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Department of Pharmacology, Institute of Translational Medicine

DRUG REFRACTORY JUVENILE MYOCLONIC EPILEPSY: NEUROPSYCHOLOGICAL PROFILE AND PSYCHIATRIC SYMPTOMS

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CONTENTS

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ABSTRACT

BACKGROUND

Juvenile myoclonic epilepsy (JME) is a common type of idiopathic generalized epilepsy with onset occurring during adolescence. JME is life-long in most individuals, but around 80% gain good seizure control with anti-epileptic drugs (AEDs). Impairments in executive function are consistently demonstrated in JME and are similar to those reported in patients with cluster B personality disorders. Moreover, a high incidence of personality and affective disorders has been reported in JME. This research aimed to profile drug-refractory JME, and address whether the executive dysfunctions and maladaptive behaviour reported in JME patients is related.

METHODS

A total of 60 patients with drug-refractory JME were administered tests of intellect, memory and executive functions. Anxiety, depression, personality traits, impact of epilepsy and perceived cognitive effects of AEDs were measured.

RESULTS

The sample as a whole presented with poorer neuropsychological functioning than published norms. Abnormal personality traits and high levels of anxiety were associated with the worse intellectual and executive functioning. Half of the cohort exhibited moderate to severe anxiety symptoms.

CONCLUSIONS

This research indicates that specific patterns of executive dysfunctions are related to maladaptive behaviour in drug-refractory JME. This research has identified a possible subgroup of patients that present with a more severe type of JME, and may be distinguished by genetic stratification. Finally, the current research confirms the breadth of deficits in drug-refractory JME, and highlights that it is more than just executive function difficulties that must be targeted to support individuals through education and employment.

RELATED PUBLICATIONS

JOURNAL ARTICLES

Walsh, J., Thomas, R.H., Church, C., Rees, M.I., Marson, A.G. and Baker, G.A. (2014). Executive functions and psychiatric symptoms in drug-refractory juvenile myoclonic epilepsy. *Epilepsy and Behavior* 35, 72-77.

Thomas, R.H., Walsh, J., Sills, G.J., Church, C., Marson, A.G., Baker, G.A. and Rees, M.I. (2014). A comprehensive neuropsychological description of cognition in drug-refractory juvenile myoclonic epilepsy. *Epilepsy and Behavior* 36, 124-129.

POSTER PRESENTATIONS

Walsh, J., Marson, A.G., Smith, P.E.M., Rees, M.I., Baker, G.A. and Thomas, R.H. Neuroticism and executive functions in drug refractory JME. Annual Epilepsy Society Meeting, The Hague, The Netherlands, 2012.

Thomas, RH, Marson, AG, Smith, PEM, Rees, MI, Baker, GA and Walsh, J. Neuroticism and executive functions in drug refractory JME. Annual Epilepsy Society Meeting, San Diego, USA, 2012.

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CHAPTER ONE – INTRODUCTION

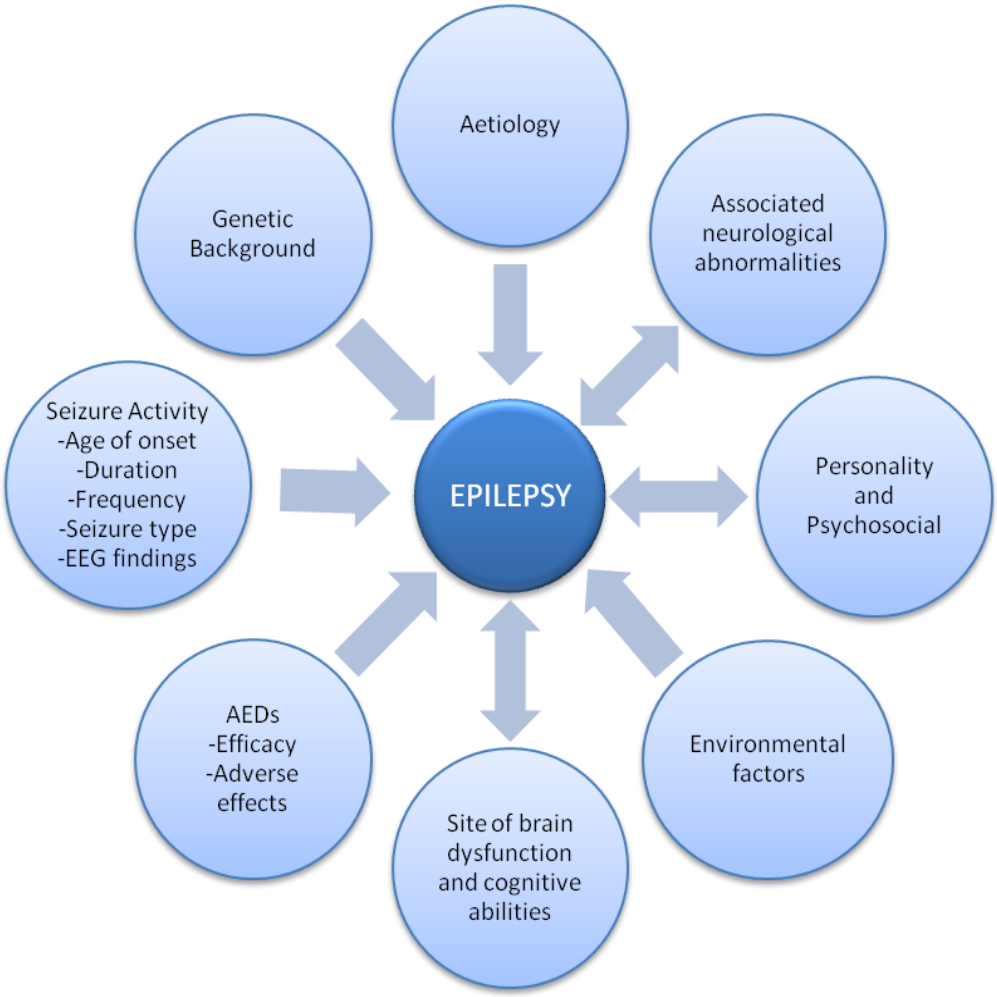
Epilepsy is a neurological disorder that is characterised by an increased predisposition to the occurrence of a transient event of abnormal paroxysmal discharges, in a group of cerebral neurons or the majority of the cortex [1]. This activity is known as an epileptic seizure. People with epilepsy (PWE) have a predisposition to epileptic seizures and must experience at least two to be diagnosed with the disorder [2]. It is associated with disturbances in neurobiological, cognitive and psychosocial functioning [3]. Epilepsy is divided into syndromes, which are usually defined by the area of the brain the activity starts in and spreads to (i.e. primary generalised, partial and secondary generalised), by the types of seizures experienced (e.g. myoclonic, tonic-clonic, absent, tonic, atonic), the age of onset and aetiology [1].

Patients who have seizures that have non-focal onset (i.e. generalised) make up 30-40% of cases [4], with the majority of these exhibiting seizure with no identifiable cause, but a genetic predisposition. This is called idiopathic generalised epilepsies (IGE) [5]. IGE is the most common form of generalised epilepsy, with several syndromes that fall under the IGE title [6]. Patients with IGE usually have normal intellectual functioning, and have no visible abnormalities on brain scans [6].

Juvenile Myoclonic Epilepsy (JME) is an IGE that accounts for 6-12% of all epilepsy cases [7] and approximately 26% of IGE cases [8]. The onset of JME can occur between the ages of 6 and 22 years, with 50% of cases presenting between the ages of 13-16 years [9]. The disorder is thought to be lifelong [10] with the majority of patients responding to treatment [11].

JME typically presents with bilateral, arrhythmic myoclonic jerks that can be single or repetitive, and usually involve the upper extremities [12]. JME is also often associated with generalised tonic-clonic seizures in around 80-97% of patients, and absence seizures in 12-54% [9]. Nevertheless myoclonic seizures must be present for a diagnosis of JME [9]. An EEG characterised by polyspike-and-wave complexes is commonly found in JME patients.

It is well documented that patients with JME show impairments in neuropsychological assessments [7, 11-16]. These impairments are multi-factorial and encompass pathophysiology, treatment, psychosocial factors, seizure -type, -duration, -severity and –onset (illustrated in figure 1.1). However, past research has assessed patients with controlled JME or mixed samples of controlled and refractory patients. The current thesis aimed to profile purely refractory JME to investigate whether these patients have worse cognition and if clinical characteristics have a bigger impact.



Adapted from [17]

Figure 1.1 The multiple and interacting factors that contribute to each individual patient's epileptic disorder

Impairments in executive functions are the most consistent finding in JME [7, 11-13, 16]. The executive dysfunctions found are similar to those reported in patients with personality disorders [18, 19]. Moreover, researchers have described structural and functional abnormalities in the frontal lobes of JME [20-22], which have also been reported in patients with personality disorders [23, 24].

It has been hypothesised that JME is not one disorder but several and past research has attempted to categorise JME patients into subgroups [25]. Research has found different levels of neuropsychological dysfunction, psychiatric disorders and different personalities in JME patients [26, 27]. One study proposed that distinct behavioural differences may be a result of specific brain dysfunctions caused by different epilepsies [28]. The current thesis aimed to examine whether executive dysfunctions and maladaptive behaviour were related, and if the different levels of dysfunction could be explained by different patterns of behaviour.

The objectives of the current thesis are to:

1. Verify the neuropsychological profile of refractory JME.
2. Examine the contribution of age of onset, duration of epilepsy, education, type of seizures, treatment, mood, impact of epilepsy and subjective view of cognitive functioning.
3. Examine whether refractory JME patients with high levels of anxiety and/or depression are more impaired on neuropsychological functioning tests than those with normal levels of anxiety and/or depression
4. Examine the relationship between personality and executive dysfunctions. Aim to provide evidence for frontal lobe involvement, and for the hypothesis that there is more than one type of JME.

An overview of epilepsy as a whole will be discussed in Chapter two. Chapter three will give a more in depth description of JME including the possible causes, diagnosis, treatment and prognosis.

Past research that has investigated the neuropsychological dysfunctions in JME will discussed in Chapter four. In addition, an analysis of the research that has investigated

the possible causes of these deficits will be given here. The chapter will discuss each of the multiple factors given above.

Chapter five will provide a detailed discussion of the current theses aims and hypotheses. The methodology employed to meet these aims will be given in Chapter six. This will be followed by the results of each of the hypotheses in Chapter seven to twelve. This thesis will end with a discussion of the findings from the current study in relation to past research, and future practise and investigation. Any limitations will also be given here.

CHAPTER TWO – EPILEPSY

Epilepsy has been documented since ancient times with reference to those who are *possessed* found in ancient scripture [29]. The WHO state that Epilepsy is the oldest condition known to mankind [30], and still remains the most common neurological disorder directly affecting 50 million people worldwide at any given time [31].

The word epilepsy comes from the Greek verb *ελαμβανειν (eng: elamvaneen),* which translated means *"to be seized by forces from without"* [32]. Epilepsy was first described as a disorder of the brain in an essay presumed to have been written by Hippocrates titled *The Sacred Disease,* in which he described a generalised epileptic seizure [29]. However, historically epilepsy was thought to be a punishment from God. Yet still today stigma remains, especially in developing countries where some people believe epilepsy is an act of witchcraft or that it is infectious [29].

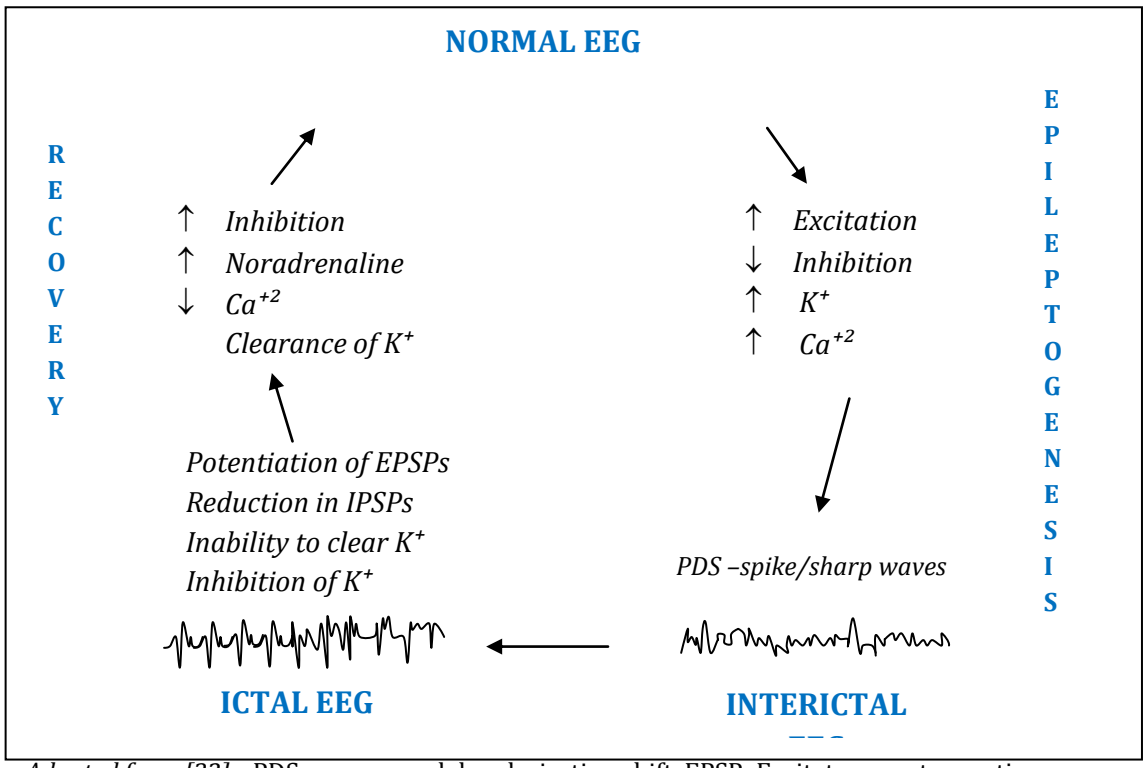
It wasn't until the 19th century that the first steps of contemporary thinking about epilepsy were taken [33]. This step was taken by John Hughlings Jackson; through detailed observations of individual cases he defined epilepsy as *"An occasional, excessive, and disorderly discharge of nerve tissue."* [32]. He also went on to highlight that epilepsy can affect anyone, at any age and from countless causes, *"This discharge occurs in all degrees; it occurs with all sorts of conditions of ill health at all ages, and under innumerable circumstances."* [32].

The accepted definition of epilepsy and of seizures provided by the International League Against Epilepsy (ILAE) is given in table 2.2 below.

2.1 HOW DO SEIZURES HAPPEN?

The events that lead to the ictal state are not fully understood, but experimental models of epilepsy show that seizures are preceded by massive depolarisation of neurons, which lead to a series of synchronised action potentials. This is called the paroxysmal depolarisation shift (PDS) [32]. The PDS can be due to several mechanisms, these may

include; changes in extracellular ion concentrations, disturbances in neuronal membranes, disturbances in excitatory or inhibitory neurotransmitters, and changes in K^+ or Ca^{2+} currents [32] (See Figure 2.1 below for an illustration of the possible processes involved in epileptogenesis). These changes may occur in an epileptiform focus (may be responsible for focal seizures), or the action potentials may spread through synaptic pathways (may be responsible for generalised seizures). Many anti-epileptic drugs (AEDs) act on one of these mechanisms. For example Carbamazepine's (CBZ) primary mode of action is to inhibit voltage-gated NA^+ channels [34].



Adapted from [32]. PDS: paroxysmal depolarisation shift, EPSP: Excitatory postsynaptic potentials, IPSP: Inhibitory postsynaptic potentials.

Figure 2.1 Possible mechanisms of interictal and ictal events

2.2 DIFFERENTIAL DIAGNOSIS

It can be a challenge to distinguish and diagnose epilepsy and non-epileptic paroxysmal events [35]. Studies have reported that a concerning 20-30% of patients are misdiagnosed with epilepsy [36, 37]. The most common conditions to be misdiagnosed as epilepsy are psychogenic non-epileptic attacks and syncope [36, 37]. Table 2.1 below highlights the possible differential diagnosis of epilepsy.

Table 2.1 Possible differential diagnosis of epilepsy

Psychogenic non-epileptic attacks	
Syncope	
Hypoglycemia	
Panic attacks	
Paroxysmal movement disorders	Acute dystonic reactions
	Hemifacial spasm
	Non-epileptic myoclonus
Sleep disorders	Parasomnias
	Cataplexy
	Hypnic jerks
	Transient ischemic attacks
Migraines	
Transient global amnesia	

Adapted from [36]

2.3 Definition and Classification of Epilepsy

Table 2.2 Definitions provided by the International League Against Epilepsy (ILAE)

A seizure	A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
Epilepsy	A brain disorder characterised by an enduring predisposition to generate epileptic seizures and by the neurologic, cognitive, psychological and social consequences of this condition.

Adapted from [3]

A person is only said to have epilepsy following the occurrence of at least two unprovoked seizures without any acute provoking event e.g. infection, brain trauma, drugs or alcohol withdrawal. A seizure involving any precursory event is referred to as provoked seizures (also known as symptomatic or reactive seizures), whereas a true epileptic seizure is referred to as unprovoked [1, 2].

Epilepsy is not a single disease, but a broad term that is used to describe a propensity to unprovoked seizures arising from a wide range of pathological causes [17]. Epilepsies are classified in two ways; firstly by the type of seizures experienced, focal or generalized, and secondly by particular patterns of symptoms and patient characteristics, which are clustered into syndromes [2, 38].

2.3.1 Epileptic Seizures

Defining seizure types is the first step in classification, but nonetheless can still be useful [38]. All seizures can be grouped into two primary types, focal and generalised.

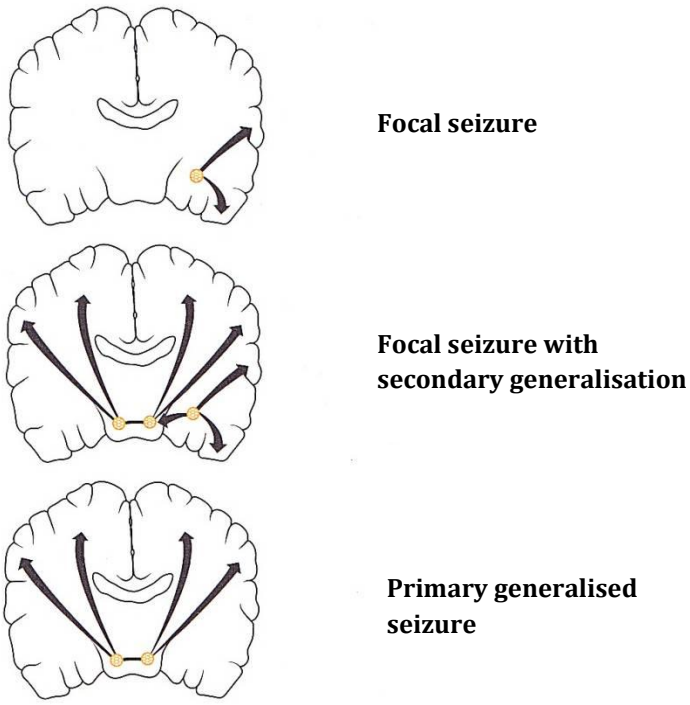


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Figure 2.2 Brain involvement during different types of seizures

2.3.1.1 Focal (partial) seizures

Focal seizures are characterised by the area of cortex the discharge of abnormal nerve cells originates [2]. The initial activation of focal seizures takes place in only part of one cerebral hemisphere [38], and can be in any of the four lobes (frontal, temporal, parietal and occipital). A seizure originating in the motor cortex of one of the frontal lobes causes contralateral contractions of the muscle. The most likely nerve cells the discharge may start in are those that control the index finger and thumb, corner of the mouth and big toe, as there are more nerve cells assigned to these muscles [2]. Seizures occurring in other lobes of the brain may be less obvious. A seizure in the parietal lobe may merely cause a perception of pins and needles or numbness in the opposite side of the body. Similarly, temporal lobe seizures may result in the feeling of déjà vu or an unpleasant smell or hallucination [2].

Focal seizures may or may not result in a loss of consciousness. Seizures in which consciousness is maintained are referred to as simple partial seizures, while those that result in loss of consciousness are referred to as complex partial seizures. Recently it has been proposed that both types of seizures should be referred to only as focal seizures with the addition of a very detailed description of what happened [2, 38]. However, the terms simple and complex partial seizures continue to be used.

Focal seizures may also develop into secondary generalised tonic-clonic seizures, in which the paroxysmal discharge spreads to central nerve cells from the original focal point. From these centralised cells the discharge spreads throughout the brain [2].

2.3.1.2 Generalised seizures

Generalised seizures can be convulsive or non-convulsive, and involve widespread bilateral discharges [39]. There are three main types of generalised seizures, namely generalised tonic-clonic seizure (GTCS), typical absence seizures (absences) and myoclonic seizures (myoclonus) [38].

Tonic-clonic seizures

GTCS are the hallmark convulsive seizures, known in lay terms as fits. They differ from secondary generalised seizures by their point of origin. GTCS begin in central nerve cells, which result in widespread involvement of the cerebral cortex. Nerve cells in the

brain stem connected to the cerebral cortex enable direct transmission to muscle fibres, resulting in the characteristic muscle contractions seen in GTCS [2, 39].

Most GTCS are sudden and happen without warning other than possibly precursory myoclonus or absences, however these may be so brief that the person or onlookers may be unaware of them [38]. GTCS begin with the tonic stage (contraction), in which the muscles of the body contract and become rigid causing the person to collapse. People often bite their tongue or inside of their cheek as their jaw contracts, and grunt or cry as the respiratory muscles contract, and air is expelled. Blood oxygen is used up rapidly with no coordinated breathing movements, resulting in cyanosis (the person becoming a dusky blue colour). Increased pressure in the thorax causes vasodilatation in the face worsening the look of cyanosis. The person may dribble as normal swallowing ceases resulting in a build up of saliva. Incontinence may also occur. [2, 32].

The clonic stage (convulsive) starts within one-two minutes of the tonic stage starting. This phase involves rhythmic movements of gradually increasing frequency of the limbs and trunk muscles. The frequency increases over 30-60 seconds, and then gradually decreases over one-two minutes. Overall the entire seizure usually lasts approximately three-five minutes, following which the person regains consciousness, yet remains confused for some time afterwards. Many people will then sleep for at least a couple of hours, and awake afterwards feeling lethargic and stiff [2, 32].

Absence Seizures

Absences were formally known as *petite mal*, which translated means *'little illness'*. This confuses people, and thus is no longer used in clinical practise. Absences can go unnoticed for a long time due to their brevity, sudden onset and conclusion. During the seizure the person will abruptly stop what they were doing or saying. Often a person may have a dazed expression, flicker their eyelids, lick their lips, and possibly fidget with their hands. Less often a person's head may drop slightly forward, but posture is maintained. [2, 32].

On average a person will experience 10-20 absences a day; however some people will experience over 50 a day. Absences predominately occur in childhood and adolescence, although they can continue into or very rarely start in adulthood [2]. In order to diagnose absences an EEG showing short bursts (usually 5-10 seconds, but occasionally

up to 20 seconds) of rhythmic generalised spike and slow wave activity is required [32].

For a list of all the known focal and generalised seizures, including the rarer types please see Table 2.3 below.

Table 2.3 Epileptic seizure types

Focal seizures	Focal sensory
	Focal motor
	Gelastic
	Hemiclonic
	Secondary generalised
Generalised seizures	Tonic-clonic
	Clonic
	Tonic
	Typical absence
	Atypical absence
	Myoclonic absence
	Spasms
	Myoclonic
	Eyelid myoclonia (with and without absences)
	Negative myoclonus
	Atonic
	Reflex (in generalised epilepsy syndromes)

Adapted from [40]

2.4 EPILEPSY SYNDROMES

Many people experience similar patterns of symptoms, onset, prognosis etc. and thus these particular patterns have been classified into epileptic syndromes. A list of syndromes was developed by the ILAE in 1989 and a proposal for an updated classification was published in 2001 [40], but has not yet achieved international acceptance. Epileptic syndromes have been divided into idiopathic (presumed genetic), symptomatic (identifiable cause) and probably symptomatic (synonymous to cryptogenic – an unidentifiable cause) [41]. Table 2.4 provides a list of the current ILAE classified epileptic syndromes divided in whether brain involvement is focal or generalised. These are then further divided by aetiology (idiopathic, symptomatic and probable symptomatic).

Table 2.4 Current ILAE classified epileptic syndromes

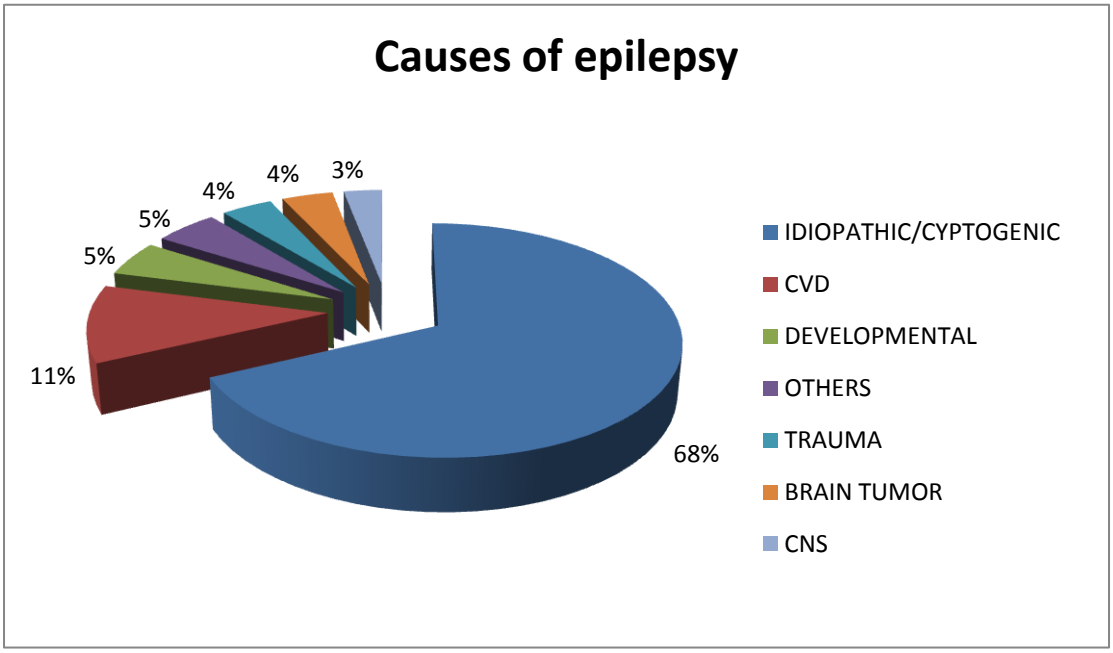
Focal	**Idiopathic**	Benign childhood epilepsy with centro-temporal spikes
		Childhood epilepsy with occipital paroxysms
		Primary reading epilepsy
	Symptomatic	Rasmussen syndrome
		Syndromes characterised by seizures with specific modes of precipitation
		Neocortical epilepsies
	Probable symptomatic	Same syndromes as Focal symptomatic, but with unidentifiable aetiology.
Generalised	**Idiopathic**	Benign neonatal convulsions
		Benign myoclonic epilepsy in infancy
		Childhood absence epilepsy
		Juvenile absence epilepsy
		Juvenile myoclonic epilepsy
		Epilepsies with GTCS
		Reflex epilepsies
	Symptomatic or probable symptomatic	West syndrome (infantile spasms)
		Lennox-Gastaut syndrome
		Landau-Kleffner syndrome
		Epilepsy with myoclonic-astatic seizures
		Epilepsies with myoclonic absences

Adapted from [40]

2.5 AETIOLOGY

2.5.1 WHAT CAUSES EPILEPSY?

There are many potential causes of epilepsy, yet for many patients the cause of their epilepsy remains unknown. In these cases the cause is assumed to be genetic or cryptogenic. A large 50 year prospective study conducted in Minnesota, USA reported 68% of the patients were presumed to have epilepsy with an unknown cause (idiopathic and cryptogenic). The remaining 38% of epilepsies were caused by central nervous system (CNS) disease, trauma, prenatal and perinatal development, cardiovascular disease (CVD), or other [42]. Figure 2.3 below illustrates the distribution of the causes found in this study. These figures are similar to those found a decade later in another USA study, a UK study and a Brazilian study, who reported 65%, 61% and 59.5% respectively had an unknown (presumed cryptogenic or idiopathic) causes [2, 43].



