who were referred for ambulatory EEG monitoring by their treating neurologist and initially invited to participate in the study were then contacted by the neuropsychology student investigator (AL) in the week preceding their EEG connection appointment. At this time, patients were provided with information regarding the research and invited to participate. Patients who expressed interest in participating or receiving further information were scheduled for an appointment with the same investigator directly following their EEG connection appointment or directly before their EEG disconnection appointment. Patients who were not available to participate in cognitive assessment during the EEG recording period were seen at any other mutually convenient time.

5.3.2 Data collection

EEG, Demography and Clinical History

All participants were interviewed on the day of their 24-hour ambulatory EEG recording using a study-designed questionnaire of clinical and demographic data (see Appendix 5). This questionnaire, together with their medical records, were reviewed to obtain their socio-demographic and epilepsy disease characteristics.

Twenty-four-hour ambulatory EEG was performed according to a standard protocol (Seneviratne et al., 2015). EEG signals were acquired with a 32-channel, Compumedics Siesta ambulatory EEG system (Compumedics Ltd, Melbourne, Australia) according to the international 10-20 system. The recording was commenced in the morning, usually between 9 am and 10 am. The patient was then allowed to resume routine activities, usually returning home wearing the small ambulatory EEG device around the waist or over the shoulder (see Figure 8). Patients were asked to complete a record of their activities during the recording period, and to signal the presence of seizures by pressing a button on the device. Patients were encouraged to have at least seven hours of sleep during the night. The recording was completed and patients were disconnected from the EEG device 24 hours later.

Figure 8. Ambulatory EEG machine fitted to the scalp and worn on the body

Neuropsychology

At the neuropsychology data collection appointment participants answered questions regarding the presence of any cognitive symptoms and their parents' education and

occupation, and underwent a cognitive assessment comprising selected subtests of the Woodcock Johnson III Tests of Cognitive Abilities (WJIII; Woodcock, 2001) and a verbal fluency task to letter (FAS task). Participants were provided with self- and informant-report forms of the Achenbach scales, and a reply-paid envelope in which to return these. The appointment was 90-120 minutes in duration. Participants were provided with feedback from their cognitive assessment in the form of a verbal summary from their treating neurologist at their next appointment. The verbal summary the patient's test scores on CHC factor domains relative to age-based normative data.

Healthy control participants

During the data collection appointment participants were asked if they had a healthy peer or sibling who may be interested in taking part in the study as a healthy participant, and for consent to call the peer or relative in subsequent weeks to follow-up regarding this request. At least one week following data collection, participants were contacted by telephone to follow-up regarding the availability of peer and sibling healthy control participants. The peer or sibling was then contacted directly by the investigator who organised a neuropsychology data collection appointment like the one described above. EEG was not performed on these healthy control participants.

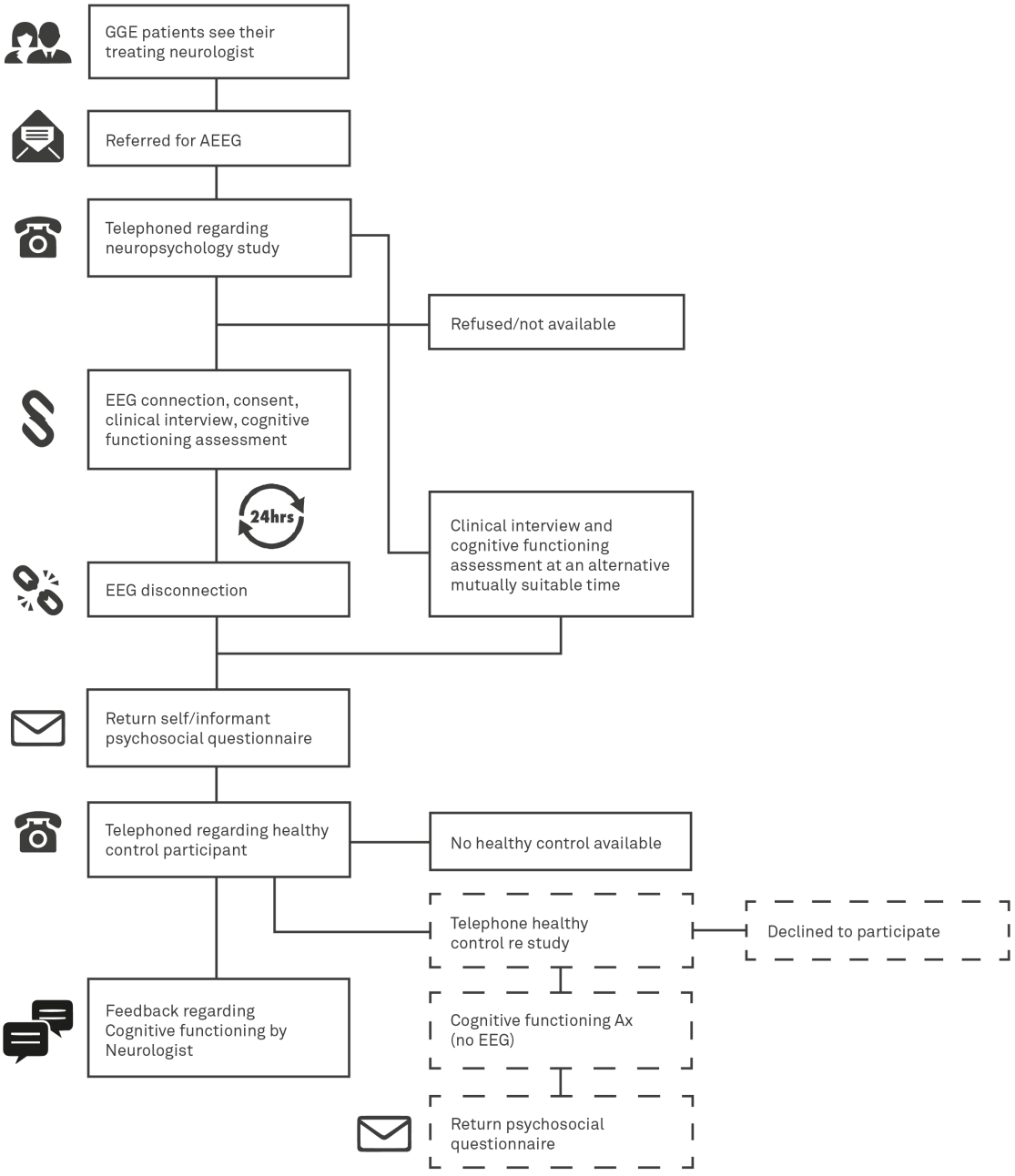

Figure 9. Recruitment flow diagram

EEG: Electroencephalogram. AEEG: Ambulatory electroencephalogram.

Potential sources of bias

As explained below, recruitment practices of this study were designed to minimise selection bias and ensure representativeness of the current study cohort at both the level of the larger study cohort, and the level of the GGE patient population more broadly.

All GGE patients seen by consultant neurologists at two large, tertiary teaching hospitals in Melbourne (St Vincent's Hospital, Melbourne and Monash Medical Centre) were invited into the larger study. These hospitals are two of nine adult tertiary teaching hospitals in Victoria, providing care to a diverse population in a wide geographic catchment (Department of Health Victoria, 2016). In addition, all patients with a diagnosis of GGE who were seen for neurological consultation during the recruitment period from the North West Region of Tasmania were invited to take part. The total population of this catchment area is approximately 114,100 (Tasmanian Health Organisations Secretariat, 2015).

There is no definitive source regarding the epidemiology of epilepsy in Victoria specifically, so it is difficult to estimate the proportion of the GGE population we are sampling in this study. However, estimates based on Australian figures are as follows. There are an estimated 250,000 Australians living with epilepsy, of whom an estimated 20% (50,000) will have a diagnosis of GGE (Department of Health Victoria, 2016; Jallon & Latour, 2005). As at December 2015, the population of Victorian and Tasmania together accounted for 27.1% of Australia's total population, at 6,483,900 (Australian Bureau of Statistics, 2015). In the absence of evidence suggesting differential rates of epilepsy between Australian states, the total population of people with GGE in these two states is estimated at 13,550.

Thus, although definitive characterisation of the GGE population in Australia is not possible, the cohort invited to take part in this study is derived from a large pool that can be considered to be representative of urban, outer metropolitan and regional areas of Australia.

All of these participants were invited to take part in the neuropsychology study, with the same criteria for inclusion as in the larger study. The researchers involved in inviting participants for neuropsychology assessment were not privy to any medical information about patients such as previous cognitive assessments or known psychological or functional issues which could be seen to bias recruitment. Further, this is a prospective study, a study type that is known to be less prone to sampling bias than retrospective studies (Pannucci & Wilkins, 2010).

The scoring of cognitive tests used in this study is standardised and requires little subjective judgment on the part of the scorer. However, in order to avoid the potential

for bias in the scoring of assessments, tests were scored immediately following the assessment and before results of the EEG assessment or clinical information were available to the neuropsychology researchers.

5.4 Measures

5.4.1 Woodcock Johnson III Tests of Cognitive Abilities

The *Woodcock Johnson III Tests of Cognitive Abilities (WJ-III)* are a battery of cognitive tests that measure general intellectual ability and specific cognitive abilities. These tests are modelled on the Cattell-Horn-Carroll (CHC) theory of cognitive abilities (McGrew & Woodcock, 2001). The Section 2.1.4 on CHC theory in Chapter 2 (page 22) above expands further on this theoretical framework. The structure and items within the WJ-III were developed in accordance with current theory and research regarding human cognitive abilities and therefore the use of the WJ-III enables comparison to other research measuring the same abilities, even when alternative tests are used. The practice of using cognitive tests such as these affords findings that are directly related to theoretical concepts rather than based in, and restricted by, the use of particular tests. In addition, the WJ-III tests have the additional advantage of simplicity of administration and reduction of unnecessary processes in test administration, such as through the use of basal and ceiling rules to limit the range of items that are required for the test to be administered. The standard procedures of the WJ-III tests are designed to avoid the need to make complex administrative and scoring decisions and have inbuilt measures to prevent common clerical errors. The use of purpose-built software to compare scores to age-based norms further reduces the likelihood of administrative error that may affect the subsequent interpretation of scores.

Test reliability refers to the consistency of measurement, and correspondingly indices of reliability measure the 'degree to which a test is free from error…or other sources of variability that affect test scores' (Strauss, Sherman & Spreen, 2006, p10). While there is no single universally preferred metric for estimating reliability, a number of widely used and accepted reliability estimation techniques reported on the WJ-III tests include standard error of measurement reported at both test and cluster level, test-retest reliabilities at extended retest intervals and inter-rater reliability. Each of these demonstrates that the WJ-III meets or exceeds basic standards of individual or group

decisions made on the basis of cognitive testing (McGrew & Woodcock, 2001; Nunnally & Bernstein, 1994). Median cluster reliabilities are frequently very high at greater than 0.9, and are therefore recommended over individual subtest scores for decision-making purposes. However, individual test reliabilities are also acceptable, with 38 of the 42 tests for which median test reliabilities are reported, at .8 or higher (McGrew & Woodcock, 2001). To reduce measurement error, cluster scores have been used in analyses presented in this thesis, with prorating of tests into clusters where scores on one of the tests assigned to a cluster were unavailable. The main reason for the unavailability of test scores was lack of tolerance of the participant to the test (e.g. one participant found the visual stimuli on a test of processing speed uncomfortable, and chose to discontinue the test). Proration was required in a small proportion of cases (<10% of all participants had one or more unavailable test scores).

Validity refers to the extent to which tests measure the relevant construct and relate meaningfully to alternative measures and concepts for defining the construct, for example a particular diagnostic criterion (Strauss & Smith, 2009). Establishing validity is central to determining the utility of a test for a specified purpose and context (Cohen & Swerdlik, 2005). Construct validity, which can be seen as a pre-requisite for content and criterion-related validity, is demonstrated in the WJ-III via confirmatory factor-analytic models (Loevinger, 1957; McGrew & Woodcock, 2001; Strauss & Smith, 2009). These demonstrate that the underlying abilities measured by the WJ-III are best described by the CHC model of a general ability (g) or seven broad-factors. The clusters of tests employed in this study encompass five of these seven broad factors, omitting Auditory Processing (Ga) and Visual-Spatial Thinking (Gv) (see Table 5 below).

The WJ-III is the only intellectual ability test for adults that has age-based Australian norms for the full range of adulthood. Age-based Australian norms were used for the interpretation of participant scores. Australian norms were developed in 2006, sampled from a total of 1,396 males and females from 13 age groups, residing in rural and urban areas of Australian states and territories (McGrew, 2008).

Table 5

Broad Narrow CHC Factors and corresponding WJ-III Test Clusters

Broad CHC Factor	Narrow Abilities Measured	Cluster of WJ-III Tests of Cognitive Abilities
Comprehension-Knowledge (Gc)	Lexical knowledge, Language development	Test 1: Verbal Comprehension
	General (verbal) information	Test 11: General Information
Long-Term Retrieval (Glr)	Associative memory	Test 2: Visual-Auditory Learning
		Test 10: Visual-Auditory Learning Delayed
	Ideational fluency	Test 12: Retrieval Fluency
Fluid Reasoning (Gf)	Induction	Test 5: Concept Formation
	General sequential reasoning	Test 15: Analysis Synthesis
Processing Speed (Gs)	Perceptual Speed	Test 6: Visual Matching
	Attention and concentration	Test 20: Pair Cancellation
Short-Term Memory (Gsm)	Working memory	Test 7: Numbers Reversed
		Test 9: Auditory Working Memory
	Memory span	Test 17: Memory for Words

Adapted from Technical Manual *Table 2.2: Broad and Narrow Abilities Measured by the WJ-III COG & WJ-III ACH*

5.4.2 Letter fluency test

The 'FAS' or letter fluency test is a short test for which the testee is asked to provide as many words as they can think of beginning with a specified letter, in a 60 second period. This task was included as a complement to Test 12 in the WJ-III tests (Retrieval Fluency) which measures category (as compared with letter) fluency. Collectively, these tests are commonly described as measures of verbal fluency, one component of 'executive function' (Strauss, 2006). Latent variable analysis has demonstrated that scores on category and letter verbal fluency tasks are moderately correlated and these tests can be conceived of in terms of the broad CHC broad abilities as measures of processing speed (Gs) and long-term retrieval (Glr) (Riva, Nichelli, & Devoti, 2000; Tombaugh, Kozak, & Rees, 1999; McGrew & Woodcock, 2001).

With respect to reliability of this test, internal reliability of the three letters F, A and S has been demonstrated, test-retest reliability is acceptable (0.7) and inter-rater reliability is extremely high (0.99; Ross, 2003; Tombaugh et al., 1999). Age-based normative data from a Canadian community sample of 1300 individuals aged 13-85 years old was used to generate age- and education-based normative standard scores on all three letters of the letter fluency task (Tombaugh et al., 1999).

5.4.3 Achenbach System of Empirically Based Assessment (ASEBA)

The Achenbach System of Empirically Based Assessment (ASEBA) includes self- and informant-report forms to assess diverse aspects of adaptive and maladaptive psychosocial functioning in children, young adults and adults (Achenbach & Rescorla, 2003). The ASEBA forms can be completed in approximately 15-20 minutes and provide individualised descriptions of respondent characteristics based on strengths and problems identified on each subscale, as well as standardised and quantitative data with respect to age-based norms. The present study employed the forms presented in Table 6.

Table 6
Forms of the Achenbach System of Empirically Based Assessment

		Subject of assessment	
		Child (ages 11-18)	Adult (ages 18-59)
Respondent type	Self	Youth Self-Report Form	Adult Self-Report Form
	Informant	Child Behavior Checklist	Adult Behavior Checklist

Responses to the ASEBA forms can be scored and interpreted via 'Syndrome Scales' and 'DSM-oriented Scales'. The Syndrome Scales were developed using a 'bottom up' approach using factor analytic measurement methods that identified syndromes of co-occurring problems for large samples of people (Achenbach & Rescorla, 2003). In contrast, the DSM-oriented Scales reflect symptoms listed in formal diagnostic categories in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Twenty-one psychologists and psychiatrists from 10 cultures with a mean of 18 years of experience rated items in the ASEBA forms for the consistency with each diagnostic category to generate these scales. Additionally,

Internalising, Externalising and Total problems Scales are global groupings of problems occurring within the self, with conflicts with other people, and a combination of the two, respectively. The adaptive functioning scale is comprised of items relating to social and vocational activities, and the substance-use scale is comprised of questions regarding frequency of tobacco, alcohol and other drug use. Scores on each of these scales can be classified as within normal range, borderline-clinical and clinical. All scales and criterion scores for each of these classifications are described in Table 7.

The use of parallel forms completed by the individual and informants enables comparison of information from two perspectives. Meta-analysis of correlations between self- and informant-report symptom report in adults suggests correlations are likely to be between .20 to .40, highlighting the need to consider both sources of information when assessing adaptive functioning (Klonsky & Oltmanns, 2002; Meyer et al., 2001). Cross-informant agreement by participants in the normative sample for ASEBA was 0.40 for the empirically based problems scales and 0.38 for the DSM-oriented scales, reinforcing the idea that different informant perspectives may provide different information.

The ASEBA adult forms have demonstrated adequate test-retest reliability at a 7-day interval, with mean correlations for the DSM-oriented scales at 0.84, with none less than 0.71. Internal consistency as measured by Cronbach's alpha was acceptable for the DSM-oriented scales, ranging from .68 - .55 (Achenbach & Rescorla, 2003).

Content validity of the ASEBA is demonstrated in a number of ways, including the utility of the problem item scores in identifying adults referred for mental health services in the preceding 12 months and the endorsement of test items as being consistent with DSM-IV diagnostic categories by the panel of expert psychologists and psychiatrists (Achenbach & Rescorla, 2003). Multiple regression analyses of problem scales presented in the Technical Manual demonstrated that the most significant variance in ASEBA scores was accounted for by referral to mental health services rather than any demographic variables (Achenbach & Rescorla, 2003).

Table 7
ASEBA Scales and Cutoff Scores

Scale Type	Normal	Borderline - Clinical	Clinical
DSM-Oriented Scale			
Depression			
Anxiety			
Avoidant personality			
ADHD problems			
Antisocial Personality			
Syndrome Scale			
Internalising			
Anxious/Depressed	T<65 <93rd%ile	T=65-69 93-97th%ile	T>=70 >97th%ile
Withdrawn			
Somatic Complaints			
Thought Problems			
Attention Problems			
Externalising			
Aggressive Behavior			
Rule-Breaking Behavior			
Intrusive			
Problem Scores			
Internalising Problems	T<60 <84th%ile	T=60-63 84-90th%ile	T>=64 >91st%ile
Externalising Problems			
Total Problems			
Adaptive functioning scale (only calculated where sufficient data exists)			
Friends			
Spouse/Partner			
Family	T>35 >8th %ile	T=30-35 3rd-7th%ile	T<30 <2nd%ile
Job			
Education			
Mean Adaptive Score			
Substance-Use Scale			
Tobacco			
Alcohol	T<65 <93rd%ile	T=65-69 93-97th%ile	T>=70 >97th%ile
Drugs			
Mean Substance-Use Score			

Regarding the utility of clinical and borderline-clinical categorical cut-off scores, the developers of the ASEBA tool used discriminant analyses to assess the extent to which scores on a measure accurately classified referred and non-referred respondents

(Achenbach & Rescorla, 2003). Based on self-reported responses, 71% were correctly classified based on syndrome scales, 77% based on DSM-oriented scales and 87% based on the 'total problems' scale which is the broadest subscale of general distress available in ASEBA. Informant report responses had marginally lower rates of correct classification at 68%, 68% and 65% for syndrome, DSM-oriented, and total problem scales respectively. Together these results suggest adequate criterion-related validity of the forms. Independent research has also demonstrated the high degree of reliability, convergent and divergent validity, sensitivity and specificity of these measures (Nakamura, Ebesutani, Bernstein, & Chorpita, 2009; Petty et al., 2008).

5.5 Data Processing and Analysis

5.5.1 EEG data processing

EEG monitoring data were analysed and coded by an experienced EEG reader (Udaya Seneviratne) with ProFusion 4 software (Compumedics Ltd, Melbourne, Australia). Ten-second pages were reviewed page-by-page on longitudinal bipolar montage with 0.5 to 70 Hz bandwidth. When an epileptiform abnormality was detected detailed analysis of the waveform was done on common average referential montage. A measuring tool incorporated in the software was used to manually measure amplitude and duration of discharges.

Each epileptiform discharge was assessed for discharge type (focal, generalised fragment, generalised paroxysm), duration (seconds), time of occurrence, state of arousal, and individual components (spike-wave, polyspike-wave and polyspike). The sleep onset and offset times were recorded. Detailed data on ED were entered into an electronic database manager. Duration and frequency data were standardised to 24 hours to adjust for minor variability in the duration of EEG monitoring. This protocol has been published in further depth elsewhere (Seneviratne, Hepworth, Cook, & Dsouza, 2015).

5.5.2 Cognitive functioning data processing

The WJ-III subtests were scored by hand as per instructions in the Manual (McGrew & Woodcock, 2001), with 10% of tests scored by two investigators to ensure consistency. Inter-rater reliability was high (97% across all items) with few clerical and no systematic or judgment errors detected. The remaining hand-scored tests were scored by a single

investigator (Amy Loughman, Nicholas Bendrups or Lib Yin Wong). Subtests scores were then entered into the WJ-III CompuScore and Profiles Program (2008, The Riverside Publishing Company, Rolling Meadows, IL, USA) to enable comparison to age-based Australian normative data and the generation of individual scored reports.

FAS scores were entered into a purpose-built spreadsheet and compared to age-based norms (Tombaugh et al., 1999).

5.5.3 Psychosocial functioning data processing

Responses to the Achenbach questionnaire were entered into the ASEBA Assessment Data Manager software (ASEBA, Burlington VT, USA), which uses age-based normative data to generate individual scores on Adaptive Functioning, Syndrome and DSM-Oriented Scales, Externalising, Internalising and Total Problems Scales. This software requires data to be entered twice to ensure accuracy.

5.5.4 Collation and analysis

Data from EEG recordings, WJ-III tests, FAS and Achenbach questionnaires were collated, processed and analysed using R software (R 3.2.0, The R Foundation for Statistical Computing) with the graphic user interface R-Studio (Version 0.98.1103, RStudio, Inc.). See Appendix 6 for a list of CRAN R packages and versions used to undertake data processing and analysis.

Frequentist statistics with a hypothesis-testing approach was used. Some post-hoc analyses were exploratory due to the lack of previous research to generate hypotheses. Specific data-analytic methods are outlined in the respective chapters (Chapters 3, 7, 8 and 9). For the meta-analysis random-effects DL (DerSimonian and Laired method) analyses were employed to pool findings across studies eligible for inclusion in the systematic review. Forest plots illustrate these findings (see Chapter 3). For analysis of primary data, sample characteristics are presented with descriptive statistics and chi-squared analyses, group comparisons were examined with covariates via analysis of covariance techniques, and multiple linear and non-parametric regression techniques were employed to predict cognitive and psychosocial outcomes from epilepsy disease characteristics.

Chapter 6: General Results

Following on from the Methodology of the overall thesis that was provided in the preceding chapter, Chapter 5, this brief General Results Chapter presents findings pertaining to the study as a whole. These results include a recruitment flow-chart of participants enrolled in various components of the study following the recruitment and eligibility process outlined in the Chapter 5, demographic and clinical characteristics of the sample, and information regarding participants that were excluded from subsequent analyses. It is intended to provide an overview of the most general results only. Results of specific analyses reflecting hypotheses presented earlier are documented in the results sections of Chapters 7-9.

During the period 2011-2015, 127 people with GGE were recruited into the larger study, 76 of whom underwent cognitive assessment as part of the neuropsychology component of the study. Detailed participant and recruitment information is presented in the participant flow diagram in Figure 10 below. Fifty-one participants in the larger study either declined to participate in cognitive assessment, were not able to be seen by an investigator at the time of their EEG appointment or were deemed ineligible. Examination of the demographic characteristics, epilepsy or general medical history revealed no systematically varying factor to suggest a selection bias, or significant or clinically meaningful differences between those people who took part in the neuropsychology study and those who did not (see Table 8, page 95). A proportion of participants seen for cognitive assessment were seen when wearing the ambulatory EEG device (29%; n=22). Although not all participants completed all components of the study, participants for whom one type of data was missing were retained in analyses of other outcomes where possible and appropriate.

As documented in Table 8 (p95), following the exclusion of those deemed ineligible or those with previous traumatic brain injury, and data recording errors, there were 127 GGE patients in the larger prognosis study, of whom 120 people were eligible for analysis of their ambulatory EEG data, 76 for their cognitive assessment data, 60 for their self-report psychosocial functioning questionnaire and 47 for their completed informant report psychosocial functioning questionnaire, and 41 participants with data available from all sources. There were no significant differences in the demographic or

epilepsy characteristics between the subgroup that took part in the neuropsychology component of the study (n=76) and the group that did not (n=51; see *Significance* column, Table 8).

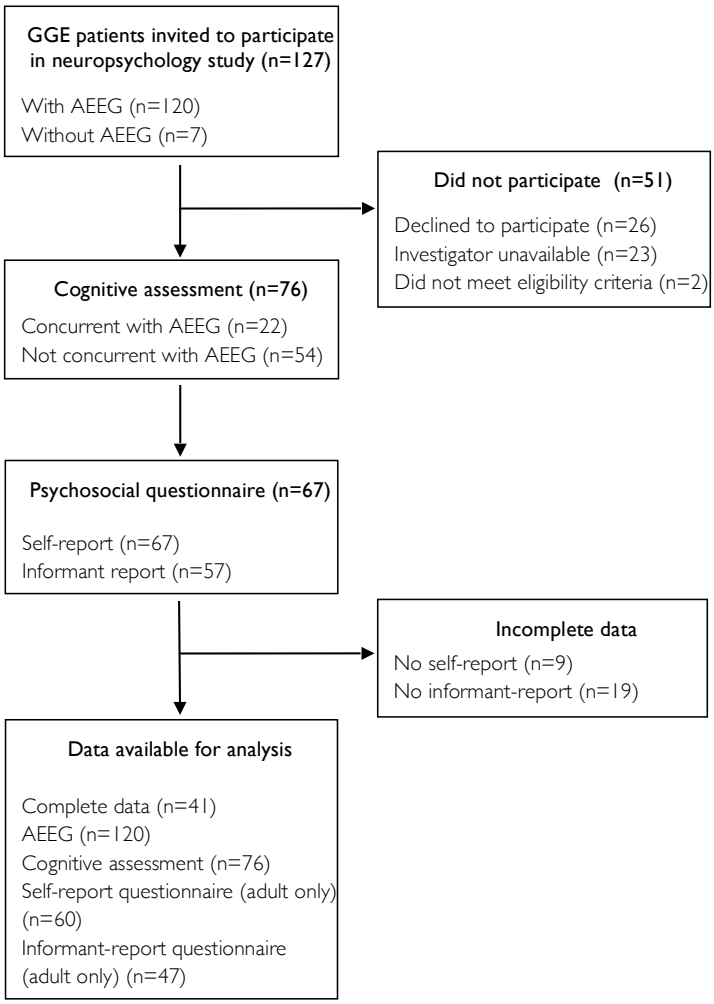

Figure 10. Participant flow diagram

AEEG: Ambulatory electroencephalogram

Table 8

Patient characteristics of AEEG only and AEEG + neuropsychology study participants.