Produced using data from [42]. CNS: Central nervous system, CVD: Cardiovascular disease.

Fig 2.3 Presumed predisposing causes of epilepsy.

Since these studies there have been great advances in imaging, consequently many of the unknown group now would be found to have underlying brain abnormalities that were not possible to see 20 years ago.

Genetic research has also become much more advance, and we now know the genes that are responsible for all of the classified Mendelian epilepsies such as benign familiar neonatal convulsions and benign adult familiar myoclonic epilepsy [44]. However the genes involved in non-Mendelian epilepsies such as the IGEs remain predominately unidentified, as complex inheritance of two or more genes are believed to be involved.

One aspect of the aetiology of epilepsy that is clear is that the earlier in life you have epilepsy the more likely genes are involved, whereas trauma, or brain disease is the most likely cause in adults [30]. The most common causes of epilepsy throughout a lifetime are genetics, pre-natal development, anoxia, trauma, tumours, infectious disease, and finally degenerative disorders [2].

2.6 EPIDEMIOLOGY AND PROGNOSIS

Epidemiological studies are important for our understanding of epilepsy, illustrating its magnitude and highlighting patterns in PWE revealing fundamental aetiological information. Additionally they enable identification of risk factors for developing epilepsy, and future prognosis [45]. However due to the cost in time and complexity very few worldwide population studies have been conducted [46]. Of the studies that have been carried out it is clear that epilepsy effects all races, both genders and all ages [47]. However, most people are diagnosed between infancy and adolescence or in older age (Figure 2.4 illustrates this nicely). Although in developing countries onset is predominately in childhood [31].

Epilepsy has been reported to affect 1-2% of the population worldwide [48], and affecting around 50 million people at any given time [30]. Around 400 per 100,000 people in the UK have active epilepsy [49]. Everyone has a 10% lifetime risk of having a single seizure, and a 3% lifetime risk of developing epilepsy [50].

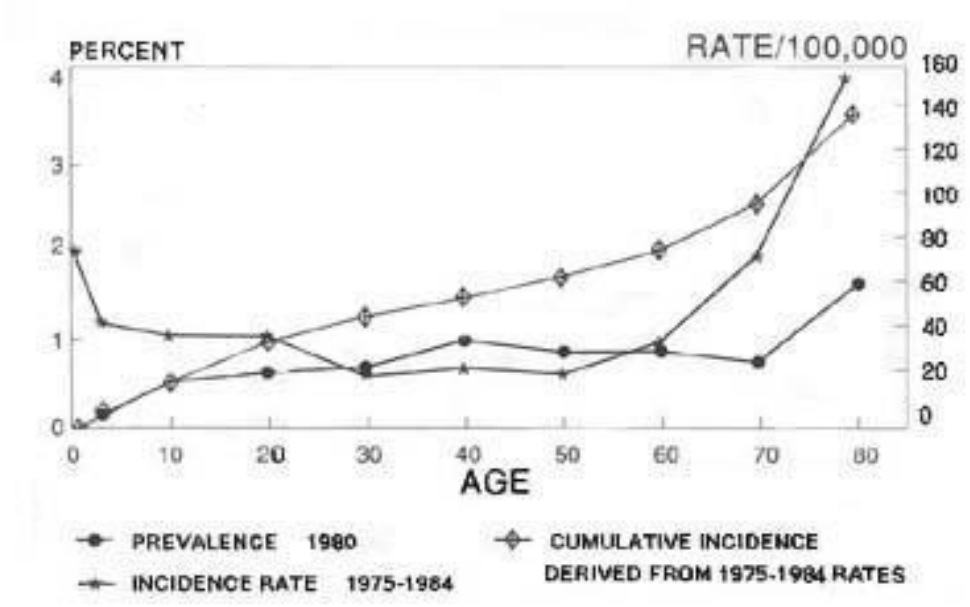


Figure 2.4 Prevalence, cumulative incidence and incidence rates of epilepsy *[51]*

2.6.1 Prevalence

Prevalence is the number of cases of a disorder within the general population at any given time [30]. It has been estimated that the worldwide prevalence of epilepsy is 8.2 per 1000 [30]. Record based epidemiology studies have reported age-adjusted prevalence rates per 1000 of 7.1 in the United States, 5.5 in the United Kingdom, 7.1 in Thailand and 17.6 in Chile [47]. Similar rates have been reported in door-to-door survey studies, which also show Central and South America have the highest reported prevalence of epilepsy in the world [47]. One review paper concluded that overall prevalence is lower in developed countries, with the lowest reported prevalence in Asia. However the low prevalence in Asia may be due to the high stigma associated with epilepsy in this region [47].

2.6.2 Incidence

Incidence is the number of new cases of a disorder in the general population at any given time [30]. It has been estimated that the incidence of epilepsy in developed countries is approximately 50 per 100,000 per year. However this number has been estimated to be double in developing countries, with reports of approximately 100 per 100,000 per year [30]. Reports from independent age-adjusted studies from across the

world report incidence rates of 16-51 in North America, 26-47 in Europe, 35 in Asia, 42-51 in Africa and 111 in Central and South America per 100,000 [47].

The trend for higher rates of epilepsy in developing countries may be explained by an increased risk of brain disease/infection such as meningitis, neurocysticerosis, malaria, pre- and peri-natal complications and malnutrition. These can result in permanent brain damage, which often leads to epilepsy [30].

2.6.3 PROGNOSIS

The outlook for many people with epilepsy is quite positive with reports of 70% achieving seizure control. For many once seizure control is achieved, medication can be stopped and the individual can remain in remission for the rest of their lives. However despite the positive prognosis, due to the cost of treatment and stigmatisation of epilepsy around 3 in 4 people with epilepsy do not receive any treatment. The majority of these cases are in developing countries [31]. For the 30% who cannot be controlled with current treatment their health, psychosocial, education, job and general quality of life can be severely diminished [30].

Epilepsy is also associated with a higher mortality rate. There are five causes of this increased mortality 1) seizure related, such as respiratory/cardio-respiratory arrest, drowning, severe head trauma etc.; 2) aetiology related, such as brain tumour/disease; 3) Treatment related, such as epilepsy surgery or medication; 4) Suicide; 5) Sudden unexplained death in epilepsy (SUDEP) [52].

2.6.4 TREATMENT

There are two main treatment options for people with epilepsy, antiepileptic drugs and surgery. An alternative treatment option that is mainly used with infants and children is known as the Ketogenic diet.

2.6.4.1 AEDs: Efficacy and side effects

There are almost 20 licensed antiepileptic drugs; however 30% of patients still remain refractory, while many controlled patients experience adverse side effect [53]. AEDs developed before 1994 are known as the old or 1st generation AEDs, the common ones include Phenytoin (PHT), Valproate (VPA), Carbamazepine (CBZ), Ethosuximide (ETX),

Primidone (PRM) and Phenobarbital (PB) [1] (for full list of AEDs, see Table 2.5 below). A large prospective study by the Veteran Administration showed that CBZ and PHT had the greatest success in controlling seizures, and overall 70% of patients were controlled on monotherapy with one of the older AEDs [54].

The AEDs developed after 1994 are known as the newer or 2nd generation AEDs, and some have been found to have similar efficacy to the older drugs while overall being safer and more tolerable [53]. The newer AEDs include, Lamotrigine (LTG), Levetiracetam (LEV), Topiramate (TPM) and Zonisamide (ZNS) (for full list see Table 2.5 below). A study that compared the newer AEDs with the older AEDs found for patients with focal seizures, the newer drug LTG was clinically better than the older generation drug CBZ [55]. For patients with generalised seizures however the older AED, VPA was found to have the most efficacy and tolerability compared to the newer AEDs LTG and TPM, respectively [4]. Table 2.6 below shows which AEDs are the first and second line treatments for different seizure types.

Table 2.5 1st and 2nd generation AEDs

1st generation	**2nd generation**
Acetazolamide Phenytoin	Eslicarbazepine acetate
Carbamazepine	Gabapentin
Clobazam	Lacosamide
Clonazepam	Lamotrigine
Ethosuximide	Levetiracetam
Phenobarbital	Oxcarbazepine
Primidone	Pregabalin
Valproate	Retigabine
Vigabatrin	Rufinamide
	Tiagabine
	Topiramate
	Zonisamide

Table 2.6 AEDs used for first and second line treatment of individual seizure types

Seizure type	First line AEDs	Adjunctive AEDs	Other AEDs that may be considered in tertiary care	AEDs that should not be offered (may worsen seizures
Generalised tonic-clonic	Carbamazepine Lamotrigine Oxcarbazepine Valproate	Clobazam* Lamotrigine Levetiracetam Valproate Topiramate		***If patient experiences absence or myoclonic seizures, or if JME is suspected do not offer:*** Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Tonic or atonic	Valproate	Lamotrigine*	Rufinamide* Topiramate*	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Absence	Ethosuximide, Lamotrigine* Valproate	Ethosuximide, Lamotrigine* Sodium Valproate	Clobazam* Clonazepam Levetiracetam* Topiramate* Zonisamide*	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Myoclonic	Levetiracetam*	Levetiracetam	Clobazam*	Carbamazepine

	Topiramate* Valproate	Topiramate* Valproate	Clonazepam Piracetam Zonisamide*	Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Focal seizures (including secondary generalised tonic clonic)	Carbamazepine, Lamotrigine Levetiracetam Oxcarbazepine Valproate	Phenobarbital, Phenytoin, Primidone, Tiagabine	Eslicarbazepine acetate Lacosamide Phenobarbital Phenytoin Pregabalin* Tiagabine Vigabatrin Zonisamide*	
Prolonged or repeated seizures and convulsive status epilepticus in the community	Buccal Midazolam, Rectal Diazepam**, Intravenous Lorazepam			
Convulsive status epilepticus in hospital	Intravenous Lorazepam, Intravenous Diazepam, Buccal Midazolam	Intravenous Phenobarbital, Phenytoin		

Adapted from NICE guidelines [56]

* At the time of NICE guidelines publication this drug did not have UK marketing authorisation for this indication and/or population.

** At the time of NICE guidelines publications this drug did not have UK marketing authorisation for this indication and/or population.

All pharmacological treatments have side effects and AEDs are no exception. Some AEDs are associated with mild adverse effects such as hair loss, dry mouth and weight gain, but others can have very severe even fatal side effects such as liver dysfunction, thrombocytopenia and hyperammonaemia [2, 53].

There are three main types of adverse effects an individual may experience and include, allergic or hypersensitivity (idiosyncratic), dose-related and chronic [2]. Around 5% of patients will experience an idiosyncratic reaction that usually results in a widespread, itchy rash. Common drugs that are associated with this are CBZ, LTG, PB and PHT. Dose-related side effects are caused by taking a dose too high or starting a drug too quickly. Side effects often caused by dose include drowsiness, unsteadiness, nausea, and blurred or double vision. Finally chronic side effects are ones that build up over time and are long lasting. These include memory impairments, changes in mood and behaviour, thickening gums, and excessive vitamin D metabolism. Additionally the most concerning chronic side effect of AEDs is the possible teratogenic effects, which include physical malformations and cognitive impairments [2]. Valproate has been significantly associated with these teratogenic effects [57-59].

Self report questionnaires have found that memory problems, tiredness and difficulty in concentrating are the most common adverse effects of AEDs. Additionally patients on polytherapy consistently report more adverse effects than those on monotherapy [60, 61]. However when patients are asked directly by the prescribing physician fewer adverse effects are reported than may be present [62]. One study assessed the use of standardised self-report tools in the clinic. They found an association between adverse events profile (AEP) and a 2.8 fold increase in AED regime change, without significant change in seizure frequency. Further, patients who completed the AEP reported improved quality of life after four months and significant drops in AEP scores were found [63].

2.6.4.2 Epilepsy Surgery

Curative surgery is predominately aimed at patients with focal epilepsies. Surgery will usually only be considered in these patients if they are refractory to drug treatment and their seizures are severe enough to have a negative impact on their quality of life [1]. For those patients who are eligible the outlook is a reasonably positive one.

Approximately 60-70% of patients who have epilepsy surgery will become seizure free, while a further 10-20% will see a great improvement in the amount of seizures they experience [2]. Table 2.7 below outlines the current epilepsy surgical procedures.

Table 2.7 Current epilepsy surgical procedures outline and outcome

Procedure	Brief description	Outcome
Vagus Nerve stimulation	For those unable or unwilling to have surgery. A pulse generator is implanted under the skin below the collar bone. Spiral electrodes are then wrapped around the Vagus nerve, which conduct the electrical signal to the Vagus nerve from the pulse generator. It is thought to desynchronise cortical activity.	25-30% reduction in seizure frequency
Lesionectomy	Involves removal of lesion and depending on location 1-2cm of surrounding tissue. Common lesions include tumours, vascular malformations, scars, or areas of focal atrophy.	80-86% seizure free
Lobectomy	Involves removal of portion or entire lobe in which the focus of epileptogenic activity lies.	Frontal lobe – 60-76% seizure free. Temporal lobe- 66% seizure free, 19% significant improvement. Parietal lobe – 64-80% seizure free. Occipital lobe – 60-72% seizure free.
Hemispherectomy	Usually performed in children with non-focal seizures that are severe and intractable. Involves	60-90% seizure free.

	disconnection (and much removal) of the entire cortex of a single hemisphere.	
Corpus Callosotomy	Involves severing of part of or all of the corpus callosum, which is the structure that connects the 2 hemispheres.	Aims to reduce not eliminate seizures. 50-80% experience significant improvements in seizure frequency.
Multiple subpial transection	Involves cutting intracortical fibres at 5mm intervals.	When used on its own only about a third of patients are seizure free. When used in conjunction with resection 48% may become seizure free, while a third experience a significant reduction in seizure frequency.

Adapted from [1]

2.6.4.3 Ketogenic Diet

The Ketogenic diet is an alternative treatment option, which involves a period of starvation in order to create a state of ketosis. This is then followed by a diet high in fat and low in carbohydrates and protein. Usually a ratio of 3-4 parts fat to 1 non fat is used. The idea of diet as a treatment of epilepsy actually dates back to the 5th century BC in reports by Hippocrates. Fasting is also mentioned in the bible (Matthew 17:14-21 and Mark 9:14-29) as a cure for seizures, with reference to Jesus telling his disciples that "demons" can only be cleansed by prayer and fasting [64].

The diet is thought to increase seizure threshold by increasing the brains energy reserves, which in turn increases neuronal stability [1]. It is predominately used in children with intractable generalised seizure, but has shown some success in adults and patients with partial seizures. Two-thirds of children on this diet either become seizure free or experience a 90% reduction in seizures, while a third show no improvement [1].

CHAPTER THREE – JUVENILE MYOCLONIC EPILEPSY

> ***"Every morning, when I had to get up, everything fell out of my hands. I broke innumerable toothbrush glasses, cups, etc."***

A patients own account in a letter written to Janz [65]

A detailed case study of a patient with JME was first written by Herpin in 1867 when he observed myoclonic jerks in his son referring to them as "secousses" [66]. Others before and after him discussed the symptoms, but the syndrome was not classified until 1957 when Janz and Christian described the disorder in detail, and termed it 'impulsive petit mal' [66, 67]. It was later known as Juvenile Myoclonic Epilepsy of Janz, but was soon shorted to Juvenile Myoclonic epilepsy or JME by the International League Against Epilepsy [68].

3.1 DEFINITION OF JME

JME is an idiopathic generalised epilepsy. It is defined as the onset of myoclonic jerks (usually bilaterally in the upper extremities) in adolescents, coupled with irregular interictal EEG characterised by polyspike-and-wave complexes. In addition to myoclonic seizures people with JME also often experience tonic clonic seizure (80-97% of patients) and less commonly, absence seizures (12-54% of patients) [7, 9]. 80% of patients are well controlled on AEDs, particularly VPA; however relapse is high if pharmacological treatment is stopped even when a patient hasn't experienced a seizure for years. It is believed to be lifelong but not progressive, and has a strong genetic aetiology [10, 69]. Table 3.1 below briefly summarises the features of JME, all of which will be discussed throughout the current chapter.

Table 3.1 Common features of Juvenile Myoclonic Epilepsy

History	No other medical history 40% with family history of idiopathic epilepsy.
Seizures	Myoclonic jerks in all. GTCS in most. Absence seizure possible.
Onset	80% between 12-18 years of age.
Precipitating factors	Sleep deprivation, alcohol intake, photic stimulation, fatigue, menstruation.
Electroencephalograph	Irregular, fast poly-spike and waves on ictal and interictal EEG.
Psychosocial symptoms	Mild-to-moderate psychopathological conditions possible, including: anxiety, depression and personality disorders.
Treatment	85-90% responds to Sodium Valproate monotherapy. Respond to few other drugs and aggravated by others.
Pharmacodependency	Relapse after drug withdrawal at any age.
Prognosis	Benign condition in most patients. 15% difficult to treat.

Adapted from [69]

3.2 PREVALENCE AND INCIDENCE

JME is a common epilepsy accounting for 26% of IGE cases, and with a prevalence of approximately 10% of all epilepsies [70]. However it has been estimated that due to the likelihood of JME being under diagnosed it may account for up to 30% of all epilepsy cases [1]. Table 3.2 below illustrates how since 1957 the prevalence has progressively increased. This trend is due to our increased understanding and awareness of JME, which has lead to it being more readily identified. Nevertheless the figure has not changed much since a report by GooBes in 1984 with studies since reporting 4-11% [69]. The prevalence of JME in the general population is 1 in a 1000 to 2000, equating to around 30,000-60,000 people in the UK diagnosed with JME [70]. The incidence of JME has been reported to be 1 in 100,000 population [9].

Table 3.2 Number of cases, prevalence and sex distribution in patients with JME

Study	Patients (*n*)	Prevalence %	Ratio of males:females
Janz et al (1957)	47	2.7	23:24
Janz (1969)	280	4.3	149:131
Gastaut et al (1973)	72	2.9	
Simonsen et al (1976)	37	2.8	21:14
Tsuboi (1977)	399	5.4	195:204
Van Heycop ten Ham (1981)	50	4.4	25:25
Asconape and Penry (1984)	15	4.0	3:12
GooBes (1984)	121	11.9	61:60

Adapted from [65]

3.3 CLINICAL MANIFESTATIONS

3.3.1 SEIZURES

The onset of JME can occur between the ages of 6 and 22 years [9] with 80% of cases presenting between the ages 12 and 18 years [66]. The three seizure types are present at different ages with absences starting at a mean age of 11.5 years. Myoclonic seizures begin one to nine years later at a mean age of 15.4 years. Finally GTCS usually follow a few months after the onset of myoclonus at a mean age of 15.5 years [66]. Not all patients will present with all three seizure types, with reports of 12-54% of patients experiencing absences and 80-97% experiencing GTCS [9].

3.3.2 PRECIPITATING FACTORS

Patients most commonly experience seizures on awakening and are often precipitated by sleep deprivation. The patient's letter to Janz (excerpt above) went on to say how she would sleep late in an attempt to control her seizures, which were stimulated by lack of sleep, *"So if I went to bed at midnight or one o'clock, say, it was impossible for me to get up at 7, 8 or 9 o'clock. If I did, then I started fidgeting like mad, and ended up with a seizure"* [65]. A 5 year prospective study of 64 patients found 51 patients reported sleep deprivation in combination with another factor, lead to seizures [10]. Table 3.3 below illustrates the precipitating factors patients reported in the Panayiotopoulos study.

Another study reported that awakening (34%) was the most common precipitating factor, which was closely followed by sleep deprivation (28%) [14]. They also reported the following precipitating factors: fasting (15%), menstruation (32% of female patients), fever (14%), colourful lights (11%), unexpected sounds and alcohol (both 2.8%). They found 80% of patients reported more than one precipitating factor [14].

JME has one of the highest percentages of patients with photosensitivity with studies reporting the figure to be approximately 20-30% of patients with JME, with a slight female preponderance to photosensitivity [8, 37]. Patients report not only the classic 'flashing lights' as a trigger but also fragmented sunlight shining through trees, and repeated patterns also known as pattern sensitive seizures. Photo- and pattern-sensitivity has been reported to cause both myoclonus and GTCS in JME patients [71].

Table 3.3 Precipitating factors reported by patients with JME

Factor	Alone or in combination (%*)
Sleep deprivation	89.9
Fatigue	42
Photosensitivity	21
Television/video games	5
Menstruation	7
Concentration	13
Stress, expectation, others	7
None	4

* Percentage of 64 patients

Adapted from [10]

3.3.3 Electroencephalograph findings

When Janz presented his review of JME he characterised the epileptic discharges as "bilaterally symmetric polyspike-wave complex(es), with fronto-central accentuation" [65]. This has been confirmed since by many [7-10, 12, 72]. The pattern usually presents with 5 to 20 generalised, often symmetrical, high frequency (10-16Hz) spikes, followed by lower frequency (2.5-5Hz) slow waves [9].

The Interictal EEG of patients with JME shows a similar pattern with generalised spike-and-wave and polyspike-and-wave complexes, but with a lower frequency of around 3-5Hz [9, 12]. The background rhythms in patients with JME are often within normal limits with isolated complexes particularly around the frontal lobe [9, 65]. A case study of ten newly diagnosed adolescents found nine to have normal background rhythms. Six of the patients showed the characteristic poly-spike and wave complexes, while the remaining four showed a variety of poly-spike and/or wave complexes following hyperventilation [73].

An interesting finding from the EEGs of JME patient's is the dominant activity in the frontocentral region, with the ictal EEG showing the onset and highest voltage within this region [9, 11], and isolated complexes during interictal period often limited to the frontal region [65]. This has been suggested to result in neuropsychological deficits of the frontal lobes [11] and will be discussed in chapter four.

3.4 AETIOLOGY

JME is an idiopathic epilepsy. Idiopathic comes from the Greek word *idios* meaning "one's own" and *pathos* meaning "suffering", and is used to describe a disease that has an unknown cause. However, although the exact cause of JME is unknown it is accepted to be an inherited disorder [66]. Entire families have been documented to have JME, indicating in these cases JME is an autosomal dominant disorder [8, 74]. In addition to these rarer cases, 40% of all JME patients have a 1st degree relative with another idiopathic epilepsy [69]. These findings suggest a strong genetic component to the disorder. Other researchers have documented focal abnormalities such as microdysgenesis in the frontal lobes [75] or neurochemical abnormalities [21, 22], and suggested these play a role in the phenotype of JME.

3.4.1 STRUCTURAL ABNORMALITIES ASSOCIATED WITH JME

Structural imaging data does not reveal any obvious pathological lesions or abnormalities in the brains of JME patients, and it is rarely associated with prenatal or traumatic lesions [76]. However with advances in imaging techniques in the last decade there has been a plethora of research indicating structural brain abnormalities [75, 77-79].

Volumetric MRI and voxel-based morphometry (VBM) are methods which have been essential in revealing abnormalities in the JME brain [79]. Tae et al reported an increase in frontal lobe volume in JME patients, which they suggest points to microdysgenesis [79]. Microdysgenesis is a term used to describe microscopic structural abnormalities [75]. This theory is supported by others, whom also speculated that microdysgenesis was the cause of the increase in grey matter volume in the mesial and basal frontal region that they found [20].

Two other independent studies have also found increased grey matter volume in the frontal cortex [75, 77], which may signify abnormalities in apoptosis during maturation. Apoptosis is a natural process, which prunes brain cells and occurs most frequently during childhood and adolescence. Thus, less apoptosis would lead to a higher volume of cells.

It is probable that these developmental disturbances are caused by genetic mutations [76]. Mutations in the EFHC1 gene have been found in JME, and linked to increased neuronal density and the formation of hyperexcitable circuits. This is due to interference of normal elimination of neurons during postnatal development [70]. However, Suzuki et al., found only 6 out of 44 families with JME had the EFHC1 mutation [80]. Nevertheless inferences regarding the cognitive impairments found in JME have been attributed to these structural abnormalities [72].

Other researchers have found abnormalities in the thalamus such as reductions in GMV and neuronal dysfunction [20, 81]. The findings of frontal and thalamic abnormalities lends support for the hypothesis that dysfunctions in the Thalamofrontal circuit is a major mechanism in JME [82]. The Thalamofrontal circuit projects from the anterior and medial thalamus to the dorsal-lateral prefrontal cortex (DLPFC). The DLPFC is an area which is highly associated with executive functioning [82, 83].

In addition to the frontal and thalamic abnormalities, researchers have reported wide spread anomalies in JME. One study reported structural and volumetric abnormalities in the frontal region, corpus callosum and hippocampus. This finding strengthens the argument that JME patients have an abnormal neural network, which is the cause of their symptoms [79].

3.4.2 Functional abnormalities

Research has not only found structural anomalies in the brains of JME patients, but also functional discrepancies [21, 22]. One study found abnormal cortical activation in patients with JME; reporting decreased activation during resting in the ventral premotor cortex, caudate, DLPFC and left medial premotor area [21]. These findings indicate widespread impairments in the frontal lobes. Moreover, during a visual working memory task, PET imaging revealed decreased activation in many regions of frontal locality particularly the DLPFC in JME patients [22].

A study by Savic et al supports the above finding that patients with JME have abnormally low levels of activity in the frontal region. They reported significantly lower concentrations of N-acetyl aspartate (NAA) in the frontal lobes of JME patients when compared with controls using Magnetic Resonance Spectroscopy (MRS) [21]. This points to either neuronal loss or a general neuronal dysfunction; dysfunction in the

regulation of N-acetyl-L-aspartate aminohydrolase leading to the degradation of NAA; or a specific mitochondria dysfunction leading to less NAA being produced [21]. The researchers suggests that all of these possibilities could be explained by cortical dysplasia, despite not finding evidence for this themselves [21]. However the reason for this lack of evidence may be due to the dysplasia being microscopic, and thus too small to be imaged using MRI (i.e. microdysgenesis as discussed above). Researchers have also found decreased NAA levels in the thalamus of the JME brain [81].

Further to classical volumetric MRI studies in JME, there have been recent applications of neuroimaging techniques assessing structural and functional connectivity in JME [84]. These approaches have shown altered thalamocortical and frontal connectivity alterations in patients compared to healthy controls [85-87], which may relate to functional connectivity alterations, and together may explain the cognitive triggering of motor seizures and frontal lobe cognitive impairments seen in patients with JME [87, 88].

The findings above highlight that the structure, volume and activity of both the frontal cortex and thalamus are abnormal in the JME brain. It is clear from the evidence that these abnormalities are the likely aetiology of the JME phenotype; however the underlying cause of these abnormalities could be either sporadic or genetic. The evidence from family and genetic studies suggest in the majority of cases it is the latter. Below is a discussion of the possible genetic culprits.

3.4.3 GENETICS

Although findings of neurochemical imbalances and structural abnormalities are of great interest in understanding JME, and help provide an explanation for the cognitive and psychological symptoms experienced by patients, it does not explain how the anomalies came about in the first place. The evidence presented above suggested that developmental disturbances could be a consequence of genetic mutations e.g. in genes that encode for apoptosis. Unfortunately JME has high genetic heterogeneity [89] making the quest to find the culprit genes difficult.

Thus far the majority of the genetic evidence from family studies have investigated linkage with many pointing to loci on Chromosome 6, in particular the region of the human leukocyte antigen (HLA) [90]. Strong evidence for this comes from independent

studies [74, 91, 92], all of which reported significant association between JME and HLA alleles. However, some studies have not found linkage to HLA in families with JME. While others have found evidence of susceptibility loci on Chromosome 15 [93]. More specifically, a gene (CHNRA7) that encodes for a receptor subunit (c7) of neuronal nicotinic acetylcholine that lies in region 15q14 [93]. In rare cases families have been found to have autosomal dominant JME. See Table 3.4 below for monogenic genes identified to date.

Table 3.4 Monogenic genes identified in families with JME

Genes	Reference
GABRA1	Cossette et al (2002); Malijevic et al (2006)
GABRD	Dibbens et al (2004)
CLCN2	Haug et al (2003) D'Agostino et al (2004)
EFHC	Suzuki etal (2004)

Adapted from [89]

Twin data has revealed high concordance rates among monozygotic twins [76]. while family studies reveal many patients with JME have a first degree relative with another IGE or abnormal EEG recording, yet for some the disorder appears sporadic [94]. The above findings highlight the genetic heterogeneity of JME and indicate that although genetics play a strong influence in its aetiology, it is not a simple Mendelian disease [76], but is the result of a complex interaction of several genetic variations and environmental factors, which have yet to be fully elucidated [89].

Overall patients with JME are clinically very similar, but it is clear from the genetic heterogeneity that it is not a single disorder [72]. The current thesis aims to take the first step in describing one of the many probably subtypes of JME based on neuropsychological profile and personality. Future projects can then take the next step of identifying the genetic aetiology of this and other subtypes.

3.5 Co-morbidities

3.5.1 Mood

Psychiatric disorders are often reported in Epilepsy with anxiety and depression being the most prevalent [95]. Researchers have found JME to be highly associated with mood disorders [27, 28, 96, 97]. One study found almost 50% of patients with JME in their sample also had a co-morbid mood or anxiety disorder [27].

3.5.2 Personality

Patients with JME are often reported to have distinct personality traits. Janz [65] first described them as *"...immature and oscillates between friendliness and mistrust, a personality which tends to cause problems where social adaptation is concerned*". Studies that have investigated personality have found cluster B personality disorders (particularly borderline) significantly more in patients with JME than healthy controls [27, 98, 99]. Another study [97] reported the occurrence of personality disorders in patients with JME to be almost double the occurrence found in a study of the general population [100].

Investigators have suggested a link between these personality traits and executive dysfunctions reported in patients with JME [7, 11-13]. Additionally, researchers have described structural and functional abnormalities in the frontal lobes of JME [20-22], which have also been reported in patients with personality disorders [23, 24]. It may be postulated from these findings that the epilepsy and psychiatric disorders are symptoms of the same aetiology. This proposal is considered further in addition to a detailed discussion of frontal lobe dysfunctions in JME in Chapter four.

3.6 Treatment

3.6.1 AEDs

The first line treatment for JME is monotherapy on VPA. It has been reported that 85-90% of patients respond to it very well with most becoming seizure free [66]. However, for women of childbearing age treatment with VPA is not recommended due to its

association with developmental delay when in utero exposure occurs [57]. It is recommended that women are treated with one of the newer AEDs, such as LEV and LTG, which have been shown to be effective and safe for women with JME [101].

VPA has many additional adverse effects some of which are weight gain, sedation and liver problems, thus researchers have recently investigated the efficacy of LEV as a first line treatment for JME. Two independent studies both reported positive findings, indicating that LEV may be a better alternative to VPA, causing less adverse effects while still producing good seizure control [102, 103]. However, studies thus far into the uses of the newer AEDs for JME have not been adequately powered or randomised [104]. Therefore conclusions must be drawn with caution.

Many patients who do not respond to monotherapy have shown promise on polytherapy, which is when a patient is on more than one drug usually VPA plus another agent [66]. Table 3.5 lists the current pharmacological treatments used for JME.

All other current AEDs have not been found to be successful in treating JME, with Phenytoin and Carbamazepine aggravating myoclonic and absence seizures [66]. Although drug therapy is very successful in JME, seizures return if medication is withdrawn [37], thus it is necessary to continue treatment for life.

Table 3.5 Pharmacological treatment for JME

First line treatment	Second line treatment
Sodium Valproate	Levetiracetam
	Lamotrigine
	Topiramate
	Clonazepam
	Primidone
	Acetazolamide

3.7 PROGNOSIS

The overall prognosis for patients with JME is positive with it becoming a benign disorder for most on appropriate treatment [66]. Over 70% of patients have controlled seizures many of which are on VPA monotherapy. Nonetheless JME is considered a lifelong disorder, since relapse rate is high following discontinuation of treatment. This is even the case for patients who have been seizure free for many years. One study reported a relapse rate of 90% after medication was withdrawn [105]. Thus it is recommended that medication is maintained for life.

CHAPTER FOUR – PATTERN AND CAUSES OF NEUROPSYCHOLOGICAL DYSFUNCTIONS IN JME

A pattern of impairment in JME has been identified, with many finding the greatest impairments in verbal memory [12, 13] and executive functions [7, 11-13]. This chapter will discuss the pattern of dysfunction that previous research has found. A discussion of the possible causes of these impairments will then be given.

4.1 PATTERN OF NEUROPSYCHOLOGICAL IMPAIRMENT

Focal epilepsies have long been linked with cognitive deficits [13]. However in the last 20-30 years researchers have shifted their attention to cognitive deficits in idiopathic epilepsies. Idiopathic epilepsies have no clear detriment to the brain and unknown pathologies. Thus, to gain a better understanding of the underlying aetiology, the causes of cognitive deficits need to be elucidated. JME is one IGE that has received attention, particularly in the last decade.

4.1.1 FRONTAL LOBE AND EXECUTIVE FUNCTIONS

Executive functions are complex cognitive processes that generate cognitive and behavioural responses, and strategies to achieve immediate or future goals [106]. Executive functions are highly associated with the frontal lobes [105].

The most consistent impairment that has been found in JME is frontal lobe dysfunction. Devinsky et al found patients with JME had impairments of several executive functions associated with the frontal lobe [11]. These included concept formation, mental flexibility, planning, and cognitive speed. Similar findings have been reported by others [7, 12-14, 16, 22, 72, 107]. One study reported that JME patients performed worse than normal controls across a neuropsychological battery, which reached significance for verbal fluency ($p = 0.030$), and semantic fluency ($p = 0.012$) [72]. Another study compared JME patients with patients with frontal lobe epilepsy (FLE), temporal lobe epilepsy (TLE) and controls [12]. They found the JME group performed significantly

worse than TLE ($p < .001$) and normal controls ($p < .001$) on the Wisconsin card sorting test (WCST; an executive function test that assesses planning, mental flexibility, concept formation, and strategy formation) and verbal fluency. In addition they found the performance of the JME group did not significantly differ from the FLE group ($p<.05$), providing strong support for frontal lobe involvement in the cognitive problems associated with JME.

Although the studies above have all found executive dysfunctions they have often differed in the pattern of impairment. It has been reported that impairments in word fluency and interference were the most consistent finding in JME [16]. Word fluency is the ability to quickly generate words beginning with a specified letter of the alphabet or words in a given semantic category. Interference is the ability to inhibit an over learned verbal response in order to generate a conflicting response. Following a review of the literature it was revealed that all studies that measured word fluency and/or inhibition found patients with JME were impaired. Table 4.1 below briefly outlines the methods and findings of these studies.

Table 4.1 Studies showing impairments in verbal fluency and/or inhibition in patients with JME

Study	Participants	Cognitive domains	Results
Pascalicchio *et al* (2007) [13]	50 patients with JME, >17 years of age and 50 healthy controls matched on age, gender and education.	Intellect, memory, language and fluency, attention and executive functioning	JME group scored sig lower on attention, immediate verbal memory, mental flexibility, control of inhibition, working memory, processing speed, verbal and visual delayed memory, naming and verbal fluency.
Iqbal *et al* (2009) [7]	8 JME patients, 8 unaffected siblings and 16 healthy controls matched on gender, age, ethnicity and education.	Intellect, memory, language, fluency, attention, executive functioning, and visuospatial ability.	JME group scored lower on verbal and executive functioning tasks than their sibling's and controls, but this only reached significance for the controls.
Sonmez *et al* (2004) [14]	35 patients with JME, >16 years of age and 35 healthy controls matched on age, gender and education.	Intellect, memory and learning, complex perceptual and construction ability, attention, language and executive functions.	The JME group's total learning score was sig lower than controls. They also scored sig lower on memory and executive functions.
Piazzini *et al* (2008) [12]	50 patients with JME, 40 with FLE, 40 with TLE and 40 healthy controls matched on age, gender, education and IQ.	Intellect and executive functions.	JME and FLE patients had significant impairments on executive functioning compared to TLE patients and controls. Linear regression analysis for the JME group showed the duration of epilepsy, seizure frequency, treatment and seizure type where not associated with neuropsychological impairments.
Devinsky *et al* (1997)[11]	15 patients with JME and 16 with TLE matched on IQ, age, age of onset and duration of epilepsy.	Executive functions and intellect	JME patients showed impairments in concept formation, mental flexibility, cognitive speed, planning and organisation. JME had sig lower scores on the

			WCST and trail making test.
De Toffol *et al* (1997) [107]	9 JME and 9 healthy controls matched on age, gender, education and handedness	Executive functions, verbal fluency and Stroop.	JME patients were significantly more impaired on all of the tests, indicating deficits in planning, fluency and inhibition (executive functions).
Swartz *et al* (1996) [22]	9 JME and 14 healthy controls matched on age, education and handedness	Immediate and delayed memory.	There was no sig difference between JME and control subjects on the IMS task, indicating both groups had normal attention. The DMS task revealed the JME group to have impaired visual working memory.
Wandschneider *et al* (2010) [16]	19 JME, 21 unaffected siblings and 21 healthy matched controls	Intellect, memory, executive functions, and prospective memory.	The JME group performed sig worse across all neuropsych tests compared to controls. The PM task revealed JME group were impaired on intention formation, completing tasks and sticking to rules.
Roebling *et al* (2009) [72]	19 JME and 20 age-, sex- and education-matched controls	Intellect, memory and executive functions.	JME group performed worse across all tests with the difference reaching sig on verbal and semantic fluency.

4.1.2 MEMORY

Past research has found memory impairments in people with JME, particularly verbal memory and/or visual memory [13, 14, 16]. One study found JME patients scored significantly lower on tests of immediate (p= .017) and delayed verbal memory (p= .013), and delayed visual memory (p= .014) compared to healthy gender, age and education matched controls [13].

There could be several causes of these impairments, some of which include AED treatment, seizure type, and frontal lobe abnormalities. Support for frontal lobe abnormalities being a cause of the memory impairments found, comes from a study by Swartz et al [22]. They reported that JME patients have a significant deficit in visual working memory compared to healthy matched controls. Moreover, with the use of PET they found significantly less uptake of 18-fluorodeoxyglucose (18FDG) in the frontal cortex compared to controls during a visual working memory task. In addition, unlike controls the PET scans of the JME patients showed activation in the medial temporal cortex during the task [22]. The authors of this study and others suggest that these findings may indicate a disorder of neuronal migration and cortical disorganisation, both of which may play a role in the impairments found and epileptogenic symptoms of JME [12, 22, 108]. All the possible causes of memory impairments in JME will be discussed in detail below in the second half of this chapter.

4.1.3 PERSONALITY

Impaired inhibition and fluidity of thought are highly associated with personality disorders, and it has been suggested that the low performance on these tasks is related to the personality traits exhibited by people with JME [16]. People with JME have often been found to have distinct personality traits [27, 98, 99]. Janz and Christian described people with JME as emotionally unstable and immature, unsteady, lacking discipline, hedonistic, having frequent and rapid mood changes, and indifferent to their disease [65].

Similar traits have been found more recently. One study comparing people with JME with healthy matched controls found 20% of the JME group (significantly more than the controls p = .008) were classified with personality disorders, displaying similar traits as described by Janz [27]. Another study compared personality disorders in JME with structural prefrontal brain abnormalities using voxel-based morphometry [20]. They

reported a significant reduction in grey matter volume in JME patients compared to healthy controls. This reduction was found in the insula (p= .006), thalamus (p= .001) and cerebellum (p= .006), and a decrease in white matter volume in the cerebellum (p= .03) was also reported. In addition they found increase grey matter volume in the right superior and medial frontal gyri (p< .001 and p= .001, respectively). Differences in brain volume were also found when the JME patients with PD were compared to JME patients without PD. The patients with PD had significantly less grey matter volume in the right thalamus than patients without (p< .001). In addition the patients with PD had increased volume in the left and right middle frontal gyri (p< .002 and p< .001, respectively), and the right orbitalfrontal gyrus (p< .004).

The findings reported by de Araujo et al [26, 27] indicate a relationship between JME and structural brain abnormalities, particularly in patients with PD. As of yet no investigation has been conducted that correlates frontal impairments and personality disorders [16, 27]. The current study will examine both frontal dysfunctions and personality disorders in order to determine whether a relationship exists between them.

4.1.4 MOOD

Co-morbid mood disorders are often found in people with JME. A study described above [27] found that almost half (49 of 100) of the participants with JME also had a mood or anxiety disorder. Another study reported that JME patients scored 1.5 standard deviations above their siblings and healthy matched controls for depression on the HADS [7]. Additionally the JME patients and their siblings scored 1 standard deviation above the healthy controls for anxiety.

It is well established that there is a relationship between mood and cognitive functioning [109]. Studies have reported that depressed individuals perform significantly worse than healthy controls on recall and acquisition [110, 111]. One study found depressed individuals had significantly impaired immediate recall and acquired significantly less information than individuals with low levels of depression. In addition, they found when anxiety co-exists not only are the above findings found, but participants also retrieved significantly less newly learned information after a 20 minute delay [112].

It has been suggested that negative mood can exacerbate memory problems in people with epilepsy [113]. However this relationship has rarely been examined in patients with JME. Considering the high percentage of JME patients with mood disorders it is important to investigate whether mood has an impact on the cognitive impairments found in these patients.

4.2 POSSIBLE CAUSES OF COGNITIVE IMPAIRMENTS

JME has been associated with cognitive deficits since Janz and Christian description in 1957, yet in the majority of cases patients maintain intellectual functioning that is within normal limits [7, 13, 72]. Despite this many researchers have found impairments in cognition [7, 11-14, 16, 22, 72, 107], and one recent study reported that JME amongst other IGE patients had significant cognitive impairments at time of diagnosis and before the onset of treatment [114].

Moreover, patient's unaffected siblings have also been found to be more impaired than healthy unrelated controls across a wide range of neuropsychological assessments [7]. These findings suggest an underlying physiological dysfunction in the brain. The latest research has suggested dysfunctions in the fronto-thalamo circuit [82], this however is beyond the scope of the current thesis. For an overview of this hypothesis please see [115]. What is clear from past research is that the cognitive deficits in JME are multi factorial. Table 4.2 gives the possible contributory factors, which will be discussed in detail for the remainder of this chapter.

Table 4.2 Factors that may influence cognitive functioning in JME

Contributory factor	
Pathophysiology	Underlying brain abnormalities, focus of epileptogenic activity
Epilepsy onset and duration	Age of onset and duration
Seizure related	Type, frequency, interictal activity and severity
Treatment related	AEDs, dose, drug interactions
Psychosocial related	Mood (depression and anxiety), personality traits, stigma, self-esteem, education/occupational attainment

4.2.1 Brain imaging and cognition

As discussed in detail in chapter three, patients with JME have been found to have increased frontal grey matter volume [75, 77]. The researchers of these findings have suggested that the increased volume is caused by a malfunction in normal developmental neuronal pruning (apoptosis), and thus leads to inefficient and/or abnormal functioning of the frontal lobes. Indeed, reduced activity in the frontal lobes of JME patients has been reported [21]. Decreased GMV and low activity in the thalamus has also been reported in JME [20, 21, 81]

The structural and functional brain abnormalities in JME has been investigated by numerous researchers [21, 22, 72, 75, 77, 79, 81, 116-118]. While several others have investigated the cognitive impairments [7, 11-14, 16, 65, 72]. Many of these researchers have speculated that the two are correlated, yet there has only been one study that has investigated both cognition and brain structure to the best of the author's knowledge.

One study found compared to healthy matched controls, patients with JME had significantly smaller right thalami ($p = .02$), and more frontal CSF ($p = .001$) indicating smaller frontal cerebral volume [82]. JME patients also had more frontal CSF ($p = .007$) than patients with Benign childhood epilepsy with centrotemporal spikes (BCECTS) who formed an active control group. In terms of cognition JME were significantly

impaired on inhibition (p= .01), and behavioural regulation (p= .03) when compared to healthy controls [82]

When Pulsipher et al., investigated the relationship between the volume abnormalities and cognition, they found that frontal tissue and thalamic volume were the only, and significant predictors of JME patients performance on the D-KEFS [82]. Specifically, frontal grey matter volume (GMV) and white matter volume (WMV) explained 57% (adjusted r^2) of the variance in category switching accuracy from the DKEFS. The standardised beta values indicated that frontal grey matter was negatively correlated, thus high GMV is associated with low ability to accurately switch between two unrelated categories (β= -2.04). Conversely, frontal white matter was positively correlated with category switching accuracy, thus decreases in WMV in the frontal lobe is associated with poor performance (β= 2.17). Similarly, a decrease in WMV (β= 1.38) explained 13% (adjusted r^2) of the variance in inhibition. Lastly, right and left thalami volume explained 39% of the variance found in performance on the card sorting test from the DKEFS. Left thalami was positively (β= 1.62), and right thalami was negatively (β= -1.54) correlated with card sorting. Therefore, increased left thalami volume is associated with poor ability to sort cards into categories, while decreased right thalami volume is associated with poor ability of this task.

This study directly correlated cognition with brain abnormalities, and gives strong support for executive dysfunctions being a symptom of the syndrome. The current thesis hope to lend support to this report by demonstrating that most of the other factors (in the Table 4.2 above) contribute little to the known neuropsychological profile in JME.

4.2.2 Epilepsy onset and duration

JME is a lifelong syndrome that begins in adolescence [8], thus the contribution that age of onset and duration of epilepsy play in cognitive impairments will be investigated in the current thesis. Studies of epilepsies that begin in childhood have revealed a negative impact of the age of onset on socioeducational development, often resulting in lower cognitive abilities, job prospects and quality of life [119]. This has rarely been documented in JME patients. Sonmez et al found no correlation between age of onset and cognitive impairments in patients with JME [14].

The findings on the impact of the duration of the disease are mixed. One study that has investigated the neuropsychological profile of JME patients, found they were significantly impaired across most neuropsychological assessments compared to healthy matched controls, and that this impairment was correlated with the duration of the disease [13]. However, this finding was not replicated in a study by Sonmez et al, or in a study by Piazzini et al, who both reported no correlation between cognition and duration of JME [12, 14].

4.2.3 SEIZURE RELATED

Seizures are sudden violent bursts of electrical discharges that focus in one region or the entire cortex of the brain, thus it is reasonable to hypothesise they may have a deleterious effect on cognition. Much research has been done over the last 30 years in order to determine whether seizures cause impairments in cognition in PWE [119-121]. Following a review of the literature it was concluded that uncontrolled seizures lead to decreased mental ability in PWE [119]. In addition, GTCS have been significantly associated with cognitive impairments, this is particularly true for prolonged GTCS i.e. convulsive status epilepticus [119].

Little research has been conducted that has examined the contribution seizures play in the known neuropsychological impairments in JME. Sonmez et al concluded from past research that when seizure control is achieved IQ levels are not changed. However the opposite is true for patients with multiple seizure types, and frequent and long lasting seizures [14]. However, these patients may have worse brain abnormalities, which result in poor seizure control and cognitive impairments. In Sonmez et al.'s own study they did not find an association between IQ and seizures [14].

The majority of JME patients have normal IQ, but have impairments in executive functions, thus one investigated the contribution seizure play in these impairments [12]. They found JME patients were significantly impaired on frontal lobe tests, compared to patients with TLE and healthy controls. Yet there was no association between these frontal lobe impairments, and the frequency or type of seizures. This suggests that seizures are not a key contributory factor.

Another factor that may have a greater impact and is related to seizures is interictal discharges. JME patients are characterised by abnormal EEG with the majority of the

activity in the frontal regions [11, 96, 122]. Although little research has revealed any significant effects of seizures on cognition in JME patients, associations have been found with abnormal interictal activity. A study by Lavandier et al reported that JME patients with interictal epileptiform EEG activity were more impaired on some frontal tasks, than JME patients without discharges [12]. Another study found more errors were made on the Stroop test (a test that assesses inhibition that is controlled by the frontal lobe) by JME patients who had paroxysmal EEGs compared to patients who had normal EEGs [14].

However a study that used video-EEG recording during a neuropsychological assessment found no increase in discharges, which the authors hypothesised, would explain the impairments found. They concluded that the neuropsychological impairments observed in the JME patients were independent of abnormal discharges [7]. Yet Iqbal et al. did find in the one patient in their study that did experience discharges at the point of learning, could not recall the information that directly corresponded to the discharge.

The mere fact of having seizures and/or paroxysmal interictal discharges, and the type of seizures experienced by JME patients may contribute to the neuropsychological impairment. Sonmez et al reported patients whom experience both myoclonic seizures and absences scored worse on tests of short term memory. In addition visual memory and recall were impaired in patients with absence seizures [14]. More recently, however a study by Piazzini et al found no association between the type of seizures JME patients experience, and the significant impairment in frontal functions they reported [12].

The research thus far does not indicate any clear association between cognitive impairment in JME and having seizures. Additionally the findings regarding the impact particular types of seizures have, are contradictory. What is clearer however is the presence of paroxysmal discharges during rest and executive dysfunctions. Interestingly, one study found EEG abnormalities in the frontal region were significantly associated with experiencing both GTCS and myoclonic seizures, a family history of epilepsy and being refractory to AED treatment [123].

Moreover, a study that compared VPA resistant JME patients to VPA sensitive patients found the refractory patients had abnormal EEGs with frontal predominance and left

temporal slowing. They suggested that the VPA sensitive patients resembled the JME syndrome described by Janz [65], while the refractory patients were a distinct subgroup of JME or possibly a different type of epilepsy altogether [124]. This suggests that it is the refractory patients that still experience paroxysmal discharges who suffer with frontal lobe impairments. This highlights the multifactorial and heterogenic nature of this syndrome.

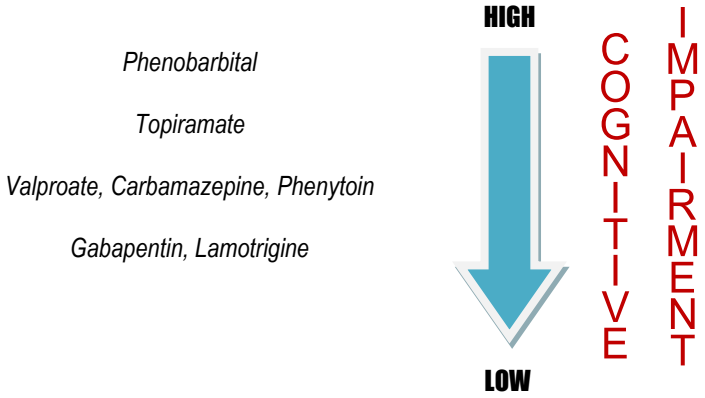
4.2.4 TREATMENT RELATED

There is much debate over the impact AED's have on cognition with many patients attributing their impairments to their medication [114]. A review of the literature reported that psychomotor speed, vigilance, memory, attention and mood are affected by AEDs [125]. However, the studies cited in the review by Hirsch et al were conducted with patients who had been diagnosed with epilepsy for many years, thus the cognitive impairments reported may be a result of years of recurrent seizures. However, a study by Taylor et al investigated the cognitive profiles of PWE before the commencement AED treatment [114]. They reported PWE were significantly impaired on over half of the test battery with the difference in memory and psychomotor speed remaining significant once sex, age and education were controlled for. This suggests that much of the cognitive impairments reported in epilepsy are not due to AEDs.

However no such study has been conducted solely with JME patients. Furthermore, due to the heterogeneity of JME, and differing responses to treatment it remains unclear whether some of the cognitive impairments described in JME patients are due to antiepileptic drug treatment. One study conducted compared JME patients with healthy age, sex and education matched controls [72]. They reported JME patients performed slightly worse on most neuropsychological tests including those of working memory, episodic memory, verbal and semantic fluency, attention, inhibition and vocabulary. The difference in performance reached significance for verbal and semantic fluency. However, both verbal and semantic fluency are associated with the functioning of the frontal lobes [12], and many suggest frontal lobe impairments are indicative of the underlining aetiology of JME.

A key factor that needs to be considered is the difference between AEDs, as a review by Meador et al demonstrated that particular AEDs have been found to be more detrimental to cognition than other AEDs [126]; Figure 4.1 below summaries their

findings. More recently a study investigated the difference between the first line treatment for JME (Valproate) with another effective JME AED (Lamotrigine) [71]. They found JME patients treated with VPA scored worse on most tests compared to those treated with LTG or no medication, and performed significantly worse on verbal memory [72]. However, another review of the literature reported that at therapeutic doses, VPA causes either mild or no cognitive impairments [127].



(Adapted from [126])

Fig 4.1 Relative cognitive effects of AEDs

It is clear that AEDs (some more than others) have an effect on cognition, with some studies showing significant impairments while others show no impairments. The exact extent they contribute to the cognitive impairments documented in JME has not been elucidated to date, and thus it remains an important question to tackle. However, one must not forget that seizure control significantly improves a patient's quality of life, thus may be deemed as more important than mild adverse effects of AEDs.

4.2.5 PSYCHOSOCIAL RELATED

4.2.5.1 Mood and personality

Mood and personality disorders are extremely common in JME. One study reported that almost 50% of JME patients in their sample also had a co-morbid mood disorder and/or anxiety disorder [27]. Mood disorders, particularly depression are correlated with cognitive impairment in healthy and clinical populations [112]. Thus the high co-

morbidity of mood disorders in JME may play a key role in the reported cognitive impairments.

In the same study by de Araujo et al. they reported 20% of their JME sample were classified as borderline, and exhibited the distinct personality traits that were first described by Janz [65], and by many since [9, 27, 98, 99]. Another study [97] reported the occurrence of personality disorders in patients with JME to be almost double that found in a study of the general population [100].

People with personality disorders such as borderline personality, have been found to have impairments in planning and inhibitions [18, 19] synonymous to the impairments found in JME patients. Furthermore, these same impairments are also found in patients with frontal lobe epilepsy (FLE) whom have a focal lesion in the frontal lobes [12]. Piazzini et al found when compared to healthy controls and patients with temporal lobe epilepsy (TLE), JME and FLE patients were significantly impaired on the WCST. However, when the performance of JME and FLE patients was compared no significant differences were found, supporting the hypotheses that JME patients have focal abnormalities in the frontal lobes.

The current thesis aims to investigate the relationship between the executive dysfunctions in JME, and personality disorders to explore whether low executive functions accounts for the personality traits or vice versa. Additionally this thesis aims to examine whether there are JME patients whom have low executive functions, but normal personality. This would provide evidence for an underlying pathological abnormality in the frontal lobes of JME, or personality traits purely being a symptom of a subtype of JME.

4.2.5.2 Education

Another factor that may impact cognition in JME patients is level of education. A study by Pascalicchio et al found significant impairments across several of the tests administered, and a positive correlation between duration of epilepsy and cognitive decline. Yet this significant correlation was lost if patients had, had more than 11 years of formal schooling and remained strong if patients had spent less than 11 years in education [13]. This indicates that education compensates for years of seizures.

4.3 CHAPTER FOUR SUMMARY

The current chapter has reviewed the literature that has investigated the neuropsychological profile of JME. The literature indicates that patients with JME for the most part maintain an IQ that is within normal limits [7, 13, 72]. Despite this, people with JME have been repeatedly found to have impairments in executive functions, particularly inhibition and verbal fluency [7, 12-14, 16, 22, 72, 107]. In addition to these impairments some researchers have reported deficits in memory [13, 14, 16], abnormal personalities [27, 98, 99], and mood disorders [27].

The literature discussed above clearly indicates that JME is a complex heterogeneous disorder, and although it is one of the most common forms of epilepsy little is still understood about its cause. One approach to gaining a better understanding of the underlying aetiology, and providing better treatment plans for patients is by determining what causes or contributes to the cognitive impairments reported in JME.

The latter half of this chapter proceeded in discussing the possible factors that may contribute to the reported impairments and abnormalities. All of these factors will be investigated in the current thesis; however there will be a particular focus on the contribution of personality and frontal lobe involvement.

CHAPTER FIVE – AIMS AND HYPOTHESES

5.1 AIMS AND OBJECTIVES OF THE CURRENT THESIS

It has been hypothesised that JME is not one disorder but several, encompassing different aetiologies, yet indistinguishable epileptic symptoms. Hence the current thesis aims to examine the relationship between the executive dysfunctions in JME and personality, and investigate whether patients with abnormal personality traits present with worse executive dysfunctions.