Demographic Characteristics	AEEG only (n=51)	AEEG + Neuropsychology (n=76)	Significance*	Test type	Effect size
Age (years)					
Range	17-55	13-58	-	-	-
Mean	28.29 (9.54)	28.96 (11.2)	p=0.73	t-test	d=-0.07
Gender (n)					
M	18 (35%)	26 (38.3%)	p=1.00		phi=0.01
F	33 (65%)	50 (61.7%)			
Syndrome (n)					
CAE	8 (16%)	10 (13%)	p=0.72	chi square	Cramer's V=0.13
JAE	17 (33%)	21 (28%)			
JME	11 (22%)	20 (26%)			
GTCSO	12 (24%)	23 (30%)			
Other	3 (6%)	2 (3%)			

* These tests compare AEEG only group (n=44) with Neuropsychology group (n=76) to establish equivalence of these.

	AEEG only (n varies)	AEEG + Neuropsychology (n=76)	Significance*	Test type	Effect size
Current AED (n)	(n=51)	(n=69^)			
None	8 (16%)	6 (9%)			
1	23 (45%)	32 (46%)	p=0.52	chi square	Cramer's V=0.14
2	17 (33%)	23 (33%)			
3	3 (8%)	8 (12%)			
Valproate	35 (63.6%)	32 (76.2%)			
Lamotrigine	20 (36.4)	15 (35.7%)			
Levetiracetam	8 (14.5%)	7 (16.7%)			
Other (Topiramate, Zonisamide, Piracetam, Carbamazepine, Clonazepam)	8 (14.5%)	10 (23.8%)	N/A: Not mutually exclusive		
History of absence seizures (n)					
No	24 (47%)	35 (51%)	p=0.83	chi square	phi=0.04
Yes	27 (53%)	34(49%)			
History of GTCS (n)					
No	4 (8%)	8 (12%)	p=0.71	chi square	phi=0.06
Yes	47 (92%)	61 (88%)			
Seizure free duration (days)	(n=58)	(n=45)			
Range	1-5290	1-9855	-	-	-
Median; IQR	90; 347.5	150; 707			
Duration ED of any length in 24hrs (s)	(n=58)	(n=45)			
Range	0-835.5	0-835.5	-	-	-
Mean	91.23 (166.11)	76.15 (146.14)	p=0.32	t-test	-0.096

* These tests compare AEEG only group with Neuropsychology group to establish equivalence of these (numbers vary on the basis of data availability). ^Detailed clinical information not available from n=7

Chapter 7: A comprehensive assessment of cognitive function in the common GGE syndromes

In the previous Chapter the descriptive characteristics of the eligible and recruited sample of GGE patients were documented. This Chapter, published in the *European Journal of Neurology,* is the first of three results chapters that address the aims and hypotheses outlined in Section 2.5. This Chapter pertains to Aim 2, the examination of cognitive functioning in GGE. In this Chapter, findings from an in-depth analysis of the cognitive functioning in this sample of 76 people with GGE are presented. Supplementary materials referred to in this publication are presented in Appendices 8 to 10.

Readers will note that executive functions have not been reported in the following chapter on cognitive function, despite the popularity of investigation of executive functions in JME in particular. This is because a number of independently replicated factor-analytic studies have now supported the coverage of these abilities within the CHC model of cognitive ability rather than as independent cognitive constructs (Jewsbury, Bowden, & Duff, 2016; Jewsbury, Bowden, & Strauss, 2016; Loring & Larrabee, 2006). Letter fluency results are presented in Appendix 7.

ORIGINAL ARTICLE

A comprehensive assessment of cognitive function in the common genetic generalized epilepsy syndromes

A. Loughman[a,b], S. C. Bowden[a,c] and W. J. D'Souza[d]

[a]*Melbourne School of Psychological Sciences, University of Melbourne, Parkville, Victoria;* [b]*School of Health and Biomedical Sciences, RMIT University, Bundoora, Victoria;* [c]*Department of Clinical Neurosciences, St Vincent's Hospital Melbourne, Fitzroy, Victoria; and* [d]*Department of Medicine, St Vincent's Hospital, The University of Melbourne, Fitzroy, Victoria, Australia*

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Background and purpose: Considered to be benign conditions, the common genetic generalized epilepsy (GGE) syndromes are now known to be frequently accompanied by cognitive dysfunction. However, unresolved issues impede clinical management of this common comorbidity, including which cognitive abilities are most affected, whether there are differences between syndromes and how seizure type and mood symptoms affect cognitive dysfunction. We provide a detailed description of cognitive ability and evaluate factors contributing to cognitive dysfunction.

Methods: A total of 76 adults with GGE were assessed with the Woodcock Johnson III Tests of Cognitive Abilities.

Results: Scores on tests of overall cognitive ability, acquired knowledge, long-term retrieval and speed of information processing were significantly below the normative mean. Long-term retrieval was a pronounced weakness with a large reduction in scores ($d = 0.84$). GGE syndrome, seizure type and the presence of recent psychopathology symptoms were not significantly associated with cognitive function.

Conclusions: This study confirms previous meta-analytic findings with a prospective study, offers new insights into the cognitive comorbidity of these common epilepsy syndromes and reinforces the need for cognitive interventions in people with GGE.

Introduction

Cognitive dysfunction has been consistently reported in people with genetic generalized epilepsy (GGE), a cluster of epilepsy syndromes representing approximately 20% of all epilepsies [1–3]. A recent meta-analysis of 26 studies showed moderate to large reductions across all cognitive factors, with the greatest deficits in information-processing speed, acquired knowledge and fluid intelligence, and working memory [4]. Questions remain regarding the nature of cognitive dysfunction in this cluster of epilepsy syndromes, making it difficult to establish the best method of prevention and treatment of this common comorbidity. It remains unclear whether patterns of cognitive impairment are similar across the main syndromes: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and GGE with generalized tonic–clonic seizures (GTCS) only (GGE-GTCSO) .

The lack of objective evidence for neuropsychological differences between these syndromes may be attributable to sampling bias in previous studies, as the majority have focused on JME [4]. Studies that have included participants with a range of GGE syndromes rarely conducted comparisons between groups. One familial study of GGE compared CAE and JME, showing few statistically significant differences in cognitive function, limited to some tests of variability in response reaction time and attentional flexibility, both lower in JME [5]. Cognitive functioning in adults with GGE is also understudied. The estimated nature and extent of dysfunction vary on the basis of the

Correspondence: A. Loughman, School of Health & Biomedical Sciences, RMIT University, Bundoora Vic. 3038, Australia (tel.: +613 9925 7374; e-mail: amy.loughman@rmit.edu.au).

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sampling and methodological characteristics of individual studies. For example, few studies conducted comprehensive cognitive assessment across all areas of function due to the testing of specific hypotheses regarding executive functioning deficits – a practice that may have led to underestimation of the extent of cognitive dysfunction [2,4].

The cause of cognitive dysfunction in epilepsy syndromes broadly and GGE more specifically is considered multifactorial and remains uncertain [2]. Possible causes include neurobiological factors, such as duration of disease, acute and cumulative effects of seizures, antiepileptic drug side-effects, epileptiform discharges and psychopathology comorbidities [6–8]. A 10-year follow-up of people with intractable epilepsy of diverse types has shown frequency of GTCS to be the strongest predictor of cognitive decline [9], although changes in antiepileptic drug use during the follow-up period confound this conclusion [10]. A related finding is the evidence of elevated rates of psychopathology in GGE [11–13]. However, to our knowledge, there are no studies that have evaluated the extent to which cognitive dysfunction and psychopathology co-occur. With improved understanding, clinical management of psychological dysfunction, both cognitive and psychopathological, and the ensuing effects on quality of life could be addressed.

This study aimed to provide a detailed characterization of cognitive function in GGE. Comprehensive measurement of cognitive ability factors and psychosocial functioning in a larger, prospective sample of adults with GGE will enable assessment of areas of relative strength and weakness, and the comparison of cognitive ability between GGE subtypes. Relationships between syndrome, seizure variables, psychopathology and cognition were also measured.

Methods

Participants and procedure

Patients were recruited prospectively as part of a larger study through epilepsy specialist clinics at two tertiary hospitals in Melbourne, Australia and a rural clinic [14]. During the period 2011–2015, 120 people with GGE were recruited into the larger prognostic study, 76 of whom underwent cognitive assessment as part of the neuropsychology component of the study (Fig. S1). The remaining 44 of those in the larger study either declined to participate in cognitive assessment or were not able to be seen by an investigator at the time of their electroencephalography (EEG) appointment. There were no significant or clinically meaningful differences between those people who took part in the current study and those from the larger study with respect to demographic or epilepsy characteristics (Table S1).

We established the diagnosis of GGE according to International League Against Epilepsy criteria, namely, the combination of consistent clinical features and a positive electroencephalogram showing generalized epileptiform discharges on at least one occasion [15,16]. All patients had EEG and brain magnetic resonance imaging performed as per routine practice of the epileptologist.

Patients with GGE were classified into the following categories: CAE, JAE, JME and GGE-GTCSO [15,16]. Medical records including EEG and neuroimaging were reviewed independently by two epilepsy specialists with any discordance on diagnosis resolved by consensus based on International League Against Epilepsy criteria. Exclusion criteria were: potentially epileptogenic structural abnormalities (such as hippocampal sclerosis), coexistent focal and generalized epilepsies, secondary bilateral synchrony and single seizure with generalized epileptiform abnormalities on EEG.

This research was approved by the Human Research Ethics Committees of participating sites. Participants provided written informed consent as per the Declaration of Helsinki. Investigators collecting cognitive data were blinded to diagnostic and other epilepsy information.

Cognitive assessment

The Woodcock Johnson III Tests of Cognitive Abilities were used to measure cognitive functioning. These tests were developed on the basis of the comprehensive Cattell–Horn–Carroll (CHC) model [17]. The CHC model has a demonstrated factor structure that explains cognitive factors underlying the majority of validated cognitive tests, including tests of executive functioning [18,19]. Subtests of the Woodcock Johnson III Tests of Cognitive Abilities are combined to form a brief measure of overall intellectual ability (an estimate of intelligence quotient) and broad CHC factors: acquired knowledge, long-term retrieval, fluid reasoning, processing speed and short-term memory as described in Table 1. Long-term retrieval is synonymous with anterograde memory or new learning. Short-term memory is also known as working memory. Participant test scores were compared with Australian age- and demographically-adjusted normative data [20].

Table 1 Broad Cattell–Horn–Carroll (CHC) factors and corresponding Woodcock Johnson III Tests of Cognitive Abilities (WJ-III)

Broad CHC factor	Narrow abilities measured	Cluster of WJ-III tests of cognitive abilities
Comprehension knowledge (Gc)	Lexical knowledge, language development	Test 1: Verbal comprehension
	General (verbal) information	Test 11: General information
Long-term retrieval (Glr)	Associative memory	Test 2: Visual-auditory learning
		Test 10: Visual-auditory learning delayed
	Ideational fluency	Test 12: Retrieval fluency
Fluid reasoning (Gf)	Induction	Test 5: Concept formation
	General sequential reasoning	Test 15: Analysis synthesis
Processing speed (Gs)	Perceptual speed	Test 6: Visual matching
	Attention and concentration	Test 20: Pair cancellation
Short-term memory (Gsm)	Working memory	Test 7: Numbers reversed
		Test 9: Auditory working memory
	Memory span	Test 17: Memory for words

Measurement of psychopathology symptoms

Following cognitive assessment, participants were invited to complete a self-report psychopathology symptom questionnaire (the Adult Self-Report form of the Achenbach System of Empirically Based Assessment) [21]. The questionnaire yields six DSM-Oriented Subscales, matched to the Diagnostic and Statistical Manual of Mental Disorders IV-TR. The Achenbach Adult Self-Report form defines *T* scores of 65–69 as corresponding to 'borderline-clinical' range and scores over 69 as 'clinical' range symptoms. This corresponds to 93rd and 97th percentile, respectively; thus, 7% of the normative reference group would be expected to disclose borderline-clinical or clinical levels of distress in each DSM-Oriented Subscale [21].

Statistical analysis

Distribution plots and one-sample *t*-tests with Bonferroni corrections for multiple comparisons were used to examine the distributional properties of standard scores on each CHC factor. To test the hypothesis of specific areas of cognitive strength and deficit in GGE, one-way within-subjects ANOVA analysis was employed to test for differences between GGE subgroups on each CHC factor, with follow-up pairwise *t*-tests if the omnibus test was significant [22].

Multivariate ANOVAS were used to test differences between GGE syndromes and seizure types (absence and GTC seizures) on each cognitive factor. Univariate ANOVAS were then used when appropriate.

A series of MANOVAS were used to compare scores on all CHC factors and a global ability index for patients with elevated (borderline-clinical or clinical level) symptom scores on any of the DSM-Oriented Subscales, with those who rated within the normal range on these subscales. Pairwise analyses followed when appropriate.

Results

A total of 76 adolescents and adults with GGE and its subsyndromes (CAE, juvenile absence epilepsy, JME, GGE-GTCSO) completed the cognitive assessment (Table 2). Two-thirds of the total sample (50 of 76 patients) completed the psychopathology symptom questionnaire. The remaining 26 did not return their questionnaire. The relative frequency of 'borderline-clinical' and 'clinical' level symptom endorsement in each of the six DSM-Oriented Subscales is shown in Table 3.

With respect to education level, the majority of the sample had completed a university degree ($n = 31$) or some vocational training ($n = 10$), a smaller proportion completing only secondary ($n = 30$) or elementary ($n = 2$) school. Most were employed ($n = 35$) or studying full-time ($n = 23$), the remainder were unemployed ($n = 11$) or did not disclose employment status ($n = 7$).

Figure 1 and Table 4 show that the sample mean of each cognitive ability lies below the normative population value in the relevant age group, except for short-term memory. One-sample *t*-tests conducted on each cognitive factor using a Bonferroni-adjusted significance value of 0.0083 (0.05/6) revealed significantly lower scores in the GGE group on overall cognitive ability, acquired knowledge and speed of information processing (small to medium effects), and long-term retrieval (large effect) compared with the norms.

One-way within-subjects ANOVA comparisons between CHC factor scores in the entire GGE sample showed significant differences between patient scores on the five cognitive factors and the global ability index ($F_{5,374} = 18.22$, $P < 0.001$, $\eta^2 = 0.19$) (Table 5). Bonferroni-corrected pairwise comparisons revealed

Table 2 Patient demographics (n = 76)

Variable	
Age (years)	
Range	13–58
Mean (SD)	29.0 (11.2)
Gender (n) (%)	
M	26 (34%)
F	50 (66%)
Syndrome (n) (%)	
CAE	10 (13%)
JAE	21 (28%)
JME	20 (26%)
GTCSO	23 (30%)
Other	2 (3%)
Current AED (n) (%)	
None	10 (13%)
1	34 (45%)
>1	32 (42%)
Lamotrigine	27
Valproate	39
Levetiracetam	14
Other AED[a]	17
History of absence seizures (n = 69[b])	
No	35 (51%)
Yes	34 (49%)
History of GTCS (n = 73[b])	
No	8 (11%)
Yes	65 (89%)
Days since last GTCS (n = 69[b])	
Range	3–9855
IQR	1340
Seizure-free duration (days) (n = 69[b])	
Range	1–9855
IQR	633.5

[a]Antiepileptic drugs (AEDs) include: Clonazepam, Topiramate, Carbamazepine, Zonisamide, Piracetam and Vimpat. NB Some clinical information was unavailable for up to seven patients. [b]Clinical information unavailable for up to n = 7 patients. CAE, childhood absence epilepsy; GTCS, generalized tonic–clonic seizure; GTCSO, genetic generalized epilepsy with generalized tonic–clonic seizures only; IQR, interquartile range; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy.

Table 3 Frequency of psychopathology symptoms (n = 50)

Symptom type	Clinical (%)	Borderline-clinical (%)	Normal (%)
Depressive	6	18	76
Anxious	4	12	84
Somatic	10	4	86
Avoidant	6	10	84
ADHD	8	14	78
Antisocial personality	0	6	94
Total problems	16	10	74

ADHD, attention deficit hyperactivity disorder.

significant, small- to medium-sized differences between mean scores on a few of the CHC factor subscales. These within-subject comparisons support the inference from Table 4 that long-term retrieval function is significantly lower than other abilities except speed of information processing, from which it is not significantly different.

A series of MANOVAS with clinical covariates as independent variables and the five cognitive functioning factors and global ability index as dependent variables revealed no significant effect of any of the following clinical covariates: GGE syndrome type ($F_{4,70}$ = 1.16, P = 0.29, η^2 = 0.09), history of absence seizures ($F_{1,66}$ = 0.30, P = 0.94, η^2 = 0.028) or history of GTCS seizures ($F_{1,70}$ = 1.24, P = 0.30, η^2 = 0.10). Table S2 shows cognitive functioning scores separately for these clinical subgroups.

A series of MANOVAS with presence or absence of the six types of psychopathology symptoms as independent variables revealed no statistically significant impact of psychopathology symptoms on cognitive function. Specifically, the models were tested with depressive, anxious, somatic, avoidant, attention deficit, antisocial and total symptoms (Tables S3–S8). The same pattern of null results was obtained when the psychopathology independent variables were reported as continuous.

Discussion

This study describes cognitive function in adults with GGE. There were three key findings. First, there was a pervasive reduction in cognitive function in people with GGE compared with the local demographically corrected norms. Performance on tests of overall cognitive ability, and the constituent scores of acquired knowledge, speed of information processing and long-term retrieval fell significantly below the normative sample by 0.42–0.84 SD units (6–13 intelligence index points). Long-term retrieval was a relative weakness compared with other cognitive functions. Fluid intelligence and short-term memory were not significantly different from normative standards. Second, we did not find any evidence for the effect of GGE syndrome, history of absence seizures or history of GTCS seizures on cognitive scores. Third, there was no evidence of poorer cognitive functioning in subgroups experiencing recent mood symptoms in any of the six DSM-Oriented Subscales.

Reductions in cognitive functioning in the current prospective cohort mirrored those reported from a recent meta-analysis in both size and direction [4]. One exception relates to the significantly greater deficit in anterograde memory reported by participants in the current study, a common subjective symptom [23], but contrasting with the meta-analytic findings that anterograde memory was relatively spared [4].

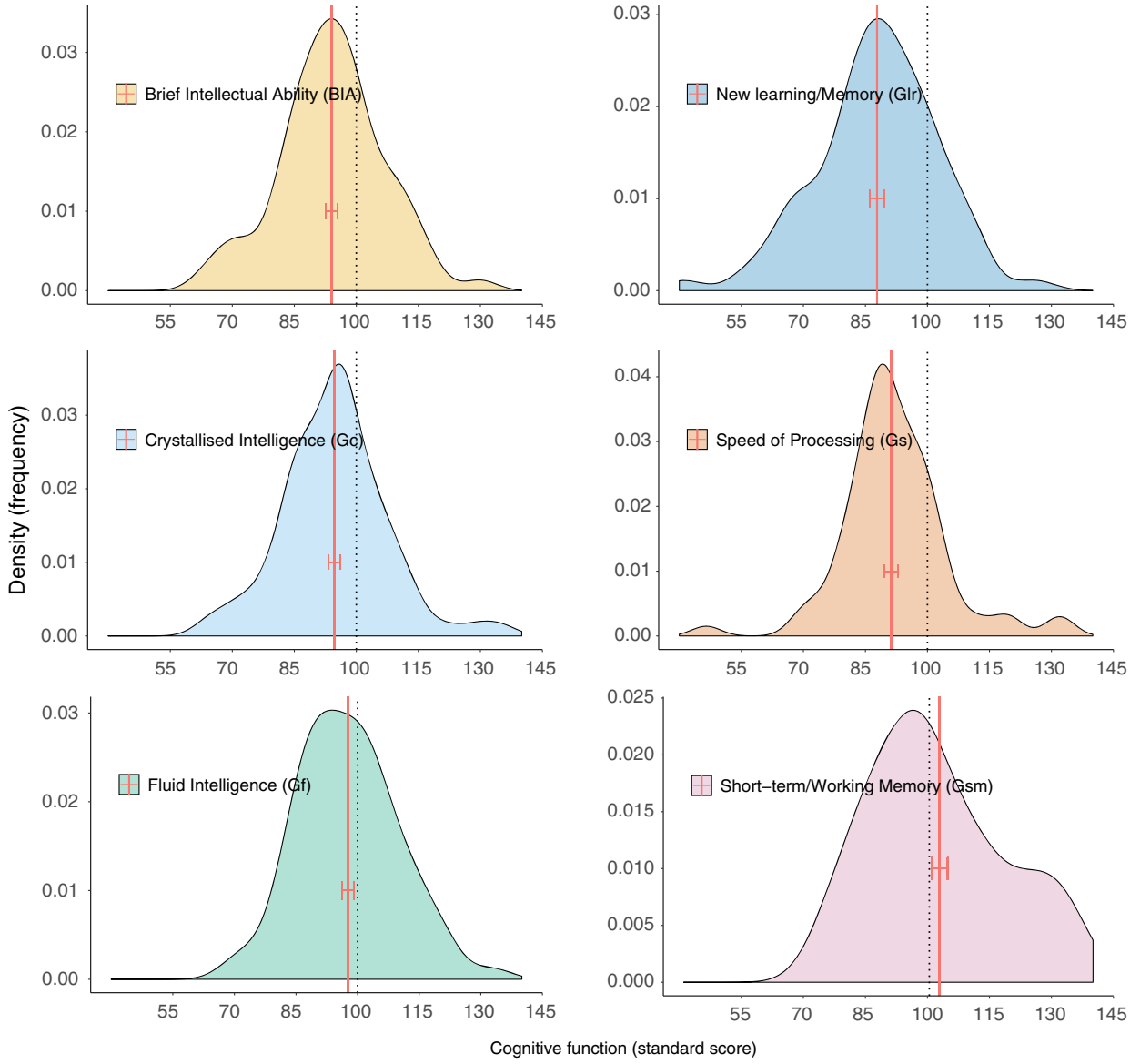

Figure 1 Distribution plots of each Cattell–Horn–Carroll (CHC) factor. (a) Brief intellectual ability; (b) new learning/memory; (c) crystallized intelligence; (d) speed of information processing; (e) fluid intelligence and (f) short-term/working memory. The normative mean of 100 is indicated by a solid vertical line, whereas the mean and distributional properties of scores on each CHC factor are indicated by the dotted line and shading. Horizontal bars refer to standard error. [Colour figure can be viewed at wileyonlinelibrary.com]

In the current sample, smaller, significant reductions were observed for overall cognitive ability, acquired knowledge and speed of information processing. No significant reduction was observed for short-term memory or fluid intelligence. Short-term memory overlaps with measures of attention and the lack of significant reduction in our sample with GGE contrasts with findings of attention deficits in children with CAE [2,24]. There are several possible explanations for this null finding. We may not have detected a difference in short-term memory function because of the relatively small proportion of people with CAE in our adult cohort. Alternatively, there may be differences in the tests used to measure short-term memory function across studies [25,26]. Although attentional deficits are commonly reported in children with CAE, it is possible that attention problems may resolve in adulthood, although this requires further investigation.

The observed reductions in speed of processing, long-term retrieval and acquired knowledge may be related. For example, a possible mechanistic pathway

Table 4 One-sample *t*-test and effect sizes for cognitive functioning in genetic generalized epilepsy (GGE) (n = 76)

Cognitive domain	GGE sample		Normative group		95% CI for mean difference	*t* (df)	*P*	Significance	Cohen's *D*	
	M	SD	M	SD						
Overall ability (BIA)	94.07	12.67	100	15	91.17–96.96	−4.08	0.0001	***	0.47	Small
Crystallized intelligence (Gc)	94.75	12.59			91.87–97.63	−3.63	0.0005	***	0.42	Small
Fluid intelligence (Gf)	97.70	12.12			94.93–100.47	−1.66	0.1019	n.s.	0.19	Small
Long-term retrieval and memory (Glr)	87.82	14.58			84.48–91.15	−7.29	0.0000	***	0.84	Large
Short-term/working memory (Gsm)	102.49	17.10			98.56–106.43	1.27	0.2107	n.s.	0.15	Small
Speed of information processing (Gs)	91.21	14.46			87.91–94.51	−5.30	0.0000	***	0.61	Medium

Two-tailed significance: n.s., not significant; *P < 0.05; **P < 0.01; ***P < 0.001. CI, confidence interval; df, degrees of freedom; M, mean.

could include a reduction in speed of information processing and memory difficulty, which together result in a difficulty in retaining learned information, reflected in the reduced acquired knowledge [27,28]. This combination of deficits has the potential for cumulative and far-reaching educational and vocational disadvantage [29].

A novel aspect of this study involved examination of effects of GGE syndrome and seizure type on cognitive ability. We found no evidence for differences in cognitive ability on the basis of GGE syndrome. This replicates previous null findings of differences between CAE and JME, and across other GGE syndromes [4,5]. However, the present study may have been underpowered to detect the observed medium-sized effect (0.7 statistical power), suggesting that future studies should aim for recruitment of at least 25 subjects per GGE syndrome group.

We found no relationship between seizure types and cognitive function. Mean differences in cognitive functioning scores between groups with and without a history of absence seizures were trivial and unlikely to be of clinical significance regardless of sample size. Therefore, the relationship between non-convulsive seizures, such as absence seizures, and history of GTCS and cognition remains a point of debate [9,30,31]. It is of course possible that the extent of seizure burden, rather than seizure type, contributes to cognitive dysfunction.

The lack of association between mood disturbance and cognitive function is surprising, given the ample evidence for this relationship in depression and other health conditions [32]. Our findings do not support the concept of shared underlying mechanisms of cognitive and psychosocial comorbidities or that mood disturbance is a key contributor to cognitive dysfunction in GGE. Nonetheless, acute mood states are known to impact retrospective symptom reports significantly due to recall biases, so the two are not entirely independent [33].

	Mean 1	SD 1	Mean 2	SD 2	*t* (df)	*P*	Significance	*d*
BIA–Gc	94.07	12.67	94.75	12.59	−0.68 (75)	1.00	n.s.	0.08
BIA–Gf			97.70	12.12	−4.14 (75)	0.00	***	0.47
BIA–Glr			87.82	14.58	5.16 (75)	0.00	***	0.59
BIA–Gs			91.21	14.46	2.23 (75)	0.43	n.s.	0.26
BIA–Gsm			102.49	17.10	−4.02 (75)	0.00	***	0.46
Gc–Gf	94.75	12.59	97.70	12.12	−2.47 (75)	0.24	n.s.	0.28
Gc–Glr			87.82	14.58	4.45 (75)	0.00	***	0.28
Gc–Gs			91.21	14.46	1.88 (75)	0.96	n.s.	0.22
Gc–Gsm			102.49	17.10	−3.75 (74)	0.01	**	0.43
Gf–Glr	97.70	12.12	87.82	14.58	6.67 (75)	0.00	***	0.76
Gf–Gs			91.21	14.46	−3.87 (75)	0.00	***	0.44
Gf–Gsm			102.49	17.10	−2.27 (74)	0.39	n.s.	0.26
Glr–Gs	87.82	14.58	91.21	14.46	−2.29 (75)	0.37	n.s.	0.79
Glr–Gsm			102.49	17.10	−6.84 (74)	0.00	***	0.26
Gs–Gsm	91.21	14.46	102.49	17.10	−4.64 (74)	0.00	***	0.54

Two-tailed significance: n.s., not significant; **P < 0.01; ***P < 0.001. df, degrees of freedom.

Table 5 Pairwise comparisons between Cattell–Horn–Carroll (CHC) factor scores within the entire genetic generalized epilepsy sample, with Bonferroni correction (see Table 4 for CHC factor domain abbreviations)

This study has a number of methodological strengths: the availability of a relatively large, prospective sample, comprehensive cognitive assessment and consideration of concurrent mood symptoms on cognition. Limitations include inadequate statistical power to detect significant small- to medium-sized differences in cognitive function between GGE syndromes and different seizure histories. Although age-matched local Australian norms were used, the accuracy of our estimates of cognitive deficits may have been improved with a large study-recruited control group. Future research should consider healthy and sibling control groups whilst retaining representation from all GGE syndromes. The inclusion of a sibling control group may enable consideration of potential underlying genetic factors unrelated to epilepsy.

Assuming a normal distribution, the reduction of overall cognitive functioning of six standard score points in this GGE sample suggests the prevalence of intellectual disability (intelligence test score of ≤70) of approximately 5.5% compared with the general population prevalence of approximately 2%. On this basis, an estimated additional 12% of people with GGE would be expected to have 'borderline' range intellectual functioning (intelligence test scores of 70–80), above the population prevalence of approximately 7%. The estimated cumulative prevalence of cognitive ability in the range of 'borderline' or intellectually disability would therefore be 17.5%. Our findings replicate previous meta-analytic findings of cognitive dysfunction in GGE in a prospective sample. The results further reinforce the need for screening of cognitive dysfunction in adults with GGE, even after initial diagnosis, and the provision of support for memory and other cognitive difficulties.

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Disclosure of conflicts of interest

As indicated above, A.L. received an Australian NHMRC Public Health Scholarship (APP1056485).

Supporting Information

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

Figure S1. Flow chart of recruitment and participation.

Table S1. Comparison of demographic and clinical information in sample with and without cognitive assessment.

Table S2. Cognitive functioning by genetic generalized epilepsy syndromes and seizure type.

Tables S3–S8. Cognitive functioning in subgroups with and without borderline-clinical/clinical symptoms.

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Chapter 8: Epileptiform Discharges and Cognitive Function

The preceding Chapter documented detailed findings regarding cognitive functioning in people with GGE, considering different latent variables of cognitive function and comparing findings from this sample to those of the meta-analysis in Chapter 3. In this Chapter, featuring an article published in *Epilepsy & Behavior*, the hypothesis that the epileptiform discharges may be amongst other factors that contribute to reduced cognitive functioning in people with GGE is explored. This work constitutes significant methodological improvement on previous investigations on the topic, due to the use of comprehensive manual reading of 24-hours of ambulatory EEG monitoring output (undertaken by Udaya Seneviratne), enabling the capture of even short epileptiform discharges. Investigating the relationships between clinical variables and cognitive outcomes is an important prerequisite to providing evidence-based prognostic advice in these conditions. Supplementary materials accompanying this publication are presented in Appendices 11 to 15.

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Epilepsy beyond seizures: Predicting enduring cognitive dysfunction in genetic generalized epilepsies

Amy Loughman [a,*], Udaya Seneviratne [c], Stephen C. Bowden [a,b], Wendyl J. D'Souza [c]

[a] Melbourne School of Psychological Sciences, University of Melbourne, Parkville, VIC 3010, Australia
[b] Department of Clinical Neurosciences, St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia
[c] Department of Medicine, St Vincent's Hospital, The University of Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia

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ABSTRACT

Reduced cognitive functioning has been documented in the genetic generalized epilepsies (GGE). Among a number of hypothesized causal mechanisms, some evidence from other epilepsy syndromes suggests the impact of epileptiform discharges. This study investigates the relationship between cognitive function in GGE and burden of epileptiform discharges within a 24-hour EEG recording, controlling for variables relevant to cognitive function in epilepsy.

As part of a larger prospective cohort study, 69 patients with EEG-confirmed GGE (11–58 years) underwent 24-hour EEG and detailed neuropsychological assessment using the Woodcock Johnson III Tests. Ten-second pages of the EEG were marked manually page-by-page on longitudinal bipolar montage with 0.5 to 70 Hz bandwidth by an experienced EEG reader. Multiple regression analyses were conducted. Epileptiform discharges were detected in 90% of patients. Less than 0.01% of electrophysiological events of two or more seconds were recognized by patients. Regression analysis demonstrated that the cumulative duration of epileptiform discharges over a 24-hour period predicted overall cognitive ability and memory function, accounting for 9.6% and 11.8% of adjusted variance, respectively. None of the epilepsy covariates included in multiple regression analysis added significantly to the model.

Duration of epileptiform discharges negatively predicts overall cognitive ability and memory function, even after accounting for other known determinants of cognition. Prolonged epileptiform discharges are common and remain unreported by patients, raising important questions regarding the management of GGE syndromes and their associated comorbidities. Further research is required to investigate causal mechanisms if we are to improve cognitive outcomes in this common group of epilepsies.

1. Introduction

Cognitive dysfunction in epilepsy is thought to reflect a combination of causal factors including the underlying disease process, seizures, antiepileptic drugs (AEDs), educational disruption, and more recently, the burden of epileptiform discharges (ED) [1,2]. Historically considered a benign disorder, genetic generalized epilepsy (GGE) has been associated with reduced outcomes across all domains of cognitive function on meta-analysis [3]. A small literature has examined consciousness during EEG activity and seizures in one GGE syndrome, childhood absence epilepsy, reporting associations between duration of long ED and absence seizures, and attention and visual memory tasks [4–6].

Studies of other epilepsy syndromes have demonstrated that ED are associated with reductions in reaction time [7], processing speed [8], memory [9], short-term memory [10], and overall IQ [9], although a recent review suggests that the impact on enduring functions remains unclear [11]. In addition, neurobiological differences between syndromes preclude the generalizability of these findings to GGE. Furthermore, EEG monitoring periods are typically of short duration and capture only wakefulness, not sleep, and EEG output is commonly described in categories such as "frequent" or "infrequent" ED, rather than in quantified terms. The possible confounding effects of other epilepsy-related variables are rarely addressed. Hence, many questions remain regarding the significance of electrophysiological abnormalities for cognitive functioning in GGE, particularly in syndromes other than childhood absence epilepsy.

We investigated the relationship between ED and cognitive function in a primarily adult GGE sample using 24-hour EEG which enabled comprehensive capture of diurnal and nocturnal events according to the circadian variation in EEG activity [12]. We used quantified EEG data by measuring the duration of all ED throughout the 24-hour recording. Given the relevance of duration of discharges in previous findings, we hypothesized that greater duration of ED would predict poorer cognitive function, independently of relevant clinical variables.

* Corresponding author at: Melbourne School of Psychological Sciences, University of Melbourne, Australia. Fax: +61 3 9347 6618.
E-mail address: amy.loughman@unimelb.edu.au (A. Loughman).

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2. Materials and methods

2.1. Participants

Patients were recruited prospectively as part of a larger prognosis study through epilepsy specialist clinics at two tertiary hospitals in Melbourne, Australia (St. Vincent's Hospital and Monash Medical Centre) and their outreach clinic (North West Regional Hospital, Tasmania). We established the diagnosis of GGE according to International League Against Epilepsy (ILAE) criteria [13,14]. All patients had EEG and brain MRI performed as per routine practice of the epileptologists. Included patients had a confirmed diagnosis of GGE based on the combination of consistent clinical features and a positive EEG showing generalized ED on at least one occasion, and consented to take part in the study. Exclusion criteria were the following: the presence of potentially epileptogenic structural abnormalities (such as hippocampal sclerosis) on MRI, coexistent focal and generalized epilepsies, secondary bilateral synchrony, and single seizure with generalized epileptiform abnormalities on EEG.

We classified patients into childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized epilepsy with generalized tonic–clonic seizures (GTCS) only (GTCSO) according to ILAE criteria [13,14]. Patients who did not fulfill the criteria of the four major syndromes were classified as "GGE unspecified". All medical records including EEG and neuroimaging were reviewed independently by two epilepsy specialists (WD & US) with any discordance on diagnosis resolved by consensus based on ILAE criteria.

2.1.1. Standard protocol approvals, registrations and patient consents

This research was approved by the Human Ethics Research Committees of all participating sites. Participants provided their written informed consent as per the Declaration of Helsinki.

2.2. Procedure

All participants were interviewed during 24-hour ambulatory EEG recording. Medical records were also reviewed to obtain their sociodemographic (age, gender, education, employment) and clinical information (seizure types, ages of onset, the date of last seizure, past history of febrile seizures, family history of febrile seizures and epilepsy in first degree relatives, history of antiepileptic drug therapy and current dosages, previous EEG findings and neuroimaging findings).

Standard protocol for 24-hour ambulatory EEG was employed as previously described [15]. Electroencephalogram signals were acquired with 32-channel, Compumedics Siesta ambulatory EEG system (Compumedics Ltd., Melbourne, Australia) according to the international 10–20 system. The recording was commenced in the morning, usually between 9 am and 10 am. The patient was then allowed to resume routine activities, returning home wearing the small ambulatory EEG device around the waist. Patients were asked to complete a record of their activities during the recording period and to signal the presence of seizures by pressing a button on the device.

Patients were encouraged to have at least 7 to 8 h of sleep during the night. The recording was ceased, and patients were disconnected from the EEG device 24 h later. Twenty-two patients completed the cognitive assessment during EEG recording. Due to patient and clinician availability, the remaining 47 completed the assessment in the week prior or following the EEG recording.

An experienced EEG reader (US) reviewed all recordings with ProFusion 4 software (Compumedics Ltd., Melbourne, Australia). Ten-second pages were reviewed page-by-page on longitudinal bipolar montage with 0.5 to 70 Hz bandwidth. When an epileptiform abnormality was detected, detailed analysis of the waveform was undertaken on common average referential montage [16]. A measuring tool incorporated in the software was used to manually measure amplitude and duration of discharges.

Each epileptiform discharge was assessed for discharge type (focal, generalized fragment, generalized paroxysm), duration (seconds), time of occurrence, state of arousal, and individual components (spike–wave, polyspike–wave, polyspike). The sleep onset and offset times were recorded. Total ED duration was obtained by adding up the total duration of all ED (in seconds) over the 24-hour period of the EEG recording. Total number of discharges was obtained by calculating the total number of ED over the 24-hour length of the EEG recording.

The Woodcock Johnson III Tests of Cognitive Abilities (WJ-III) were used to measure cognitive functioning. These tests were developed on the basis of the comprehensive Cattell–Horn–Carroll (CHC) model, which has a demonstrated factor structure that explains cognitive domains underlying the majority of validated cognitive tests, including tests of executive functioning [17,18]. "Brief Intellectual Ability" is a subscale of the WJ-III measuring overall cognitive ability that incorporates measurement of comprehension–knowledge, fluid reasoning, and processing speed, as per the CHC factor structure. Two additional broad CHC factors—short-term memory and long-term (anterograde) memory retrieval—were measured using the WJ-III tests (see Online Supporting Information for details). The CHC factor "short-term memory" is synonymous with "working memory". Long-term memory retrieval includes learning and retention of new information, and retrieval of existing knowledge.

All investigators were blinded; none of the data were available to either the person interpreting EEGs or administering/scoring cognitive tests.

Variables used as covariates in the analysis were obtained from current patient medical records and structured validated interviews. Epilepsy duration was included to account for the potential cumulative effects of disease. Antiepileptic drug therapy is considered a risk factor for cognitive dysfunction, and such side effects are commonly reported by patients [19]. A continuous variable—number of AEDs currently prescribed—was dichotomized to 2 levels: 1) No AED or monotherapy, and 2) polytherapy (>1 AED). There was insufficient power to include monotherapy as a separate level. Additionally, current use of valproate, levetiracetam and lamotrigine was included to account for possible side-effects specific to each of these most frequently used AEDs. Three seizure variables were also included as covariates given the previously demonstrated association of this seizure type with reductions in cognitive function: history of absence seizures, days since last GTCS, and seizure-free duration [5,20]. The impact of education level on cognitive function is well known and was included as a covariate to account for the possibility that any association between ED and cognitive function was not simply reflecting this relationship [21].

2.3. Analysis

Standard linear regression was used to test associations between duration of ED and the three cognitive outcomes: overall cognitive functioning, short-term memory, and long-term memory retrieval. Tests of these three a priori hypotheses that duration of ED would be negatively associated with cognitive outcomes were conducted using Bonferroni-adjusted alpha levels of 0.017 per test (0.05/3).

We used single and multiple linear models to explore other possible hypotheses regarding associations between number of ED and the three cognitive outcomes, the potential role of covariates, and time of day variables. Corrections for multiple comparisons were not made for these exploratory analyses to ensure that potentially important findings were not overlooked [22]. Analyses were conducted using R version 3.2.0 and the *lm.beta* and *gvlma* packages.

3. Results

3.1. Demographic and clinical outcomes

Sixty-nine people with EEG-confirmed GGE were recruited prospectively into the study (23 males; mean age: 28.6 years, SD: 11.5; see Table 1). Genetic generalized epilepsy syndromes were distributed approximately evenly within the sample, with a slight bias against CAE due to our predominantly adult sample (84% above 18 years of age). The majority of patients were prescribed AED treatment (91%; n = 63), most commonly valproate (n = 47; only n = 17 on doses above 800 mg), lamotrigine (n = 25), and levetiracetam (n = 13), and approximately 20% were prescribed one of the following less common agents: clonazepam (n = 2), zonisamide (n = 5), topiramate (n = 4), carbamazepine (n = 4), piracetam (n = 1), and lacosamide (n = 1). A history of absence seizures was found in 50% of the patients. Seizure-free duration ranged from 1 to 9855 days (median: 150, interquartile range: 707 days).

Epileptiform discharges of any length during the 24-hour monitoring period were recorded in 62 patients; ED 2 s or longer occurred in 37 patients (see Table 2 and Fig. 1 for details). A smaller number (n = 14) showed one or more focal ED. Only 2 patients reported experiencing symptoms during ED, reporting a total of 3 events, accounting for 0.01% of all long ED (≥2 s) recorded on EEG. Our sample had lower overall cognitive and long-term memory retrieval function than age-based Australian norms (0.5–1.0 SD, respectively), and average short-term memory function (Fig. 2).

3.2. Prediction of cognitive function

Simple linear regression analyses (Fig. 3) revealed that the total duration of ED during the EEG monitoring period significantly predicted overall cognitive ability (BIA) and explained 9.6% of the variance in cognitive test scores (standardized β coefficient = −0.33, adjusted $R^2 = 0.096$, $F(1, 67) = 8.2$, $p = 0.005$). Total duration of ED significantly predicted memory function (Glr) and explained 11.8% of the variance of scores (standardized β coefficient = −0.36, adjusted $R^2 = 0.118$, $F(1, 67) = 10.03$, $p = 0.002$). Short-term memory ability was not significantly predicted by total duration of ED.

The influence of the covariates of epilepsy duration, AED polytherapy, AED type, history of absence seizures, days since last GTCS, and seizure-free duration was examined using standard multiple regression analysis to predict the two significant outcomes: overall cognitive ability and new-learning and memory (all ps > 0.05).

As expected, lower education level (less than 12 years of schooling) significantly predicted lower overall cognitive ability; however, this did not account for the significance or magnitude of prediction by epileptiform discharge duration (education level standardized β coefficient = −0.35, t = −3. 27, p < 0.01). Educational level accounted for an additional 12.42% above 10.94% accounted for by ED duration. Order of entry into the hierarchical regression did not significantly alter these results. Lower education level was not a significant covariate in the prediction of memory function (p > 0.05).

Table 1
Patient characteristics.

Age (years)	Range 11–58 Mean 28.6 (11.5)
Gender (n)	M n = 23 (33%) F n = 46 (67%)
Syndrome (n)	CAE n = 8 (12%) JAE n = 19 (27%) JME n = 19 (27%) GTCSO n = 21 (30%) Other n = 2 (3%)
Current AED (n)	None n = 6 (9%) 1 n = 32 (46%) >1 n = 31 (45%)
History of absence seizures (n)	No n = 35 (50%) Yes n = 34 (50%)
History of GTCS (n)	No n = 8 Yes n = 61
Days since last GTCS	Range 3–9855 days Mean 1175 days (5813)
Age of epilepsy onset	Range 2–26 Mean 13.1 years (5.2)
Seizure-free duration	Range 1–9855 days Mean 737 days (1555)
Epilepsy state	Active n = 50 Remission on AED n = 17 Remission off AED n = 2

Percentages have been rounded to 1 decimal place.
CAE: Childhood absence epilepsy.
JAE: Juvenile absence epilepsy.
JME: Juvenile myoclonic epilepsy.
GTCSO: Genetic generalized epilepsy with generalized tonic–clonic seizures (GTCS) only.
AED: Antiepileptic drug.

Table 2
EEG and cognitive functioning.

Total duration ED of any length in 24 h (s)	Range 0–1248 Mean 101.7 (209.0)
Total duration ED ≥ 2 s in 24 h (s)	Range 0–1076 Mean 57.6 (178.3)
Total number ED of any length in 24 h	Range 0–319 events Mean 50.7 (70.0) None n = 7 (10.1%)
Total number ED in 24 h ≥ 2 s	Range 0–150 events Mean 21.4 (29.4) None n = 32 (46.4%)
Duration of individual ED (s)	Mean 1.4 (1.3) Range 0.4–8.3
Number events recognized by patient	Total 3 (0.01% of events ≥2 s)
Brief Intellectual Ability	Range 63–119 Mean 92.4 (11.8)
Anterograde memory	Range 41–112 Mean 86.3 (13.9)
Short-term memory	Range 74–141 Mean 102.4 (17.6)

Note: cognitive functioning is displayed in standard scores: Mean: 100; SD: 15.
ED: Epileptiform discharge.
Total duration of ED refers to the cumulative duration of all ED recorded during the 24-hour period.
Total number of ED refers to the count of all ED recorded during the 24-hour period.

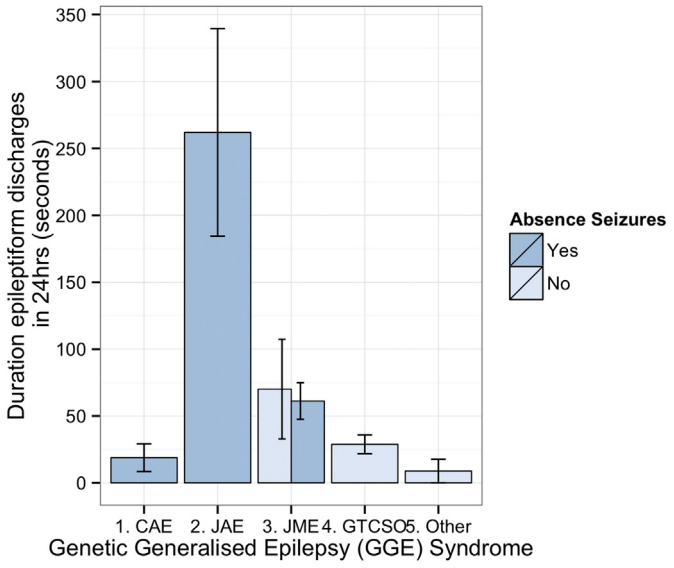

Fig. 1. Duration of epileptiform discharges by GGE syndrome and history of absence seizures (±standard error). Duration of epileptiform discharges was greatest for JAE patients.

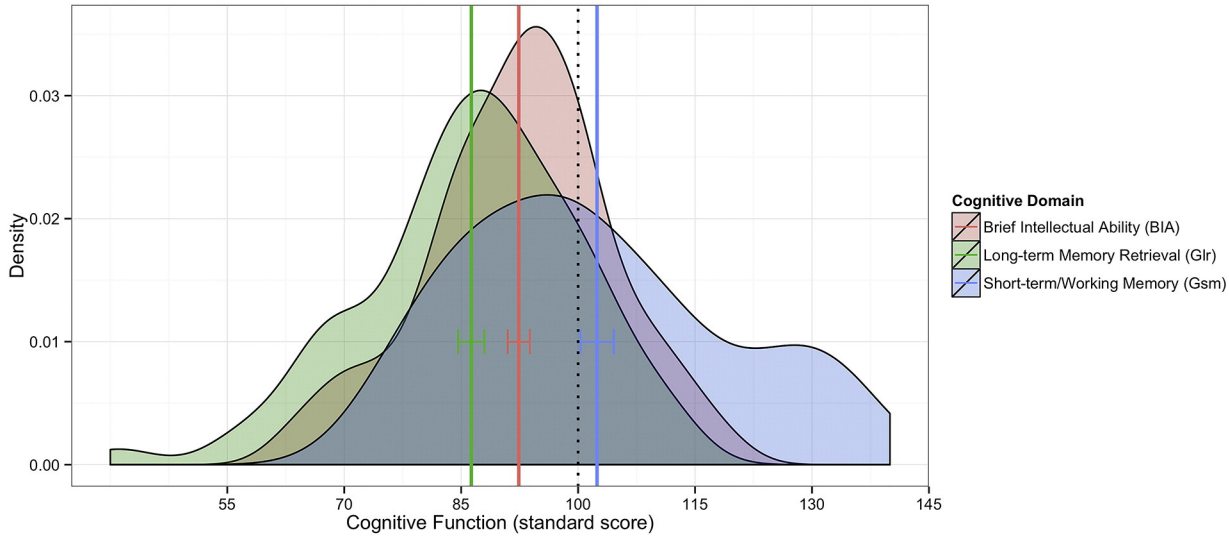

Fig. 2. Distribution of cognitive ability in GGE. Fig. 2 shows reduced overall cognitive ability and new learning and memory but not short-term memory function in GGE patients relative to age-based normative data. The age-based mean is denoted by the red vertical line through the standard score of 100. The color-coded mean (with standard error bars) and a smoothed kernel distribution plot of each cognitive domain show the distribution of scores. The y-axis quantifies the density of each score (0–1). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Having established our primary hypotheses, we conducted follow-up analyses to explore the relationship between the number of discharges and cognitive function. See Table 3 for statistical details of all subsequent analyses. The total number of discharges significantly predicts a small proportion of overall cognitive ability while there was a trend towards total number of discharges predicting a small proportion of memory function. Short-term memory ability was not significantly predicted by total number of ED. Multiple linear regression analyses to examine effects of clinical covariates in conjunction with total number of discharges as predictor were not undertaken due to the weak effects from the simple linear regression.

We also considered the differential impact of total duration of ED during wakefulness and sleep. Epileptiform discharges during wakefulness significantly predicted a small proportion of variance of BIA while ED during sleep predicted a larger proportion of the variance. The inverse pattern was true of prediction of Glr scores, with total duration of discharges during wakefulness accounting for a larger proportion of memory function than those during sleep. These models were not compared statistically.

Post-hoc comparison of ED in those 22 patients who had concurrent EEG and cognitive assessment revealed that only two of these showed ED during cognitive assessment, and that the ED duration during testing was comparable to the average duration experienced by each of these patients throughout the remainder of their EEG. Further, there were no significant differences between cognitive test scores for the group with concurrent EEG and the group who was not assessed concurrently (details available in Supplementary Table 2). This was not consistent with a potential precipitating effect of cognitive testing which is one documented cause of EEG changes in a proportion of GGE patients [23].

All regression analyses satisfied assumptions of linear regression analysis, namely normality of distribution of residuals, heteroscedasticity, skewness, kurtosis and multicollinearity. Details and illustrative QQ plots are available in Supplementary material (Supplementary Table 3 and Supplementary Figs. 1 and 2, respectively).

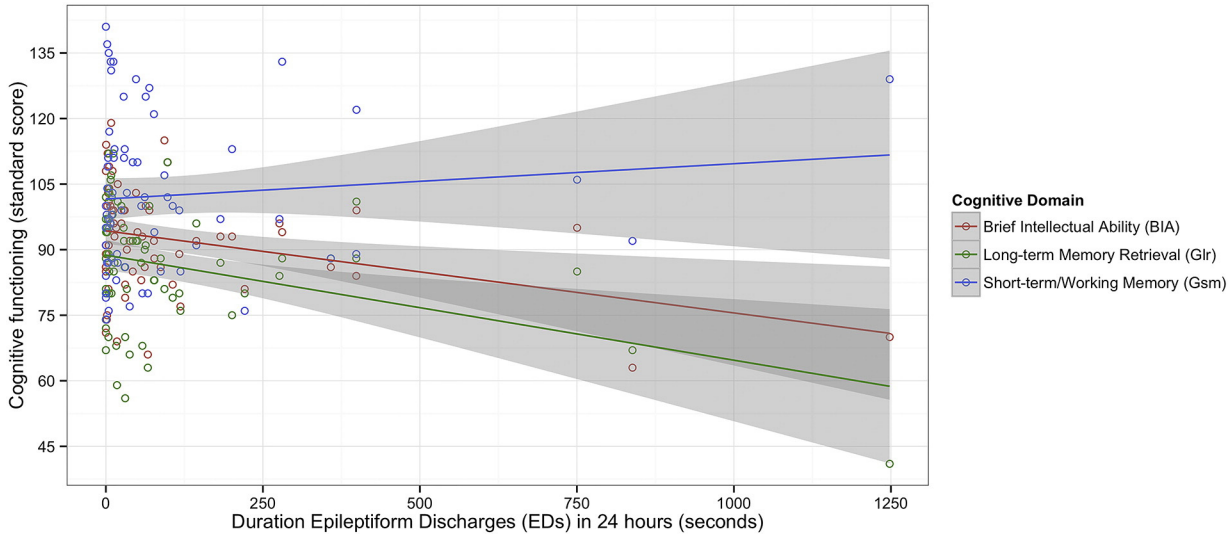

Fig. 3. Prediction of cognitive ability outcomes by duration of ED (linear regression).

Table 3
Standard simple and multiple regression predicting cognitive ability from number of ED and total duration (during wakefulness and sleep).