The objectives of the current thesis are to:

1. Verify the neuropsychological profile of JME.
2. Examine the contribution of age of onset, duration of epilepsy, education, type of seizures, seizure frequency, treatment, mood, impact of epilepsy and subjective view of cognitive functioning.
3. Examine the impact of high levels of anxiety and/or depression on neuropsychological functioning in a refractory JME sample.
4. Examine the relationship between personality and executive dysfunctions. Aim to provide evidence for frontal lobe involvement, and for the hypothesis that there is more than one type of JME.

The hypotheses of the current thesis will be given below, along with a brief discussion of the research that led to them.

5.2 HYPOTHESIS ONE – NEUROPSYCHOLOGICAL PROFILE

Chapter four discussed in detail past research that has investigated the neuropsychological profile of JME. From this review of the literature it was concluded that the most consistent deficits found in JME are impairments in inhibition and verbal fluency, both of which are executive functions and associated with the frontal lobes [128]. The current thesis aims to confirm these impairments.

It is thus hypothesised that the participants whom are drug-refractory will be significantly impaired on inhibition and verbal fluency. Secondly, as the patient group investigated in the current thesis consists of only refractory patients it is hypothesised that other cognitive impairments will be revealed.

5.3 HYPOTHESIS TWO – OTHER CONTRIBUTORY FACTORS

Although the current thesis has hypothesised that personality plays a key role in the executive dysfunctions in JME, other factors cannot be ignored. Especially as not all JME patients have an abnormal personality, and studies that have examined non-refractory and refractory patients as one group have still found significant impairments. Therefore, there must be other factors contributing to these impairments.

The current thesis aims to examine the impact the following factors have on the neuropsychological impairments:

5.3.1 AGE OF ONSET

Age of onset has been found to impact cognition in epilepsy patients in general, with studies reporting early onset having a negative impact on cognition [119]. However, another study did not find this to be the case in JME [14]. Thus the present thesis will investigate this with the current sample.

5.3.2 DURATION OF EPILEPSY

The findings on the impact of duration of epilepsy in JME have been inconsistent. One controlled study investigating the neuropsychological profile of JME found that the significant impairments found in JME compared to healthy matched controls were

correlated with the duration of epilepsy [13]. However, this finding was not replicated by two other independent controlled studies [12, 14]. The current thesis will investigate the impact of the duration of epilepsy with the current sample.

5.3.3 TYPE OF SEIZURES

JME is associated with myoclonus, GTCS and Absences. It has been reported that impairments in short term memory is associated with experiencing both myoclonus and absences [14]. This finding has not be consistently reported in JME [12], and is unlike the findings for epilepsy in general, for which GTCS are associated with cognitive impairments. However, the current sample consists of only refractory patients, many of whom experience myoclonus and/or absences daily. Reasonably it would not be unexpected to find this level of seizure activity negatively impacting cognition. Thus the current thesis aims to investigate the impact of seizure type.

5.3.4 TREATMENT

Research to date indicates that some AEDs may be related to significant impairments in cognition. However, with regards to JME patients there has been no study that has exclusively investigated the effects of AEDs, and thus it remains an important question to tackle. Therefore, the current thesis will examine the contribution the AEDs prescribed to the current sample have on cognition.

5.3.5EDUCATION

Past research suggests that years of education and/or level of education has a positive impact on neuropsychological test scores [12], and may compensate for years of seizures [13]. The current thesis aims to investigate the contribution years and the levels of education have on the cognition of the current sample. Years of education will also be controlled for when investigating the first hypothesis.

5.4 HYPOTHESIS THREE – PSYCHIATRIC SYMPTOMS AND NEUROPSYCHOLOGICAL FUNCTIONING

Mood disorders have been correlated with cognitive impairments in healthy and clinical populations [112]. Mood and anxiety disorders have been reported highly in JME, with one study reporting 50% of their sampling being classified with a mood

disorder [27]. Thus it is important to investigate the impact the high co-morbidity of mood disorders has on the cognitive impairments reported.

5.5 Hypothesis four – Personality and executive functions

Abnormal personality traits have been repeatedly reported in studies of JME [9, 27, 65, 98, 99]. The personality traits reported are synonymous to those described in borderline personality disorder [18, 19], and one JME study reported a high percentage of JME patients were classified as borderline [27]. Moreover, borderline personality disorder is associated with executive dysfunctions. Finally, the executive dysfunctions found in JME are similar to those found in frontal lobe epilepsy, which is a focal epileptic disorder. It therefore follows that the personality traits in JME may be related to the executive dysfunctions, and the personality traits may be a result of an underlying frontal lobe abnormality.

As of yet no investigation has been conducted that correlates frontal dysfunctions and specific personality traits in drug-refractory JME [16, 27]. It has been hypothesised that JME is not one disorder but several, encompassing different aetiologies, yet indistinguishable epileptic symptoms. Hence the current thesis aims to examine the relationship between the executive dysfunctions in JME and personality traits, and investigate whether patients with abnormal personality traits have a different type of JME to those with normal personality traits

5.6 SUMMARY OF CHAPTER FIVE

The current thesis has four main hypotheses, which will be investigated:

1. The refractory JME sample will be significantly impaired on inhibition and verbal fluency.
2. Clinical characteristics and mood will have an impact on any cognitive impairments found in the refractory JME sample.
3. Refractory JME patients with high levels of anxiety and/or depression will be more impaired on neuropsychological functioning than those with normal levels of anxiety and/or depression
4. Participants with abnormal personality traits as determined by the EPQ-BV will be more impaired on executive functions than participants with normal personality traits

Details of how the aims and hypothesis of the current thesis will be investigated will be given in detail in Chapter six.

CHAPTER SIX – DESIGN AND METHODS

6.1 OVERVIEW OF THE CHAPTER

This chapter will outline the methodology used to investigate the neuropsychological profile of patients with refractory JME. The methodology was designed to investigate refractory JME patients, and assess whether JME patients with abnormal personalities are more impaired on executive functions and cognition than JME patients with a personality profile within normal limits. In addition, the methodology was designed to assess the impact of the following factors:

i. Seizure type and frequency
ii. AEDs
iii. Age of epilepsy onset
iv. Family history of epilepsy
v. History of febrile seizures
vi. Age
vii. Years in education

The design, participants and procedure of the current thesis will be given in this chapter and split into the following sections:

1. General methodology
2. Recruitment and description of participants
3. Neuropsychological tools utilised
4. Procedure
5. An outline of the statistical analysis conducted

6.2 General Methodology

6.2.1 Recap of Aims and Hypothesis

The main aim of the current thesis is to investigate the relationship between the reported neuropsychological deficits in patients with JME, and the abnormal personality traits these patients are described to have. Additionally, the aim is to assess the impact of the contributory factors listed above and discussed in detail in Chapter four. Finally, the current thesis aims to examine the neuropsychological, social and clinical profile of JME patients who do not respond on AED treatment [13].

6.2.2 Contribution of the thesis author J.W.

18 participants were collected by research assistants at the University of Liverpool as part of the MRC funded ReJuMEC study. A further 21 participants were recruited and assessed by Dr Rhys Thomas as part of Wales Epilepsy Study. The author, J.W conducted 21 assessments, and arranged and confirmed each by letter and telephone. The author spent 62 hours conducting testing face to face, 51 hours of scoring and 16 hours of preparing feedback. J.W travelled a total of 2416.8 miles to carry out the assessments, equating to an average of 115 miles per assessment. This constitutes an average of 2.5 hours of travelling per participant and 48 hours spent travelling overall. In addition, J.W. arranged travel and accommodation required for the long distance assessments.

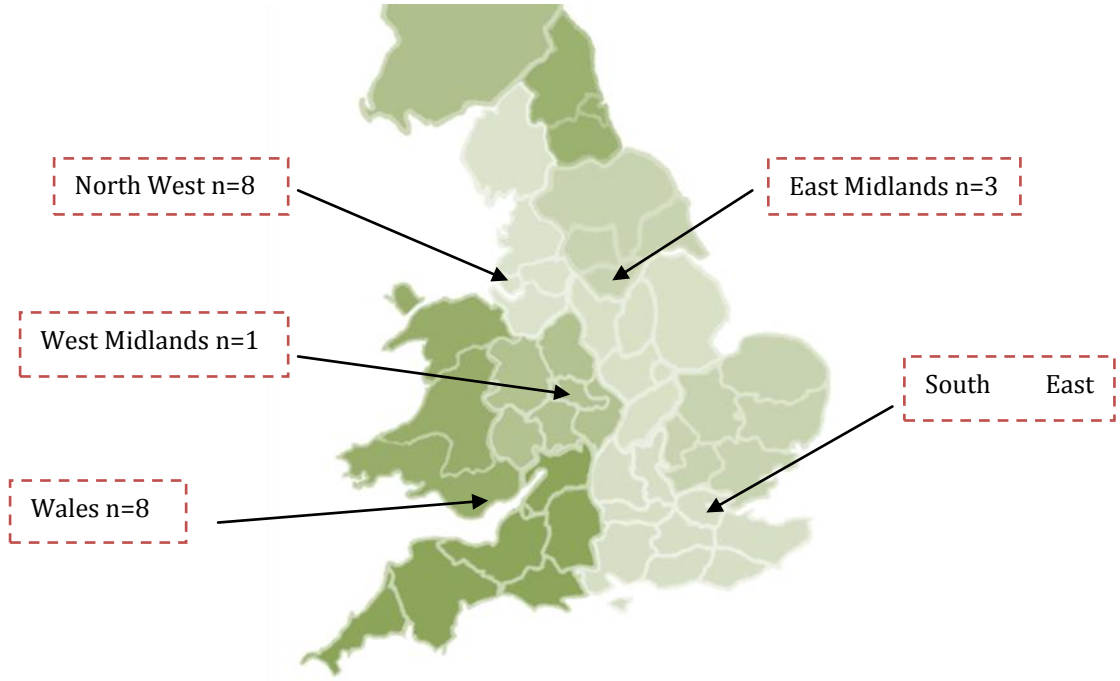


Fig. 6.1 Number of neuropsychological assessments conducted across the UK by the author J.W

6.2.3 ETHICS

Ethical approval was granted by the North West 1 Research Ethics Committee – Cheshire, in 2009 for the study titled 'Juvenile Myoclonic Epilepsy Cohort' (Ref: 09/H1017/55). Several amendments, including inclusion of seizure diaries, choice of length of EEG, and changes to the patient information sheet to the original application were made and granted between 2009-2010. With regards to the current study the author submitted a substantial amendment that was approved in January 2011. The amendment was for the inclusion of the 'Eysenck Personality Questionnaire-Brief Version' [129], so that the personalities of participants could be assessed. A research passport was obtained to gain Research and Development (R&D) approval from 11 NHS organisations. An honorary contract was granted by R&D at the University Hospital of Wales. Indemnity was covered by the University of Liverpool.

6.3 RECRUITMENT

6.3.1 PARTICIPANTS

In total 78 patients were recruited from five different epilepsy outpatient clinics across England and Wales. Four of these patients were excluded from the study as their seizures were controlled with AED treatment. One patient was excluded due to their inability to complete the assessment due to problems caused by an additional clinical illness. Four patients did not attend their pre-arranged neuropsychological assessment, and either could not be contacted afterwards or did not wish to arrange a follow up appointment. Three patients that were recruited by physicians could not be contacted due to insufficient details or change of address. Finally, six patients no longer wished to take part in the study once contacted following initial recruitment.

Therefore data from 60 (45 female:15 male) patients with refractory JME were used in the analysis. Patients were classified as refractory if they experience ≥1 myoclonic and/or absence and/or tonic-clonic seizure per month despite prior or current exposure to a dose of at least 1000mg of Sodium Valproate (VPA). The definition of drug-refractory epilepsy varies greatly in the literature [130] and has not been defined in JME research. The criteria used were based on a combination of the knowledge of sodium valproate being effective in 85–90% of the patients with most becoming seizure-free [66], the criteria used by others [131, 132] and clinical experience of members of the ReJuMEC group. .Exclusion criteria included abnormal MRI brain scan, alcoholism, a history of drug abuse, and/or neurological disorder besides epilepsy. In addition none of the patients had experienced a GTCS within the 24 hours prior to the neuropsychological assessment. For full demographic and clinical characteristics of the participants please see Tables 7.1 and 7.2.

Participants were recruited during routine outpatient appointments with epilepsy specialists based in major neurological departments in the UK. Table 6.2 below gives a list of sites and number of patients tested at each site. Written informed consent was obtained for all participants by either the enrolling neurologist or specialist epilepsy nurse, or the author J.W.

Table 6.2 Hospitals involved in recruitment and number of patients assessed at each site

Hospital	***n***
Walton Centre, Liverpool	23
University Hospital Wales, Cardiff	32
Kings College London	1
Royal Hallamshire Hospital, Sheffield	3
Queen Elizabeth Hospital, Birmingham	1
Total number of participants	**60**

6.4 PROCEDURE

The participants were given full instructions of what the study entailed by either the recruiting physician or the author J.W. There were four components that participants were asked to complete, namely a three month prospective seizure diary, a 48 hour ambulatory EEG, a battery of neuropsychological assessments and a blood sample (for use in future research). Once recruited participants details were passed on to the study co-ordinator who forwarded their details to the relevant parties. Participants were then contacted separately to undergo the EEG, neuropsychological assessments and to give blood. Participants were not obliged to give blood to take part in the other components.

6.4.1 PARTICIPANTS RECRUITED AS PART OF THE REJUMEC STUDY

18 of the participants were recruited and assessed as part of a multicentre study of refractory JME, prior to the author's involvement. These participants were all recruited by epilepsy consultants or epilepsy specialist nurses at the Walton Centre, Liverpool during outpatient clinics. The study was explained by the recruiting physician and informed written consent was obtained. A blood sample was taken (if consent was given to do so) by nurses in the outpatient clinic at the time of enrolment into the study. An EEG was then arranged by the Clinical Trials Unit in the Walton Centre. The neuropsychological assessment was arranged, conducted and scored by a research

assistant to Prof G. Baker at the University of Liverpool. The assessments were all carried out in the Clinical Trials Unit in the Walton Centre. The same research assistant conducted all the assessments.

6.4.2 Participants recruited as part of the Wales Epilepsy Study

21 participants were recruited and assessed as part of the Wales Epilepsy Study. Participants from this study were given a neuropsychological assessment and asked for a blood sample. They were not given seizure diaries or an EEG. Dr R. Thomas recruited, gained written consent, took blood or saliva samples, and conducted and scored the neuropsychological assessment for all 21 participants.

6.4.3 Participants recruited and/or assessed by the author

Eight of the participants assessed by J.W were recruited as part of the ReJuMEC study in the same way as described above. However, not all participants were recruited and assessed at the Walton Centre. Five of these eight participants were recruited by consultant neurologists at the Royal Hallamshire Hospital, Sheffield; Kings College Hospital, London; and Queen Elizabeth Hospital, Birmingham. The blood samples, seizure diaries and EEGs were all organised by the appropriate hospital. The neuropsychological assessment however was arranged and conducted by the author at the recruiting hospital. Furthermore, these assessments were scored and feedback provided by the author.

A further eight participants were recruited by Dr R. Thomas at the University Hospital of Wales, Cardiff. Written informed consent and blood samples were obtained by Dr R. Thomas. The neuropsychological assessments of these participants were arranged by both the author and an administrative member of staff at Swansea University. The neuropsychological assessments were conducted at the University Hospital of Wales, Cardiff by the author. These assessments were also scored and feedback provided by J.W.

Finally the author recruited one participant from an outpatient clinic at the Walton Centre, Liverpool. No EEG was conducted, seizure diary given, or blood taken from this participant. Informed written consent was obtained by the author prior to conducting

the neuropsychological assessment, which was carried out at the participant's home. Lone worker policy was utilised for this assessment to ensure the safety of the author. A letter was sent out to patients at the Walton Centre who met the inclusive criteria explaining the study and asking for volunteers. Unfortunately no participants were gained through this method.

To follow is a brief description of the seizure diary, neurophysiology and genetic components of the study. These components were not carried out by the author, however some of the data particularly from the seizure dairies was utilised in the analysis conducted by the author. A detailed description of the neuropsychological assessment will then be given.

6.4.4 Seizure diary

In order to gain a detailed account of any ongoing seizure activity participants were asked to complete a seizure diary for three months. Participants were supplied with a diary whereby they simply had to tick what seizure type (if any) they experienced each day.

6.4.5 Genetics

Blood samples were collected from 52 participants and saliva from 1. These samples were not utilised in the current thesis, but were obtained for future research. Participants gave informed consent to take a DNA sample, which was taken by a qualified nurse or doctor. Participants were not required to give blood/saliva to take part in the current thesis study.

6.4.6 Neuropsychology

A standardised battery of neuropsychometric tests was administered to each participant. The battery was chosen to enable evaluation of intellectual ability, language functioning, verbal and non-verbal memory, frontal lobe mediated executive functions, depression, generalised anxiety, patient-perceived cognitive impairment, psychosocial impact of JME and personality. Table 6.3 below outlines the assessments used and the abilities assessed.

Table 6.3 Neuropsychological assessments and questionnaires administered and the abilities/difficulties assessed

Assessment	Reference	Description of measures
Wechsler Adult Scale of Intelligence 3rd edition (WAIS-III)	*[133]*	Measures adult intellectual functional: • Verbal IQ • Performance IQ • Full Scale IQ • Working Memory • Processing Speed
Wechsler Memory Scale 3rd edition (WMS-III)	*[134]*	Measures adult memory ability: • General Memory • Working Memory • Immediate Memory • Visual Immediate Memory • Auditory Immediate Memory • Visual Delayed Memory • Auditory Delayed Memory • Auditory Recognition Delayed Memory
Delis-Kaplan executive function system (D-KEFS)	*[135]*	Measures frontal lobe mediated executive functions: • Verbal Fluency • Inhibition
Boston Naming Test (BNT)		Measures visual naming ability
Behavioural Assessment of the Dysexecutive Syndrome (BADS)	*[136]*	Measures frontal lobe mediated executive functions: • Planning • Inhibition • Strategy Formation
Eysneck Personality Questionnaire –	*[129, 137]*	Measures Personality: • Extroversion

Brief Version (EPQ-BV)		• Neuroticism
Hospital Anxiety and Depression Scale (HADS)	*[138]*	Measures Mood: • Anxiety • Depression
Aldenkamp-Baker Neuropsychological assessment scale (ABNAS)	*[139]*	Measures patient-perceived cognitive impairments: • Fatigue • Slowing • Memory • Concentration • Motor • Language
Impact of Epilepsy	*[140]*	Measures psychosocial impact of epilepsy

Wechsler adult scale of intelligence 3rd edition (WAIS-III) [133]

The WAIS-III is a thoroughly validated assessment in normal populations [141], and clinical populations including epilepsy [142]. It is a test that was developed to assess a wide range of abilities in an individual, which together provide a detailed insight into an individual's intellectual strengths and weaknesses. Furthermore, it has been used repeatedly in JME research [7, 12, 13, 96], thus in the present thesis it was chosen to determine the intellectual functioning of refractory JME patients. The accompanying manual provides normative data and scoring instructions [133].

Thirteen subtests from the WAIS-III were administered namely, Picture Completion, Vocabulary, Digit Symbol, Similarities, Block Design, Arithmetic, Matrix Reasoning, Digit Span, Information, Comprehension, Picture Arrangement, Letter-Number Sequence and Symbol Search. From these subtests Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), Working Memory (WKM) and Processing Speed index scores were obtained for each participant and used in the statistical analyses. Scaled scores were calculated using WAIS-WMS writer software for each of the subtests for comparison.

Six subtests are combined to calculate the VIQ score, namely Vocabulary, Similarities, Arithmetic, Digit Span, Information and Comprehension. These subtests are measures of acquired knowledge, verbal reasoning, and attention to verbal material. An individual with a deficit in VIQ may be problems with responding to a verbal request, this may have implications in the workplace and in social relations. For samples of each of these subtests please see Table 6.4 below.

The Vocabulary subtest is designed to measure an individual's vocabulary level. For the Vocabulary subtest participants are asked to define a list of words of increasing difficulty. For each item a score of zero, one or two can be given depending on how well the participant defines the word.

The Similarities subtest is designed to measure abstract thinking. For this participants are verbally presented with two words and asked to explain how they are similar. Again a score of zero, one or two can be given depending on how well the participant can explain how the two words are similar.

The Arithmetic subtest is designed to measure numerical skills, concentration and anxiety. For this subtest participants are verbally presented an arithmetic problem, which they must solve mentally. Their answer must be given within a specified time of between 15-120 seconds depending on the complexity of the problem. If an answer is not given within this time frame a score of zero is given regardless of whether their response is correct or not. Each item carries a score of zero or one, with the exception of the final two items for which a score of zero, one or two can be given depending on the speed of the response.

The Digit Span subtest is designed to measure working memory and anxiety. The subtest has two sections (digit forward and digit backward). For the digit forward section participants are verbally presented with a series of digits and asked to repeat them back in exactly the same order as they were presented. A maximum of eight items with a total of 16 unique trials can be presented. The initial item contains two digits, and then for each item thereafter a digit is added up to a maximum of nine digits. Participants can proceed to the next item if one of the two trials is repeated correctly. The section is discontinued if the participant scores a zero on both trials of an item. A score of zero, one or two can be given for each item. For the digit backward section participants are given a series of digits in exactly the same way as the digit forward

section, but this time participants are asked to repeat the series of digits backwards. The digit backward section is slightly shorter with a possible seven items and 14 trials available. The maximum amount of digits in a trail is eight. The same discontinue rule and scoring applies to the digit backward, as the digit forward.

The information subtest is designed to measures an individual's range of knowledge. For this participants are asked up to 28 general knowledge questions. Each item carries a score of zero or one.

The comprehension subtest is designed to measure judgment and social understanding. For this subtest participants are verbally presented with questions regarding everyday problems and social norms. Responses are scored on how well they describe what they would do or why certain things are the way they are in society. For five of the items participants are required to give more than one reason or idea in order to obtain a perfect score. Each item carries a score of zero, one or two.

Table 6.4 Sample items for the verbal subtests of the WAIS

Subtest	Sample item
Vocabulary	What does WINTER mean?
Similarities	In what way are PIANO and DRUM alike?
Arithmetic	What is FOUR POUNDS PLUS FIVE POUNDS?
Digit Span	1. 1 1-7
	2 6-3
	2. 1 5-8-2
	2 6-9-4
Information	What is a THERMOMETER?
Comprehension	What is the thing to do IF YOU FIND AN ENVELOPE IN THE STREET THAT IS SEALED, ADDRESSED AND HAS A NEW STAMP ON IT?

Five subtests are combined to calculate the PIQ score namely, Picture Completion, Digit Symbol-coding, Block Design, Matrix Reasoning and Picture Arrangement. These subtest are measures of fluid reasoning, spatial processing, attention to detail and

visual-motor functioning [133]. An individual with a deficit in PIQ may struggle with convergent thinking; this may cause problems in formal education. For samples of each of these subtests please see Table 6.5 below.

The Picture Completion subtest is designed to measure attention to detail. For this subtest participants are presented with a series of incomplete pictures (Figure 6.2). For each item the participant is asked what important part is missing in the picture. A maximum of 25 pictures of increasing difficultly can be presented. Each item carries a score of zero or one.

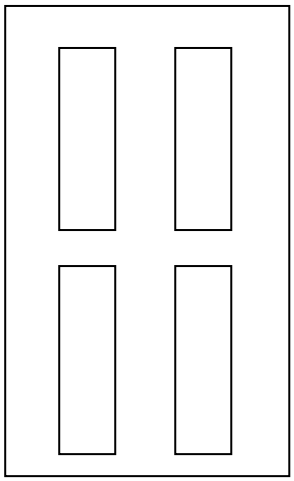


Figure 6.2 Sample item for the picture completion subtest from the WAIS - a door with the handle missing

The Digit Symbol-Coding subtest is designed to measure visual-motor functioning and processing speed. For this subtest participants are presented with boxes with the number 1-9 along the top and symbols in the boxes below. They are then directed half way down the page where there are more boxes with the numbers 1-9 in a random order, but this time the boxes underneath are empty (Figure 6.3). Thus participants are asked to fill in these boxes by drawing a symbol using the code at the top of the page. They are asked to work as quickly as they can without skipping any boxes until they are asked to stop. Participants are stopped after 120 seconds if they do not fill in all the empty boxes. A score of one is given for every correct symbol draw within the time frame.

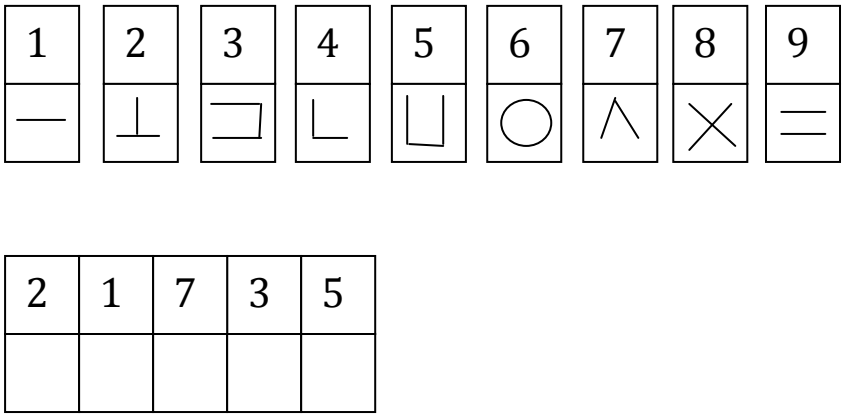


Figure 6.3 Sample of Digit Symbol-coding subtest from the WAIS

The block design subtest is designed to measure nonverbal reasoning. For this subtest participants are presented with nine identical blocks. The blocks are coloured in red and white. Some sides are all red, some sides are all white and some sides are half red and half white. Participants are asked to copy a printed design with the blocks. For items 1-6 a score of zero, one and two can be given. For items 7- 14 a score of zero, four, five, six and seven can be given depending on how quickly the participant arranges the blocks in the correct design.

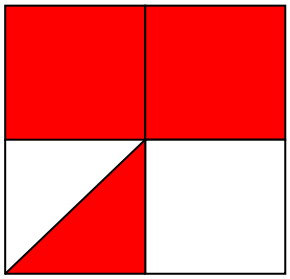


Figure 6.4 Sample item of the block design subtest from the WAIS

The Matrix Reasoning subtest is designed to measure an individual's ability to analyse part-whole relationships. For this subtest participants are presented with a series of printed patterns that are incomplete, and five options to complete the pattern. They are asked to look at each pattern carefully and say which of the five possible options best completes the pattern. Each item carries a score of zero or one.

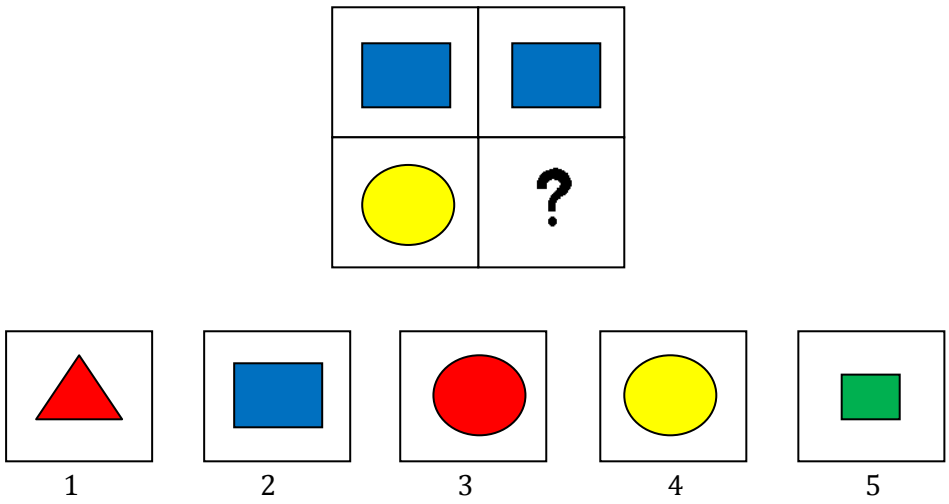


Figure 6.5 Sample item of the Matrix Reasoning subtest from the WAIS

The Picture Arrangement subtest is designed to measure planning ability. For this subtest participants are given a number of cards with pictures on them, and asked to arrange them in an order that makes sense.

Participant's FSIQ score is calculated from their VIQ and PIQ scores. WKM score is calculated from participant's performance on the digit span and letter-number subtests. Finally their processing speed score is calculated from the digit symbol-coding and symbol search subtests.

Wechsler memory scale 3rd edition (WMS-III) [134]

The WMS-III is a thoroughly validated in normal populations [134], and clinical populations including epilepsy [143, 144]. The WMS has been used repeatedly in JME research [13, 14, 72] and was chosen to determine immediate and delayed recall ability. Ten subtests were administered namely, Logical memory, Verbal paired associates, Faces, Family Picture, Letter number sequencing and Spatial Span. From these subtests General Memory, Working Memory, Immediate Memory, Visual Immediate and Delayed, Auditory Immediate and Delayed, and Auditory Recognition Delayed Memory index scores were obtained for each participant and used in the statistical analysis. Scaled scores were calculated using WAIS-WMS writer software for each of the subtests for comparison.

Auditory memory (immediate and delayed) was calculated from the Logical Memory and Verbal Paired Associates scores. These subtests are measures of memory functioning when information is presented orally. An individual with a deficit in auditory immediate memory may have problems with learning; this may have implications in all aspects of life when stimuli are presented in the auditory modality [134]. If an individual has a deficit in auditory delay memory they may experience a high rate of forgetting. For samples of each of these subtests please see Table 6.5 below.

For the Logical Memory subtest participants are read out two stories and asked to immediately recall as much of each of the stories as they can. Story one is read out first and recalled, followed by story two. Once the participant has recalled story two the story is read out again and the participant is asked to recall it once more. Participants are then asked to recall both stories following a 30 minute delay.

For the Verbal Paired Associates subtests participant are read out a list of eight word pairs. The first word of each pair is then repeated and the participant is asked to say which word goes with BANK for example. The list of pairs is read out four times and recalled four times (once every time the list is read out). Participants are then asked to recall the pairs once more after a 30 minute delay.

Table 6.5 Sample items for the Verbal memory subtests of the WMS

Subtest	Sample item
Logical Memory	Anna Thompson of South London who was employed as a cook in a school canteen.....
Verbal Paired Associates	Truck-Arrow Insect-Acorn Reptile-Clown

Visual memory (immediate and delayed) was calculated from the Faces and Family Pictures scores. These subtests are measures of memory functioning when information is presented visually. Similar problems in learning and forgetting that were described above in relation to auditory memory apply to visual memory. In addition to this the

delayed visual subtests comprise of one recall paradigm (family pictures) and one recognition paradigm (faces). Thus a difference in performance on the two subtests may suggest meaningful differences in memory functioning. For example, a low score on the Family Pictures subtest, and high score on the Faces subtest may indicate a retrieval problem [134].

For the Faces subtest participants are presented with 24 faces for two seconds one at a time, which they are asked to remember. They are then presented with a group of 48 faces, and asked to say yes if a face is one from the group I asked them to remember or no if it is a new face. A score of zero or one can be given, depending on if the participant correctly identifies each face. Following a 30 minute delay participants are asked to correctly pick out the faces they were asked to remember from a new group of 48 faces. The scoring is the same as the immediate recall task.

For the Family pictures subtest participants were first presented with a picture of a family of five family members (Grandfather, Grandmother, Father, Mother, Son and Daughter) and a dog. They are then presented with four scenes with these family members and the dog in them for 10 seconds each. They are then asked to recall who was in the scene, where they were and what they were doing for each scene. Following a 30 minute delay participants are then asked to recall the four scenes again. For each correctly recalled character a score of one is given. For each correctly recalled location of a character a further score of one is given. Finally for each activity recalled a score of zero, one or two is given, depending on how accurately the participant describes what each character was doing. The scoring is the same for the immediate and delayed recall.

Auditory Recognition Delayed Memory was calculated from the Logical Memory recognition score and the Verbal Paired Associates recognition score. For the Logical Memory recognition participants were asked 15 question on story one and 15 question on story two. They were asked to simply say whether the statement is true or not. For the Verbal Paired Associates recognition participants were read out a list of 24 word pairs, which contained both the pairs they had learnt and new pairs. Participants were asked to say ‘yes’ if the pair was one they had learnt or ‘no’ if it was a new word pair. Please see Table 6.6 below for samples of the recognition subtests.

Table 6.6 Samples of the recognition subtests from the WMS

Subtest	Sample item
Logical Memory Recognition	Was the women's name Anna Thompson?
Verbal Paired Associates Recognition	Rose-Bag Queen-Thumb Elephant-Glass

Immediate memory was calculated from the immediate recall scores from the Logical Memory, Verbal Paired Associates, Faces and Family Pictures subtests. General memory was calculated from the delayed recall scores from the Logical Memory, Verbal Paired Associates and Family Pictures subtests.

Delis-Kaplan executive function system (D-KEFS)[135]

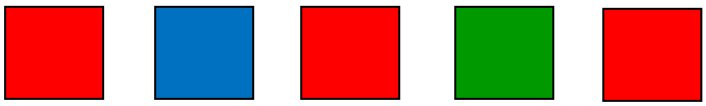
The D-KEFS was chosen to assess language, fluency, attention and executive functions. It is also a thoroughly validated test [145], and comes with normative data and a scoring manual [135]. The subtests administered were Verbal Fluency, which included Letter, Category and Category Switching; and Colour-Word Interference, which included an adaptation of the Stroop Test [146].

The Verbal Fluency subtest was used to examine the patient's ability to generate words fluently. The letter task included naming as many words as possible in 60 seconds beginning with a particular letter. This was repeated for the letters F, A and S. For the category task participants were asked to name as many animals as they could, followed by as many boys' names as they could, both in 60 seconds. Lastly, for the category switching task participants were asked to switch between saying as many fruits, and as many pieces of furniture as they could in 60 seconds. The number of words generated and rule breaks were calculated and used in the analyses.

The Colour-Word Interference task was used to examine patient's ability to inhibit an over learned verbal response in order to generate a conflicting response of naming the dissonant ink colours in which the words are printed. The task includes 4 trials. For trial one the examinee is to simply say the colour of the ink squares are printed in. For

trial two they are asked to read a sequence of colour words printed in black ink. For trial three participants must name the colour of the ink of non matching colour words. Finally, for trial four participants were asked to do the same as the previous trial with the additional task of reading the written word not the ink colour if the word was in a box. The time it took participants to complete each trial and the number of mistakes and corrections were used in the analyses. See Figure 5.6 below for illustrations of each of the trials.

Trial one:



Trial two:

green red blue green blue

Trial three:

blue green blue red blue

Trial four:

green blue green blue red

Figure 6.6 Sample of each of the four trials in the Colour-Word Interference task from the D-KEFS

Boston naming test (BNT)

The BNT was chosen to assess visual naming ability. The standard form was used in the present study. Participants were presented with pictures and asked to name the object depicted. All participants in the current study were administered items 30-60. If a

participant was incorrect on any of the items 30-38 they were administered items in reverse order from 29 until 8 consecutive correct responses. The number of correct responses was used in the analyses.

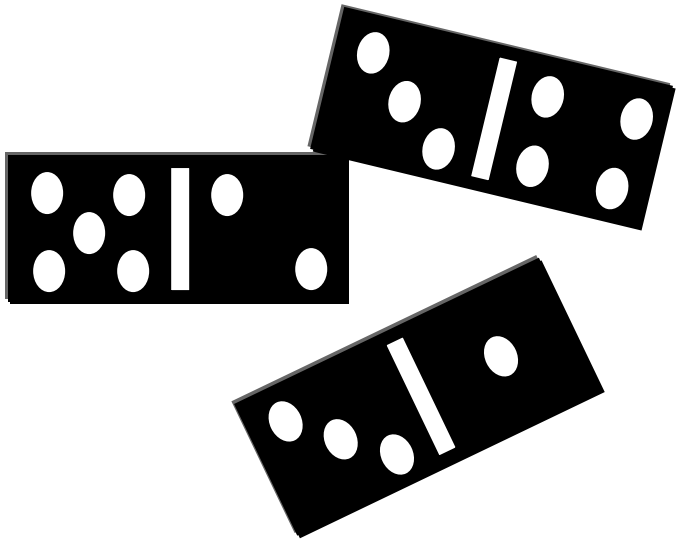


Figure 6.7 Sample item from the Boston Naming Test

Behavioural Assessment of the Dysexcutive Syndrome (BADS) [136]

The BADS was included as an additional test of executive functions that has good ecological validity [147]. The BADS comes with normative data and a scoring manual [136]. The subtests administered were the Rule Shift, Key Search and Zoo Map. For each test a profile score was calculated and used in the analyses. For classification of profile scores see Table 6.7 below.

Table 6.7 Classification of profile scores

Profile score	Classification
4	Above average
3	Average
2	Below average
1	Borderline
0	Impaired

The Rule Shift was chosen to assess the participant's ability to follow and shift between rules. The test comprises of two trials. In the first trial participants were presented with 21 spiral bound non-picture playing cards and the rule 'Say yes to red cards and no to black cards', which was both read out to them and placed in front of them for the duration of the trial. The examiner turned over the playing cards one at a time, waiting for the participant's response before turning over the next card. In the second trial participants were presented with the same playing cards, but a different rule 'Say Yes if the card that has just been turned over is the same colour as the previously turned card and no if it is a different colour', which was read out and placed in front of them. The examiner turned over the playing cards one at a time, waiting for the participant's response before turning over the next card. In both trials the number of errors and time taken was recorded A profile score was calculated based on the performance on the second trial.

The key Search was chosen to assess strategy formation and participant's ability to self-monitor. Participants were presented with an A4 piece of paper with a 10cm square in the middle and a small black dot 5cm below it. The participants were told to 'imagine the square is a large field, which you have lost your keys in. Draw a line starting from the black dot to show where you would walk to search the field to make absolutely certain that you would find your keys. Tell me when you are finished.' The time taken was recorded, and this and the strategy used was used to calculate a profile score.

The Zoo Map was included to assess planning ability. This task consisted of two trials. In both trials participants were presented with an A4 piece of paper, which had a map of a zoo on it. Above the map were instructions of six locations (out of 12) on the map they were required to visit. They were also given a set of rules they must obey when planning their route around the zoo. They rules included; starting at the entrance, finishing at the picnic area, only using paths once unless the path has a dotted pattern in which case the path can be used twice, and only using the monorail once. In the first trial participants are not given any instructions other than the rules and a list of six locations they must visit in an order they choose. In the second trial as well as the rules they are given the order in which they must visit the six locations. The time taken and number of rules broken was recorded and used to calculate a profile score.

Eysenck Personality Questionnaire – Breif Version (EPQ-BV) [129, 137]

The EPQ-BV was included to examine the presence of personality disorders (PDs) in JME, and whether PDs are related to severity of seizures, cognitive impairments and executive dysfunction. The EPQ-BV [129] is a 24-item short version of the EPQ-R, which was developed from the original Eysneck and Eysneck EPQ [148]. It is a self-report questionnaire that measures two personality dimensions, namely extroversion (E) and neuroticism (N).

The EPQ-BV was chosen over previous versions of the EPQ [148] due to the brevity and likert scale format. Alternative personality tool have been employed in the few previous studies that have investigated personality in JME i.e. the Minnesota Multiphasic Personality Inventory (MMPI) [149], the Structured Clinical Interview for the DSM-IV (SCID) [26, 27] and the Youth Self-report (YSR) and Weinberger Adjustment Inventory (WAI) [98]. The above personality assessments were not used for the following reasons: the YSR and WAI were designed for participants aged between 10-17 years, thus both were not appropriate for the current sample. The MMPI was eliminated as it contains 567 questions with the facility to answer only "true" or "false". Finally the SCID could not be used as a Psychiatrist is required to administer it, and thus was too costly in time and money for the current investigation.

The EPQ-BV is quick and easy to administer and complete, and appropriate for the age range of the current sample. Moreover, it has good re-test reliability and validity [129]. The coefficient alpha scores for the EPQ-BV have been reported to be .92 and .90 for E and N, respectively [129, 137]. The EPQ-BV is scored on a likert scale from A (not at all) to E (extremely), where A=1, B=2, C=3, D=4 and E=5. Items 13 and 19 are reverse scored. Table 5.8 below gives a sample of the EPQ-BV.

Table 6.8 Sample of EPQ-BV

Sub-scale	Sample Question	Response	Score
Extroversion	*Are you a talkative person?*	• Not at all • Slightly • Moderately • Very much • Extremely	1 2 3 4 5
Neuroticism	*Does your mood often go up and down?*		

Hospital anxiety and depression scale (HADS) [138]

The HADS was chosen to assess the participant's level of anxiety and depression. Mood has long been found to be a factor in cognitive performance, thus the HADS was used to examine the impact mood has on the cognitive performance in the current sample. The HADS is well established as a reliable tool for measuring anxiety and depression in patient groups [150]. Acceptable internal consistencies and high re-test reliability correlations have been reported internationally [151, 152]. Another advantage is its' brevity, especially when participants are already faced with a lengthy and tiring assessment.

The HADS is a self-report questionnaire that consists of seven questions for the depression subscale, and seven questions for the anxiety subscale. Participants are asked to rate each item based on how they have been feeling in the previous week on a 4-point likert scale. Anxiety and depression items are scored separately with each item carrying a score of 0-3. An overall score for either subscale of 0-7 equates to normal levels, 8-10 to mild levels, 11-14 to moderate levels, and 15-21 to severe levels of anxiety or depression (Table 6.9 presents a sample of both subscales). The scores for both subscales were used in the analyses.

Table 6.9 Sample of HADS

Sub-scale	Sample Question	Response	Score
Anxiety	I feel tense or 'wound up'	• Most of the time	3
		• A lot of the time	2
		• Time to time	1
		• None of the time	0
Depression	I still enjoy the things I use to enjoy	• Definitely as much	0
		• Not quite as much	1
		• Only a little	2
		• Hardly at all	3

Aldenkamp-Baker Neuropsychological assessment scale (ABNAS) [139]

The ABNAS was included to assess the relationship between patients perceived level of cognitive effects of their AEDs, and their actual level of cognition based on an objective neuropsychological assessment. The ABNAS is a self-report questionnaire that has been found to be a valid instrument for identifying drug induced cognitive impairments in patients with epilepsy [139].

The ABNAS assesses six aspects of cognition that are sensitive to neurotoxicity of AEDs, namely Fatigue, Slowing, Memory, Concentration, Motor and Language. The Scale consists of five items for both the fatigue and slowing subscales, four items for the memory and concentration subscales, and three items for the motor and language subscales. Participants were asked to rate to what extent 24 statement are true to them on a 4-point likert scale (0=no problem to 3=a serious problem). A score for each of the subscales was totalled. Each subscale score was then added together to produce an overall total score, which ranged from 0-72. The total score was used in the analysis. For a sample of the ABNAS please see Table 6.10 below.

Table 6.10 Sample questions for each of the subscales from the ABNAS

Sub-scale	Sample Question	Response and score
Fatigue	I am less enthusiastic about day to day activities	• No problem = 0 • Mild problem = 1 • Moderate problem = 2 • Serious problem = 3
Slowing	My mind does not work as fast as it should	
Memory	I have difficulties remembering people's names	
Concentration	I have difficulties in following books or films	
Motor	I feel clumsy	
Language	I have problems finding the correct words	
Total score		**0-72**

Impact of Epilepsy Scale (IES) [140]

The impact of epilepsy scale was utilised to assess the impact of epilepsy and AED treatment on various aspects of participant's daily lives, including their relationships with friends and family, social life, employment, health, self-esteem, plans for the future and standard of living. Acceptable alpha coefficients have been reported for the scale [140]. In addition high correlations between psychological wellbeing and perceived impact of epilepsy, indicate good construct validity [140].

It is comprised of 10 items rated on a 4-point likert scale from 'a lot' to 'not at all'. With the exception of items one and five, which have an additional option of 'not applicable'. A score of 8-20 represents mild impact, 21-30 represents moderate impact, and a score of 31-40 represented severe impact. For a sample of the IES please see Table 6.11 below. The total score was used in the analyses.

Table 6.11 Sample questions from the Impact of Epilepsy Scale

	Sample Question	Response	Score
Impact of epilepsy scale	To what extent have your personal relationships been affected?	• A lot • A moderate amount • A small amount • Not at all	4 3 2 1

6.5 Statistical analysis

6.5.1 Power calculation

A power calculation was conducted by the author J.W using Minitab 16 statistical package. The primary outcome measure was verbal inhibition from the D-KEFS. This outcome measure was chosen as it is the most consistent executive function impairment reported in JME [16]. The power calculation revealed that 32 participants were needed to detect a significance difference of 2.22 between the refractory JME group and manual means, setting the probability of making a type 1 error at 0.05.

6.5.2 DATA ENTRY

The data collected from the 60 participant's was inputted into a database designed and maintained by the author. All the assessments were scored according to the manuals provided with each of the tests, and checked before being entered into a database using the Statistical Package for Social Sciences (SPSS) version 19.0.

6.5.3 STATISTICAL PROCEDURE USED

Due to the number of multiple comparisons being made, and to reduce the likelihood of making Type I error the significance level was set at $p < .01$ for all independent sample t-tests. Bonferroni correction was not applied as this would have given too conservative a value ($0.05/41 = p<.001$) due to the number of inferential statistics conducted, and therefore would have increased the likelihood of making a Type II error. The use of a significance level of $p<.01$ has been used by others [114, 153]

6.5.3.1 Demographic and clinical characteristics

Demographic characteristics that were recorded and used in the analyses were gender, age, years of education, level of education (school, college or university), WAIS full IQ index score, and employment status. For the continuous variables histograms were produced and skew and standard error statistics. Means and standard deviations were reported for data that met the normal distribution. If data were considered skewed from the normal distribution the median and inter-quartile ranges were reported. The latter applied to the variables age and years of education. The mean and standard deviation were reported for the WAIS IQ index score.

Clinical characteristics that were recorded and used in the analyses were age of onset, duration of epilepsy, family history, history of febrile seizure, photosensitivity, seizure type, seizure frequency, number of AEDs, and AED type. For the continuous variables histograms were produced and skew and standard error statistics. Means and standard deviations were reported for data that met the normal distribution. If data was considered skewed from the normal distribution the median and inter-quartile ranges were reported. The latter applied to the variables age of onset and duration of epilepsy.

6.5.3.2 Neuropsychological profile

The neuropsychological assessment administered to all the participants produced an age adjusted score for each cognitive domain assessed. The spread of these scores was determined by visual analysis of histograms, and consideration of the skew and standard error statistics. Each of the index score from the WAIS and WMS were normally disturbed apart from processing speed. Therefore the means and standard deviations were used to describe central tendency for all but processing speed, for which the median and inter-quartile range was reported.

For the subtests of the WAIS and WMS the same procedure was carried out. For the variables digit-symbol coding, faces (immediate and delayed recognition), family pictures (delayed recall) and spatial span the median and inter-quartile ranges were reported. The remaining subtests were normally distributed, and thus their means and standard deviations were reported.

In order to compare the participant's scores to a healthy population, z-scores were calculated based on the means and standard deviations given by the assessment manuals.

To control for and assess the impact of education, intellectual functioning scores were correlated with years in education using Pearson's R correlation coefficients. Pearson's was chosen as the scores fitted assumptions of normality. Post hoc t-tests were run for any variables that were highly correlated.

6.5.3.3 Impact of contributory factors on neuropsychological profile

In order to determine the impact of the contributory factors outlined in Table 4.2 (and described in detail in Chapter four) on the neuropsychological profile of the sample, bivariate correlation and regression analyses were conducted. Standard linear regression was chosen to assess the predictive power of the variables and to identify which factors significantly contributed to the explanation of variance in cognition. This analysis has been utilised in previous reports investigating the neuropsychological profile of JME patients.

For each cognitive test with a z-score >1.00 SD below published norms a univariant regression was run for each clinical and mood variable (age of onset, duration of epilepsy, types of seizures, frequency of seizure types, number of AEDs, HADS depression score and HADS anxiety score). Multivariable regression with forward variable selection was then run for further investigation of any cognitive test with more than one significant predictor.

Post-hoc analyses of significant findings were assessed using independent sample t-tests.

6.5.3.4 Personality and neuropsychological functioning

To assess whether an abnormal personality is related to neuropsychological functioning, the data from the EPQ-BV was dichotomised into 'high' and 'normal' neuroticism, and 'low' and 'normal' extroversion. The neuroticism scores were split into ≥40 for females, and ≥37 males. A score of 40 or above for females and 37 or above for males is one standard deviation above the means given by Sato [137]. The extroversion score was split into ≤33 for both males and females. A score of 33 or less is one standard deviation below the means given by Sato [137].

The performance across the battery of the participants in each personality group was compared to published norms using z-scores. Their performance was then compared across groups with independent sample t-tests.

Patients were then grouped into those with high neuroticism and/or low extroversion, and those with normal levels of neuroticism and extroversion. These two groups were coded as abnormal personality and normal personality, respectively. To assess the effect of abnormal personality traits overall on neuropsychological functioning, one sample t tests were conducted between published norms and abnormal personality group, and normal personality group.

Three additional executive function tests were administered to half of the sample, namely the rule shift, key search and zoo map from the BADS. The samples mean scores were compared to manual means by one sample t-tests. A significant difference was found for the zoo map. Pearson's correlation was conducted between zoo map score

and personality, psychiatric characteristics, clinical characteristics and years of education. A significant correlation between neuroticism and zoo map score. Post-hoc independent t-tests were conducted to investigate the effect of neuroticism on zoo map performance.

6.5.3.5 Severity of executive dysfunction

Executive function tests were divided into six executive functions, and the z-scores of each of the tests were calculated. In concordance with previous research [154, 155] a z-score of ≤-1 (one or more standard deviations below the manual means) on at one of the tests within each of the six domains was categorised as having executive dysfunction in relation to that domain. As naming ability was measured by only one test a z-score of ≤-1 on the Boston naming test was categorised as executive dysfunction in relation to naming ability. If two domains were found to meet these criteria the patient was said to have mild executive dysfunction. If three or four domains met the criteria the patient was said to have moderate executive dysfunction. If five or more domains met the criteria the patient was said to have severe executive dysfunction.

CHAPTER SEVEN – RESULTS: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

7.1 DEMOGRAPHIC CHARACTERISTICS (TABLE 7.1)

In total 60 patients diagnosed with refractory JME were assessed on their intellectual functioning, memory, and executive functions. In addition patient's psychological wellbeing and personality were also examined. Prior to assessment demographic and clinical history was recorded. The demographic and clinical characteristics of the current sample are displayed in Tables 7.1 and 7.2, respectively.

The majority of the sample were female (75%) and had a median age of 31 years (range 19 – 67 years). All patients had achieved at least a secondary school education with the median number of years of formal education being 13.0 years; 38% had a college educational and 13% graduated from University. Sixty-seven percent were currently in employment, 5% in education and the remainder were unemployed.

Table 7.1 Participants' demographic characteristics

		n = 60
Gender	*Female*	45 (75.0%)
	Male	15 (25.0%)
Age	*Median*	31.00
	IQR	24.00, 38.75
Number of years in formal education	*Median*	13.00
	IQR	11.00, 13.00
Level of education (n=40)	*School*	20 (50.0%)
	College	15 (37.5%)
	University	5 (12.5%)
WAIS full scale IQ	*Mean*	89.25
	SD	15.24
Employment status (n=39)	*Employed*	26 (66.7%)
	Unemployed	11 (28.2%)
	Full time education	2 (5.13%)

SD, standard deviation; IQR, Inter-quartile range; WAIS, Wechsler Adult Intelligent Scale

7.2 Clinical characteristics (table 7.2)

The clinical characteristics of the current sample of JME are in concordance with JME profiles reported previously [13, 14, 16]. The median age of onset was 12.00 years, with the median duration of epilepsy being 21.00 years. All of the patients (100%) had or continue to experience myoclonic seizure. The majority of patients also had experienced GTCS (96%), and almost two thirds had experienced absences (70%). In addition two patients had experienced atonic/astatic seizures, while another single patient had experienced drop attacks. Photosensitivity was reported by nine of the patients.

Two-thirds returned seizure diaries; 50% continued to experience at least one myoclonic seizure per day (only 7.5% reported abatement of these seizures) (Fig 7.1). In contrast, 37.5% of the patients had controlled GTCS, and 5% had never had a GTCS. The frequency of GTCS for the remaining 57.5% ranged between one per week to one per year (Fig 7.2). Forty percent of the patients had never experienced an absence

seizure. However, for those who did, they were found to be very frequent. 25% experienced one or more per day and all together 50% experienced one or more per month, while only 5% were controlled (Fig 7.3).

A small minority of the sample had a history of febrile seizures (n=6, 11.1%). A family history of epilepsy was more prevalent with 25 patients (43.9%) reporting at least one member of their family had or has epilepsy. Of these 25 patients about two thirds of them reported one family member related by at least the 3rd degree having also been diagnosed with epilepsy, while nearly a quarter of these patients reported two or more cases of epilepsy in their families.

Table 7.2 Participant's clinical characteristics

Duration of epilepsy (years) (n = 57)	*Median*	20.00
	IQR	9.50, 30.00
Onset of epilepsy (years) (n= 57)	*Median*	13.00
	IQR	9.00, 15.00
Types of seizure	*Myoclonic*	60 (100%)
	GTCS (n=54)	52 (96.3%)
	Absences (n-54)	38 (70.4%)
	Other	2 (3.4%)
Family history (n=57)		25 (43.9%)
History of febrile seizures (n=54)		6 (11.1%)
Photosensitive (n=33)		9 (27.3%)
Number of AEDs	*1*	28 (46.7%)
	2	20 (33.3%)
	3 or more	12 (20.0%)
AED type	*VPA*	35
	LEV	25
	LTG	18
	TPM	10
	ZNS	4
	CLB	10
	CBZ	2

IQR, Inter-quartile range; Myo, myoclonic seizures; Ab, absence seizures; TC, tonic clonic seizures; VPA, Sodium Valproate; LEV, Levetiracetam; LTG, Lamotrigine; TPM, Topiramate; ZNS, Zonisamide; CLB, Clobazam ; CBZ, Carbamezepine.