	β	SE	R^2	F	df	p
Cognitive domain	Number of epileptiform discharges					
Brief Cognitive Ability	−.247	0.020	.047	4.368	(1,67)	.040*
New learning and memory	−.234	0.024	.041	3.898	(1,67)	.052
Short-term memory	−.007	0.030	−.014	.055	(1,67)	.814
	Total duration of epileptiform discharges during wakefulness					
Brief Cognitive Ability	−.268	0.011	.058	5.19	(1,67)	.026*
New learning and memory	−.373	0.013	.126	10.84	(1,67)	.0016**
	Total duration of epileptiform discharges during sleep					
Brief Cognitive Ability	−.348	0.013	.108	9.254	(1,67)	.003**
New learning and memory	−.288	0.016	.069	6.07	(1,67)	.016*

β = Standardized beta; SE = Standard error of the beta coefficient; R^2 = Adjusted R^2.
* $p < .05$.
** $p < .01$.

4. Discussion

4.1. Key findings

The results of our study demonstrate that increased cumulative duration of ED over 24 h was predictive of reduced overall cognitive function and memory in GGE. This relationship does not appear to be explained by lifetime or current history of absence seizures, days since last GTCS, epilepsy duration, AED type or AED polytherapy, or other known threats to cognitive function in epilepsy. Further, the vast majority of even relatively long ED of at least 2 s (99.9%) were asymptomatic. No association was observed between ED and short-term memory function, which was at an age-expected level in our sample. Cumulative duration of ED during sleep explained a greater proportion of variance associated with an estimate of IQ than duration during wakefulness, while the inverse was true of long-term memory function.

The finding that scores on short-term memory tests were not reduced is surprising given that this is a commonly reported deficit in epilepsy. However, a recent meta-analysis of cognition in GGE shows that although on average, short-term memory can be reduced by 0.48–0.90 standard deviation units, consistent with our findings, approximately one third of studies did not reveal a reduction in short-term memory function in their GGE samples [3].

The large majority of studies examining EEG and cognition to date have investigated so-called "transient cognitive impairment" (TCI), a real-time disruption of reaction time and sustained attention caused by ED or seizures [2,7]. Although replicated in CAE groups, it is noted that TCI in other syndromes remains a controversial finding, with null results reported by a number of studies [8,24–26]. The aim of this study was not to examine this transient phenomenon; however, in order to consider this hypothesis, a subsample of 22 patients undertook cognitive assessment during the EEG recording period. Epileptiform discharges occurred during the assessment in only two of these patients, making it unlikely that real-time disruptions to attentional or other cognitive processes explain our findings. Further, as mentioned above, we did not find any relationship between short-term memory and ED, a cognitive function which is particularly susceptible to TCI [27].

In addition, our finding of impairment in more stable cognitive processes that rely on systems developed over the longer term suggests that ED are related to more enduring deficits. The observed relationship may reflect the critical impact of ED at three overlapping time points: 1) during sensitive periods of cognitive development in these child and adolescent onset epilepsies, 2) ongoing disruption to cognition throughout the course of the disease, or 3) as a cumulative source of neural damage and potential cognitive deterioration. The fact that GGE is not known to be associated with a deteriorating course and the independence of disease duration in our results provides weight towards the first, developmental model of cognitive dysfunction, that is, disruption to the development cognitive processes and skills during childhood and adolescence. This has important implications for treatment efforts, which may need to occur more intensively during a critical period of development, or which may benefit the patient equally at any point in life.

It is possible that the finding of differential relationship of IQ and ED during sleep, and memory and ED during wakefulness reflects the long-term impact of under-recognized epileptiform abnormalities during sleep. We have demonstrated that most ED go unrecognized by the individual in whom they are occurring — although there may, of course, be signs that are apparent to a careful observer, especially when interacting with a patient. In this case, and given that routine EEG is obtained more frequently than overnight or longer ambulatory monitoring, it is quite possible that ED occurring during sleep are even less recognized than those during wakefulness. They may, therefore, have been occurring undetected for an extended period of time and represent a source of disruption to the development of the broad cognitive skills encompassed by IQ. However, this requires replication and we hesitate to emphasize this relatively small finding.

A question that may be raised when considering these findings is the issue of what exactly the ED represents. The distinction between ED as interictal activity, compared with those considered "subclinical seizures" or indeed seizures, is arbitrary [28]. In 37 of our patients, events of 2 or more seconds in duration were observed, thus, meeting commonly used electrophysiological definitions of seizure activity [29]. However, the accompaniment of an EEG event with a clinical sign or symptom is both a formal and working definition of a seizure [30]. The use of concurrent video monitoring may elucidate any subtle behavioral signs of recorded ED. However, in practical and clinical terms, the distinction between interictal and ictal may be inconsequential and purely a matter of measurement precision. Importantly, only two of our patients reported experiencing seizure symptoms during these recorded paroxysms, accounting for less than 0.01% of all recorded discharges of 2 s or longer. The real issue at hand is that ED appear to be below the threshold of subjective awareness, so patient reported or caregiver-observed seizures may not be a sufficient measure of disease burden. That these electrophysiological events are associated with reduced cognitive function is sufficient to warrant further investigation, even if they are only apparent on EEG [31].

An alternative explanation is that these findings represent epiphenomena of the underlying disease process or shared genetic predisposition for epilepsy and reduced cognitive function, a recently debated topic [32,33]. There is some evidence for cognitive reductions in unaffected first-degree relatives of people with GGE, providing some support for a genetic underpinning of cognitive findings in these epilepsies [34–36]. Although not as comprehensively examined with 24-hour recordings, ED have also been observed in unaffected siblings, making it difficult to exclude the possibility of a causative role of these in compromising cognitive processes [37,38]. An extension of our detailed EEG and neuropsychology measurement protocol to a sibling sample may enable the appraisal of these possibilities in future research.

4.2. Strengths

This study builds on existing knowledge regarding negative relationships between ED and cognition with a number of methodological enhancements [6,8,9]. The most significant of these is the precise quantification of ED during the 24-hour recording period, rather than an estimation of ED in a shorter time frame. To our knowledge, this is the first time that quantified 24-hour EEG was completed according to a uniform protocol and used prospectively to investigate the association between ED and cognition. This extended recording enables the capture of ED during natural sleep as well as wakefulness and ensures that epileptiform variations with daily activity, as well as with circadian rhythms, are comprehensively sampled. An additional strength lies in

the detailed measurement of primary cognitive domains beyond reaction time and attention using a valid and reliable battery of tests [39].

Finally, our prospectively recruited sample was a well-characterized cohort comprised exclusively of patients with GGE syndromes, meaning that our findings pertain specifically to this group of common syndromes [15,16]. Our relatively large sample size enabled the inclusion of covariates to examine the possible influence of other explanatory variables.

4.3. Limitations

One downside to the naturalistic setting that ambulatory EEG monitoring affords is that, in the absence of concurrent video monitoring, we are unable to definitively exclude the possibility of transient cognitive effects of ED or to observe the possible occurrence of subtle behavioral manifestations of ED and better classify these as interictal or ictal in traditional terms. Also, ED occurrence may vary on a daily basis, and we have only sampled a single 24-hour period. We were also unable to draw conclusions regarding the impact of patient-reported seizures and ED on cognition due to this cohort's relatively well-controlled epilepsy, with mean reported seizure-free duration in excess of 2 years.

Future research would benefit from longitudinal follow-up beginning at the point of disease onset in order to assess the trajectory of risk from ED and other epilepsy factors and to elucidate a possible trajectory underlying our cross-sectional findings such as a developmental model of ED-related cognitive dysfunction. This has important implications for treatment which may need to occur more intensively during a critical period of cognitive development or which may benefit the patient even at later stages of life.

4.4. Implications of the findings

Seizure management is subject to patient- and clinician-reporting bias and does not take into consideration all the explanatory and predictive factors relating to disease burden and psychopathological comorbidities [40]. In combination with previously reported findings, these data raise the possibility that the focus of treatment practices should, therefore, extend beyond the traditional goal of managing seizures. Impaired cognition is a particularly under-recognized, adverse prognostic outcome in epilepsy, despite the known relationship between cognitive status, educational and vocational opportunity and success, quality of life, and mental health [28].

4.5. Conclusion

Our study documents a possible contributing factor for reduced cognitive function in GGE syndromes. These findings raise important questions regarding whether EEG epileptiform discharge burden, even in the absence of reported seizures, should be considered “high risk” for comorbidities warranting consideration of AED therapy. This represents a paradigm shift from our current focus exclusively on seizure management in GGE. Our findings provide a rationale for the investigation of ED as a potential marker for psychosocial comorbidities of GGE. Further, this study demonstrates that information from 24-hour EEG has the potential for prognostic as well as diagnostic applications to stratify the risk of cognitive dysfunction.

At a public health level, a greater understanding of the significance and relevance of ED will assist in mitigating the burden of epilepsy given that cognitive dysfunction occurs in an estimated 25% of people with GGE. Epileptiform discharges have also been implicated in other neurological conditions such autism, attention deficit hyperactivity disorder, and language disorders [11]. Examining the occurrence of ED in these conditions and healthy control groups may contribute to an understanding of the role of altered electrophysiological states on cognitive disorders more broadly.

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Author contributions

Loughman, A., Seneviratne, U., Bowden, S.C. and D'Souza, W.J.

WD conceived and designed the study. US designed and conducted EEG analyses. SB and AL selected the tests of cognitive function and the data analysis strategy. AL conducted the data analysis. AL and US drafted the manuscript. All authors discussed the results and implications, and commented on the manuscript at all stages.

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Chapter 9: Self and Informant Report Ratings of Psychopathology in Genetic Generalised Epilepsy

The previous Chapter presented the final analyses regarding cognitive functioning in GGE, examining the association between cognitive outcomes and clinical characteristics, epileptiform discharges in particular. Having established the nature of cognitive functioning in GGE, areas of deficits and possible contributing factors in Chapters 7 and 8, the reader is now invited to peruse the findings regarding psychosocial function, the other key topic of this thesis. In this Chapter, psychopathology signs and symptoms are examined, as rated by people with GGE and their friends and relatives. The differences between self- and informant- report are assessed, resulting in recommendations for optimal screening practices. This chapter was published in the journal *Epilepsy & Behavior*. Supplementary materials accompanying this publication are presented in Appendices 16 to 18. Secondary findings regarding adaptive functioning and substance-use are presented in Appendices 19 and 20.

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Self and informant report ratings of psychopathology in genetic generalized epilepsy

Amy Loughman [a,b,*], Stephen C. Bowden [a,c], Wendyl J. D'Souza [d]

[a] Melbourne School of Psychological Sciences, University of Melbourne, Parkville, VIC 3010, Australia
[b] School of Health & Biomedical Sciences, RMIT University, PO Box 71, Bundoora, VIC 3083, Australia
[c] Department of Clinical Neurosciences, St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia
[d] Department of Medicine, St Vincent's Hospital, The University of Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia

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ABSTRACT

The psychological sequelae of genetic generalized epilepsies (GGE) is of growing research interest, with up to a third of all adults with GGE experiencing significant psychiatric comorbidity according to a recent systematic review. A number of unexplored questions remain. Firstly, there is insufficient evidence to determine relative prevalence of psychopathology between GGE syndromes. Secondly, the degree to which self-report and informant-report questionnaires accord in adults with epilepsy is unknown. Finally, while epilepsy severity is one likely predictor of worse psychopathology in GGE, evidence regarding other possible contributing factors such as epilepsy duration and antiepileptic drugs (AEDs) has been equivocal. The potential impact of subclinical epileptiform discharges remains unexplored.

Self-report psychopathology symptoms across six DSM-Oriented Subscales were prospectively measured in 60 adults with GGE, with informant-report provided for a subset of 47. We assessed the burden of symptoms from both self- and informant-report, and the relationship between clinical epilepsy variables and self-reported symptoms.

Results showed elevated symptoms in almost half of the sample overall. Depression and anxiety were the most commonly reported types of symptoms. There was a trend towards greater symptoms endorsement by self-report, and relatively modest interrater agreement. Symptoms of ADHD were significantly positively associated with number of AEDs currently prescribed. Other psychopathology symptoms were not significantly predicted by epilepsy duration, seizure-free duration or total duration of epileptiform discharges over a 24-hour period.

The high prevalence of psychological needs suggests that routine screening of psychopathology and provision of psychoeducation may be essential to improving patient care and outcomes. Further investigation is required to better understand predictive and causal factors for psychopathology in GGE.

1. Introduction

The cognitive, psychological, and psychosocial sequelae of the genetic generalized epilepsies (GGE) is a topic of recent research interest, with accumulating evidence suggesting that GGE is not the benign condition as once thought [1,2]. A recent systematic review found that clinically significant psychiatric comorbidity may occur in up to half of all children and a third of all adults with the condition [3]. As is the case with psychiatric symptoms in the general population, the most common comorbidities in adults with GGE were depression and anxiety, followed by conditions such as addiction, impulse control, and psychotic disorders [3,4]. It is unclear whether this survey encompasses the full burden of undiagnosed and untreated dimensional psychopathological symptoms or is limited to patients with existing diagnoses, since many studies did not prospectively measure symptoms.

The significance of these outcomes for quality of life in epilepsy is well-recognized, and improving these patient outcomes has become an important clinical goal [5,6]. Indeed, several authors have posited that psychological and behavioral comorbidities such as mood disorders are intimately related to the epilepsy, and that the relationship is best understood as bidirectional; i.e. epilepsy is a risk factor for mood disorder and mood disorder is a risk factor for epilepsy [7,8]. While a neurobiological underpinning to psychopathology is considered likely, specific causal relationships are rarely identified, which may be due - at least in part - to the heterogeneity of epilepsy as a condition and that studies have mostly focused on epilepsy-related risk factors [9]. Epilepsy severity has been identified as one likely predictor of poor

* Corresponding author at: Melbourne School of Psychological Sciences, University of Melbourne, Australia.
E-mail address: amy.loughman@unimelb.edu.au (A. Loughman).

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psychosocial outcomes in adults with GGE, with findings of other factors such as longer epilepsy duration and antiepileptic drug (AED) treatment proving equivocal - both negative and null associations with psychopathological outcome have been reported [3]. Finally, while subclinical epileptiform discharges (ED) are known to disrupt cognitive functioning in epilepsy and bear a relationship to depression in epilepsy [10,11], their potential role in mood and psychosocial functioning in GGE and other epilepsies remains unexplored.

In a large, prospectively recruited sample of adults with GGE, we aimed to a) assess the burden of psychopathology across different symptom types on the basis of both categorical and dimensional outcomes; b) consider a self- and informant-report version of a comprehensive symptom severity questionnaire; c) examine the relationship between ED and other clinical variables and psychopathological symptom ratings. On the basis of previous research, we anticipated that the questionnaire would identify a 30% prevalence of people with GGE vulnerable to psychopathological comorbidity.

2. Methods

2.1. Participants and procedure

As part of a larger study regarding the prognosis and EEG characteristics of GGE [12], adults with EEG-confirmed GGE completed the Adult Self-Report form of the Achenbach System of Empirically Based Assessment. We established the diagnosis of GGE and classified patients into childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized epilepsy with generalized tonic-clonic seizures (GTCS) only (GTCSO) according to ILAE criteria [13,14]. Patients who did not fulfill the criteria of the four major syndromes were classified as "GGE unspecified". All medical records including EEG and neuroimaging were reviewed independently by two epilepsy specialists (authors WD & US) with any discordance on diagnosis resolved by consensus based on ILAE criteria. The Achenbach System comprises screening questionnaires that produce DSM-Oriented Subscales that are designed to be consistent with DSM-IV diagnostic criteria for depression, anxiety, somatization, avoidant personality, attention deficit, and antisocial personality [15]. The Achenbach System is intended to screen for these domains of functioning, not to provide psychiatric diagnosis such as that resulting from a structured clinical interview. Participating patients were asked to provide the Adult Behavior Checklist, the informant version of the same form, to a partner or close friend to complete. Frequencies of elevated symptoms in the GGE sample were contrasted with 7% prevalence in the normative sample of the Achenbach measure. Cognitive functioning data were collected using the Woodcock Johnson III Tests of Ability [16] and compared to Australian age-based norms provided by the test software.

History of psychiatric diagnosis and prescription of psychotropic medication information was collected from the medical record. Epilepsy history was collected according to the research protocol and included seizure type, frequency, epilepsy age of onset, and AED currently used. In addition, patients underwent 24-hour ambulatory EEG following standard protocol as previously described [12]. An experienced EEG reader (author US) reviewed all recordings with ProFusion 4 software (Compumedics Ltd., Melbourne, Australia). Ten-second pages were reviewed page-by-page on longitudinal bipolar montage with 0.5 to 70 Hz bandwidth. When an epileptiform abnormality was detected, detailed analysis of the waveform was undertaken on common average referential montage [17]. A measuring tool incorporated in the software was used to manually measure amplitude and duration of discharges.

Participants were excluded if they had another significant neurological condition, or structural abnormalities apparent on brain MRI. This research was approved by the Human Ethics Research Committees of participating sites. Participants provided written informed consent as per the Declaration of Helsinki.

2.2. Statistical analysis

To maximize the representativeness of the final dataset, data were retained from all participants, even if they were unable to provide an informant report questionnaire. The equivalence of the demographic characteristics of the group with both self- and informant- report available (the paired data group) and the total sample was evaluated using *t*-tests and chi-squared tests as appropriate. One sample *t*-tests with Bonferroni corrections were used to compare GGE scores with those of the Achenbach measure normative sample. Multivariate analysis of variance (MANOVA) tests on the paired data group were used to examine the concordance of self- and informant-report T-scores across the six DSM-Oriented Subscales and appropriately control for the family-wise error rate. Kappa statistics were calculated for comparison of interrater classifications of normal, borderline-clinical, and clinical range classifications. Finally, associations between epilepsy variables and psychopathology symptom endorsement were assessed using Spearman correlation coefficients and multiple linear regression. We used an alpha level of 0.05 for all statistical tests.

3. Results

3.1. Patient characteristics

Prospective recruitment yielded 60 people with EEG-confirmed GGE (18 males; mean age: 31.6, SD: 11.0). For a subset of 47, a family member or close friend also completed the corresponding Adult Behavior Checklist. The majority of informant-report questionnaires were completed by spouses/partners (43%), and parents or adult children (36%). Smaller proportions were completed by friends (8%), siblings (4%) or were not reported (9%). The group with both self- and informant-report data available (the paired data group) was compared to those with only self-report data available. A higher proportion of males was in the self-report only group than in the paired data group ($\chi 2\ (1) = 5.41$, $p = 0.02$). No other significant differences were found on any demographic or epilepsy variables to suggest that these groups differed systematically (see Supplementary Table 1 for these analyses). For this reason, subsequent analyses were conducted on the entire sample ($n = 60$).

Aside from a slight bias against CAE due to our predominantly adult sample, GGE syndromes were distributed approximately evenly within the sample (Table 1a). The majority of patients were prescribed AED treatment (95.2%), and 50% had a history of absence seizures (Table 1b). Seizure-free duration ranged from 1 to 9855 days (median: 129, interquartile range: 660 days). Detailed clinical data were unavailable from a small minority of patients (available *n* marked in Table 1b). A summary with one-sample *t*-tests comparing patient scores to age-

Table 1a
Demographic characteristics.

Variables	Total sample ($n = 60$)	Paired data ($n = 47$)	Unpaired self-report only data ($n = 13$)	Sig. (2-tailed)*
Age (years)				
Range	18–58	18–58	18–57	–
Mean (standard deviation)	31.62 (10.95)	31.11 (10.80)	33.46 (11.73)	NS
Gender (*n*)				
M	18 (30%)	18 (38.3%)	13 (100%)	$p = 0.02$
F	42 (70%)	29 (61.7%)	0 (0%)	
Syndrome (*n*)				
CAE	6 (10%)	6 (12.8%)	0 (0%)	
JAE	17 (28.3%)	13 (40.4%)	4 (30.8%)	
JME	16 (26.7%)	12 (25.5%)	4 (30.8%)	NS
GTCSO	20 (33.3%)	16 (34.0%)	4 (30.8%)	
Other	1 (1.7%)	0 (0%)	1 (0.8%)	

* These tests compare paired data group ($n = 47$) with self-report only group ($n = 13$) to establish equivalence of these.

Table 1b
Clinical information.

Current AED (*n*)	(*n* = 56)	(*n* = 43)	(*n* = 13)	
None	3 (4.76%)	1 (1.8%)	2	
1	27 (42.86%)	20 (36.4%)	6	NS
2	22 (33.33%)	26 (29.1%)	5	
3	4 (6.35%)	4	0	
	(*n* = 55)	(*n* = 42)	(*n* = 11)	
Valproate	35 (63.6%)	32 (76.2%)	3 (27.3%)	
Lamotrigine	20 (36.4)	15 (35.7%)	5 (45.5%)	
Levetiracetam	8 (14.5%)	7 (16.7%)	3 (27.3%)	–
Other (Topiramate, Zonisamide, Piracetam, Carbamazepine, Clonazepam)	8 (14.5%)	10 (23.8%)	5 (45.5%)	
Age epilepsy onset (years)	*n* = 60	*n* = 47	*n* = 13	
Range	2.5–31	2.5–31	8–24	–
Mean (standard deviation)	14.46 (5.62)	14.38 (5.94)	14.77 (4.60)	NS
Epilepsy duration (years)				
Range	1–46	0–46	2–33	–
Mean (standard deviation)	17.01 (12.24)	16.00 (12.61)	18.15 (11.29)	NS
History of absence seizures (*n*)	(*n* = 55)	(*n* = 42)	(*n* = 13)	
No	28 (50.9%)	19 (45.2%)	9 (69.2%)	NS
Yes	27 (49.1%)	23 (54.8%)	4 (30.8)	
History of GTCS (*n*)	(*n* = 58)	(*n* = 45)	(*n* = 13)	
No	5 (8.6%)	2 (4.4%)	3 (23.1%0	NS
Yes	53 (91.4%)	43 (95.6%)	10 (76.9%)	
Seizure free duration (days)	(*n* = 58)	(*n* = 45)	(*n* = 13)	
Range	1–9855	1–5110	1–9855	–
Median; IQR	129; 660.25	150; 463	92; 723	NS
Total duration EDs of any length in 24 h (s)	(*n* = 58)	(*n* = 45)	(*n* = 13)	
Range	0–835.5	0–835.5	0–750.3	–
Mean	91.23 (166.11)	76.15 (146.14)	143.4 (221.27)	NS

based Australian norms is presented in Table 1c. These comparisons, reported in further detail in a manuscript currently under review, show significant moderate to large reductions in overall cognitive ability.

3.2. Psychopathology symptom ratings

3.2.1. Frequency of borderline-clinical and clinical level of distress

The Achenbach measures define scores between T = 65 and T = 69 to correspond to 'borderline-clinical' range, and scores T > 69 to be 'clinical' range symptoms. This corresponds to the 93rd and 97th percentiles in the normative population respectively; thus 7% of the normative reference group would be expected to endorse borderline-clinical or clinical levels of distress in each DSM-oriented Subscale [15]. Twenty-five of the participants in the full sample (41.7%) self-reported borderline-clinical or clinical level symptoms on one or more of the six DSM-Oriented Subscales. In comparison, only 15 participants (25%) had a previous or currently diagnosed psychiatric illness. Of these previous or existing diagnoses, 14 (23.3% of full sample) were depressive disorders, eight (13.3%) anxiety disorders, one (1.6%) obsessive-compulsive disorder, and one (1.6%) eating disorder. Of the 15 people with an existing diagnosis, 11 had the provision of some form of treatment documented on their medical record (psychotropic medication or psychological treatment).

Fig. 1 depicts the relative frequencies of normal, borderline-clinical, and clinical levels of self- and informant-reported distress across each of the DSM-Oriented Subscales in the paired dataset. Between 15 and 28% of GGE respondents endorsed experiencing elevated levels of symptoms across the five most common categories: depressive, anxiety, somatic, avoidant personality, and attention deficit/hyperactivity symptoms. Anti-social personality problems were endorsed relatively less frequently (4%).

Depressive symptoms were the most commonly reported symptom type, with 28% of GGE respondents endorsing borderline-clinical or clinical degree of distress of this type, significantly more than expected on the basis of normative data ($\chi^2(2) = 13.98$, $p < 0.01$). Attention deficit and hyperactivity symptoms (ADH) were also significantly more common than in the normative reference group, with 22% endorsing a borderline-clinical or clinical level of symptom severity ($\chi^2(2) = 6.75$, $p = 0.03$). Attention deficit/hyperactivity symptom severity was not related to history of absence seizures or to particular GGE subtypes (all p's > 0.05). Anxiety, somatic symptoms, and avoidant personality problems were approximately equally prevalent, with 15%, 20%, and 16% of respondents scoring above the normal range, respectively. These proportions were not significantly higher than expected on the basis of the normative group.

On the basis of informant report, 0–25% of GGE patients scored within the borderline-clinical or clinical range across the DSM categories. Depression was the most frequently recognized type of distress by informants as well as by patients themselves. Avoidant personality signs were the next most commonly recognized, with 22% of patients scoring in the borderline-clinical or clinical range according to their informants. Anxiety, somatic, and ADH signs were endorsed by informants at 11%, 8% and 8% respectively. No informants endorsed signs of antisocial personality problems in their friend/relative with GGE.

3.2.2. Mean self- and informant-report T-scores on DSM-oriented subscales

Table 2a and Fig. 2 illustrate the mean T-scores by self and informant raters on each of the six DSM categories. The normative mean is T = 50, and the borderline-clinical range corresponds to T = 65 (>93rd %ile). A series of Bonferroni-corrected one-sample *t*-tests revealed that self- and informant rated mean scores were significantly above the normative mean for all DSM-Oriented Subscales (see Table 2b). A multivariate analysis of variance (MANOVA) test revealed no significant differences between self- and informant-reports of signs and symptoms on any of the six DSM-Oriented Subscales when accounting for the family-wise error rate using this statistic ($F(6,86) = 2.10$, $p = 0.06$). As this *p*-value shows, there is a trend towards differences between self- and informant-report mean scores on Anxiety, Somatic, and ADH subscales, which is also reflected in non-overlapping error bars in Fig. 2.

Fig. 1 illustrates higher frequency of borderline-clinical or clinical level symptom endorsement than in the normative sample, and Fig. 2 shows mean scores significantly above the normative mean, together reflecting high levels of psychological distress across all DSM categories in this GGE patient group.

Table 1c
Cognitive functioning.

Cognitive domain	GGE sample		Normative group		95% CI for mean difference	t (df)	P	Sig.
	M	SD	M	SD				
Overall ability (BIA)	94.64	11.00	100	15	91.51–97.77	−3.45	<0.01	**
Crystallized intelligence (Gc)	94.44	10.83			91.36–97.52	−3.63	<0.001	***
Fluid intelligence (Gf)	98.32	11.56			95.03–101.61	−1.03	0.31	–
Long-term retrieval and memory (Glr)	89.24	12.31			85.74–92.74	−6.18	<0.001	***
Short-term/Working memory (Gsm)	102.69	15.61			98.21–107.17	1.21	0.23	–
Speed of information processing (Gs)	92.47	9.88			89.66–95.28	−5.39	<0.001	***

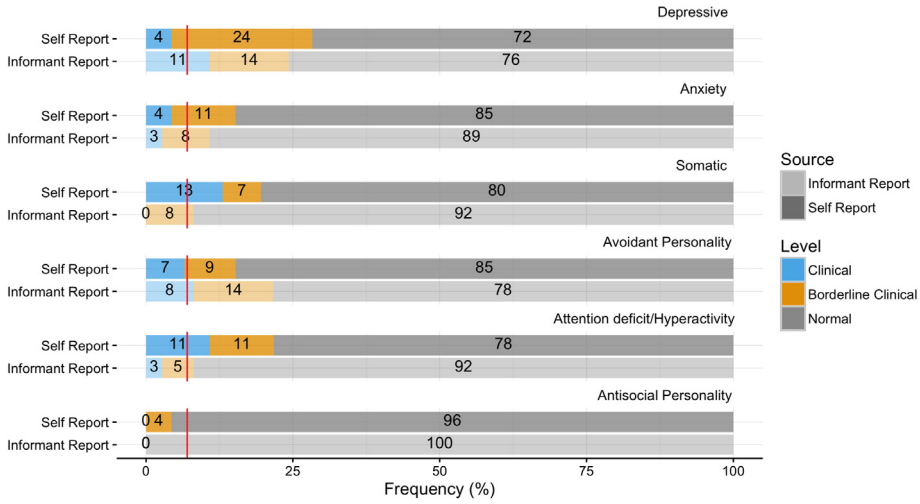

Fig. 1. Rates of borderline-clinical and clinical signs and symptoms in paired data group. Borderline-clinical and Clinical levels of distress of Depressive and Attention deficit/Hyperactivity symptoms are significantly higher than that of the normative sample (7%; denoted by the red vertical line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Concordance between self- and informant-report

Table 3 displays squared-weighted kappa statistics (K) representing the degree of categorical agreement between self- and informant-report ratings leading to normal, borderline-clinical, and clinical categories for five of the six DSM-oriented scales. The kappa K for Antisocial Personality could not be calculated due to the rarity of this symptom. The squared weighting takes into account the ordinal nature of the levels of symptom endorsement, and considers the distance between discrepant ratings. For example, the difference between normal and clinical ratings is greater than between borderline-clinical and clinical ratings. Based on Cohen's guidelines of interpretation of magnitude of agreement between observers using Kappa, agreement between self- and informant-report scoring can be interpreted as 'slight' (Depressive, Anxiety, ADH Subscales) to 'fair' (Somatic and Avoidant Subscales) [18,19].

3.4. Predictors of psychosocial dysfunction

Bivariate scatterplots for each of the DSM-Oriented Subscales with epilepsy characteristics revealed non-normal relationships (see Supplementary Figs. 1–6). A moderately large, positive significant Spearman correlation was observed between number of AEDs currently prescribed and ADHD symptoms ($r = 0.30$, $p = 0.024$; Table 4). To ensure that a potentially significant predictor was not missed, forward stepwise multiple regression analyses were conducted using three other clinical variables (seizure-free duration; epilepsy duration; total duration of ED over 24 h) as predictors of each DSM-oriented subscale but none were significant (see Supplementary Table 2).

Table 2a
Self- and Informant-report scores on DSM-Oriented Subscales.

	Self-report		Informant-report	
DSM-oriented subscale	M	SD	M	SD
Depressive	58.89	7.90	58.30	7.78
Anxiety	57.74	7.76	54.96	6.03
Somatic	59.37	9.02	56.30	5.79
Avoidant	58.07	8.20	57.26	7.04
ADHD	59.17	7.44	56.22	5.82
Antisocial personality	53.96	5.03	52.68	3.74

4. Discussion

The results of this study indicate a high prevalence of self-reported and informant-reported psychopathology across all six DSM-Oriented Subscales. Almost half of our sample endorsed experiencing levels of symptomatology in the borderline-clinical or clinical range on one or more of the Subscales. This contrasted with approximately 18% who had previously or were currently being treated for a psychiatric condition. Depressive symptoms were the most common, with up to 28% of the GGE participants reporting borderline-clinical or clinical range symptoms. All symptom types were endorsed at a higher rate than in the normative sample by both self- and informant-report. Anxiety, somatic, avoidant personality, and ADH symptom ratings were also elevated relative to normative sample rates. The average T-scores of the GGE sample were above the normative mean on all DSM-Oriented Subscales. These rates of symptoms are comparable to those of similar studies in a recent systematic review, and elevated compared to those reported in studies citing rates of existing diagnoses (rather than those prospectively measured) [3]. For example, the only study of adult patients with GGE across subtypes to use validated psychopathology measures included in that review reported psychiatric diagnosis in

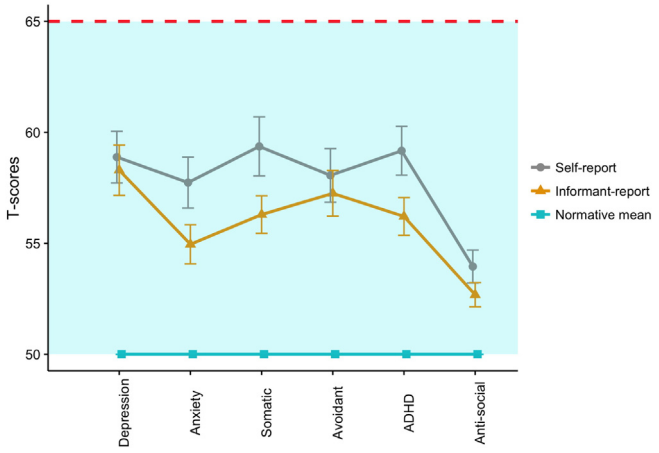

Fig. 2. Mean and standard error of the mean of self- and informant-report ratings of each DSM-oriented subscale (paired data group; $n = 47$). Mean scores across all symptom ratings were above the normative mean of T = 50 and below the borderline-clinical cut-off score of 65.

Table 2b
One-sample *t*-tests comparing self- and informant-report scores to normative mean (T = 50).

	95% CI (T-score)			*n*	t	df	Sig. (2 tailed)
Self-report DSM-oriented subscale							
Depressive	56.59	–	61.48	60	7.40	58	$p < 0.001$
Anxiety	55.48	–	59.51		7.44		$p < 0.001$
Somatic	56.35	–	61.38		7.06		$p < 0.001$
Avoidant	56.00	–	60.44		7.40		$p < 0.001$
ADHD	56.93	–	61.21		8.47		$p < 0.001$
Antisocial personality	52.81	–	56.31		5.22		$p < 0.001$
Informant-report DSM-oriented subscale							
Depressive	56.01	–	60.58	47	7.31	46	$p < 0.001$
Anxiety	53.19	–	56.73		5.64		$p < 0.001$
Somatic	54.60	–	58.00		7.45		$p < 0.001$
Avoidant	55.19	–	59.32		7.07		$p < 0.001$
ADHD	54.50	–	57.92		7.32		$p < 0.001$
Antisocial personality	51.58	–	53.78		4.92		$p < 0.001$

26% of their sample [4]. Similar high rates of psychopathology were observed in adult JME samples, such as that reported by Perini and colleagues with a diagnosis rate of 22% [20]. In comparing the findings of the current study with these previous studies, it is noted that the screening tool used in the current study was not equivalent to a DSM diagnosis obtained by a method such as structured clinical interview as presented by some of the previous research.

On the basis of informant-report, a lower proportion of patients had scores in the borderline-clinical or clinical range across all Subscales (Figs. 1 and 2). There was relatively low concordance between raters, particularly in Depressive, Anxiety, and ADHD Subscales (Table 3), suggesting that information regarding psychosocial functioning of GGE patients differs depending on the provider of the information. This finding broadly replicated population-level surveys, which showed modest cross-informant correlations, and greater concordance with externalizing problems (e.g. aggressive behavior; hyperactivity) relative to internalizing emotional distress (e.g. depression and anxiety) [21]. We found a trend towards increased sensitivity of self-reported ratings relative to informant-reported ratings (Table 2a and 2b; Figs. 1 and 2). Comparison of these findings with objective assessment by mental health professionals would be required to ascertain the relative reliability of self- and informant-report. However one implication of our findings may be that recognition of distress by the close friends and relatives around people with GGE could be improved. While self-report measures may therefore be the optimal method of screening for psychopathology, informant-report from a close friend or relative should be considered a suitable alternative in the event that self-report is unavailable or unsuitable, since at least in direction if not in magnitude, informant-report mirrors self-reported symptom ratings.

Attention deficit/hyperactivity disorder symptoms were positively associated with the number of AEDs in current use. This finding accords with a previously reported association between polytherapy and worse ADHD symptoms in studies of children and those with epilepsy and severe intellectual disability [22,23]. Specific AEDs may also have differential impacts on attention deficit symptoms, with some known to improve symptoms (e.g. lamotrigine, carbamazepine) and others to have exacerbating effects (e.g. phenobarbital, gabapentin, topiramate), although individual responses vary significantly [24]. It is worth noting that few of our patients were on any of these agents, and none were being prescribed AEDs for the purpose of alleviating mood or psychiatric symptoms. It is therefore unlikely that any relationship between symptoms and AEDs is due to reverse causality. However, it is possible that some behavioral features occurring with higher prevalence in ADHD such as insomnia and substance use may contribute to seizure frequency and therefore to increased need for AED treatment. There may also be pharmacokinetic interaction effects or general dose-related neurotoxicity that may be underlying the relationship with polytherapy. Further research conducted in larger samples should investigate potential interactions or cumulative side-effects of AEDs, and attempt to separate these effects from other factors associated with polytherapy (such as seizure severity).

Table 3
Interrater concordance.

Agreement between self- and informant-report ratings $n = 47$			
Subscale	Kappa κ	*p*-Value	Magnitude
Depressive	0.19	0.17	slight
Anxiety	−0.1	0.47	slight
Somatic	0.33*	0.02	fair
Avoidant	0.39*	<0.01	fair
ADHD	0.37*	<0.01	fair
Antisocial personality	N/A	N/A	N/A

* $p < 0.05$

We found no evidence to suggest that the duration of seizure freedom, duration of epilepsy (representing cumulative effect of disease) or epileptiform discharges are related to mood disorders in GGE, once again prompting further consideration of other potential risk factors for psychopathology. These risk factors may include more general predisposing and precipitating factors such as family history, and situational and lifestyle factors [11]. The measurement of these broader risk factors in future research may assist in delineating possible interactions between these and clinical epilepsy variables, and inform the priorities for clinical therapeutic practices.

Alongside increased prevalence of psychopathology in GGE, cognitive deficits are also common [2]. While it is possible that attention deficit psychopathology symptoms such as those observed in the current cohort are due to impaired cognitive functioning such as working memory, this hypothesis is not supported by the data in Table 1c showing intact short-term/working memory relative to age-based local norms.

The investigation of the clinical relevance of ED to psychopathology in GGE is novel. This study did not reveal any evidence for a relationship between burden of ED and retrospective report of symptom severity in the previous 6 months. However, it should be noted that we did not measure acute mood states, nor did we have a concurrent EEG and mood measurement design such as that used to measure ED and cognition [25]. Our null findings do not exclude the possibility that ED may have different importance on acute mood states, in other epilepsy syndromes, or in people with a greater ED burden. Only 33% of our sample experienced >60 s of discharges over the 24-hour recording period. The possible impact of ED on psychopathology has not been examined in generalized epilepsies or in adults. However findings from other conditions are suggestive of a relationship between ED and psychopathology. In children with ADHD (without epilepsy), a higher prevalence of sleep ED is reported, with greater burden of focal than generalized spike-wave discharges (as seen preferentially in the present GGE sample) [26]. In another pediatric sample, a double-blind placebo-controlled trial of the use of AEDs for reduction of interictal epileptiform discharges (IEDs) found that behavioral disturbances were significantly improved in children with focal epilepsy when IEDs were reduced [27]. We did not find evidence for such a relationship between ED and mood in adults with generalized epilepsies.

A limitation of this study is the lack of a demographically-matched healthy control group, which would have been preferable to the age-matched normative data provided by the Achenbach software program that was used. Further, the unavailability of detailed clinical and EEG data from approximately 10% of patients meant that the sample size was reduced for these analyses. The measurement of psychopathology symptoms in this study using a well-validated comprehensive symptom checklist provided breadth, and the benefit of comparing two perspectives (patient and informant). However the Achenbach questionnaires used in this study were not administered alongside a structured psychiatric interview (the current gold-standard) and can be considered a detailed screening tool rather than a diagnostic instrument. It is also noted

Table 4
Spearman correlation coefficients.

Spearman correlations between DSM-Oriented Subscale scores and clinical variables						
	Depressive	Anxiety	Somatic	Avoidant	ADHD	Antisocial personality
Number of AEDs	0.25	0.08	0.22	0.23	0.30*	0.13
Seizure free duration	−0.07	0.14	−0.05	0.04	−0.01	0.13
Epilepsy duration	0.11	0.11	0.15	−0.01	−0.04	0.17
Total ED duration over 24 h	−0.02	−0.1	−0.06	−0.06	0	−0.1

* $p < 0.05$.

that the Achenbach questionnaires do not include a symptom validity measure.

Our findings add further evidence that the burden of psychopathology in people with GGE is high. Mood disorders are readily treatable and should be prioritized in the management of GGE [28,29]. Comprehensive assessment and early intervention is increasingly recommended as good practice by leading epilepsy clinicians and a consensus document published in 2011 outlines recommended actions in managing neuropsychiatric comorbidities of epilepsy [28,30–32]. The most optimal clinical protocol for screening, referral, and treatment of psychopathology in terms of what is feasible and effective will inevitably vary based on context and the availability of resources. One strategy may be to identify the health professionals responsible for each of the roles in the clinical workflow within each primary health care and specialist epilepsy treatment setting. Explicitly allocating responsibility for psychosocial services may result in improve coverage of the currently high proportion of unmet patient needs [28]. For example, even in large samples recruited from North American tertiary centers and surrounding community clinics, less than a quarter of children with CAE experiencing affective, anxiety or suicidal problems were receiving treatment [33]. The relative lack of expertise of treating clinicians has been identified as a significant limitation to the recognition of psychopathology in epilepsy [31]. Education of primary care and specialist clinicians regarding screening practices for psychopathology in particular may therefore improve clinician confidence and enable greater patient access to specialist psychological services where these are available. Psychopathology symptoms are eminently treatable, in people with epilepsy as in the general population, and the benefits to quality of life have been well demonstrated. For this reason, efforts to identify and treat psychopathology should be considered a paramount goal in patient care.

5. Conclusion

In summary, these results indicate a high prevalence of psychological needs in patients with GGE. Depressive symptoms were the most common; however anxiety, avoidant personality, and attention deficit problems also occurred frequently. Our results suggest that patients may have more insight into these problems than their families. Antiepileptic drug polytherapy may be a risk factor for attention deficit symptoms. Routine screening of psychopathology and the provision of psychoeducation to patients and families is essential.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.11.014.

Disclosures

AL, SB and WD state that they have no disclosures relevant to this manuscript.

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Chapter 10: General Discussion

The previous Chapter documented findings regarding psychopathological outcomes in GGE. This General Discussion brings together conclusions from all investigations in this thesis, and provides a contextualisation of these findings in relation to the broader literature and some of the relevant current debates within the epilepsy research community. In the spirit of evidence-based practice and the translation of research to application, this Chapter, and thesis, culminates in an integration of these findings into existing (and suggestions for future) clinical guidelines and other practical applications.

10.1 Summary of findings

To refresh the reader's memory, the findings from this thesis were presented in the form of two systematic reviews (Chapters 3 and 4), one general results chapter (Chapter 6), and three results chapters addressing targeted primary research questions (Chapters 7, 8 and 9). The following summary of results will be framed around the aims and each of the four key hypotheses stated in Section 2.5 (page 44).

Overall, it can be concluded that cognitive and psychosocial problems are common in people with GGE. Regarding cognitive function, the meta-analysis of 26 studies (Chapter 3) and the primary analysis of prospective data from a sample of 76 adults and adolescents with GGE (Chapter 7) revealed small to moderately large reductions across most cognitive factors relative to that of healthy control participants and local, representative age-based normative data (Woodcock, 2008). In the primary data study, the most affected cognitive factor was long-term retrieval and memory function, followed by relatively smaller reductions in overall cognitive ability, acquired knowledge and processing speed. No significant differences between people with GGE and age-based normative data were apparent for short-term memory or fluid intelligence. There were no observed differences in cognitive ability between the GGE subtypes, although a larger sample size would have provided more confidence in this conclusion.

One of the aims of this thesis was to investigate the relationship between clinical features of the seizure disorder and cognitive functioning to determine whether risk or protective factors for psychosocial sequelae could be established. Firstly, the study highlighted the

high frequency of EDs in adults with GGE, and the extent to which these occur outside of conscious experience. This is an issue of particular concern since we found further evidence of a relationship between EDs and cognitive function, indicating that these subtle and unnoticed events may not be entirely benign. Two significant findings emerged from the investigation of epileptiform discharges. Firstly, cumulative burden of discharges over a 24-hour monitoring period was positively correlated with new learning and memory, and a composite measure of overall cognitive ability. Secondly, the relationships between epileptiform discharges and cognitive function were not explained by other epilepsy variables, as demonstrated by non-significant contributions of seizure history type, days since last GTCS, epilepsy duration, and number or type of AED currently prescribed to cognitive outcomes. Surprisingly, there was no observed relationship between reductions in cognitive performance and the presence or severity of self-reported psychopathology. Although replication is required, together these null findings suggest that the underlying epilepsy disease, rather than seizure characteristics or medication side-effects may be the primary causes of psychological sequelae.

Psychopathology symptoms were common, endorsed by approximately 50% of our sample. The prevalence of the clusters of symptoms reported (e.g. depressive, anxious) mirrored the relative frequency of the respective psychopathology symptoms in the general population. Symptoms were identified with greater sensitivity by people with GGE than by the family member or friend that they nominated to complete the informant-report questionnaire. Depressive symptoms were the most commonly endorsed of the psychopathology symptom types, with almost a third of our sample reporting a clinically significant degree of depressive symptoms. Anxiety and somatic symptoms, avoidant personality and attention deficit problems were also endorsed by a larger proportion of our sample than would be expected on the basis of normative data. A moderately large positive association was observed between the number of AEDs currently prescribed and more severe attention deficit symptoms, however no other epilepsy factors were found to predict psychopathology symptoms of any type.

10.2 Findings in context

10.2.1 Integration of findings with existing literature

Each of the Chapters 7, 8 and 9 included Discussion sections in which the respective findings were evaluated in light of previous literature. The following section of the current Chapter will expand on and synthesise the integration of this study's primary findings within the existing scientific literature. The examination of the implications of these findings will progressively broaden to consider how these findings relate to existing and future clinical guidelines, and the discourse regarding the conceptualisation of GGE as distinct syndromes or a spectrum of epilepsies.

Cognition and Psychosocial functioning

As the narrative synthesis in Chapter 2 and meta-analytic work in Chapter 3 indicated, the existing literature regarding cognitive function in GGE could be summarised as demonstrating widespread reductions across all cognitive factors and across all GGE syndromes, with no demonstrable differences between the four main diagnostic subtypes. This null finding between GGE syndromes can be contrasted to conclusions of a number of individual studies, many of which focus on the cognitive dysexecutive features of JME specifically (e.g. Piazzini, Turner, Vignoli, Canger, & Canevini, 2008; Pulsipher et al., 2009). Our findings of deficits of up to Cohen's d = 0.84 on measures of cognitive ability do replicate individual studies of people with GGE, although only a few studies have measured a comparable array of cognitive factors (Loughman, Bowden, & D'Souza, 2014). Importantly, the overall finding of reduced functioning across a broad range of factors was replicated in the current study.

As discussed in Chapter 7, there were some notable differences between mean effects for respective cognitive factors to indicate areas of relative strength and weakness in people with GGE, at least at the group level. These differences between performances on cognitive factors were slightly different to results that emerged from the meta-analysis of 26 studies. As noted in Section 10.1 (page 121), the primary difference between the prospective cohort study (Chapter 7) in the present thesis and findings from the meta-analysis (Chapter 3) was in the effect size for reduction in memory function. A larger reduction in mean memory score was observed in the prospect study than in the meta-analysis (d = 0.84, a value which fell outside of the meta-analytic 95% confidence interval

of effect estimation of 0.20-0.63). As noted in Chapter 3, there was a trend towards worse memory performance in samples of adults with GGE relative to those of children with GGE. Our sample had a higher average age than participants in most of the previous studies, so the greater observed memory deficit may reflect the progression of memory dysfunction over the lifespan in GGE. Cognitive function was less impaired in our sample than the confidence interval estimates from the meta-analysis for acquired knowledge, fluid intelligence, processing speed and short-term memory function.

To some extent, differences between the meta-analysis and prospective study findings are to be expected. The meta-analysis combines 26 studies, which were found to be at least moderately heterogeneous, and the average of these therefore may not be replicated by a single study. The heterogeneity of sampling and methodology between the study presented in Chapter 7 and other studies is most likely to underpin the differences we found. For example, most of the sample reported in Chapter 7 were adults, whereas this was true of only approximately half of the studies included in the meta-analysis. One of the methodological limitations of the current prospective study, that is, the use of normative healthy control data rather than a demographically-matched control group, may also have contributed to the observed differences. The use of a matched control group may have more effectively accounted for possible reduced socioeconomic status in the GGE sample measured here that may have contributed to the observed reductions in cognitive ability. For example, a strong family history of disability due to epilepsy may result in reduced educational and vocational opportunity and vulnerability to reduced cognitive attainment regardless of epilepsy disease status. However, practical constraints prevented the recruitment of a sufficiently large demographically matched and representative control group to improve on the local normative data that was available (McGrew, 2008).

There may also be an element of simple error variance associated with the necessary post-hoc categorisation of tests by a single cognitive factor which was the strategy used to integrate findings in the meta-analysis. Not many tests truly assess one single ability in isolation; multiple cognitive factors often underpin the successful completion of a cognitive test. In contrast, in the prospective study, cognitive factors were measured using subscales comprising two or more tests, each developed with the aim of testing one cognitive factor.

As documented in Chapter 9, psychosocial dysfunction in the form of increased prevalence of psychopathology symptoms were observed. Consistent with the previous literature, the prevalence in the GGE sample measured was higher than would be expected in the normative population. In the systematic review presented in Chapter 4, an estimated 50% of children and 30% of adults with GGE were found to experience clinically significant psychopathology. These findings were replicated in the cohort study presented in Chapter 9, with up to 50% of our adult sample endorsing Borderline-clinical or Clinical degrees of symptom severity - a more lenient criterion of severity than those used in previous studies (e.g. Meeting DSM diagnostic criteria). Estimates derived from the systematic review would suggest approximately 30% would be expected to score within the Clinical range.

One strength of the measurement of psychopathology in the present study was the examination of both dimensional and categorical outcomes. The Achenbach questionnaires have validated cut-off scores for borderline-clinical degree of symptom report and these scores were used to establish categories to estimate the frequency of clinically relevant distress. However, consideration of the scores on each of the DSM-oriented scales of the AESBA also enabled a more nuanced view of the range of symptoms. The systematic review in Chapter 4 and primary analyses in Chapter 9 revealed that the relative prevalence of symptom types mirrors those in the general population. Depression was the most common symptom endorsement followed by anxiety then somatic, attentional and thought disorders, in that order.

It is relevant to note that the study of psychopathology presented in Chapter 9 was cross-sectional and measured symptoms experienced only in the previous six months. We did not measure long-term outcomes, or change in symptomatology over time. We also focussed on psychopathological symptoms rather than general life outcomes such as marriage, work and financial status. As discussed in Chapter 2, psychopathology and psychosocial function were within the intended scope of this thesis, whereas quality of life or the attainment of specific social milestones were not.

One unique aspect of the current study was the consideration of the relationship between cognitive and psychosocial functioning. Whilst a strong positive relationship between the two seemed logical and was supported by previous literature in other conditions, we did not observe any such relationship in our sample. As noted in Chapter 7, there is some

precedent for this null finding. Psychopathology symptomatology can impact perceptions about ability (including cognitive ability) more commonly than it impacts ability when measured objectively (Elixhauser, Leidy, Meador, Means, & Willian, 1999). Although psychopathology symptoms were frequently endorsed in our sample, there are at least two caveats on the interpretation of this null finding as evidence against a relationship between cognitive functioning and psychopathology in GGE. Firstly, a relatively small proportion of our sample endorsed experiencing a degree of distress that would be likely to meet criteria for a diagnosis of an Axis 1 disorder from a semi-structured interview. Therefore the observed null relationship between cognition and psychopathology symptoms may not remain true for more severe psychological distress, which, on the basis of ours and other findings occurs in a greater proportion of people with GGE than in the general population (Loughman, Bendrups, & D'Souza, 2016; Wirrell et al., 1997). Secondly, the Achenbach psychopathology questionnaire used in Chapter 9 refers to the previous six months, and not to current mood states. For this reason, endorsement of clinically significant depressive symptoms for example, could relate to a period of time which is recent but has since ended. On the other hand, cognitive assessment refers to current - not retrospective - ability. This slight incongruence of timeframe of measurement may therefore contribute to the lack of observed relationship between cognitive function and psychopathology symptoms.

The contribution of epileptiform discharges and other factors

As outlined in Chapter 5, ED were measured using manual reading of each page of a 24-hour ambulatory EEG recording (by Udaya Seneviratne, an epileptologist on the larger study). This provided a higher degree of precision and detail than has been available in previous work examining ED. In the larger study, several elelectrophysiologically-focussed publications resulted from this detailed characterisation of ED in GGE (e.g. See Seneviratne, Cook, & Dsouza, 2015; Seneviratne, Hepworth, Cook, & D'Souza, 2015). In this thesis, detailed information about ED in GGE was used in conjunction with the assessment cognitive functions and psychopathology to consider the potential role of epileptiform abnormalities on these common psychological comorbidities of epilepsy.

Regarding cognition, we found significant negative relationships between total duration of ED over 24 hours and new learning and memory scores, and on a composite of

overall cognitive ability. ED predicted approximately 10% of variance of both cognitive outcomes, a small to medium effect size (Cohen, 1988). There was no significant relationship observed between total duration of ED and short-term memory function. As discussed in Chapter 8, there are no comparable studies with which to compare these findings in GGE. However, there are three studies in people with GGE to provide some context with which to integrate the current findings. Firstly, in order of chronology, a study by Needham and colleagues in 1969 compared a group of children and adults with idiopathic epilepsy (focal as well as generalised), and two groups of relatives without epilepsy, one with and one without epileptiform discharges on EEG. The epilepsy group performed more poorly than non-epilepsy family-relative groups, and there was no difference between the two relative groups. Thus, Needham and colleagues found no evidence for a detrimental effect of the presence of epileptiform discharges in relatives of people with epilepsy. The authors conclude that EEG abnormalities do not influence intellectual functioning, however it is important to note that they did not report conducting an EEG in their epilepsy sample, nor did they quantify the degree of epileptiform discharge in the relatives.