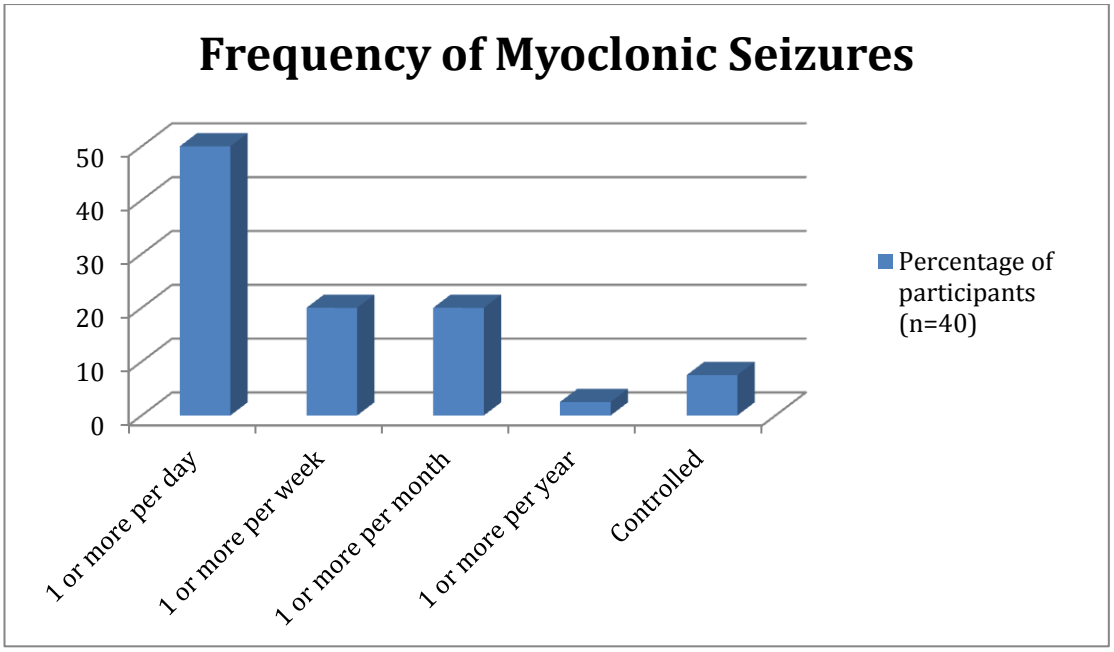


Figure 7.1 Frequency of myoclonic seizures (n=40)

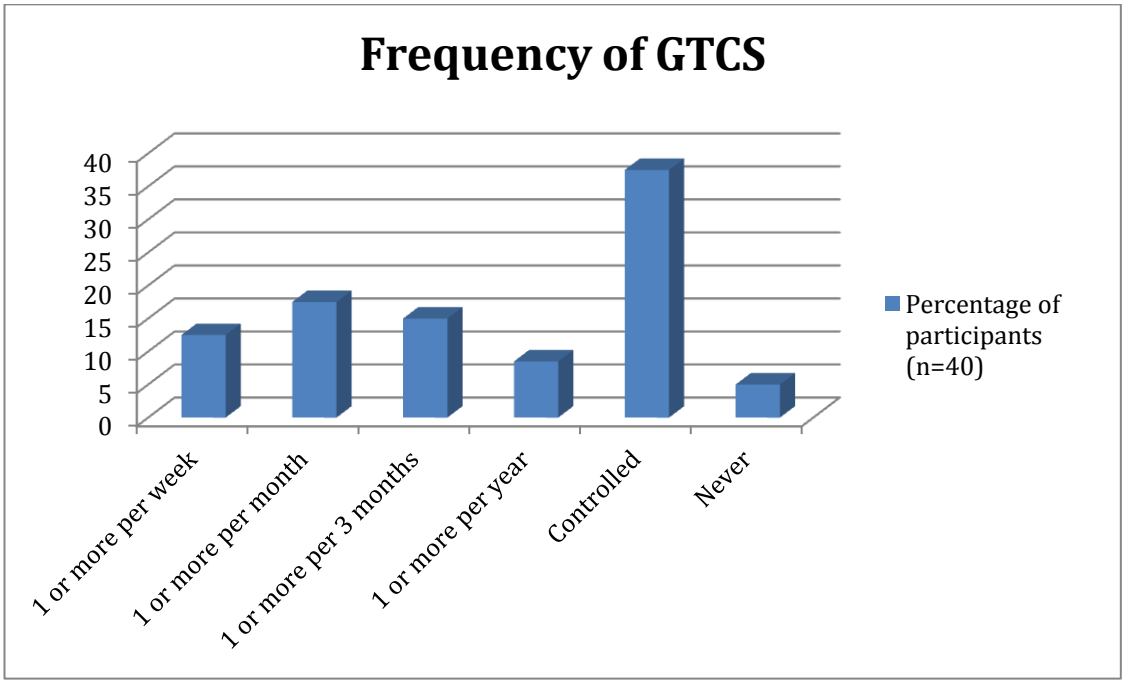


Figure 7.2 Frequency of GTCS (n=40)

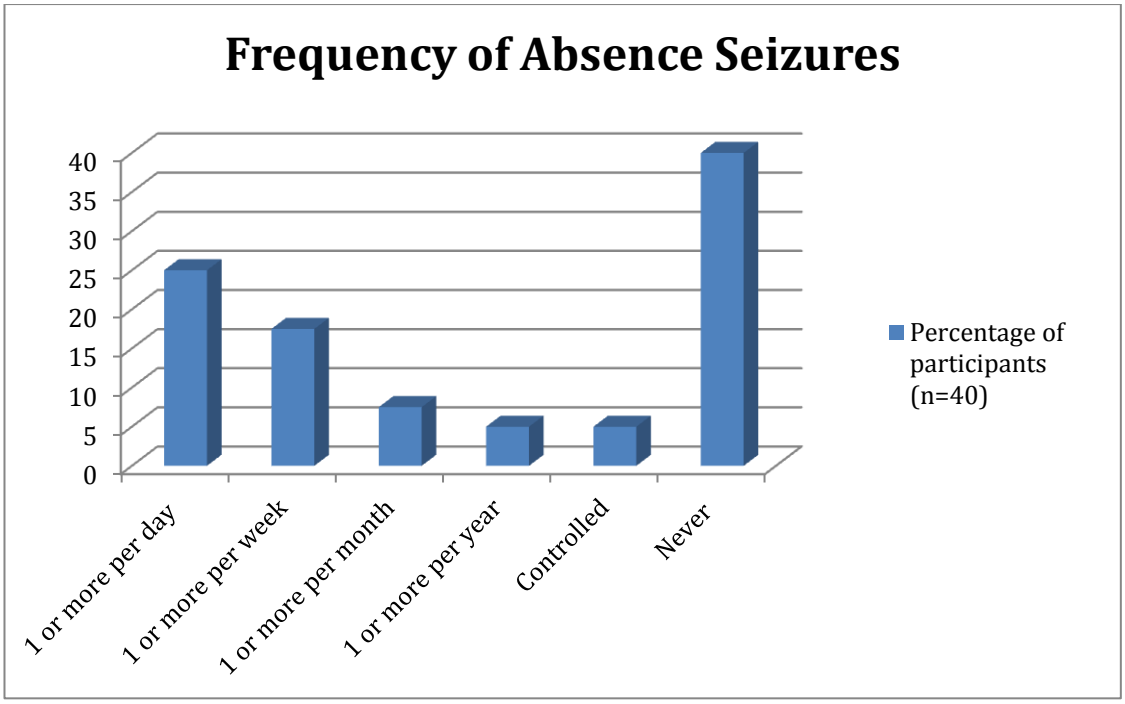


Figure 7.3 Frequency of absence seizures (n=40)

7.2.1 Anti-epileptic medication at testing

In the current sample seven different AED's were prescribed, with VPA being the most common. As would be expected in a refractory sample, over half of the patients were on polytherapy (n=32), while 28 patients (47%) were on monotherapy; 20 (33%) were taking two; 11 (18%) were taking three; and one individual was taking four. The monotherapy AEDs were valproate (n=17, mean daily dose 1464mg); lamotrigine (n=5, mean daily dose 300mg); levetiracetam (n=4, mean daily dose 2500mg); and zonisamide and topiramate were both taken by single individuals. Of the people taking two AEDs there were 12 different combinations, the most common of which was valproate and levetiracetam (n=5) followed by valproate and lamotrigine (n=3). There were six different combinations of three AEDs taken concurrently, four of these included clobazam as an adjunct.

7.3 PERCEIVED EFFECTS OF AEDS ON COGNITIVE FUNCTIONING

Perceived cognitive functioning assessed with the ABNAS (see method chapter for description). Means reported by Aldenkamp et al [156] were used for comparison with the current sample. They reported a mean of 19.46 and standard deviation of 15.8 from

a sample of 96 people with epilepsy (consisting of 55 well controlled patients on monotherapy and 41 refractory patients on polytherapy) [156]. One sample t-tests were conducted with a test value of 19.46 to compare the current samples ABNAS scores to the means reported by Aldenkamp et al. The findings from these tests are displayed in Table 7.3 below

Table 7.3 Current samples ABNAS score compared to healthy means

	N	Mean (SD)	Sig.
Total ABNAS score	35	36.9 (16.0)	< .001 ***

***P ≤.001

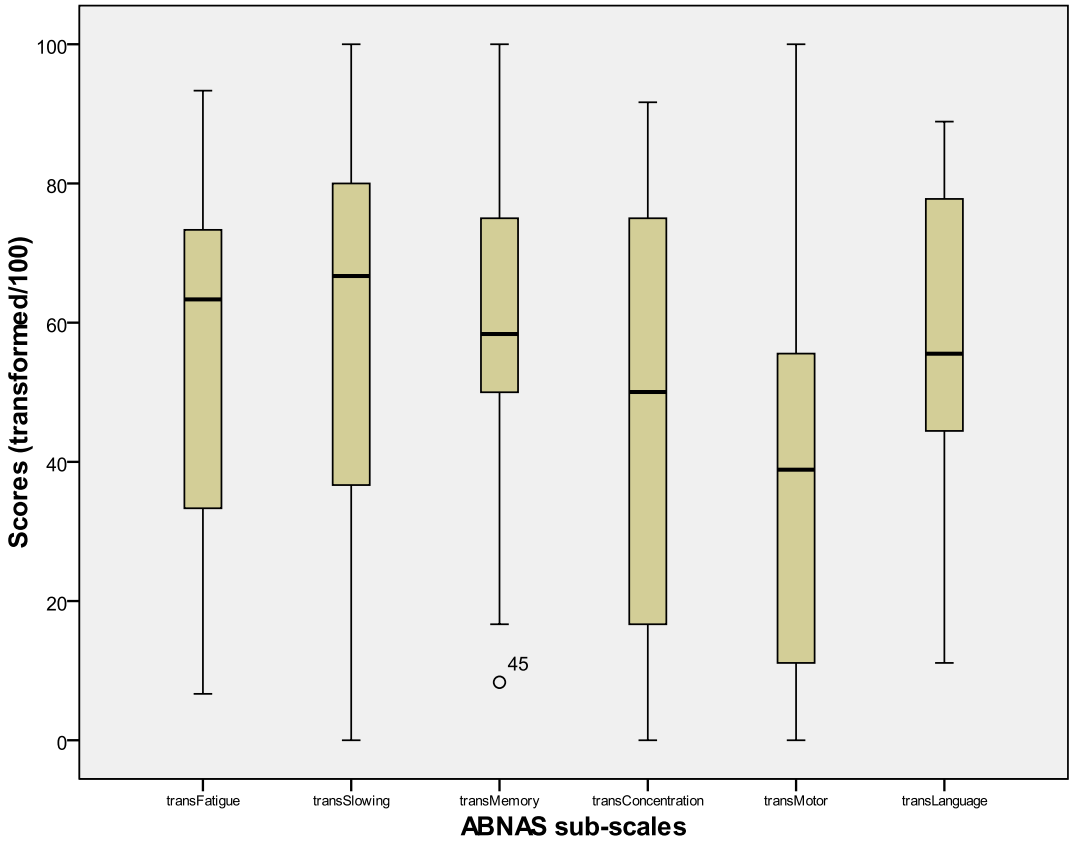


Figure 7.4 Current samples scores across the six sub-scales of the ABNAS

Figure 7.4 illustrates the current samples scores across the six sub-scales of the ABNAS. The box plots indicates that the least subjective complaint reported on average was motor abilities. The most subjective complaint reported on average was mental slowing. However, both motor and mental slowing produced the largest range of scores.

CHAPTER EIGHT – RESULTS: NEUROPSYCHOLOGICAL PROFILE

Hypothesis one: SIGNIFICANT IMPAIRMENTS IN 1) INHIBITION 2) VERBAL FLUENCY. AS THE PATIENT GROUP INVESTIGATED IN THE CURRENT THESIS CONSISTS OF ONLY REFRACTORY PATIENTS IT IS HYPOTHESISED THAT OTHER COGNITIVE IMPAIRMENTS MAY BE REVEALED.

Previous investigations have consistently reported impairments in neuropsychological functions in patients diagnosed with JME [7, 11-14, 16, 22, 72, 106, 154, 157]. Therefore the current study hypothesised that significant impairments would be found for inhibition and verbal fluency. To investigate this hypothesis participants were administered a series of neuropsychological assessments. The means and standard deviations of these assessments are displayed in Table 8.1 below.

No control group was recruited in the current study. Therefore, in order to compare the participant's scores to the mean scores of a healthy population, z scores were calculated based on the means and standard deviations given by the assessment manuals. Each of the assessments provides standardised scores for the ages 16-89. The z scores were calculated using the following equation:

$$Z = \frac{x - \bar{x}}{s}$$

The z scores for the WAIS, WMS and D-KEFS are given in table 8.1. Box plots of these scores are also presented (figures 8.1-8.3) to better illustrate the current samples scores, compared the standardised means.

8.1 Intellectual function

The mean FSIQ was 89 for the cohort (range 55 - 117). VIQ, PIQ, PS, WM and the FSIQ (Table 8.1) were all lower in people with drug-refractory epilepsy than standardised means; PS was lowest. Eight participants (13%) returned FSIQs two SDs below the mean (i.e. an IQ of 70 or below).

Table 8.1: Intellectual functioning as measured by the WAIS of patients with drug-refractory JME compared to healthy standardized controls.

Neuropsychological test	Mean (SD) scaled score	Standardised norms (SD)	Mean adjusted z score
Full Scale IQ	89.2 (15.37)	100 (15)	-.718
Verbal IQ	88.8 (15.30)	100 (15)	-.689
Performance IQ	91.4 (15.25)	100 (15)	-.570
Processing Speed	86.0 (79.5, 99.0) [a]	100 (15)	-.930
WAIS Working Memory	88.8 (18.41)	100 (15)	-.644
Vocabulary	8.4 (3.23)	10 (3)	-.532
Similarities	8.0 (3.13)	10 (3)	-.673
Arithmetic	7.9 (3.63)	10 (3)	-.842
Digit Span	8.5 (2.85)	10 (3)	-.485
Information	8.3 (2.89)	10 (3)	-.577
Comprehension	8.0 (3.65)	10 (3)	-.661
Picture Completion	9.1 (3.37)	10 (3)	-.300
Digit Symbol-coding	7.0 (5.0, 7.0) [a]	10 (3)	**-1.00**
Block Design	8.6 (2.51)	10 (3)	-.468
Matrix Reasoning	9.6 (3.19)	10 (3)	-.135
Picture Arrangement	8.3 (2.88)	10 (3)	-.574
Letter-Number Sequencing	8.7 (3.59)	10 (3)	-.425
Symbol Search	8.3 (3.32)	10 (3)	-.553

[a] Median and inter-quartile range

8.2 Memory performance

Immediate memory (particularly immediate visual memory), delayed visual memory, general memory and WM were all lower in participants than published norms (Table 8.2). The lowest scores were seen in immediate visual memory (mean= 88). Of the subtests that compose these measures patients scored worse on verbal paired associates, faces, family pictures (immediate and delayed) and spatial span.

Table 8.2: Memory function as measured by the WMS of patients with drug-refractory JME compared to healthy standardized controls**.**

Cognitive Test	JME means (SD)	Standardised norms (SD)	Mean adjusted z-score
Immediate Memory	90.5 (13.07)	100 (15)	-.635
Immediate Visual Memory	87.6 (14.11)	100 (15)	-.827
Delayed Visual Memory	88.2 (19.44)	100 (15)	-.679
Immediate Auditory Memory	95.8 (12.50)	100 (15)	-.277
Auditory Recognition Memory	100.4 (14.72)	100 (15)	.039
General Memory	95.2 (13.43)	100 (15)	-.321
WMS Working Memory	90.4 (15.45)	100 (15)	-.644
Logical Memory: immediate recall	9.8 (2.94)	10 (3)	-.056
Logical Memory: delayed recall	10.5 (2.58)	10 (3)	.230
Verbal Paired Associates: immediate recall	8.6 (2.54)	10 (3)	-.459
Verbal Paired Associates: Delayed	9.6 (2.60)	10 (3)	-.132

recall			
Faces: immediate recognition	8.0 (7.0, 9.0) [a]	10 (3)	-.670
Faces: delayed recognition	9.0 (7.0, 11.0) [a]	10 (3)	-.310
Family Pictures: immediate recall	7.6 (2.83)	10 (3)	-.793
Family Pictures: delayed recall	8.0 (5.0, 10.0) [a]	10 (3)	-.780
Spatial Span	8.0 (6.0, 10.0) [a]	10 (3)	-.707

[a] Media and inter-quartile range

8.3 Executive function

Participants scored worse on all tests of verbal fluency and executive function (Table 8.3). The two most poorly performed tests were inhibition switching and the BNT.

Table 8.3: Executive functioning of patients with drug-refractory JME compared to healthy standardized controls.

Cognitive test	JME mean (SD)	Published norms (SD)	Mean adjusted z-scores
Letter Fluency	7.4 (3.30)	10 (3)	-.867
Category Fluency	7.9 (4.24)	10 (3)	-.707
Category Switch	8.6 (3.88)	10 (3)	-.477
Category Accuracy	9.2 (3.69)	10 (3)	-.259
Inhibition	7.8 (4.33)	10 (3)	-.740
Inhibition switch	6.0 (4.48)	10 (3)	**-1.34**
BNT	49.1 (9.0)	55.5 (3.9)	**-1.64**

The performance of the current sample compared to standardised norms illustrated in Figures 8.1-8.3 below. The index scores for the WAIS and WMS, and scores from the D-KEFS are displayed alongside the standardised norms.

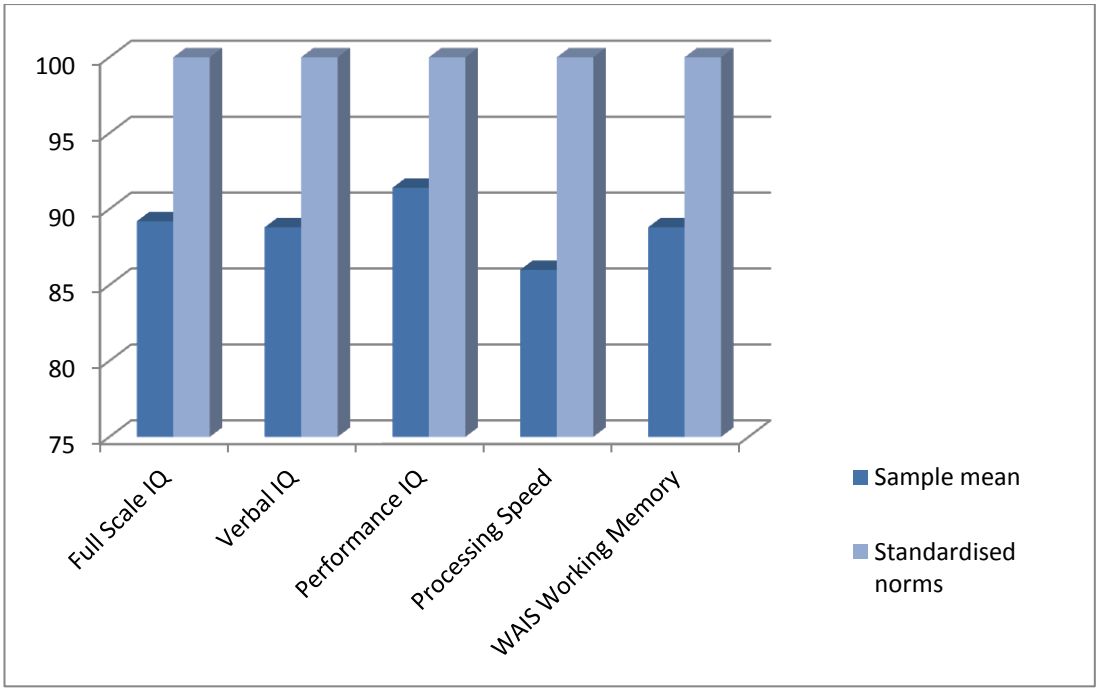


Figure 8.1 Mean WAIS index scores and standardised norms

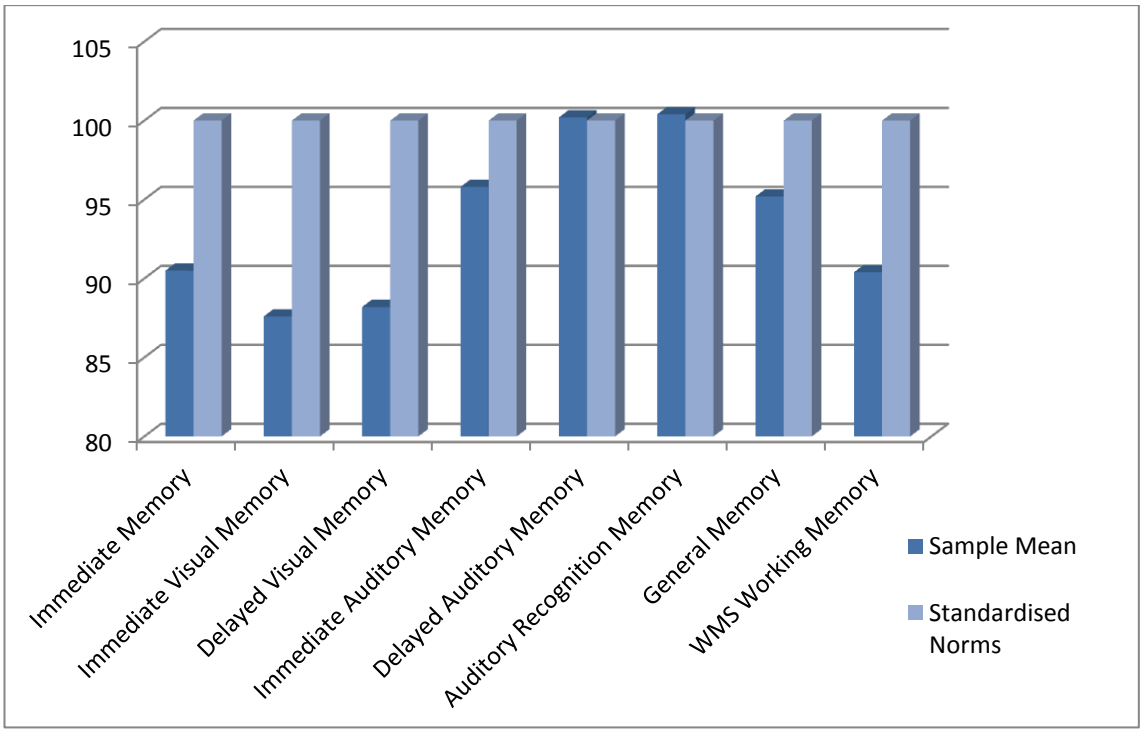


Figure 8.2 Mean WMS index scores and standardised norms

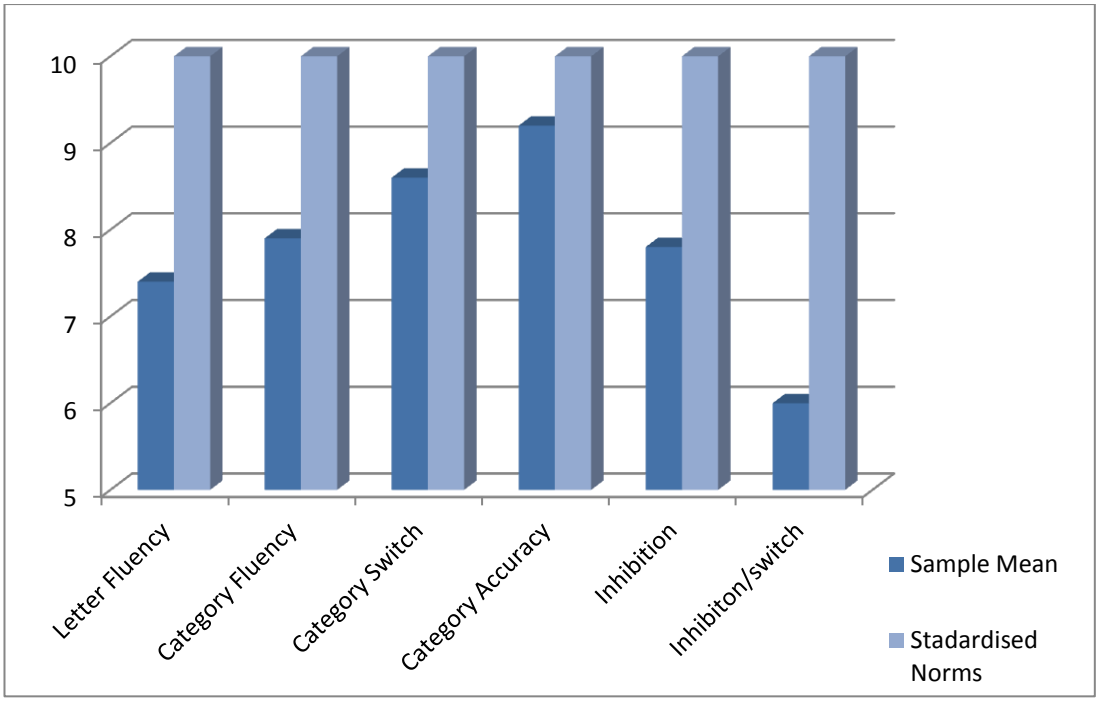


Figure 8.3 Mean D-KEFS scores and standardised norms

8.4 Education

To control for and assess the impact of education intellectual functioning, memory and executive function scores were correlated with years in education using Pearson's R correlation coefficients. This revealed significant relationships between years of education and verbal IQ [r= .497, *df*= 40, p< .001], full scale IQ [r= .422 *df*= 39, p<.05], auditory immediate memory [r= .340, *df*= 39, p<.05], auditory delayed memory [r= .373, *df*= 39, p< .05], and verbal inhibition [r= .375, *df*= 37, p< .05].

Post hoc t-tests were run to investigate these relationships. The sample was split into those who had received ≥11 years of education, and those who had received <11 years of education. The means and SDs of the two groups for the five correlated variables (full scale IQ, verbal IQ, auditory immediate and delayed memory, verbal inhibition) were compared. The t-tests with alpha level set at p< .01 revealed significant differences in verbal IQ, auditory immediate memory and auditory delayed memory. The difference in full scale IQ scores and verbal inhibition scores failed to reach significance. Those with ≥11 years of education had significantly higher verbal IQ scores [t(39)= 2.018, p< .05], auditory immediate memory [t(38)= 2.261, p< .05] and auditory delayed memory [t(38)= 2.504, p< .05] than those with <11 years of education.

When the scores of the two groups were compared to manual means the performance of patients with ≥11 years of education did not significantly differ for auditory immediate (p= .612) or delayed (p= .159) memory. However, their performance was significantly poorer for verbal IQ (p= .019). The patients with <11 years of education performed significantly worse than manual means on all three cognitive domains; verbal IQ (p< .001), auditory immediate (p= .007) and delayed (p= .044) memory. Thus, receiving formal education for ≥11 years protects against impairments in auditory immediate and delayed memory, but it does not protect against significantly worse performance on verbal IQ. However, although patients with ≥11 years of education performed worse they still scored within the normal range for verbal IQ (mean = 91.22), while those with <11 years of education scored at the lower end of the below average range (mean = 81.72).

CHAPTER NINE – CONTRIBUTORY FACTORS

HYPOTHESIS TWO: CLINICAL CHARACTERISTICS AND MOOD WILL HAVE AN IMPACT ON ANY COGNITIVE IMPAIRMENTS FOUND IN THE REFRACTORY JME SAMPLE.

It is clear from past research that the cognitive deficits in JME are multi factorial, encompassing pathophysiology, clinical factors, treatment and psychosocial factors (discussed in detail in chapter four).

The current thesis seeks to assess the impact of clinical and psychosocial factors on the neuropsychological functioning of JME patients. From the analysis of the neuropsychological assessments, it was found that the current sample scored more than one standard deviation below published norms in the three tests (digit symbol coding, BNT and inhibition switching). Therefore multiple linear regressions were conducted to assess the impact of clinical factors and mood on the scores of these three tests (Table 9.1, 9.2 and 9.3 summarises these regression analyses).

Firstly, univariant regressions were run to investigate the contribution of each of the clinical and mood variables on the scores for the three tests. The variables investigated included age of onset, duration of epilepsy (log transformation), types of seizures, frequency of myoclonic seizures, frequency of GTCS, frequency of absence seizures, number of AEDs prescribed, HADS depression score and HADS anxiety score. The results of these analyses are presented in Table 9.1-9.3 below.

For the following regression analyses the assumptions of homogeneity, normality and multicollinearity were assessed by inspection of the residual scatter plot, residual histogram and tolerance. Standardised residuals and Cook's distance were checked for any outliers having undue influence of each model. Each of these assumptions was met in the analyses below.