In Siren and colleagues' 2007 work with 11 children with CAE and JAE, the authors examined the relationship between duration of epileptiform discharges and performance on a number of concurrently administered computerised tasks assessing fine motor dexterity, sustained attention, visual memory and spatial memory. Their study found a significant negative association between duration of discharges during testing of visual memory at epilepsy onset and before AED commencement, and no other significant findings with respect to epileptiform discharges. Siren and colleagues conducted a second assessment of these children approximately 10 months later, following commencement of their AED treatment. At this time, approximately half of the group had no further EEG abnormalities and performance on a number of cognitive measures had improved in the whole sample. It is unclear from the reporting of this study whether the follow-up assessment was undertaken concurrently with EEG, however no relationship was reported between discharges and the second cognitive assessment.

In order to interpret our findings in this context, it is significant to note a number of important differences between the sample reported in Siren and colleagues' study, compared to the study reported in Chapter 8. The former comprised a group of children

with new-onset absence epilepsies, before AED therapy (Siren et al., 2007). Whilst there was a degree of overlap between the cognitive functions assessed in the two studies, the present study did not assess fine-motor fluency. Nonetheless, the present study did replicate the relationship found between discharges and visual memory performance by Siren and colleagues, although this could be coincidental and requires further study. One notable difference in findings between the present study and that of Siren and colleagues relates to overall intelligence. Scores on composite measures of verbal and performance IQ in the new-onset Siren sample were average, whereas our adult sample showed a reduction from the population average in overall intelligence of 0.47 standard deviation units. Our adult sample had significantly longer duration of disease than Siren's new-onset sample, so these discrepant intelligence findings may reflect in part the contributions of chronic epilepsy and ED and long-term AED use.

Finally, a recent study by Dlugos and colleagues (2013) also examined pre-treatment epileptiform discharges and cognition as part of a randomised controlled trial of AEDs in children with childhood absence epilepsy. The authors administered the Wisconsin Card Sorting Test and the Conners' Continuous Performance Task and related scores on these to the length of the longest duration of EEG discharge that was observed during a one-hour routine EEG conducted on a separate occasion (not simultaneously). Higher omission errors were observed on the Conners' test of sustained attention in children in whom EEG events longer than 20 seconds were recorded. Events of this duration substantially exceed minimum criterion for a seizure (2-3 seconds; Seneviratne et al., 2012). Although EEG recording did not occur at the same time as cognitive assessment, it is reasonable to assume that such long absences were occurring regularly for those children and that errors of omission may have been explained by events of this nature occurring during testing (Dlugos et al., 2013). Again, this pre-treatment CAE sample is significantly different from our relatively well-controlled adult GGE sample. As reported in Chapter 7, a mean reduction in attentional abilities was not observed in the present cohort. Similarly, there was no relationship observed between attention and epileptiform discharges (Chapter 8). Given substantial sample differences, any inference regarding reasons for these discrepant findings should be considered speculative. One possible explanation of the different findings reflect an evolution of problems across the lifespan whereby inattention is seen in children and overall ability - including acquired knowledge, speed of processing and memory become compromised later in life. As discussed in

Chapter 7, the mechanism underlying the observed pattern of cognitive deficits may comprise a cumulative effect of reduced speed of processing and memory function impacting on capacity to learn knowledge and resulting in reduced acquired knowledge and educational opportunity.

The present study also considered several aspects of epileptiform discharges including the relative contribution of their number compared with duration, and whether they occurred during sleep or wakefulness. Two other studies (not of people with GGE) measured discharges occurring during sleep and wakefulness. Ebus and colleagues (2012) found that people with discharges comprising more than 10% of the measured EEG during wakefulness had reduced processing speed, short term verbal memory and visual motor integration. In contrast, no relationship was observed between cognition and ED during sleep. In part, this finding mirrors our findings that ED occurring during wakefulness significantly predicted a larger proportion of variance associated with memory function than with overall cognitive ability. We additionally found the inverse pattern for ED during sleep. However as noted in Chapter 8, the sleep and wakefulness models were not compared statistically in the present study and may not represent a meaningful finding. Our findings also broadly replicated those observed by Lv and colleagues (2013) who reported a significant negative relationship between ED in both sleep and wakefulness on composite scores of overall cognitive ability and memory function alike. They report finding no differences between the contribution of ED on cognitive function during sleep and wakefulness. Clearly, a conclusion on the issue of relative significance of sleep versus waking ED is not possible without further investigation.

As discussed in some detail in Chapter 2 and Chapter 8, the investigation of epileptiform discharges and cognition in this thesis is distinct from 'transient cognitive impairment' (TCI): the phenomenon of immediate disruption of cognitive functions due to real-time epileptiform activity (Aarts, Binnie, Smit, & Wilkins, 2984). The significant points of difference of the present study compared with TCI methodology include the following factors 1) cognitive assessment occurring on an adjacent day to EEG monitoring in the majority of participants, 2) the evaluation of ED over the course of a full 24-hour period, and 3) the decision to assess enduring functions rather than those typically associated with TCI and the lack of video monitoring. However, as noted in Chapter 8, a subgroup

of 22 patients did undertake cognitive assessment concurrently with EEG monitoring. This subgroup enables a consideration of the possible contribution of TCI to our findings. We established that this subgroup was comparable to the larger sample with respect to cognitive function scores and ED. That is, their cognitive performance was similarly reduced relative to age-based normative data, and ED was observed with similar frequency in the complete sample. However only two of the 22 people with concurrent assessment experienced ED during testing, making it unlikely that concurrent discharges underlie the relationship we observed between ED and cognitive function scores. Therefore, although the study was not designed specifically to investigate TCI, findings do not support the occurrence of the phenomenon in GGE - certainly not as the primary explanation for cognitive deficits.

The significant advancement in methodology of ambulatory EEG monitoring represents as much of a contribution to this literature as the results that have emerged from this study. No other studies have counted the number of discharges on EEG, or measured duration with a comparably high degree of precision as the present study. As discussed in Chapter 2 and Chapter 8, previous work on the topic has typically estimated the burden of epileptiform discharge by sampling a small proportion of EEG output during a one-hour monitoring period. Categorising the data into groups experiencing less than or greater than 1% or 10% of the sampled period with EEG abnormalities was a common approach in previous studies (Aldenkamp & Arends, 2004; Tromp et al., 2003).

10.2.2 Integration with existing guidelines

Our findings demonstrate that guidelines for the clinical management of epilepsy should include acknowledgement of the prevalence of cognitive and psychosocial dysfunction, and stronger recommendations regarding screening and services for these common psychological sequelae of GGE. As discussed in Section 2.3.1 (page 28), the American Epilepsy Society guidelines state that children with epilepsy are at greatest risk of cognitive dysfunction. Our findings do accord with this, with the exception of memory function which may decline from childhood to middle and older adulthood. The Epilepsy Society of Australia should include guidelines about these common conditions, not only on topics of controversy. The UK's NICE guidelines recommend providing access to information about potential psychosocial issues, however the guidelines do not provide any such resources or specify what they should contain. Further detail regarding

the prevalence of cognitive and psychosocial comorbidity and recommendations about where to obtain relevant assistance would further bolster the NICE guidelines.

Although risk factors for psychological comorbidities of epilepsy continue to be investigated, a discussion of these risk factors in clinical guidelines may assist clinicians towards considering the most likely causes of dysfunction. In their guidelines, the AES cites epileptiform activity as a risk factor for cognitive and behavioural dysfunction (Society, 2012a, 2012b), and if this hypothesis gains further support, it may be useful to consider recommending regular EEG for the purposes of monitoring ED, not only seizures. Other guidelines do not currently mention ED in the context of cognition, but perhaps should consider those patients with a high burden of ED to be at increased risk for cognitive dysfunction in particular. With respect to recommended screening procedures, the inclusion of an informant report may be suggested as a viable alternative when self-report is not available or if there are concerns regarding the reliability of patient self-report.

Guidelines and other clinical education tools may also be improved by listing strategies for common cognitive difficulties in the event that a psychologist or other appropriately trained professional is not available to provide this. Part of the psychoeducation should include the destigmatisation of cognitive difficulties, given the long history of stigmatisation of other components of epilepsy, and the fact that negative stereotypes have a negative impact on cognition (Kit, Tuokko, & Mateer, 2008). Indeed, memory difficulties are challenging to discuss since the public understanding of them confounds memory failure with presumption of progressive decline and loss of function such as in dementia (Sargeant & Unkenstein, 2001). This known taboo topic needs to be countered with frank, destigmatising conversations. Psychoeducational strategies may be useful in normalising and contextualising occasional memory failures (Sargeant & Unkenstein, 2001). For example, explanations about how cognitive difficulties can occur, such as memory failure that can occur due to lapse of attention, and the fact that memory symptoms may resolve rather than necessarily being permanent or progressive. Cognitive remediation strategies for minimising the impact of cognitive difficulties on daily life should be framed as a 'crutch' rather than as a hallmark of confirmed disability.

In summary, the overall findings from this thesis echo those of other recent scientific publications stating the need for routine neuropsychological assessment. In particular,

the findings of dynamic risk of deficits in various aspects of mental function (both cognitive and mood) over the lifespan support Devinsky's 2003 recommendation of an informal enquiry into current mental health status at every point throughout patient care (Devinsky, 2003). Whilst the cost of comprehensive routine neuropsychological assessment may be prohibitive in many settings, brief screening of cognition may be sufficient to improve the identification of people experiencing cognitive difficulties relative to current standard practice.

10.2.3 GGE as one or many syndromes: The neuropsychological perspective

As discussed in Chapter 3, there has been insufficient previous investigation of GGE syndromes separately to date, to state conclusively whether there are differences in their cognitive characteristics. Whilst this was not a formal aim of the current thesis, this issue was examined in Chapter 7 when the overall cognitive ability, long-term memory and short-term memory function of GGE syndrome groups were compared. As mentioned in that Chapter, the study was somewhat underpowered to detect possible medium-sized differences between syndromes (0.7 statistical power). Of the four primary syndromes, the JME group had the highest overall cognitive ability score by an effect size of approximately 0.3 (Cohen's d), although as noted in Chapter 7, statistical significance of this difference could not be established with our sample. Further investigation with samples with at least 25 participants per syndrome would be required to establish statistically significant differences based on the estimated effects reported in Chapter 7. On the basis of the available cognitive evidence therefore, there is no strong support for the distinct syndromes in GGE. No significant differences were observed between the syndromes with respect to psychopathological symptoms.

10.3 Limitations

The present series of studies aimed to provide detailed description of cognitive and psychosocial functioning in GGE whilst overcoming some of the methodological limitations of previous research. In particular, the use of detailed quantified EEG during a 24-hour period of ambulatory monitoring comprises a significant development and increase in precision, as discussed in detail in Chapter 5 and Chapter 8. The measurement of six key cognitive factors and six of the most common psychopathology symptom

types in a relatively large sample spanning all GGE syndromes is another important strength.

The comparison of syndromes and seizure history with respect to cognitive outcomes was limited by statistical power in this thesis. The implications of this are discussed in Chapter 7 and in Section 10.2.3 (page 132). An additional limitation was the unavailability of a small proportion of data from some participants. There is an inherent challenge in human clinical studies when collecting multiple types of data from different sources. Due to varying participation rates in each component of the study, it was not possible to ensure that every person seen for EEG also had all clinical data available at the time of analysis, completed a cognitive assessment, the self-report psychosocial functioning questionnaire and had an informant return their respective psychosocial functioning questionnaire. In order to maximise representativeness of the sample, all eligible participants were retained in the study - regardless of their data completion. The availability of data from each and every enrolled participant may have provided more statistical power in some of the analyses. However we were able to compare groups on baseline characteristics to ensure that the incomplete data did not reflect obvious selection bias from certain types of participants only participating in some parts of the study.

As mentioned in Chapter 8, one methodological limitation in the examination of epileptiform discharges was the absence of video monitoring. Video monitoring during cognitive testing and the remainder of the ambulatory EEG monitoring period may have afforded a more detailed characterisation of any behavioural features that may have accompanied some of the recorded epileptiform discharges and further informed the delineation between subclinical and clinical seizure activity (Aldenkamp et al., 1996). Instead, patients were asked to indicate the occurrence of any subjectively experienced events, which replicates common clinical practice of asking adults patients to report the occurrence of seizures and determining seizure control - at least in part - on this basis.

The sample comprised adults with relatively well-controlled seizures and with mean seizure-free duration of more than 2 years. This fact does serve to fill an important gap in the literature on GGE, which is relatively sparse with respect to outcomes in adulthood. However the generalisability of our findings may be limited to similar GGE populations. By definition, cross-sectional research cannot measure lifetime trajectories. Although

childhood and adolescence has been the traditional focus of GGE syndromes, there may well be ongoing changes to the conditions and psychosocial co-morbidities during the course of adulthood and ageing. Longitudinal research with repeated measurement of epileptiform discharges and comprehensive assessment of cognition and psychopathology would therefore be a significant asset to future research.

10.4 Practical applications

In order to address the aforementioned limitations and to advance knowledge in this field, future research would benefit from larger sample size, greater breadth of psychological functioning measures and neuroimaging. These aims may be best facilitated through collaborative projects and data linkage, given the practical challenges of large-scale recruitment and also the limitations to generalisability of samples derived from a single clinical centre or geographic location. A larger study may be able to consider broader aspects of psychosocial function such as quality of life, and vocational and social outcomes. Although time-intensive to measure in both research settings and in clinical practice, a holistic appreciation of outcomes associated with GGE would be assisted by the measurement of some other components of psychological wellbeing and factors contributing to the overall life outcomes listed previously. Relevant predictive factors may include individual and family adaptive styles in addition to routinely collected data on the metrics of medical and seizure severity. Regarding neuroimaging, the development of new techniques has led to a growing body of literature regarding neurobiological substrates of JME (e.g. (O'Muircheartaigh et al., 2011; Vollmar et al., 2011) and could be more broadly applied to other GGE syndromes to improve insights into these conditions. For example, some authors postulate that abnormal functional connectivity in the default mode network of people with GGE may be linked to the social cognitive impairments that have been reported previously (McGill et al., 2012).

In light of the potential role of ED in cognitive dysfunction, and the high prevalence of both ED and cognitive dysfunction as demonstrated in this thesis, future work should consider the risks and benefits of treatment of ED once this relationship is more firmly established. There is limited work on ED treatment to date. One example is a small study of 12 children in a 16-week placebo controlled trial of AEDs demonstrated significant reductions in EDs and behavioural problems, but no improvement in cognition

(Marston, Besag, Binnie, & Fowler, 1993). There does not appear to be any such work in adults.

In spite of what appears to be heightened recognition of the importance of early detection, screening and intervention of psychopathology and cognitive dysfunction in epilepsy, some estimates reveal that as few as 23-33% of children with comorbid disorders receive mental health services (Caplan et al., 2005; Caplan et al., 2008). As mentioned briefly in Section 10.2.2 (page 130), greater dissemination of information and support for clinicians may assist with translating research findings to clinical practice. Lack of expertise in clinicians and their limited ability to recognise, diagnose and treat psychological dysfunction was identified as a major barrier to the access of services, suggesting that clinician education in screening in order to improve confidence with referral is one avenue for progress (Devinsky, 2003).

More broadly, psychosocial outcomes may be reframed as the perspectives held by individuals and societies regarding living with chronic illness. For example, the 'shifting perspectives model' states that living with chronic illness is a dynamic state of change between illness-in-the-foreground and wellness-in-the-foreground where each serves different functions for the individual, and requires different support from healthcare providers (Paterson, 2001). Psychological approaches such as mindfulness and Acceptance and Commitment Therapy (ACT) are part of the trend towards a focus on mental health and away from a focus on mental illness (Keyes, 2005). These approaches and therapies fit within a broader cultural context of the biopsychosocial model of medicine and attitudinal shifts towards preventative health practices and lifestyle recommendations for health and wellbeing (Engel, 1989; Yeh & Kong, 2013). In this context, the balance between recognition of difficulties, reduction of stigma, and reframing of perspectives on life with chronic illnesses should be more possible than it has ever been.

10.5 Conclusion

In conclusion, cognitive and psychosocial sequelae are common in GGE. This appears to be the case in all syndromes and in adults as well as in children. The now significant body of evidence should result in improved recognition of psychological comorbidites in people with these common epilepsy syndromes and help recognition of comorbidities

throughout the lifespan. Future research to replicate and extend the findings presented in this thesis may further improve understanding, prognosis and clinical management of GGE.

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Appendices

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See next page for Appendices.]

Appendix 1

Search Terms Systematic Review (Chapter 3)

Database	Epilepsy keywords/MeSh headings	Boolean	Cognition keywords	Other
Scopus (no date restriction available)	KEY ("idiopathic generali? epilepsy") OR KEY ("childhood absence epilepsy") or key ("juvenile absence epilepsy") or key ("juvenile myoclonic epilepsy") or key ("idiopathic epilepsy with generali? tonic clonic seizures") and not (key ("partial epilepsy") or key ("cryptogenic epilepsy") or key ("symptomatic epilepsy") or key("temporal lobe epilepsy"))	and	(KEY("cognition") or key ("cognitive function") or key ("neuropsychology") or key ("memory") or key ("executive function"))	
Medline (1989-2013)	MH:exp=Epilepsy NOT NOT MH:exp=Epilepsy, Complex Partial NOT MH:exp=Epilepsy, Frontal Lobe NOT MH:exp=Epilepsy, Partial, Motor NOT MH:exp=Epilepsy, Partial, Sensory NOT MH:exp=Epilepsy, Temporal Lobe NOT MH:exp=Epilepsy, Benign Neonatal NOT MH:exp=Epilepsy, Post-Traumatic NOT MH:exp=Epilepsy, Reflex NOT MH:exp=Landau-Kleffner Syndrome NOT MH:exp=Seizures, Febrile NOT MH:exp=Status Epilepticus OR TS="idiopathic generalized epilepsy"	and	TS=cognition OR TS="cognitive function" OR TS="cognitive impairment" OR TS="memory" OR TS="executive function"OR (MH="cognition" OR MH="executive function" OR MH="neuropsychology" OR MH="neuropsychological tests"	[excluding] MeSH Headings=(ANTERIOR TEMPORAL LOBECTOMY OR EPILEPSY TEMPORAL LOBE OR AMYGDALA OR EPILEPSIES PARTIAL OR INFANT OR EPILEPSY COMPLEX PARTIAL) AND Languages=(ENGLISH) AND [excluding] MeSH Headings=(BRAIN NEOPLASMS OR POSTOPERATIVE COMPLICATIONS)

Appendix 2

Tests and corresponding CHC factors (Chapter 3)

Test name	CHC factor	Test name	CHC factor
Adult Memory and Information Processing Battery (Figure - delayed recall)	glr	D-KEFS Category Switching Accuracy	gs
Adult Memory and Information Processing Battery (Figure - delayed recall)	glr	D-KEFS Correct Card Sorts	gf
Adult Memory and Information Processing Battery (List learning - delayed recall)	glr	D-KEFS Inhibition	gs
Adult Memory and Information Processing Battery (Word List - delayed recall)	glr	D&P - People delayed	glr
Attention Network Test (Overall mean RT)	gs	D&P - Shapes delayed	glr
Beery-Buktenica Devt Test of Visual-Motor Integration	gv	Digit Span (backward)	gsm
Block Design	gf	Digit Span (forward)	gsm
Block recall	glr	Digit Span (forward+backwards)	gsm
Block Span (backward)	gsm	Digit Span (unspecified)	gsm
Block Span (forward)	gsm	Facial recognition test	glr
Block Span (unspecified)	gsm	Finger tapping	gs
BNT	gc	Finger tapping (Right;taps per minute)	gs
Brixton Spatial Anticipation Test	gf	Five-Point test (number figures)	gv
California Verbal Learning Test (Delayed Recall)	glr	Gordon Diagnostic System - Vigilance task	gsm
Category fluency	gs	Grooved Peg Board (Dominant Hand time)	gs
Clock drawing test	gv	Hayling Sentence Completion task	gs
CMS - Dot locations subtest (30min recall)	glr	Judgment of line orientation	gv
CMS - Stories subtest (30min recall)	glr	KABC-Hand Movements	gsm
Coding (number correct)	gs	Letter fluency	gs
Cognitive Estimates Test	gc	Matching Familiar Figures Test (time)	gs
Complex Figure recall - Delayed	glr	Matrix Reasoning	gf
Complex motor control (Mean ITI-Con)	gs	McKenna Naming task	gc
Continuous Performance Task (AX - Correct)	gs	Memory Assessment Scale (Delayed word recall)	glr
Continuous Performance Task (Deg.X - Correct)	gs	Memory Assessment Scale (Visual reproduction)	glr
Continuous Performance Task (Lo - Correct)	gs	MWT-A Vocabulary Test	gc
Continuous Performance Task (Overall Index)	gs	NART	gc
Continuous Performance Task (Tones - Correct)	gs	RCFT (delay)	glr

Test name	CHC factor	Test name	CHC factor
Corsi Block Tapping Test	gsm	Rey Auditory Verbal Learning Test (Delayed recall)	glr
Rey-Osterrieth Complex Figure (Copy)	gv	WAIS - III Matrix Reasoning	gf
Rey-Osterrieth Complex Figure (Delayed recall)	glr	WAIS - III Picture Arrangement	gf
Simple copy (cube)	gv	WAIS - III Picture Completion	gv
SLQ	gc	WAIS - III Similarities	gc
Spatial Span	gsm	WAIS - III Symbol Search	gs
Speed of Capactiy of Language Processing (SCOLP) - Comprehension	gs	WAIS - III Vocabulary	gc
Speed of Capactiy of Language Processing (SCOLP) - Word	gs	WAIS - Similarities	gc
Story Recall - Delayed	glr	WAIS - Vocabulary	gc
Stroop (interference)	gs	WAIS-VIQ	gc
Stroop (time to completion)	gs	Warrington Recognition Memory Test - Faces	glr
Stroop test (Colour-Word correct)	gs	Warrington Recognition Memory Test - Words	glr
TAP Tonic Alertness test (time)	gs	WASI - FSIQ	g
Test of Everyday Attention - Elevator Counting with Distraction	gsm	WASI - PIQ	gf
TMT-A (time)	gs	WASI - VIQ	gc
TMT-B (Time)	gs	WCST (Categories)	gf
Token Test	gc	Weschler Arithmetic	gsm
Total Nonverbal Short-Term Memory (Memory for Objects; Bead Memory subtests)	glr	Weschler Block Design	gf
Total Verbal Reasoning (Vocabulary; Comprehension & Absurdities subtests)	gc	Weschler Digit Symbol/Coding	gs
Total Verbal Short-Term Memory (Memory for Sentences; Digit Span forwards and backwards)	gsm	Weschler Memory Scale - Total recall score	glr
Tower of London (total % completed)	gf	Weschler Picture Completion	gf
Verbal Learning Delayed recall	glr	WISC_III FSIQ	g
Verbal Learning Memory test (German, delayed recall)	glr	WISC_III PIQ	gf
Vocabulary	gc	WISC_III Shortform	g
WAIS - Arithmetic	gsm	WISC_III VIQ	gc
WAIS - FSIQ	g	WISC_R FSIQ	g
WAIS - III Arithmetic	gsm	WISC_R PIQ	gf
WAIS - III Block Design	gf	WISC_R VIQ	gc
WAIS - III Comprehension	gc	WISC-R Arithmetic	gsm
WAIS - III Digit Span	gsm	WISC-R Block Design	gf
WAIS - III Digit Symbol	gs	WISC-R Coding	gs

Test name	CHC factor	Test name	CHC factor
WAIS - III Information	gc	WISC-R Comprehension	gc
WAIS - III Letter-Number sequence	gsm	WISC-R Digit Span	gsm
WISC-R FSIQ	g	WMS - R Logical Memory (Delayed recall)	glr
WISC-R Information	gc	WMS - R Visual Reproduction (Delayed recall)	glr
WISC-R Mazes	gv	WRAML - 2 Story delayed recall	glr
WISC-R Object Assembly	gv	WRAT-3 Math	gc
WISC-R Picture Completion	gf	WRAT-3 Reading	gc
WISC-R Similarities	gc	WRAT-3 Spelling	gc
WISC-R Vocabulary	gc	WTAR	gc

Appendix 3

Author-specified tests of executive function (Chapter 3)

Test author specified tests of executive function
Block Span (backward)
Category fluency (Animals)
Category fluency (People and fruit)
D-KEFS Category Switching Accuracy
D-KEFS Correct Card Sorts
D-KEFS Inhibition
Digit Span (backward)
Five-Point test (number figures)
Hayling Sentence Completion task
Letter fluency
Rey-Osterrieth Complex Figure (Copy)
Stroop (interference)
Stroop (time to completion)
Stroop test (Colour-Word correct)
Stroop test (errors)
TMT-B (Time)
Tower of London (total % completed)
Tower of London (total)
WAIS - III Letter-Number sequence
WCST (Categories)
Weschler Digit Symbol/Coding
WISC-R Mazes

Appendix 4

Methodologic detail from included studies (Chapter 4)

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
1	GGE heterogenous; localisation-related epilepsy, healthy first degree cousins	CBCL	By consensus. Criteria not specified	T-score ≥65 'at risk'/clinical cut-off for behavioural problem scales. ≥35 for competence scales	All CBCL subscale means within normal range. Total problems 55.30 (12.16), Internalising 56.74 (11.96), Externalising 52.23 (11.43). Total competence 45.02 (10.11)	Healthy control group:47.26 (11.09), Internalising 48.71 (9.85), Externalising 47.31 (10.64). Total competence 50.94 (9.15)
2~	GGE heterogeneous; partial epilepsies	K-SADS	ILAE 1989	DSM-IV	55% psychiatric diagnosis; 26% disruptive disorder; 13% anxiety/affective disorder; 16% comorbid disruptive and anxiety/affective disorders; 0% cases schizophrenia-like psychosis.	HC - 18% psychiatric diagnosis. CPS - 63% psychiatric diagnosis; 25% disruptive disorder; 13% anxiety/affective disorder; 14% comorbid disruptive and anxiety/affective disorders; 10% schizophrenia-like psychosis.
3~	CAE; Complex partial seizure disorder	K-SADS; CBCL; Childrens Depression Inventory; Multidimensional Anxiety Scale for Children	ILAE 1989	DSM-IV	85% anxiety disorder; 50% anxiety only; 35% anxiety with comorbid disruptive behaviour problem; 15% depression; 5% depression only; 10% depression with comorbid disruptive behaviour problem; 0% cases anxiety with comorbid depression; 0% cases anxiety with comorbid depression only; 0% cases anxiety with comorbid depression and disruptive behaviour problem.	HC - rates not presented. CPS - 51% anxiety disorder; 27% anxiety only; 24% anxiety with comorbid disruptive behaviour problem; 21.6% depression; 5.4% depression only; 16.2% depression with comorbid disruptive behaviour problem; 27% anxiety with comorbid depression; 5.4% anxiety with comorbid depression only; 21.6% anxiety with comorbid depression and disruptive behaviour problem.

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
4~	CAE	K-SADS; CBCL	ILAE 1989	DSM-IV; CBCL borderline-clinical cut-off	61% psychiatric diagnosis; 26% ADHD; 20% affective/anxiety disorder. Elevated CBCL subscales: 40% total problems; 36.9% internalising ; 26.2% externalising; 37.5% attention; 34.4% somatic complaints; 23.4% social problems; 20.3% thought problems; 14.1% withdrawn; 17.2% anxious/depressed; 9.4% aggressive; 14.1% delinquent.	HC - 15% psychiatric diagnosis; 6% ADHD; 7% affective/anxiety. Elevated CBCL subscales: 11.8% total problems; 15.7% internalising; 6.9% externalising; 4.9% attention; 5.9% somatic complaints; 5.9% social problems; 3.9% thought problems; 2.9% withdrawn; 7.8% anxious/depressed; 2.0% aggressive; 6.9% delinquent.
5	CAE	CBCL (Withdrawn, Social problems, Thought problems, Somatic complaints, and Anxious/Depressed scales)	ILAE 1989 equivalent	Comparison of means	All CBCL subscale means within normal range (T: 56.8-60.3), but significant differences between CAE and HC for: attention problems, withdrawal, social problems, and thought problems subscales. No differences for somatic complaints or anxiety/depression. Effect sizes between 0.36-1.15 compared to HC.	HC - All CBCL subscale means within normal range (T: 51.1-54.9). T1D - All CBCL subscale means within normal range T1D (T: 51.1-56.4).
6	GGE heterogeneous	Child Behavior Profile (Achenbach, 1978, 1979; Achenbach and Edelbrock, 1978, 1979)	ILAE 1989 equivalent	Comparison of means (T-score: ≥60 borderline-clinical cut-off)	CBCL agression and social competence subscales within normal range (T: 57.9 and 37.0 respectively). Total Behavior Problem score T: 65.3. GGE group behaviour scores not significantly different from other epilepsy groups.	n/a

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
7	JME, CAE, JAE	Study-designed psychosocial questionnaire (education, employment, family and social situation, self-reported psychiatric comorbidities); Quality of Life in Epilepsy Inventory (QOLIE-31)	ILAE 1989 with modification to classify all pts with myoclonic jerks as JME	Comparison of endorsement to items on psychosocial questionnaire, mean scores on QOLIE-31 range 0-100.	JME: 71% university qualification, 80% never unemployed for >1yr, 80%% 'wealthy or sufficient' financial situation, 90% 'satisfying social situation', 90% good 'integration into social context'. Current or previous depression 19%, anxiety disorder 4.9%. Overall quality of life 71.1 (3)	CAE/JAE: 34% university qualification, 73% never unemployed >1yr, 76% 'wealthy or sufficient' financial situation, 78% 'satisfying social situation', 90% good 'integration into social context'. current or previous depression 10%, anxiety disorder 10%, psychosis 2%.
8	GGE heterogeneous; partial epilepsies	K-SADS	Unspecified	DSM-IV	13% depressive disorder; 26.1% anxiety disorder; 1.9% psychotic disorder; 17.4% ADHD; 17.4% oppositional defiant disorder; 8.7% conduct disorder; 0% cases tic disorder.	HC - 4% depressive disorder; 22% anxiety disorder; 2% psychotic disorder; 10% ADHD; 2% oppositional defiant disorder; 0% conduct disorder; 2% tic disorder. Focal epilepsy - 23.3% depressive disorder; 36.7% anxiety disorder; 2% psychotic disorder; 30% ADHD; 10% oppositional defiant disorder; No cases conduct disorder; 16.7% tic disorder.

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
9	GGE heterogeneous	CBCL (Total problems, Internalising, and Externalising scales)	Unspecified	Comparison of means	CBCL: total problems 56 (11.18); internalising 56.45 (11.68); externalising 50.36 (12.6) all within normal range.	HC - CBCL: total problems 42.87 (14.14); internalising 44.25 (14.54); externalising 45.14 (8.34) all within normal range. HC scores on total problems and internalising significantly lower than GGE.
10~	GGE heterogeneous; partial epilepsies	K-SADS; CBCL	ICD-10	DSM-IV; CBCL (T: ≥65)	59.6% psychiatric diagnosis; 23.5% of those with a psychiatric diagnosis receiving treatment. CBCL: total problems 54.2 (13.4); internalising 52.2 (12.6); externalising 48.9 (11.5); 25% clinically significant total problems; 15% clinically significant internalising problems; 12.5% clinically significant externalising problems.	CPS - 61.3% psychiatric diagnosis; 40.3% of those with a psychiatric diagnosis receiving treatment. CBCL: total problems 55.1 (13.8); internalising 53.5 (11.3); externalising 49.4 (13.2); 22.9% clinically significant total problems; 14.6% clinically significant internalising problems; 14.6% clinically significant externalising problems.

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
11	JME	Youth Self Report (YSR); Weinberger Adjustment Inventory (WAI)	ILAE 1989	YSR borderline-clinical cut-off, and clinical cut-off	20% in clinical range, and 12% in borderline-clinical range for internalising or externalising; 20% in clinical range, and 4% in borderline-clinical range for internalising; 4% in clinical range, and 12% in borderline-clinical range for externalising. Within internalising: 8% borderline-clinical for withdrawal; 4% borderline-clinical for somatic complaints; 8% clinical, and 4% borderline-clinical for anxiety and depression; 8% borderline-clinical for social problems; 4% borderline-clinical for thought problems. Within externalising: 4% clinical, and 8% borderline-clinical for attention problems; 4% borderline-clinical for delinquency.	n/a
12	CAE	BASC (Anxiety and Depression subscales)	ILAE 1989	1.5 SD above normative sample mean	11% clinical range anxiety; 24% clinical range depression. BASC scores: anxiety 50.7 (9.3); depression 40.5 (12.9).	HC - Rates not reported. BASC scores: anxiety 43.3(7.5); depression 50.4 (12.9).
13	GGE heterogeneous	n/a	ILAE 1989/2001	ICD-10	26.1% any psychiatric disorder; 13.4% mood disorder; 7.6% neurotic, stress-related, and somatoform disorders.	n/a

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
14^	JME	Modified version of Wirrell et al. (1997) measure	Equivalent to ILAE 1989 [myoclonic seizures and >=1 GTCS, Normal background EEG with bursts of gen'd spike and wave >= 3 Hz]	n/a	During the 20+ year follow up period: 61% had been medicated for mood disturbance at some stage. At time of follow up: 87% had graduated high school; 70% had completed additional education; 69% were employed and self sufficient (31% unemployed). Although there were no population norms for their measure, the authors noted Province unemployment to be 7% at the time of the study.	n/a
15^	GTSCO	Modified version of Wirrell et al. (1997) measure	Equivalent to ILAE 1989 [GTCS only; normal background EEG with bursts of gen'd spike and wave >2.5Hz]	n/a	27% any psychiatric diagnosis; 40% had not graduated high school; 38% pregnancy outside a stable relationship; 23% living alone; 33% unemployed; 7% criminal conviction; 55-65% reported satisfaction with their lives, friendships and social activities.	n/a
16	GGE heterogeneous (50% JME)	n/a	Equivalent to ILAE 1989	n/a	During follow up period: >30% diagnosed and treated for mental disorder; 24% medicated for depression; 17% medicated for anxiety; 2% medicated for obsessive-compulsive symptoms; 2% medicated for psychotic symptoms; 10% unemployed.	n/a

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
17	JME	SCID 1; SCID 2; K-SADS-PL [if aged under 18 years]	ILAE 1989	DSM-IV	62% psychiatric disorder; 24% anxiety disorder; 19% depressive disorder; 2% alcohol abuse; 9.2% personality disorder.	n/a
18*	JME	SCID 1; SCID 2; GAF	ILAE 1989	DSM-IV/DSM-III-R	49% Axis 1 disorder; 23% anxiety disorder; 19% mood disorder; 7% somatoform disorder; 3% schizophrenia; 2% alcohol abuse; 5% Axis 2 disorder; 20% mild-moderate personality disorder; GAF: 61.2 (16.0).	HC - 18% Axis 1 disorder; 8% anxiety; 6% mood; 1% schizophrenia; 3% alcohol abuse; 4% personality disorder; GAF: 84.5 (12.1).
19*	JME; TLE	SCID 1	ILAE 1989	DSM-IV	49% Axis 1 disorder; 23% anxiety disorder; 19% mood disorder; 7% somatoform disorder; 3% psychotic disorder; 5% two Axis 1 disorders; 2% alcohol abuse.	TLE - 50% Axis 1 disorder; 14.1% anxiety disorder; 25.8% mood disorder; 4.7% somatoform disorder; 15.8% psychotic disorder; 10.6% two Axis 1 disorders.
20	GGE; TLE	SCID 1; Yale–Brown Obsessive Compulsive Scale (Y-BOCS); BDI	ILAE 1989	DSM-IV; Y-BOCS Severity Scale; BDI >14	48.1% at least one Axis 1 disorder; 3.7% (1 individual) diagnosis of OCD; 11.1% (3 individuals) clinically meaningful obsessive-compulsive symptoms.	HC - 16.7% at least one Axis 1 disorder; 0% diagnosis of OCD. TLE - 75.9% at least one Axis 1 disorder; 10.3% (3 individuals) diagnosis of OCD; 34.5% (10 individuals) clinically meaningful obsessive-compulsive symptoms.
21	JME	n/a	ILAE 1989	DSM-IV	"Non-resistant" patients - 19% any psychiatric disorder; 10% personality disorder; 2.6% generalised anxiety disorder. "Resistant" patients - 58.3% any psychiatric disorder; 25% personality disorder; 12.5% generalised anxiety disorder.	n/a

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
22*	JME	SCID 1; SCID 2; K-SADS-PL [if aged under 18 years]; STAI	ILAE 1989	DSM-IV	47.6% any psychiatric disorder; 16.9% personality disorder, 16.9% generalised anxiety disorder; 12.3% mood disorder; 1.5% psychotic disorder.	n/a
23	JME	MMPI	ILAE 1989	n/a	No significant difference in subscale scores between GGE and healthy control participants.	See GGE symptom rates column.
24*	GGE; symptomatic focal epilepsy	Liverpool Adverse Events Profile (LAEP) [Brazilian version]; HADS [Brazilian version]; QoLIE-31 [Brazilian version]	ILAE 1989	LAEP score range 0-100, >45 considered 'toxicity' from AED.	Reported LAEP scores: Sleepiness 47.0 (42.38), Memory problems 41.9 (43.07). HADS and QoLIE not reported.	Reported LAEP scores: Sleepiness 60.1 (41.19), Memory problems 56.3 (43.69).
25	GGE; symptomatic focal epilepsy	BDI; Self-rating Depressive Scale (SDS); Washington Psychosocial Seizure Inventory (WPSI)	n/a	n/a	BDI: 4.3 (5.9); SDS: 32.9 (7.9); WPSI: 4.6 (8.5).	Simple focal epilepsy - BDI: 13.3 (9.8); SDS: 40.3 (8.6); WIP: 6.9 (7.2). CPS - BDI: 10.2 (7.6); SDS: 37.8 (7.8); WIP: 17.6 (14.9). Secondary generalised epilepsy - BDI: 10.3 (9.1); SDS: 37.4 (12.0); WIP: 7.1 (9.2).
26	JME	BDI [Brazilian version]; STAI [Brazilian version]; Temperament and Character Inventory (TCI)	ILAE 1989	Comparison of means	No rates or scores reported for BDI or STAI; depression, state anxiety, and trait anxiety scores significantly higher in JME than HC; with BDI and STAI as covariates, TCI scales Novelty Seeking and Harm Avoidance higher in JME than HC.	See GGE symptom rates column.

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
27	GGE heterogeneous	Study-designed interview regarding impact of epilepsy; standard Social Status questionnaires from Swedish SCB census	ILAE 1985/1991	Qualitative descriptions of outcomes	34.5% no close friend; 15.5% saw friends once a month or less often; 64.1% rarely met co-workers outside their jobs; 22.4% never participated in sports or other physical activities; 17.2% had sleeping problems.	7.9% no close friend; 5.8% saw friends once a month or less often; 40.6% rarely met co-workers outside their jobs; 12.4% never participated in sports or other physical activities; 7.7% had sleeping problems.
28	JME; TLE	Social Stress and Support Inverview (Jenkins et al., 1981); BDI; NEO Five-Factor Inventory; Bear Fedio Questionnaire; Morning type/Evening type Questionnaire	n/a	n/a	No rates or scores reported.	n/a
29	JME; TLE	SADS; BDI; STAIX1; STAIX2	ILAE 1989	DSM-III-R; comparison of means	22.2% psychiatric disorder; BDI and STAI results unclear, but anxiety was higher in JME than in an unspecified control group.	T1D - 10% psychiatric disorder. TLE - 80% psychiatric disorder; BDI and STAI results unclear, but TLE scores higher than all other groups.
30	GGE; TLE	BDI-II; QOLIE-31	n/a	Comparison of means	BDI-II: 8.3 (8.3) ; QOLIE-31 54.3 (18.3).	TLE - BDI-II: 15.5 (10.2); QOLIE-31: 47.8 (20.7).
31	JME	BDI; QOLIE-31-P	n/a	Comparison of means	QOLIE-31: 68.2 (15.89); BDI scores not reported.	n/a
32	GGE heterogenous; idiopathic partial epilepsy	BDI [Arabic version]; Aggressive Behavior Scale; Eysenck Personality Inventory	ILAE 1991	Not reported [however, Arabic version of BDI >16 indcates clinically significant depression (Fawzi, 2012)]	BDI: 17.5 (12.35).	HC - BDI: 8.59 (8.10).Idiopathic partial epilepsy - BDI: 20.81 (9.60)

ID #	Syndrome/s	Psychiatric/psychosocial measures	GGE diagnostic criteria	Psychiatric diagnostic criteria/Clinical cut-off used	Symptom rate/diagnosis rate/outcome GGE	Symptom rate/diagnosis rate/outcome Comparison Groups
33	JME	SCID 1; SCID 2	ILAE 1989	DSM-IV	At time of study: 35% any psychiatric diagnosis; 19% Axis I disorder; 23% personality disorder. In their lifetime: 47% any psychiatric diagnosis; 30% Axis I disorder; 26% personality disorder.	n/a
34^	CAE; JAE	Study-designed psychosocial interview (educational attainment, behaviour, pregnancy, relationships, substance use, self-reported psychiatric difficulties, employment and financial security).	ILAE 1989 equivalent	n/a	25% described themselves as loners; 16% continued to have emotional difficulties at follow up; 50% completing higher education were employed in their field of study; compared with JRA, absence epilepsy reported poorer relationships with siblings, had fewer regular social outings, worked for fewer months of the year, were more likely to have an unskilled job, were less often employed in upper management or professional positions, and more frequently reported poor job satisfaction.	JRA - 11% described themselves as loners; 7% continued to have emotional difficulties at follow up; 86% completing higher education were employed in their field of study.

Appendix 5

Clinical and demographic interview questionnaire (Chapter 5)

1	Date of assessment	
2	Name	
3	Study ID no	
4	UR number (hospital)	
5	DOB	
6	Age	
7	Gender 1male 2female	
8	Phone no	
9	Consultant : mc/wds/us/other	
10	Cohort: 1incident 2prevalent 3newly diagnosed drug-naive	
11	Syndrome 1cae 2jae 3jme 4gtcso 5other	
12	Sz types & onset age GTCS: 1yes/2no GTCS onset age:	
	Myoclonus: 1yes/2no Myoclonus onset age:	
	Absences : 1yes/2no Absence onset age:	
	EMA: 1yes/2no EMA onset age:	
	Myoclonic absence: 1yes/ 2no MA onset age:	
13	Sz type & last sz (how many days ago) GTCS: 1yes/ 2 no Last GTCS how many days ago:	
	Myoclonus: 1yes/ 2no Last myoclonus how many days ago:	
	Absences: 1yes/ 2no Last absence how many days ago:	
	EMA: 1yes/ 2no Lat EMA how many days ago:	
	Myoclonic absence : 1yes/ 2no Last MA how many days ago:	

14	On AED: 1yes/ 2no If y-current AEDs & total daily dose Valproate: Lamotrigine: Topiramate: Levetiracetam: Zonisamide: Ethosuximide: Phenytoin: Clonazepam: Carbamazepine: Primidone: Phenobarbitone: If n- ceased how many days ago:	
15	Steady state valproate level:	
16	FH epilepsy (in first degree relatives): 1yes/ 2no	
17	PH of FS: 1yes/2no	
18	FH of FS (in first degree relatives): 1yes/ 2no	
19	Epilepsy state: 1active 2remission on aed 3remission off aed	
20	Current occupation: 1managers 2professionals 3technicians and trades workers 4community and personal service workers 5clerical and administrative workers 6sales workers 7machinery operators and drivers 8labourers 9student 0unemployed	
21	Education level: 1postgraduate degree level 2graduate diploma and graduate certificate level 3bachelor degree level 4advanced diploma and diploma level 5certificate level 6secondary education 7primary education 8pre-primary education 9other education	
22	Current marital status: 1single 2other stable relationship 3de facto 4married	
23	Coexisting PNES 1yes on clinical impression 2yes confirmed on vem 3no	
24	Drivers licence: 1yes/ 2no	

Appendix 6

R packages and versions (Chapter 5)

Package	Version	Package	Version
acepack	1.3-3.3	memoise	0.2.1
AICcmodavg	2.0-3	mime	0.4
bitops	1.0-6	minqa	1.2.4
car	2.1-1	mnormt	1.5-3
caTools	1.17.1	munsell	0.4.2
chron	2.3-47	nloptr	1.0.4
coda	0.18-1	pander	0.6.0
colorspace	1.2-6	pbkrtest	0.4-4
crayon	1.3.1	plyr	1.8.3
curl	0.9.4	ppcor	1.1
descr	1.1.2	praise	1.0.0
dichromat	2.0-0	proto	0.3-10
digest	0.6.8	psych	1.5.8
evaluate	0.8	quantreg	5.19
formatR	1.2.1	R6	2.1.1
Formula	1.2-1	RColorBrewer	1.1-2
gdata	2.17.0	Rcpp	0.12.2
ggplot2	1.0.1	RcppArmadillo	0.6.200.2.0
gridExtra	2.0.0	RcppEigen	0.3.2.5.1
gtable	0.1.2	RCurl	1.95-4.7
gtools	3.5.0	reshape	0.8.5
gvlma	1.0.0.2	reshape2	1.4.1
heplots	1.0-16	rjags	Mar-15
highr	0.5.1	rmarkdown	0.8.1
Hmisc	3.17-0	rstudio	0.98.1103
htmltools	0.2.6	scales	0.3.0
httr	1.0.0	SparseM	1.7
jsonlite	0.9.19	stringi	1.0-1
knitr	1.11	stringr	1.0.0
labeling	0.3	swirl	2.2.21
latticeExtra	0.6-26	testthat	0.11.0
lm.beta	1.5-1	unmarked	0.11-0
lme4	1.1-10	VGAM	1.0-0
lmSupport	2.9.2	xtable	1.8-0
lsr	0.5	yaml	2.1.13
magrittr	1.5		
manipulate	1.0.1		
markdown	0.7.7		
MatrixModels	0.4-1		

Appendix 7

Letter fluency results (Chapter 7)

As outlined in Chapter 5, Letter fluency was assessed using the Controlled Oral Word Association Task (COWAT), and the letters F, A and S. Total scores across the 3 letters was calculated and compared to normative age- and education-based Canadian data from Tombaugh and colleagues (1996). Standard scores were then calculated.

As seen in the table below, GGE patients scored 0.7 standard score points below the normative mean on average. A one-sample t-test comparing patient scores to the definitional mean of Z=0 revealed a statistically significant reduction in patient scores ($t(63)=-4.83$, $p<0.001$). The 95% confidence interval and estimated effect size accords with previous estimates of cognitive deficits of up to 1 standard deviation points below the mean in GGE patients.

COWAT Z-Scores	
Mean (SD)	-0.70 (1.17)
95% CI	-0.99 - -0.41
Min	-5.6
Max	2.20
N	64

Appendix 8

Online Table 1 (Chapter 7)

Demographic information	AEEG only (n=51)	AEEG + Neuropsychology (n=76)	p value*	Test type	Effect size
Age (years)					
Range	17-55	13-58	-	-	-
Mean	28.29 (9.54)	28.96 (11.2)	p=0.73	t-test	d=-0.07
Gender (n)					
M	18 (35%)	26 (38.3%)	p=1.00		phi=0.01
F	33 (65%)	50 (61.7%)			
Syndrome (n)					
CAE	8 (16%)	10 (13%)	p=0.72	chi square	Cramer's V=0.13
JAE	17 (33%)	21 (28%)			
JME	11 (22%)	20 (26%)			
GTCSO	12 (24%)	23 (30%)			
Other	3 (6%)	2 (3%)			

* These tests compare AEEG only group (n=44) with Neuropsychology group (n=76) to establish equivalence of these.

Clinical information	AEEG only (n varies)	AEEG + Neuropsychology (n varies)	p value*	Test type	Effect size
Current AED (n)	(n=51)	(n=69^)			
None	8 (16%)	6 (9%)			
1	23 (45%)	32 (46%)	p=0.52	chi square	Cramer's V=0.14
2	17 (33%)	23 (33%)			
3	3 (8%)	8 (12%)			
Valproate	35 (63.6%)	32 (76.2%)			
Lamotrigine	20 (36.4)	15 (35.7%)			
Levetiracetam	8 (14.5%)	7 (16.7%)			
Other (Topiramate, Zonisamide, Piracetam, Carbamazepine, Clonazepam)	8 (14.5%)	10 (23.8%)	N/A: Not mutually exclusive		
History of absence seizures (n)					
No	24 (47%)	35 (51%)	p=0.83	chi square	phi=0.04
Yes	27 (53%)	34(49%)			
History of GTCS (n)					
No	4 (8%)	8 (12%)	p=0.71	chi square	phi=0.06
Yes	47 (92%)	61 (88%)			
Seizure free duration (days)	(n=58)	(n=45)			
Range	1-5290	1-9855	-	-	-
Median; IQR	90; 347.5	150; 707			
Duration ED of any length in 24hrs (s)	(n=58)	(n=45)			
Range	0-835.5	0-835.5	-	-	-
Mean	91.23 (166.11)	76.15 (146.14)	p=0.32	t-test	-0.096

* These tests compare AEEG only group with Neuropsychology group to establish equivalence of these (numbers vary on the basis of data availability). ^Detailed clinical information not available from n=7

Appendix 9

Online Table II (Chapter 7)

	BIA	Gc	Gf	Glr	Gs	Gsm
GGE Syndrome (F(4, 70)=1.16, p=0.29, η2=0.09; medium effect)						
Childhood absence epilepsy (n=10)						
Range	81-130	73-135	84-133	70-126	59-67	85-120
Mean (SD)	94 (14.39)	93.6 (17.24)	99.9 (15.72)	88.4 (16.89)	91.2 (12.29)	98.2 (12.9)
Juvenile absence epilepsy (n=21)						
Range	63-116	64-121	80-117	41-112	46.5-131.5	76-135
Mean (SD)	93.38 (13.91)	93.62 (13.9)	97.71 (9.24)	89.38 (16.44)	90.88 (17.69)	104.67 (16.03)
Juvenile myoclonic epilepsy (n=20)						
Range	82-119	87-129	77-123	66-112	75-113	77-141
Mean (SD)	97.8 (10.23)	100 (10.53)	99.3 (11.79)	91.8 (10.72)	92.25 (8.66)	111.85 (16.03)
GGE with GTCS only (n=23)						
Range	66-114	71-113	70-120	56-109	33-132.5	74-137
Mean (SD)	92.91 (12.25)	92.52 (10.12)	96.91 (12.72)	84.83 (13.39)	91.3 (16.89)	95.32 (17.22)
Other GGE (n=2)						
Range	69-86	78-93	72-87	59-67	73-93.5	84-89
Mean (SD)	77.5 (12.02)	85.5 (10.61)	79.5 (10.61)	63 (5.66)	83.25 (14.5)	86.5 (3.54)
Absence seizures (F(1, 66)= 0.30, p=0.94, η2=0.028; small effect)						
History of absence seizures (n=34)						
Range	63-130	64-135	77-133	41-126	46.5-131.5	76-135
Mean (SD)	93 (13.12)	94.03 (15.42)	97.5 (11.75)	88.29 (15.25)	90.78 (15.1)	104.24 (14.69)
No history of absence seizures (n=35)						0.25 (d)
Range	66-119	71-113	70-120	56-112	33-132.5	74-141
Mean (SD)	93.31 (12.15)	94.77 (10.29)	96.99 (12.27)	85.8 (14.18)	90.57 (14.47)	100.97 (20.05)
GTCS (F(1,70)=1.24, p=0.30, η2=0.10; medium effect)						
History of GTCS (n=65)						
Range	63-119	67-129	70-123	41-112	33-132.5	74-137
Mean (SD)	93.23 (12)	94.62 (11.63)	96.65 (11.46)	86.78 (14.5)	90.28 (14.96)	102.12 (17.15)
No history of GTCS (n=8)						
Range	74-130	64-135	84-133	80-126	87-120	85-141
Mean (SD)	96.12 (17.26)	94.62 (11.63)	101.88 (16.47)	94.38 (14.45)	98.75 (10.49)	106 (18.74)

Appendix 10

Online Tables III-VIII (Chapter 7)

III	Depressive Sx Present n=12		Depressive Sx Absent n=38					
Cognitive Domain	M	SD	M	SD	n	Pillai	F (6,42)	Sig. (2 tailed)
Overall ability (BIA)	92.67	9.01	95.26	11.60				
Crystallised intelligence	93.33	8.56	94.79	11.54				
Fluid intelligence	99.25	13.06	98.03	11.22				
Long-term retrieval and memory	86.83	12.24	90.00	12.40	50	0.1	0.76	0.6049
Speed of information processing	89.71	6.19	93.34	10.71				
Short-term/Working memory	97.93	12.32	104.13	16.30				

IV	Anxiety Sx Present n=7		Anxiety Sx Absent n=43					
Cognitive Domain	M	SD	M	SD	n	Pillai	F (6,42)	Sig. (2 tailed)
Overall ability (BIA)	94.44	10.95	95.04	11.94				
Crystallised intelligence	94.88	5.00	94.36	11.66				
Fluid intelligence	104.62	12.35	97.12	11.16				
Long-term retrieval and memory	87.50	9.35	89.57	12.87	50	0.18	1.49	0.204
Short-term/Working memory	95.12	13.11	104.17	15.77				
Speed of information processing	91.62	8.98	92.63	10.14				

V	Somatic Sx Present n=6		Somatic Sx Absent n=43					
Cognitive Domain	M	SD	M	SD	n	Pillai	F (6,42)	Sig. (2 tailed)
Overall ability (BIA)	90	13.24	95.40	10.58				
Crystallised intelligence	93.86	12.69	94.53	10.67				
Fluid intelligence	93.14	13.06	99.16	11.24				
Long-term retrieval and memory	84.29	16.19	90.05	11.60	49	0.08	0.58	0.7474
Short-term/Working memory	99.5	16.45	103.14	15.64				
Speed of information processing	90.93	10.98	92.72	9.81				

VI	Avoidant Sx Present n=8		Avoidant Sx Absent n=42					
Cognitive Domain	M	SD	M	SD	n	Pillai	F (6,42)	Sig. (2 tailed)
Overall ability (BIA)	95	7.93	94.57	11.57				
Crystallised intelligence	94.00	6.48	94.52	11.54				
Fluid intelligence	101.12	10.87	97.79	11.74				
Long-term retrieval and memory	92.88	6.42	88.55	13.08	50	0.14	1.13	0.3626
Short-term/Working memory	94.00	12.55	104.39	15.71				
Speed of information processing	92.75	6.93	92.42	10.42				

VII	ADHD Sx Present n=10			ADHD Sx Absent n=39					
Cognitive Domain	M	SD		M	SD	n	Pillai	F (6,42)	Sig. (2 tailed)
Overall ability (BIA)	98.27	12.81	93.62	93.62	10.39				
Crystallised intelligence	96.18	7.67	93.95	93.95	11.61				
Fluid intelligence	100.73	12.35	97.64	97.64	11.40				
Long-term retrieval and memory	89.73	16.43	89.10	89.10	11.15	49	0.1	0.75	0.6521
Short-term/Working memory	101.10	17.70		103.10	15.26				
Speed of information processing	94.73	11.16		91.93	9.55				

VIII	Antisocial Sx Present n=3			Antisocial Sx Absent n=46					
Cognitive Domain	M	SD		M	SD	n	Pillai	F (6,42)	Sig. (2 tailed)
Overall ability (BIA)	90	8.72		94.94	11.14				
Crystallised intelligence	94.67	7.09		94.43	11.08				
Fluid intelligence	95.00	9.17		98.53	11.75				
Long-term retrieval and memory	89.15	12.67		90.67	4.67	49	0.09	0.70	0.6521
Short-term/Working memory	91.00	4.36		103.76	15.79				
Speed of information processing	88.83	8.61		92.70	10.00				

Appendix 11

Subtests of the Woodcock Johnson III Tests of Cognitive Ability (Chapter 8)

Cluster ability	Subtest	Description of test
Overall Cognitive Ability (BIA) - Comprehension Knowledge – (Gc) - Fluid Reasoning – (Gf) - Processing Speed – (Gs)	1. Verbal Comprehension	Naming pictured objects; finding synonyms and antonyms; completing analogies.
	5. Concept Formation	Identifying rules for geometric figures.
	6. Visual Matching	Speeded task to identify identical numbers.
Short-term memory (Gsm)	7. Numbers Reversed	Verbally repeat numbers in reverse order.
	17. Memory for Words	Repeating words in their stated order.
Anterograde memory (Glr)	2. Visual-Auditory Learning	Learn and remember a growing list of word/symbol associations.
	12. Retrieval Fluency	Stating words from categories in 1 minute.