Table 9.1 Univariant analysis of digit symbol coding score

Variables	Pearson's correlation	R^2	Sig of model	beta	t
Age	.113	-.005	.402	-	-
Duration of epilepsy	-.186	.017	.166	-	-
Seizures	.171	.009	.241	-	-
Myoclonic frequency	-.345	.096	.029*	-.750	-2.263
Tonic clonic frequency	-.082	.019	.615	-	-
Absence frequency	-.071	-.021	.662	-	-
Number of AEDs	-.403	.148	.001**	-.403	-3.353
Depression	-.206	.015	.222	-	-
Anxiety	-.218	.020	.195	-	-

*P<.05, **p<.01

Table 9.2 Univariant analysis of BNT score

Variables	Pearson's correlation	R^2	Sig of model	beta	t
Age	-.061	.015	.661	-	-
Duration of epilepsy	-.103	.008	.460	-	-
Seizures	-.131	.005	.382	-	-
Myoclonic frequency	-.159	.002	.341	-	-
Tonic clonic frequency	-.085	.020	.612	-	-
Absence frequency	.247	.036	.129	-	-
Number of AEDs	-.289	.067	.029*	-3.393	-2.241
Depression	-.068	-.025	.694	-	-
Anxiety	-.242	.031	.155	-	-

*P<.05

Table 9.3 Univariant analysis of inhibition switching score

Variables	Pearson's correlation	R^2	Sig of model	beta	t
Age	.122	-.004	.380	-	-
Duration of epilepsy	-.229	.034	.096	-	-
Seizures	.109	-.011	.473	-	-
Myoclonic frequency	-.230	.026	.171	-	-
Tonic clonic frequency	.144	-.007	.395	-	-
Absence frequency	-.050	-.026	.770	-	-
Number of AEDs	-.229	.035	.087	-	-
Depression	-.103	-.020	.562		
Anxiety	.020	-.031	.913		

The univariant regressions revealed that the frequency of myoclonic seizures and number of AEDs prescribed were significant independent predictors of performance on the digit symbol coding test. A multivariable regression with forward variable selection was then run to investigate the contribution of these two significant variables (number of AEDs and frequency of myoclonic seizures) on the participants' digit symbol coding score. This analysis revealed that only the number of AEDs prescribed was entered into the regression and explained 31.1% of the variance. The beta value indicated a negative association; therefore being on polytherapy was associated with a lower score on the digit symbol coding test.

Table 9.4 Forward multivariable regression analysis of digit symbol coding score

Variables entered	Pearson's correlation	R^2	Sig of model	beta	t
Number of AEDs	-.606	.331	.005*	-.606	-3.228

*P<.01

The univariant regression analyses revealed only one significant independent predictor of naming ability, therefore a multivariable regression was not conducted. Number of AEDs explained 6.7% of the variance in naming ability. The beta value indicated a negative association; therefore being on polytherapy was associated with a lower naming ability.

On further inspection of the results it was found that the number of AEDs prescribed was a significant independent predictor of naming ability (p =.007), and explained 17.9% of the variance in performance on the BNT. The beta value indicated a negative association; therefore being on polytherapy was associated with low naming ability.

Post-hoc independent t-tests revealed that patients on polytherapy performed significantly worse than those on one AED (p= .007). The means indicated that patients on one AED scored close to healthy means (mean= 52.5), while patients on polytherapy scored more than two standard deviations below healthy means (mean= 46.3). These results indicate polytherapy is associated with impaired naming ability.

The univariant regressions revealed that none of the clinical or mood variables assessed significantly predicted inhibition switching score. Thus unknown variables are contributing to the impairment in inhibiting the natural response and the mental flexibility to switch between rules.

9.1 SUMMARY OF CHAPTER NINE

The current chapter has investigated the impact of clinical characteristics and psychosocial variables on cognition. The regression analyses revealed the key contributory factor was number of AEDs prescribed, indicating that receiving polytherapy is associated with worse neuropsychological functioning.

No clinical or mood variable significantly explained the variance in the consistently found impairment in switching between inhibiting a response and not inhibiting a response. The final two results chapters will investigate the impact of mood further and finally the impact of personality traits.

CHAPTER TEN- PSYCHIATRIC SYMPTOMS AND NEUROPSYCHOLOGICAL FUNCTIONING

Hypothesis three: Refractory JME patients with high levels of anxiety and/or depression will be more impaired on neuropsychological functioning than those with normal levels of anxiety and/or depression

Both depression and anxiety have been found to be associated with neuropsychological impairments [112]. JME patients have been reported to have high levels of depression and anxiety [27]. Thus to investigate whether high levels of anxiety and/or depression in JME is associated with neuropsychological impairments, the HADS was administered.

Forty-nine percent of the patients scored in the moderate to severe range for anxiety symptoms and 16% for depressive symptoms. Nine (24%) people had mild anxiety; 15 (41%) people had moderate anxiety; and three (8.1%) had severe anxiety symptoms. In contrast, seven (19%) people had mild depressive symptoms; five (14%) had moderate depressive symptoms; and one (2.7%) had severe depressive symptoms.

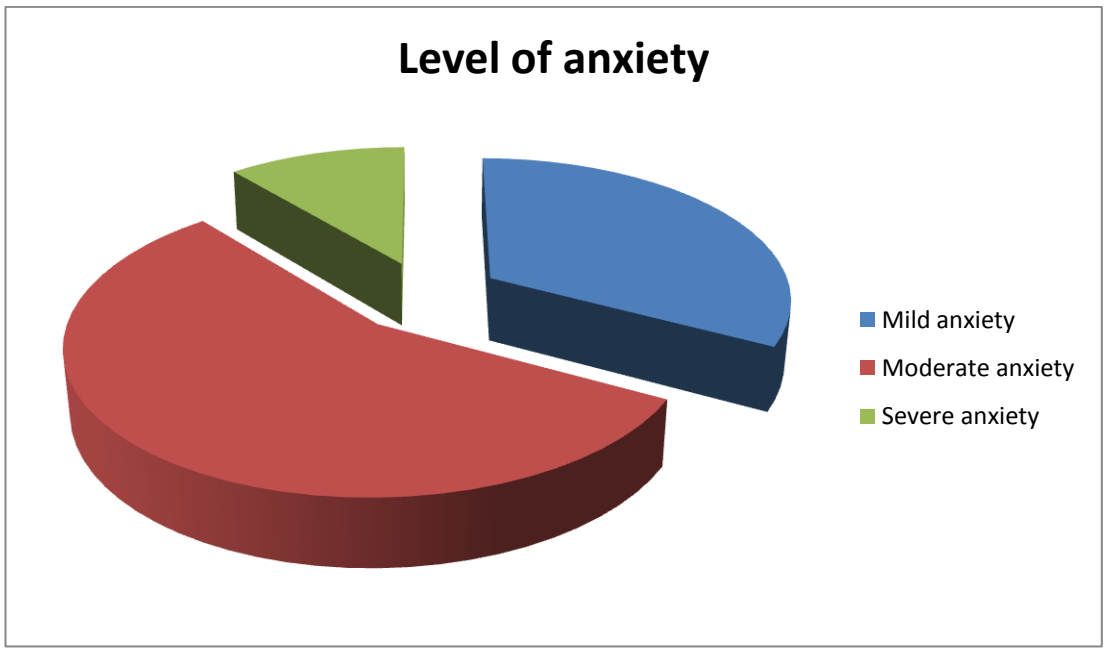


Figure 10.1 Level of anxiety across the refractory JME sample

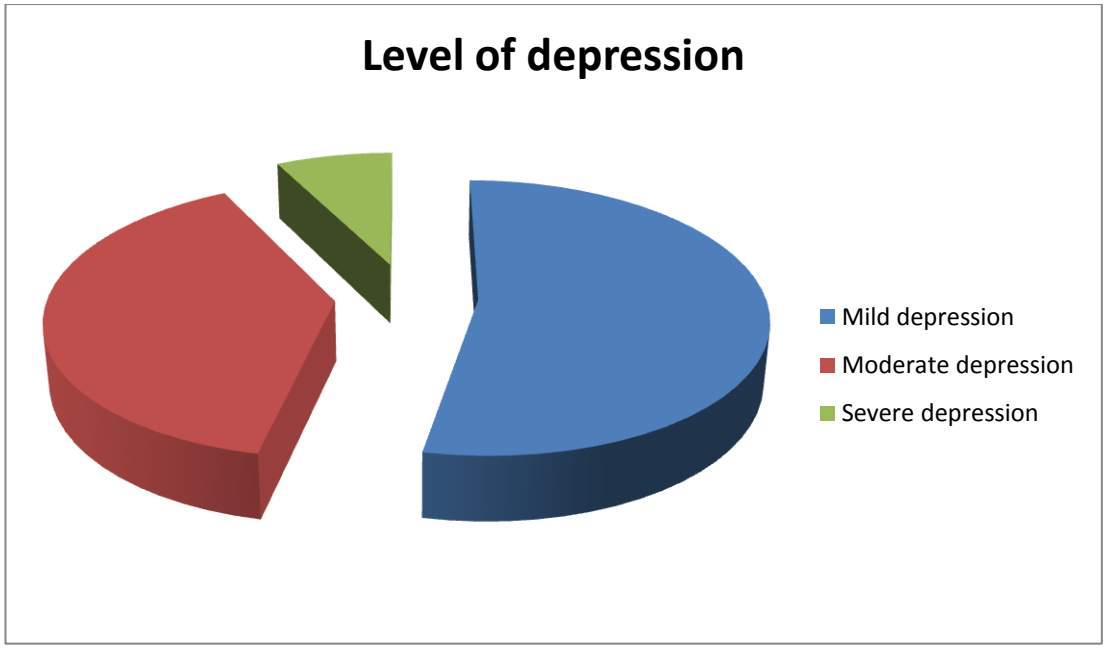


Figure 10.2 Level of depression across the refractory JME sample

Higher anxiety scores were significantly correlated with poorer function on tests of vocabulary, similarities, information, picture completion, verbal IQ, performance IQ, full-scale IQ, and letter fluency. Independent t-tests revealed significantly poorer function on the WAIS subtests vocabulary ($p = .004$) and information ($p = .010$). People with high anxiety scores had, on average, 2.77 points lower on vocabulary ($d = 1.02$) and 2.40 points lower on the information subtest ($d = 0.89$) compared with people with drug-refractory JME and less extreme HADS anxiety scores. Anxiety remained a significant independent predictor of performance on the information subtest when correlated clinical and demographic characteristics (duration of epilepsy and years of education) were controlled for and explained 19% ($p = .003$) of the variance. No clinical or demographic characteristics significantly correlated with performance on the information subtest.

Although the other test scores were not statistically significant, the real-life difference may be substantial, and medium effect sizes were found. People with high anxiety scores had, on average, 9.10 points lower on verbal IQ ($d = 0.627$, $p = .065$) and 9.00 points lower on full-scale IQ ($d = 0.654$, $p = .058$) compared with people with lower anxiety scores. Higher depression scores were significantly correlated with poorer function on category fluency. Independent t-tests revealed a non-significant difference; however, this was likely to be due to the small number of the cohort presenting with high depressive symptoms. People with higher depression scores had, on average, 2.97

points lower on category fluency (d = 0.918) compared with people with less extreme HADS depression scores.

10.1 Summary of Chapter ten

A higher proportion of patients presented with high anxiety symptoms than high depression symptoms. Real life differences in cognitive functioning were found between patients with high anxiety and depressive symptoms and those with levels of anxiety and depression within normal range.

CHAPTER ELEVEN – PERSONALITY, NEUROPSYCHOLOGICAL FUNCTIONING AND EXECUTIVE FUNCTIONS

HYPOTHESIS FOUR: PARTICIPANTS WITH AN ABNORMAL PERSONALITY TRAITS, AS DETERMINED BY THE EYSENCK PERSONALITY QUESTIONNAIRE-BRIEF VERSION (EPQ-BV) WILL BE MORE IMPAIRED ON EXECUTIVE FUNCTIONS THAN PARTICIPANTS WITH NORMAL PERSONALITY TRAITS.

Patients with JME have been described as having abnormal personalities [27, 98, 99]. To investigate whether an abnormal personality is related to neuropsychological functioning, the EPQ-BV was administered. Participants were considered to have abnormal personalities if they were found to have high levels of neuroticism and/or low levels of extroversion.

One sample t-tests (Table 11.1) were run to compare the current refractory sample with the mean neurosis and extroversion values reported by Sato [137]. The data file was dichotomised into males and females. The EPQ-BV identified that females with drug-refractory JME had pathologically high neuroticism scores and low extroversion scores (introvert trait). The males also scores in the introverted range but not in the pathological range for neuroticism (Table 11.1).

Table 11.1 Current sample EPQ-BV scores compared to norms reported by Sato [137]

	Neuroticism			**Extroversion**		
	Sample Means	**Sato Norms**	**p value**	**Sample Means**	**Sato Norms**	**p value**
Males	33.09 (10.34)	26.93 (9.96)	.076	33.72 (12.51)	42.58 (9.11)	.041*
Females	39.00 (11.51)	30.54 (9.38)	.001 ***	30.63 (9.94)	42.09 (8.97)	<.001 ***

N=38, *P ≤.05, **P ≤.01, ***P ≤.001

Independent sample t-tests were run to compare the scores of those with high and normal neuroticism, and those with low and normal extroversion. Due to the number of multiple comparisons being made, and reduce the likelihood of making Type I error the significance level was set at p< .01. Bonferroni correction was not applied as this would have given too conservative a value (0.05/41= p<0.001) due to the number of inferential statistics conducted, and therefore would have increased the likelihood of making Type II error. The use of a significance level of p<.01 has been used by others [114, 153].

11.1 Neuroticism Vs Neuropsychological Functioning

The impact of neuroticism on neuropsychological functioning was investigated by splitting the current sample in to those with 'high neuroticism' and those with 'normal neuroticism'. Participants were considered to have abnormally high neurosis if they scored more than one standard deviation above the means reported [137], based on 257 healthy volunteers. Levels of neuroticism differ in healthy males and females, with females exhibiting higher levels of neurosis. Therefore a score ≥40 for females and ≥37 for males was considered abnormal in the current sample.

Tables 11.2-11.3 below display the means and z-score for each test, illustrating whether the scores of participants in the two groups was lower than published norms. The p value for the comparison between the two groups ('high' neurosis Vs 'normal' neurosis) is also given.

Table 11.2 Intellectual functioning as measured by the WAIS of patients with drug-refractory JME and high/normal levels of neuroticism compared to healthy standardized controls.

Cognitive test	High neuroticism		Normal neuroticism		Neurotic Vs non-neurotic
	Mean score	**Mean adjusted z-score**	**Mean score**	**Mean adjusted z-scores**	**Sig.**
Full Scale IQ	84.6	-1.03	90.7	-0.62	.224
Verbal IQ	83.6	-1.09	92.0	-0.53	.072
Performance IQ	90.1	-0.66	90.6	-0.63	.925
Processing Speed[α]	88.5	-0.77	81.0	-1.27	.940[α]
Vocabulary	7.00	-1.00	9.23	-0.26	.021
Similarities	7.94	-0.69	8.14	-0.62	.833
Arithmetic	7.69	-0.77	8.45	-0.52	.304
Digit Span	7.56	-0.81	8.82	-0.39	.173
Information	7.06	-0.98	9.23	-0.26	.037
Comprehension	**6.50**	-1.17	8.64	-0.45	.043
Picture Completion	9.44	-0.19	9.05	-0.32	.754
Digit Symbol-coding[α]	7.50	-0.83	**6.00**	-1.33	.956[α]
Block Design	8.27	-0.58	8.64	-0.47	.652
Matrix Reasoning	9.00	-0.33	9.59	-0.12	.597
Picture Arrangement	8.13	-0.62	8.27	-0.58	.881
Letter-Number Sequencing	8.31	-0.56	8.59	-0.47	.815
Symbol Search	7.31	-0.90	8.19	-0.60	.480

[α] Mann-Whitney U Test

Table 11.3 Memory function as measured by the WMS of patients with drug-refractory JME and high/normal levels of neuroticism compared to healthy standardized controls.

Cognitive test	High neuroticism		Normal neuroticism		Neurotic Vs non-neurotic
	Mean score	Mean adjusted z-score	Mean score	Mean adjusted z-score	Sig.
Immediate Memory	87.8	-0.81	89.0	-0.73	.811
Immediate Visual Memory	85.8	-0.95	85.4	-0.97	.933
Delayed Visual Memory	87.1	-0.86	89.2	-0.72	
Immediate Auditory Memory	92.8	-0.48	95.9	-0.27	.462
Delayed Auditory Memory	98.9	-0.07	100.1	0.01	.800
Auditory Recognition Memory	95.9	-0.27	100.7	0.05	.348
General Memory	91.8	-0.55	94.9	-0.34	.529
WMS Working Memory	88.4	-0.77	89.6	-0.69	.819
Logical Memory: immediate recall	9.25	-0.25	10.5	0.17	.811
Logical Memory: delayed recall	10.1	0.03	11.0	0.33	.377
Verbal Paired Associates: immediate recall	8.31	-0.56	8.14	-0.62	.821
Verbal Paired Associates: Delayed recall	9.63	-0.12	8.86	-0.38	.407
Faces: immediate recognition[a]	8.00	-0.67	8.00	-0.67	.759[a]
Faces: delayed recognition[a]	8.00	-0.67	9.00	0.33	.122[a]
Family Pictures: immediate recall	7.38	-0.87	7.36	-0.88	.991
Family Pictures: delayed recall[a]	8.00	-0.67	8.00	-0.67	.797[a]
Spatial Span	7.56	-0.81	7.86	-0.71	.777

[a] Mann-Whitney U Test

People with drug-refractory JME and high neuroticism scores scored worse across the battery of intellect and memory than published norms and patients with neuroticism scores within normal limits. Patients with neuroticism scores within normal limits also scored worse than published norms across much of the battery. These finding support the earlier finding that patients with refractory JME have lower neuropsychological functioning, and indicate that also having a neurotic personality exacerbates this lower ability.

Independent sample t-tests revealed no significant difference between neurotic and non-neurotic patients in the number of years of education they received, age of onset, duration of epilepsy, the number of AEDs they were currently prescribed and levels of depression. People with JME and higher neuroticism scores reported more anxiety symptoms and more concentration and motor difficulties compared with those with less extreme neuroticism scores (anxiety: $p = .001$, $d = 1.57$; ABNAS concentration: $p= .007$, $d= 1.18$; ABNAS motor: $p= .006$, $d= 1.41$). Both groups reported their epilepsy has a moderate impact on their lives.

11.2 Extroversion Vs Neuropsychological Functioning

In order to examine whether patients with low extroversion were more impaired on neuropsychological functioning, the data file was dichotomised into 'low extroversion' and 'normal extroversion'. Participants were considered to have abnormally low levels of extroversion if they scored more than one standard deviation below the reported means [137]. Levels of extroversion have not been found to differ significantly in males and females, therefore a score of ≤33 for both males and females was considered abnormal.

Tables 11.4-11.5 below display the means and z-scores for each test, illustrating whether the scores of participants in the two groups was significantly lower than published norms. The p value for the comparison between the two groups ('low' extroversion Vs 'normal' extroversion) is also given.

Table 11.4 Intellectual functioning as measured by the WAIS of patients with drug-refractory JME and low/normal levels of extroversion compared to healthy standardized controls.

Cognitive test	Introverted		Normal extroversion		Introvert Vs non-introvert
	Mean score	Mean adjusted z-score	Mean score	Mean adjusted z-score	Sig.
Full Scale IQ	86.2	-0.92	91.4	-0.57	.319
Verbal IQ	86.3	-0.91	92.2	-0.52	.219
Performance IQ	89.4	-0.71	92.1	-0.53	.623
Processing Speed[a]	84.0	-1.07	82.5	-1.17	.632[a]
Vocabulary	7.96	-0.68	8.86	-0.38	.378
Similarities	7.71	-0.76	8.64	-0.45	.329
Arithmetic	7.88	-0.71	8.57	-0.48	.667
Digit Span	7.92	-0.69	8.93	-0.36	.252
Information	7.67	-0.78	9.43	-0.19	.093
Comprehension	7.25	-0.92	8.57	-0.48	.229
Picture Completion	9.25	-0.25	9.14	-0.29	.929
Digit Symbol-coding[a]	7.00	-1.00	**6.00**	-1.33	.988[a]
Block Design	8.00	-0.67	9.29	-0.27	.115
Matrix Reasoning	9.50	-0.17	9.07	-0.31	.708
Picture Arrangement	7.71	-0.76	9.07	-0.31	.170
Letter-Number Sequencing	8.46	-0.51	8.50	-0.50	.971
Symbol Search	7.26	-0.91	8.71	-0.43	.250

[a] Mann-Whitney U Test

Table 11.5 Memory function as measured by the WMS of patients with drug-refractory JME and low/normal levels of extroversion compared to healthy standardized controls.

Cognitive test	Introverted		Normal extroversion		Introvert Vs non-introvert
	Mean score	Mean adjusted z-score	Mean score	Mean adjusted z-score	Sig.
Immediate Memory	88.3	-0.78	88.7	-0.75	.933
Immediate Visual Memory	.85.8	-0.97	85.0	-1.00	.767
Delayed Visual Memory	87.7	-0.82	89.3	-0.71	.767
Immediate Auditory Memory	93.8	-0.41	95.9	-0.94	.634
Delayed Auditory Memory	99.7	-0.02	99.4	-0.04	.961
Auditory Recognition Memory	98.7	-0.09	98.6	-0.09	.979
General Memory	93.1	-0.46	94.2	-0.39	.823
WMS Working Memory	89.0	-0.73	89.4	-0.71	.939
Logical Memory: immediate recall	9.88	-0.04	10.1	0.03	.790
Logical Memory: delayed recall	10.6	0.20	10.5	0.17	.896
Verbal Paired Associates: immediate recall	8.04	-0.65	8.50	-0.50	.565
Verbal Paired Associates: Delayed recall	9.13	-0.29	9.29	-0.24	.865
Faces: immediate recognition[a]	8.00	-0.67	8.50	-0.50	.540[a]
Faces: delayed recognition[a]	8.00	-0.67	9.00	-0.33	.223[a]
Family Pictures: immediate recall	7.54	-0.82	7.07	-0.98	.638
Family Pictures: delayed recall[a]	9.00	-0.33	7.50	-0.83	.654[a]
Spatial Span	7.67	-0.80	7.86	-0.71	.861

[a] Mann-Whitney U Test

People with drug-refractory JME and high introversion scores scored worse across the battery of intellect and memory than published norms and patients with introversion scores within normal limits. Patients with extroversion scores within normal limits also scored slightly worse than published norms across much of the battery.

Independent sample t-tests revealed no significant difference between introverted and non-introverted patients in the number of years of education they received, age of onset, duration of epilepsy, the number of AEDs currently prescribed, the number of cognitive complaints and levels of depression or anxiety. Both groups reported their epilepsy has a moderate impact on their lives.

11.3 Executive Functions

Tables 11.6-11.7 below display the means and z-scores for each executive function test, illustrating whether the scores of participants with extreme neuroticism and/or introversion scores was lower than published norms. The p value for the comparison between the groups is also given.

Table 11.6 Executive functioning as measured by the D-KEFS and BNT of patients with drug-refractory JME and high/normal levels of neuroticism compared to healthy standardized controls.

Cognitive test	High neuroticism		Normal neuroticism		Neurotic Vs non-neurotic
	Mean score	**Mean adjusted z-score**	**Mean score**	**Mean adjusted z-score**	**Sig.**
Letter fluency	**6.75**	-1.08	7.41	-0.86	.557
Category fluency	7.38	-0.87	8.05	-0.65	.643
Category switching	8.75	-0.42	9.05	-0.32	.820
Category accuracy	9.19	-0.27	10.0	0.00	.548
Verbal inhibition	7.53	-0.82	7.82	-0.73	.846
Inhibition switch	**6.00**	-1.33	**5.95**	-1.35	.968
Boston naming test[a]	**48.0**	-1.92	53.5	-0.53	.312[a]

[a]Mann-Whitney U Test

Table 11.6 above indicated that both groups scored >1 standard deviation below published norms on the inhibition switching test. Patients with high neuroticism scores also scored >1 standard deviation below published norms on the letter fluency test and BNT. Scores within the borderline range have been highlighted in bold in Table 11.6 above.

Table 11.7 Executive functioning as measured by the D-KEFS and BNT of patients with drug-refractory JME and low/normal levels of extroversion compared to healthy standardized controls.

Cognitive test	Introverted		Normal extroversion		Introvert Vs non-introvert
	Mean score	**Mean adjusted z-score**	**Mean score**	**Mean adjusted z-score**	**Sig.**
Letter Fluency	**6.79**	-1.07	7.71	-0.76	.421
Category fluency	7.38	-0.87	8.43	-0.52	.475
Category switching	8.33	-0.56	9.93	-0.02	.225
Category accuracy	9.04	-0.32	10.8	0.27	.151
Verbal inhibition	7.04	-0.99	8.92	-0.36	.208
Inhibition switching	**5.91**	-1.36	**6.08**	-1.31	.708
Boston naming test[a]	**49.5**	-1.54	54.0	-0.38	.427[a]

[a] Mann-Whitney U Test

Table 11.7 indicated that both groups scored >1 standard deviation below published norms on the inhibition switching test. Patients with low extroversion scores also scored >1 standard deviation below published norms on the letter fluency test and BNT. Scores within the borderline range have been highlighted in bold in Tables 11.7 above.

The analyses presented in Table 11.6 and 11.7 above indicated that neurotic and introverted patients have lower executive functioning than patients with less extreme scores. Figures 11.1 to 11.2 were produced to illustrate any differences between introverted and neurotic patients. In addition patients were classified as having an 'abnormal' personality if they were highly neurotic and/or introverted, and classified as

having a ‘normal’ personality if they scored in the normal range for neuroticism and extroversion. The scores of patients classified with ‘abnormal’ and ‘normal’ personalities are included in Figures 11.1 to 11.2

[fig 11.1-Personality and executive functions line graphs to be inserted here-landscape]

[fig 11.2 Personality and executive functions line graphs to be inserted here – landscape]

Figure 11.3 illustrates the difference in naming ability between patients with different personality traits.

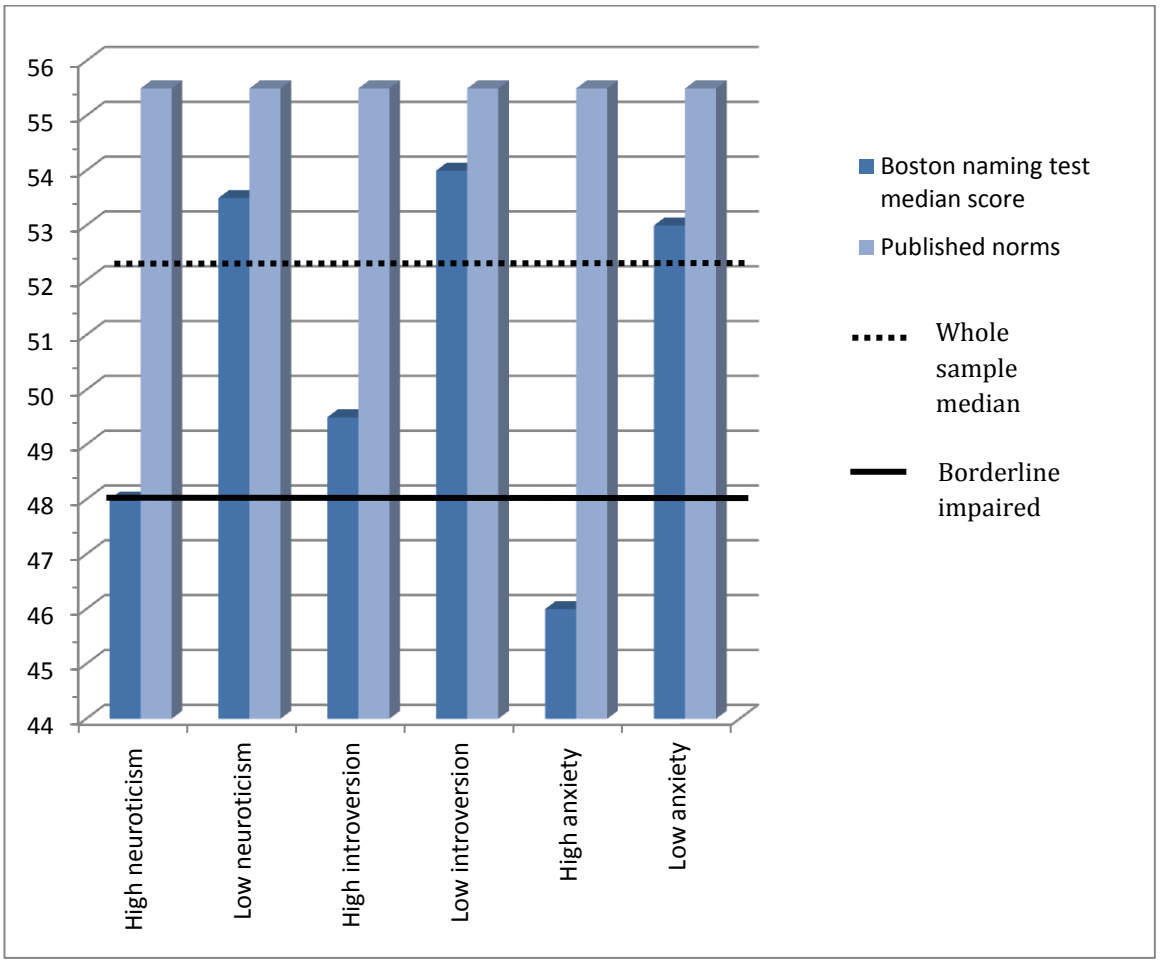


Figure 11.3: Boston Naming Test performance (median scores) of people with drug-refractory JME and different personality traits

11.4 Preliminary findings with the BADS

Just over half the sample was also administered some of the subtests from the BADS. These included the rule shift, key search and zoo map.