BIA: Brief Intellectual Ability; Gc: Crystallised Intelligence/Acquired Knowledge; Gf: Fluid Intelligence; Gs: Speed of Information Processing; Gsm: Short-term Memory; Glr: New Learning and Memory Function

Appendix 12

Cognitive functioning scores by concurrent and non-concurrent EEG group (Chapter 8)

Cognitive Factor	**Concurrent Group (n=22)**	**Non-concurrent Group (n=47)**	**p-value**
BIA	91.0 (14.1)	94.2 (11.8)	0.36
Glr	82.6 (17.5)	89.1 (12.8)	0.13
Gsm	100.3 (19.5)	103.7 (16.6)	0.49

Appendix 13

Regression diagnostics for simple and multiple regression analyses (from R packages gvlma) (Chapter 8)

BIA - Simple regression

Assumptions test	Value	p-value	Decision
Global Stat	1.4565	0.8343	Assumptions acceptable.
Skewness	0.4432	0.5056	Assumptions acceptable.
Kurtosis	0.0455	0.8311	Assumptions acceptable.
Link Function	0.0971	0.7553	Assumptions acceptable.
Heteroscedasticity	0.8707	0.3508	Assumptions acceptable.

Glr - Simple regression

Assumptions test	Value	p-value	Decision
Global Stat	6.2017	0.18458	Assumptions acceptable.
Skewness	1.4408	0.23001	Assumptions acceptable.
Kurtosis	0.3347	0.56291	Assumptions acceptable.
Link Function	3.0933	0.07862	Assumptions acceptable.
Heteroscedasticity	1.3329	0.24828	Assumptions acceptable.

Gsm - Simple regression

Assumptions test	Value	p-value	Decision
Global Stat	5.6602	0.226	Assumptions acceptable.
Skewness	2.4203	0.1198	Assumptions acceptable.
Kurtosis	1.439	0.2303	Assumptions acceptable.
Link Function	1.2824	0.2574	Assumptions acceptable.
Heteroscedasticity	0.5186	0.4714	Assumptions acceptable.

BIA – Multiple regression

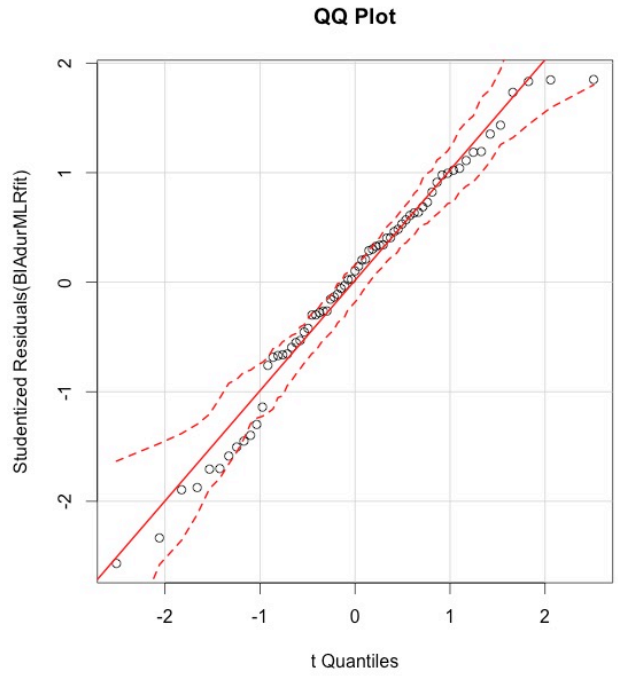
Assumptions test	Value	p-value	Decision
Global Stat	1.9257	0.7494	Assumptions acceptable.
Skewness	0.4289	0.5125	Assumptions acceptable.
Kurtosis	0.1625	0.6869	Assumptions acceptable.
Link Function	0.6426	0.4228	Assumptions acceptable.
Heteroscedasticity	0.6917	0.4056	Assumptions acceptable.

Test of multicollinearity – Variance inflation factors

	Total ED duration	Absence	Polytherapy	Age
Value	1.142279	1.127006	1.086923	1.057449.
Interpretation (Square root of value under 2 is acceptable)	Acceptable	Acceptable	Acceptable	Acceptable

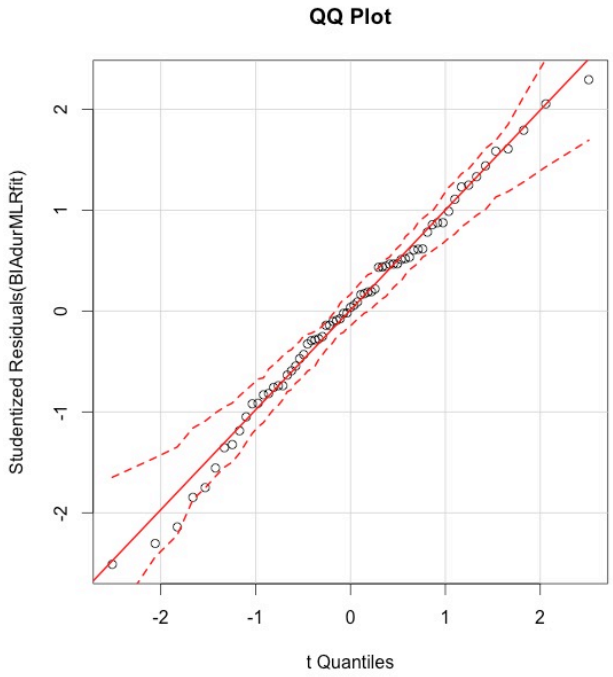
Appendix 14

QQ plot of studentized residuals for prediction of BIA by duration of epileptiform discharges (Chapter 8)



Appendix 15

QQ plot of studentized residuals for prediction of GIr by duration of epileptiform discharges (Chapter 8)



Appendix 16

Equivalence analyses for demographic and clinical information (Chapter 9)

Variables	Total sample (n=60)	Paired data (n=47)	Unpaired self-report only data (n=13)	Statistics	Sig. (2-tailed)*
Age (years)					
Range	18-58	18-58	18-57	-	-
Mean	31.62 (10.95)	31.11 (10.80)	33.46 (11.73)	t (58)=0.68	p=0.50
Gender (n)					
M	18 (30%)	18 (38.3%)	13 (100%)	χ^2 (1)=5.41	p=0.002
F	42 (70%)	29 (61.7%)	0 (0%)		
Syndrome (n)					
CAE	6 (10%)	6 (12.8%)	0 (0%)		
JAE	17 (28.3%)	13 (40.4%)	4 (30.8%)		
JME	16 (26.7%)	12 (25.5%)	4 (30.8%)	χ2 (4)=5.45	p=0.24
GTCSO	20 (33.3%)	16 (34.0%)	4 (30.8%)		
Other	1 (1.7%)	0 (0%)	1 (0.8%)		
Detailed clinical information	**Total sample (n=56)**	**Paired data (n=43)**	**Unpaired self-report only data (n=13)**	**Statistics**	**Sig. (2-tailed)***
Current AED (n)					
None	3 (4.76%)	1 (1.8%)	2		
1	27 (42.86%)	20 (36.4%)	6		
2	22 (33.33%)	26 (29.1%)	5	χ2 (3)=3.08	p=0.38
3	4 (6.35%)	4	0		
	(n=55)	**(n=42)**	**(n=13)**		
Valproate	35 (63.6%)	32 (76.2%)			
Lamotrigine	20 (36.4)	15 (35.7%)			
Levetiracetam	8 (14.5%)	7 (16.7%)		-	-
Other (Topiramate, Zonisamide, Piracetam, Carbamazepine, Clonazepam)	8 (14.5%)	10 (23.8%)			
History of absence seizures (n)	**(n=55)**	**(n=42)**	**(n=13)**		
No	28 (50.9%)	19 (45.2%)	9 (69.2%)	χ2 (1)=1.43	p=0.23
Yes	27 (49.1%)	23 (54.8%)	4 (30.8)		
History of GTCS (n)	(n=58)	(n=45)	(n=13)		
No	5 (8.6%)	2 (4.4%)	3 (23.1%0	χ2 (1)=2.39	p=0.12
Yes	53 (91.4%)	43 (95.6%)	10 (76.9%)		
Seizure free duration (days)	**(n=58)**	**(n=45)**	**(n=13)**		
Range	1-9855	1-5110	1-9855	n/a	
Median, IQR	129, 660.25	150, 463	92; 723	t (12.71)=-1.25	p=0.23
Total duration ED of any length in 24hrs (s)	(n=58)	(n=45)	(n=13)		
Range	0-835.5	0-835.5	0-750.3	n/a	
Mean	91.23 (166.11)	76.15 (146.14)	143.4 (221.27)	t (15.15)=-1.03	p=0.32

*These tests compare paired data group (n varies) with self-report only group (n=13) to establish equivalence of these.

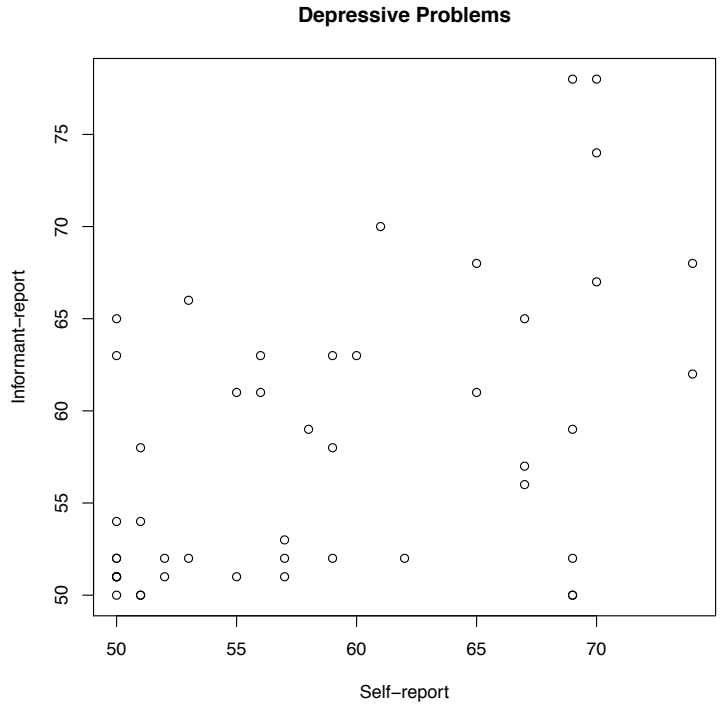
Appendix 17

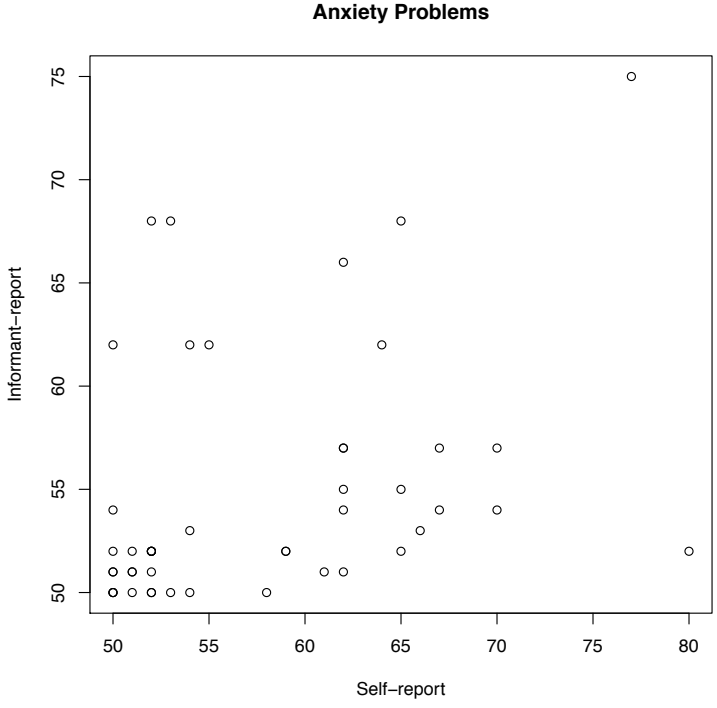
Prediction of psychopathology symptoms scores by seizure variables (Chapter 9)

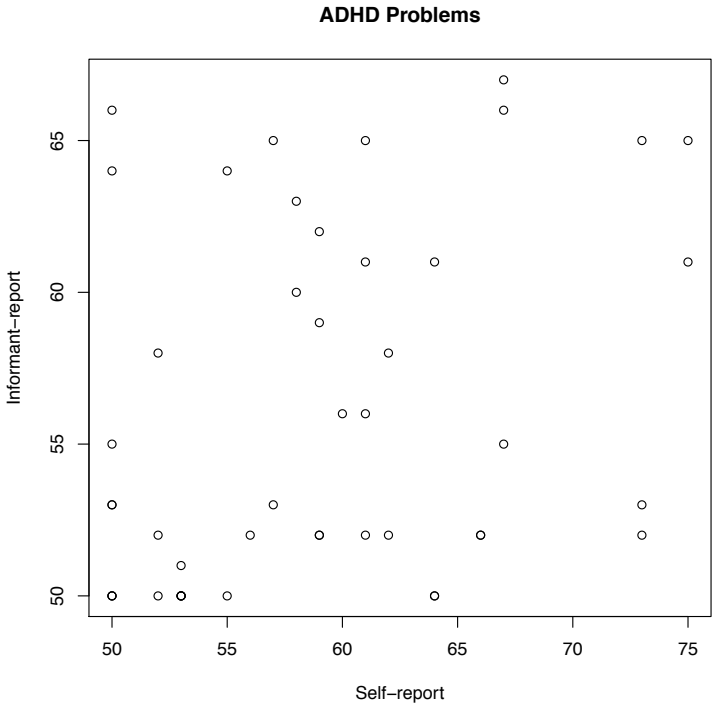
	β	SE	t	p
Variable		Depressive symptoms		
Seizure-free duration	0.00	0.00	-0.54	0.59
Epilepsy duration	0.10	0.11	0.90	0.37
Total duration of epileptiform discharges over 24 hours	0.00	0.01	-0.59	0.56
Overall model	F(3,52)=0.41, R^2=0.23, p=0.75			
		Anxious symptoms		
Seizure-free duration	<0.01	<0.01	0.70	0.49
Epilepsy duration	0.06	0.09	0.73	0.49
Total duration of epileptiform discharges over 24 hours	-0.01	0.01	-1.06	0.29
Overall model	F(3,52)=0.83, R^2=0.04, p=0.49.			
		Somatic symptoms		
Seizure-free duration	<-0.01	<0.01	-1.07	0.29
Epilepsy duration	0.17	0.11	1.52	0.14
Total duration of epileptiform discharges over 24 hours	<-0.01	<0.01	-0.93	0.36
Overall model	F(3,52)=1.20, R^2=0.06, p=0.31			
		Avoidant symptoms		
Seizure-free duration	<0.01	<0.01	0.09	0.93
Epilepsy duration	<0.01	<0.01	-0.27	0.79
Total duration of epileptiform discharges over 24 hours	<0.01	<0.01	-1.17	0.25
Overall model	F(3,52)=0.51, R^2=0.0.03, p=0.68			
		ADHD symptoms		
Seizure-free duration	<-0.01	<0.01	-0.94	0.35
Epilepsy duration	<-0.01	0.09	-0.18	0.86
Total duration of epileptiform discharges over 24 hours	<-0.01	<0.01	-0.79	0.43
Overall model	F(3,52)=0.49, R^2=0.03, p=0.69			
		Anti-social behaviour		
Seizure-free duration	0.00	0.00	-0.54	0.59
Epilepsy duration	0.10	0.11	0.90	0.37
Total duration of epileptiform discharges over 24 hours	0.00	0.01	-0.59	0.56
Overall model	F(3,52)=0.41), R^2=0.23, p=0.75			

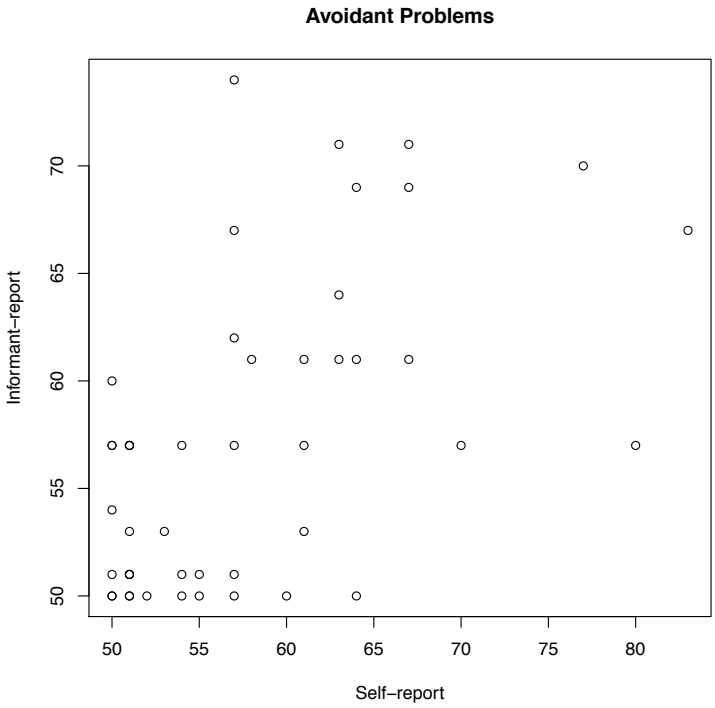
Appendix 18

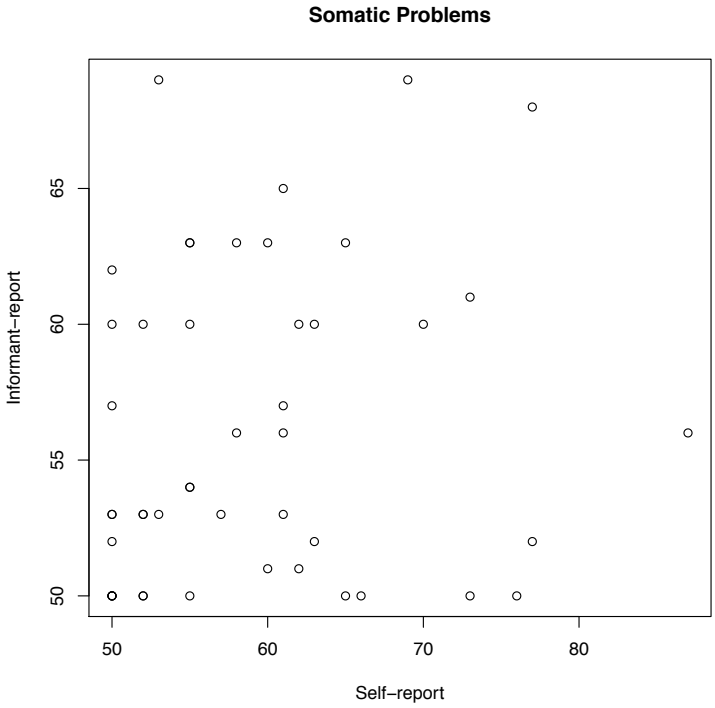
Bivariate scatterplots of self and informant report scores on all DSM subscales (Chapter 9)

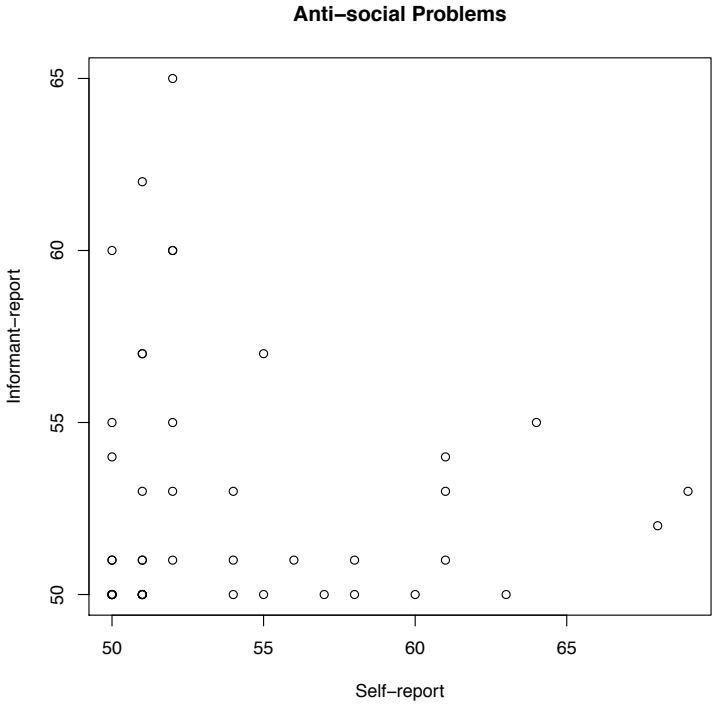





ADHD Problems
Informant−report
Self−report
50
55
60
65
70
75


Avoidant Problems
Informant−report
Self−report
50
55
60
65
70
75
80


Somatic Problems
Informant−report
Self−report
50
55
60
65
50
60
70
80


Anti−social Problems
Informant−report
Self−report
50
55
60
65
50
55
60
65

Appendix 19

Adaptive functioning in GGE (Chapter 9)

Paired samples self- and informant-report scores on Adaptive Functioning subscales

	Self-Report			Informant-Report		
Adaptive functioning Subscale	M	SD	n	M	SD	n
Friends	37.87	22.15	47	39.45	21.93	47
Spouse	31.71	24.6	31	32.65	23.95	31
Family	39.6	22.86	48			
Job (previous 6 months only)	32.64	24.24	33	N/A		
Education(previous 6 months only)	28.04	26.26	25			
Mean Adaptive Scale	38.71	22.56	48			

As seen in Table 7 of the Methods Chapter (page 88), the normal range for Adaptive Functioning Subscale scores is T>35. A series of Bonferroni-corrected one-sample t-tests showed no significant differences between our sample from the normative mean value of T=35 (all ps>0.05).

The informant-report measures include subscales for Friends and Spouse (where applicable), but not Family, Job, Education or Mean Adaptive Functioning Scale. Comparison of self- and informant reported scores on adaptive function scales were therefore not undertaken.

Appendix 20

Substance-use in GGE (Chapter 9)

Paired samples self- and informant-report scores on Substance-Use subscales

	Self-Report			Informant-Report			95% CI for Mean Difference					
Substance-Use Subscale	M	SD	n	M	SD	n			t	df	Cohen's *d*	Sig. (2 tailed)
Tobacco	51.57	4.47	47	51.62	4.72	48	-0.58	0.41	-0.35	46	0.05	NS
Alcohol	53.89	5.49	46	54.74	6.24	47	-1.99	0.08	-1.86	45	0.27	NS
Drugs	50.64	3.09	47	50.47	3.21	47	-0.44	-0.79	0.57	45	0.08	NS
Any Substance-Use	52.3	4.17	46	53.3	4.15	46	-1.93	-0.38	-3.02	44	0.43	P=0.006

As seen in Table 7 of the Methods Chapter (page 88), the normal range for Substance-Use scales is T<65. All subscale means in the current sample fell below this score, suggesting no apparent elevation in substance-use problems in GGE. For overall substance-use, informant-report scores were significantly higher than self-report, with moderately large effect size. This suggests greater insight or willingness to disclose substance-use history in informants compared to patients.