Rule shift – assesses perseveration and mental flexibility i.e. the ability to adjust behaviour to meet demands of a changing situation

Key search – assesses planning ability

Zoo map – assesses ability to plan independently and follow a pre-formulated plan, while abiding by a set of rules.

A Pearson's correlation was conducted to investigate whether personality, clinical characteristics or mood was associated with performance on the BADS. This revealed significant correlations between neuroticism and the raw scores on both version one ($r = -.540$, $p = .038$) and two ($r = -.591$, $p = .020$) of the zoo map. People with high neuroticism scores scored, on average, 5.00 points lower compared with people with drug-refractory JME and less extreme neuroticism scores (Fig. 11.5). No other variables were significantly correlated with the zoo map.

The zoo map is an executive function test with good ecological validity, thus the findings presented above indicate that refractory JME patients with neurotic personalities may experience problems with planning and following rules in their daily lives. This finding warrants further study, but must be taken with caution as unfortunately only a small number (n=15) of individuals in the current sample were administered both the zoo map and the EPQ-BV.

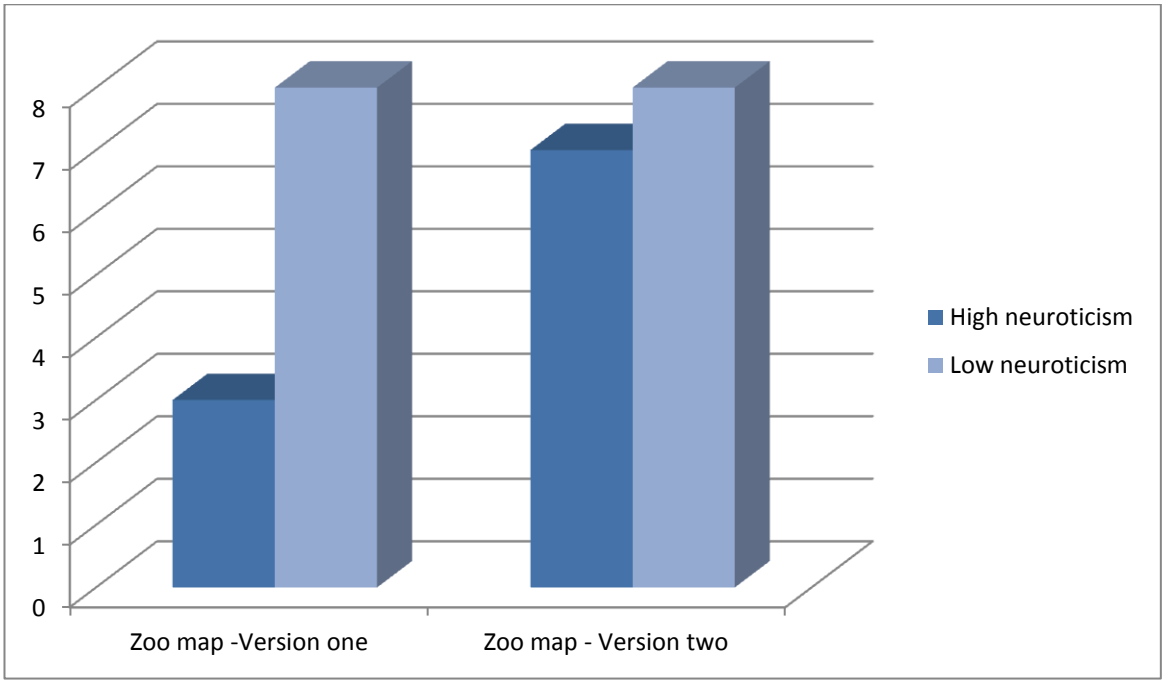


Figure 11.5: Median scores on version one and two of the Zoo Map for drug-refractory JME with high and low neuroticism scores.

11.5 Severity of executive dysfunctions

The severity of executive dysfunctions in the current sample was assessed by inspection of the samples z scores (calculated using manual means). The following tests were used to measure six executive and attention domains:

- Working memory, mental control of auditory-visual stimuli and attention span: assessed using the digit span and letter-number sequencing.
- Visual working memory, mental control of visual-spatial stimuli and attention: assessed using the symbol search, digit-symbol coding and spatial span.
- Verbal fluency: assessed using the letter fluency and category fluency,
- The ability to switch between categories: assessed using category switching and category accuracy.
- The ability to inhibit responses to visual-verbal stimuli: assessed using the colour-word interference test (verbal inhibition and inhibition switch)
- Naming ability: assessed using the Boston naming test

In concordance with previous research [154, 155] a z-score of ≤-1 (one or more standard deviations below the manual means) on at least one of the tests within each of the six domains was categorised as dysfunction in relation to that domain. As naming ability was measured by only one test a z-score of ≤-1 on the Boston naming test was categorised as executive dysfunction in relation to naming ability. If two domains were found to meet these criteria the patient was said to have mild executive dysfunction. If three or four domains met the criteria the patient was said to have moderate executive dysfunction. If five or more domains met the criteria the patient was said to have severe executive dysfunction.

Of the 60 refractory patients in the current sample (2 patient was excluded from this analysis due to missing data), 83% demonstrated a degree of executive/attentional dysfunction, which was moderate-severe in 66% of patients (38/58 patients). When a more conservative value of ≤ 2 SD below manual means were applied to each test 45% of the patients presented with a degree of executive dysfunction, and 28% presented with moderate to severe dysfunction. These percentage are lower than that previously reported in a JME sample [154]. However the previous study was conducted in Brazil thus there may be cultural differences. Moreover IQ was found to be significantly correlated with all of the executive function tests, and although Moschettea and

Valente's sample had a very similar mean IQ as the current sample (91.5 and 89., respectively) the current sample received on average almost three more years of formal education than their sample (13 years Vs. 10.1 years).

Extreme EPQ-BV scores were found to exacerbate the level of dysfunction in the current sample, and, when the more conservative value of two SD below published norms was applied, people with extreme EPQ-BV scores demonstrated the greatest level of executive dysfunction impairment; 54% presented with dysfunction, and 39% had moderate to severe dysfunction. This degree of dysfunction was not seen in any individual with unremarkable EPQ-BV scores; only one (8.3%) person had moderate dysfunction, and three (25%) had mild dysfunction.

11.6 SUMMARY OF CHAPTER ELEVEN

The current chapter investigated whether the abnormal personality exhibited by JME patients is related to the neuropsychological impairments previously reported [7, 11-14, 16].

The refractory JME sample was found to be significantly introverted compared to the healthy means reported by Sato [129]. In addition the females were also found to be significantly neurotic. When patients were split into neurotic Vs non-neurotic and introverted Vs non-introverted significant differences in neuropsychological functioning were found. Both neurotic and introverted patients scored worse across the majority of the battery. Moreover both neurotic and introverted patients were found to perform in the borderline range for letter fluency and the BNT. This suggests the common finding of impaired letter fluency in JME samples may be due to abnormal personality.

Preliminary analysis with the BADS revealed that the current sample scored significantly worse than manual means on the zoo map. Further, when the zoo map was correlated with personality, mood and clinical characteristics it was found that only neuroticism was significantly correlated with zoo map score. Post hoc analyses confirmed that patients with neurotic personalities perform significantly worse than healthy means and non-neurotic patients.

Overall this chapter has highlighted that refractory JME patients experience executive dysfunctions. It was found that 66% of the current sample experienced moderate to severe executive dysfunction. However 54% of patients with extreme personality scores compared to 1 participant of those with normal personality scores were classified as having moderate to severe executive dysfunction. In addition personality was found to be related to executive functions commonly found in JME, and points towards an association between neuroticism and real life planning ability. Abnormal personality is associated with frontal lobe abnormalities, thus the same frontal lobe abnormalities may be the cause of the executive dysfunctions in this subset of JME patients. However, thus far no cause has been found for the consistent impairment in switching between inhibiting a response and not inhibiting a response.

CHAPTER TWELVE – SUMMARY OF RESULTS

Overall the current sample performed worse than published norms across the battery. Worse performance was found even when education was controlled for.

Polytherapy was found to be associated with worse performance on neuropsychological test and explained a proportion of the variance. Subjective effect of AEDs was also associated with cognitive performance.

Anxiety was associated with verbal IQ, performance IQ, full scale IQ and letter fluency. Both anxious and non-anxious patients performed significantly worse than manual means, but anxious patients performed significantly worse than non-anxious patients. Depression was found to be associated with category fluency. Both depressed and non-depressed patients scored significantly worse than manual means on category fluency, but depressed patients scored significantly worse than non-depressed patients.

Introverts and neurotic patients perform worse than published norms across the battery and presented with the worse executive dysfunctions. 54% of patients with extreme personality scores compared to 1 participant of those with normal personality scores were classified as having moderate to severe executive dysfunction

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CHAPTER THIRTEEN – DISCUSSION

13.1 NEUROPSYCHOLOGICAL PROFILE

Several studies in the past decade have investigated the neuropsychological profile of JME patients. Previous research has compared JME patients to healthy controls [7, 12-14, 72], unaffected siblings [7, 16], and patients with other epilepsy syndromes [11, 12]. The current thesis (to the best of the author's knowledge) was the first study to profile patients solely with drug refractory JME, it was expected that more impairments may be revealed in this sample.

Following a review of the literature it was found that JME patients consistently perform worse across tests of intellect, memory and executive functions. However, the difference in performance was only consistently significant on executive function tests, in particular verbal fluency and inhibition. The same finding was reported by Wandschneider et al [16] when they reviewed the literature. The current thesis also supports this, finding significant impairments in both verbal fluency and inhibition.

The drug-refractory JME cohort had significantly worse neuropsychological functioning than published norms and 66% were classified as having moderate to severe executive dysfunctions. A previous study [154] that applied the same criteria when examining the severity of executive dysfunctions found a higher percentage of patients had dysfunction than the current study. However, three of the six executive and attention tests differed between the current and Moschetta and Valente study [154], thus the tests administered in the earlier study may be more sensitive to the frontal dysfunctions in JME patients. In addition, the patients in the current study received on average three more years of formal education than the patients in the Moschetta study, which may have improved the performance of the current patients.

The current sample performed worse than published norms across the majority of the test battery, however only three tests were found to have a z-score of <1.00 SD below published norms; digit-symbol coding test, inhibition switching test and BNT. This is inconsistent with previous studies that have also reported impairments in verbal

memory [12, 13]. However, when the current sample was split into those who had 11 or more years of education, and those who had less than 11 years of education, there were significant differences in performance on verbal IQ, auditory immediate and auditory delayed memory.

On inspection of the means both groups still performed within normal limits on verbal immediate and delayed memory, albeit patients with more years of education scored higher. Conversely, performance on verbal IQ for both groups was significantly lower than manual means. Yet those who received more years of education remained within normal limits, while those with <11 years education scored at the lower end of the below average range and <1.00 SD below published norms (z = -1.22). These results indicate that verbal memory is not impaired in JME, and education level is the sole contributor to the current samples performance. However, the current samples verbal IQ scores were lower despite education level, thus other factors may be involved. Other factors will be discussed further below.

13.1.1 Refractory JME Vs controlled JME

One of the aims of the current thesis was to compare refractory patients to controlled JME patients. Unfortunately a controlled JME group was not possible to recruit for reasons which will be discussed in the limitations section below. Therefore to compare the neuropsychological functioning of the current sample with controlled patients the means reported by Pascalicchio et al. [13] were used. Table 13.1 gives the p values from the one sample t-tests conducted.

The refractory sample scored significantly lower across the majority of the subtests from the WAIS when compared to controlled patients. In addition the executive function tests revealed the current sample performed significantly worse on verbal inhibition and the Boston naming test. However there was no significant difference found between the two patient groups on the letter fluency task.

Thus overall the neuropsychological functioning of the refractory patients was worse than Pascalicchio et al's controlled sample. The worse performance of the current sample was despite them receiving significantly more years of education compared to the controlled JME group. On average the refractory patients received 1.62 years more of formal education. However there was also a significant difference between the

duration of epilepsy of both groups. The refractory sample had epilepsy for 7.45 years longer on average, which was significantly longer than the controlled patients.

The results in Table 13.1 indicate that refractory patients have worse neuropsychological functioning compared to controlled JME patients. However it must be noted that the controlled patients were not matched to the current sample, and both the current thesis and Pascalicchio et al [13] found years of education and duration of epilepsy to effect performance.

Table 13.1 Neuropsychological functioning of current refractory JME sample compared to a controlled JME sample (means reported in Pascalicchio et al [13])

	Current sample Vs Pascalicchio JME sample
Vocabulary	.603
Similarities	< .001
Arithmetic	< .001
Digit Span	.001
Information	< .001
Comprehension	< .001
Picture Completion	< .001
Digit Symbol-coding	< .001
Block Design	< .001
Matrix Reasoning	.001
Picture Arrangement	.227
LN Sequencing	.002
Symbol Search	<.001
Letter fluency	.147
Boston naming test	< .001

13.2 CONTRIBUTORY FACTORS

13.2.1 Clinical characteristics

Past JME studies that have investigated the impact of clinical variables have been contradictory. One study concluded no clinical variable significantly predicted neuropsychological functioning found in JME patients [12]. A recent study found performance on executive function tests were significantly correlated with duration of epilepsy, frequency of myoclonic and GTCS [154]. Another study also found duration of epilepsy was associated with neuropsychological functioning [13]. They reported as the duration of epilepsy increased, the degree of impairment increased. In the current study duration of epilepsy was significantly correlated with immediate memory (overall and auditory), attention, visual working memory (Digit symbol coding and symbol search) and inhibition switching. On average, people in the current sample with low inhibition switching scores had JME for 8 years 8 months longer than those with higher inhibition switching scores. In addition, experiencing all three seizure types (myoclonic, GTCS and absences) was significantly correlated with worse performance on letter fluency and verbal inhibition.

Of the three cognitive tests (digit-symbol coding, BNT and inhibition switching) that gave scores <1.00 SD below the published norms, number of AEDs was found to be the sole significant predictor of digit-symbol coding and BNT. Significant negative correlations were found, which indicated that polytherapy was associated with worse performance. In contrast a large study of refractory epilepsy found no difference between adverse events profiles (including cognition items) of those on monotherapy compared to those on polytherapy [158]. However, they did not use any objective measures of cognition and the sample consisted of mainly focal epilepsy patients, both factors making it difficult to compare to the current findings. Unfortunately, due to the number of different AED combinations prescribed in the current sample it was not possible to tease out the effects of the separate AEDs.

In line with past research the current study found that measures of attention were more often correlated with clinical variables than executive functions. In addition planning and inhibition (when combined with mental flexibility) were not affected by clinical variables [154]. No clinical or mood variable predicted performance on inhibition switching, and the finding that on average all patients perform within the

borderline range on this test provides further support for an underlying frontal lobe abnormality.

13.2.2 Affective symptoms

Studies that have investigated the neuropsychiatric profiles of JME patients have found a high proportion of mood disorders, particularly anxiety and depression [27, 28, 96].

Measures

In the current investigation the HADS was administered to investigate anxiety and depression. Past studies of JME [26-28] have often chosen to use the Scheduled Clinical Interview for the DSM-IV axis I, but this requires a psychiatrist to administer thus is costly in time and money. The HADS on the other hand can be administered by anyone, takes the patient 10 minutes to complete and has been used in a JME study that was similar to the current investigation [7]. Further, a study that compared depression tools concluded that that the HADS should be chosen over other self-completed questionnaires for use with epilepsy patients [159], and it has been found to have good internal and test-retest reliability in non-neurological clinical groups [152]. Finally, a study that assessed the HADS as a screening tool found the probability of a case defined by the HADS being found a case using the SCID was 80%. Therefore, for the purposes of the current study the HADS was deemed the optimal choice.

Affective symptoms and cognition

In the current sample almost half of the patients (48.6%) were found to have moderate to severe levels of anxiety. Consistent with previous research, a smaller percentage of patients (16.2%) were found to have moderate to severe levels of depression. However, the percentage of patients with high levels of anxiety is higher than previously reported [27]. This may to be due to the current sample being drug refractory or the use of different assessment tools.

The higher level of anxiety found in the current sample may contribute to the range of neuropsychological impairments found. To investigate the impact of mood on cognition HADS anxiety and depression scores were correlated with patients score across the neuropsychological battery. This revealed significant negative correlations between anxiety and verbal IQ, performance IQ, full scale IQ and letter fluency. In addition, the analysis revealed a significant negative correlation between depression and category fluency. Thus high levels of anxiety were correlated with lower intellect and phonetic

mental fluidity, and high levels of depression were associated with lower semantic mental fluidity.

The correlations with anxiety were further investigated by dichotomising patients into those with 'high anxiety' and 'normal anxiety'. This revealed that within the current refractory sample, both anxious and non-anxious patients have lower neuropsychological functioning than published norms. However the non-anxious group scored within the average range on all four cognitive measures. The anxious patients scored within the low average range for performance IQ, full scale IQ and verbal IQ, although the latter two were at the lower end of the low average range. In addition anxious patients scored within the borderline range for letter fluency.

The regression analyses reported in chapter nine revealed that anxiety is not a significant independent predictor of the tests investigated, past research has found that anxiety is associated with health related quality of life in patients with epilepsy [160], therefore patients' anxiety level should be considered when treating JME patients.

Depression was also further investigated by splitting patients into two groups, namely 'high depression' and 'normal depression'. This revealed that both depressed and non-depressed patients scored significantly lower than manual means on category fluency. However, on inspection of the means it was found that although the non-depressed patients scored lower than the published norms their performance was still within normal limits. Conversely, the high depression group performance was in the impaired range, but a significant difference was not found. However, it must be noted that the 'high depression' group consisted of only six patients verses 30 in the 'normal depression' group, thus the result must be interpreted with caution. In a regression analysis depression was not a significant independent predicator of category fluency performance, but number of AEDs prescribed was and explained 18.2% of the variance in category fluency performance.

Both anxiety and depression were not associated with current AED treatment, number of AEDs prescribed, age of onset, duration of epilepsy, or seizure types. This suggests that both anxiety and depression are at least in part associated with the underlying brain abnormalities in JME.

13.3 PERSONALITY

When Janz first described JME he described the patients as immature, emotionally unstable, hedonistic and indifferent to their disease [65]. Since, studies have found a high percentage of axis II personality disorders (particularly cluster B) and axis I psychiatric disorders (particularly anxiety and depression) in JME samples, and significantly more than in healthy controls [27, 98, 99].

13.3.1 Past studies

It is unclear how anatomically bounded a function 'personality is, but it has been proposed that the abnormal personality exhibited by JME patients is related to the frontal lobe dysfunctions reported in these patients [16, 20, 26, 97]. Previous research has found a reduction in grey matter volume in the thalamus and increased volume in the right frontal gyri in JME patients compared to healthy controls. These differences were exacerbated in patients with cluster B personality disorders who had further significant volume differences in these areas compared to JME patients without personality disorders [20].

Other studies have investigated whether personality is related to structural and functional abnormalities in the frontal lobes [20, 26] and focal epilepsies [27]. Or whether structural brain abnormalities [72, 82], functional brain abnormalities [22, 72] and focal epilepsies [11, 12] are related to neuropsychological functioning.

A study that compared JME patients to patients with FLE and TLE (both focal epilepsies) found JME patients performed significantly worse than patients with TLE and healthy matched controls on verbal fluency, metal flexibility, planning and perseveration. When JME patients were compared to FLE no significant differences were found [12]. This was despite the administered tests being measures of frontal lobe functioning and patients with FLE having lesions in the frontal lobe. This study clearly indicates a frontal lobe abnormality in JME.

Studies that have compared JME patients with localised epilepsies and healthy controls have found significant differences. One study found 70% of JME patients had an axis I or axis II disorder, and significantly more of each compared to healthy matched controls [27]. In another study they compared this JME sample to patients with TLE they found axis I psychiatric disorders in 50% of patients in both groups [28]. However,

TLE is associated with emotional problems due to lesions in the limbic region of the brain, thus a high percentage of mood disorders are expected. To the contrary, JME is an idiopathic epilepsy and by definition has no physical brain abnormalities. In this study they found an association between anxiety disorders and JME, and between psychosis and TLE. They suggested that these distinct behavioural differences may be a result of specific brain dysfunctions caused by the different epilepsies [28].

Past research has proposed that the abnormal personality exhibited by patients with JME is related to the executive dysfunctions reported in these patients [16, 20, 26, 97]. A previous study touched on this by examining correlations between executive functioning and history of psychiatric disorders [154]. To the best of the author's knowledge, the current thesis is the first study to investigate the relationship between dysexecutive functions and specific personality traits in patients with drug-refractory JME.

13.3.2 Current study

The current study found worse neuropsychological performance across the battery. However significant impairments were found for inhibition, mental flexibility and naming ability across the whole sample. The common finding of impaired verbal fluency was not revealed in the sample as a whole, but it was when patients were divided by personality traits.

Neurotic patients remained impaired on the processes above in addition to impairment in verbal fluency. To the contrary, non-neurotic patients only remained impaired on inhibition and mental flexibility. Using a published method of stratifying executive dysfunctions in JME [154], the majority of patients, regardless of EPQ-BV scores, exhibited executive dysfunction. However, when a more conservative analysis was used, over half of the patients with JME and high EPQ-BV scores had dysfunction, with 39% presenting with moderate to severe dysfunction. Conversely, no patient with low EPQ-BV scores presented with severe dysfunction, and only one participant had moderate dysfunction.

People with drug-refractory JME and a high anxiety score had significantly poorer intellectual functioning and naming ability. All patients performed worse than published norms on naming ability, but only those with high anxiety scores performed

within the borderline-impaired range and those with high neuroticism scores performed extremely closely to this range. Preliminary findings with the BADS revealed significant correlations between poorer planning ability and only a high neuroticism score. The planning ability of those with high neuroticism scores was marginally lower when given the order of places to visit (zoo map version two), but when given a list of places to visit with no guidance on order, patients with high neuroticism scores, struggled considerably. As already mentioned this is only a preliminary finding due to the small number of patients who were administered both the BADS and the EPQ-BV. Thus future research is encouraged to include the zoo map in studies of JME and personality.

Not one patient with abnormal personality traits was found to have normal performance across all executive functions, however only a third of patients with normal personality traits scored within the average to high average range across all executive function tests. This indicates that patients with normal personality traits also have impaired executive functions. However, this finding may be due to the limited personality traits examined in the current study. It is hoped that these findings will be used to highlight that abnormal personality in JME is related to patient's frontal lobe functioning. If possible future research should use a more comprehensive assessment of personality (i.e. SCID).

Further research is encouraged particularly investigating the genetic and imaging differences in JME patients with abnormal personality traits. The current findings suggest a subgroup of patients who have a more severe type of JME, which may be distinguished by genetic aetiology.

13.4 QUALITY OF LIFE

Patients with drug-refractory JME are most likely to use clinical services and represent the cohort of JME patients with the greatest social burden. Therefore, until more AEDs have been developed, treatment of refractory JME must focus on achieving the best quality of life possible for these patients. In the current study polytherapy was associated with significantly worse performance across much of the battery. In addition, polytherapy was associated with high levels of fatigue, which may influence

an individual's ability to work. In support of this it was found that patients who were unemployed had significantly high levels of fatigue, whereas those who were employed had normal levels of fatigue. Although adequate seizure control is the main goal, a patient's ability to work and their cognitive functioning must be considered.

The current study and past research [27, 28] has shown high levels of anxiety are present in JME patients, and the current study indicates that anxiety is related to intellect and executive functions. Thus treating anxiety as well as the seizure may improve cognition and therefore quality of life.

Furthermore, the current study revealed that patients with abnormal personality traits were impaired on verbal fluency, mental flexibility, inhibition, planning and naming ability. However, when patients had a normal personality, executive functions where improved, although mental flexibility and inhibition remained impaired.

Being neurotic and/or introverted, highly anxious and having impaired executive functions may impact on an individual's ability to interact with others, and may have a detrimental effect on their personal and working relationships. Thus more research must be done to elucidate the cause of abnormal personality traits and affective symptoms in JME, but for now treatments such as psychotherapy may improve day to day life.

13.5 LIMITATIONS AND SUGGESTIONS FOR FUTURE STUDY

The biggest limitation to the current study was not all of the patients completed the EPQ-BV. This was added to the battery by the author when JW joined the ReJuMEC project. All the patients tested by the author were administered the EPQ-BV during testing, and all patients already tested or tested as part of the Wales epilepsy study were posted a copy of the questionnaire. If it was not returned within a month a second copy was sent. Unfortunately despite the effort to get as many patients to complete the questionnaire it was not possible to get everyone to complete it.

A limitation of the EPQ-BV itself is that it only assesses two dimensions of personality. A particular set of executive dysfunctions were found to be associated with

neuroticism. However not all impairments were explained by neuroticism, and some patients who were classified as having normal personality by the EPQ-BV were also found to have executive dysfunctions. Thus these patients with normal personality may in fact have different personality traits not assessed by the EPQ-BV. JME is a heterogeneous disorder and different genetic aetiologies may result in different personality traits and levels of impairment. Despite this the EPQ-BV has been a worthwhile tool for the current thesis. This is the first study that has investigated the relationship between specific personality traits and frontal lobe functions in drug-refractory JME, and has revealed frontal dysfunctions are associated with personality traits. In addition due to the comprehensive battery administered to the patients the brevity of the EPQ-BV made it an appropriate choice.

The current study also aimed to profile drug-refractory JME, as this has not yet been done, thus a long battery of assessments were required. However, it is suggested that future research that seeks to explore personality and frontal functions should focus the neuropsychological battery on executive function tests. In particular tests of mental flexibility, planning, inhibition, verbal fluency and naming ability should be administered. The executive function tests should be given in combination with a comprehensive personality and psychiatric assessment such as the SCID, which has already been shown as a valid tool in JME research [26-28].

Finally, there were several limitation related to the sample. Firstly the current study did not have a control group. A healthy control group was not used as the aim was to profile drug-refractory JME. However an additional sample of patients with controlled JME was desired, and data collection from such patients was attempted. However, patients with controlled JME very rarely have appointments at tertiary centres, which is where the patients for the current study were recruited. The author did attempt to find controlled patients by studying the medical records of every patient at the Walton centre who was diagnosed with JME. In addition JW attended weekly epilepsy clinics. Any patient that was identified through medical records or clinics was contacted by letter. Unfortunately only a handful of controlled patients responded to the letters and were tested, thus there were too few for reliable comparison with the refractory sample.

Secondly, the size of the sample was limited by loss of funding. The original study was funded by the MRC and only a few months following JW joining the project the funding

was stopped. This limited resources and time available for JW to recruit and test patients for the study. As a consequence, the statistical tests conducted and their resulting power was limited.

CHAPTER FOURTEEN – SUMMARY OF THESIS

Refractory JME patients have worse neuropsychological functioning than healthy controls and are impaired on attention and executive functions. Overall cognitive functioning within the average range (but worse than healthy controls) with specific frontal lobe dysfunctions is consistent with JME samples of controlled and mixed patients [7, 11-14, 16, 22, 106, 154]. The current study found worse performance on some cognitive domains, explained by: fewer years of education, polytherapy, and duration of epilepsy.

People with drug-refractory JME performed least well on tests of mental flexibility and inhibition. People with the poorest naming ability also had high anxiety scores and reported high levels of cognitive problems. Furthermore, they had a higher mean neuroticism score with a small to medium effect size. People with the lowest inhibition switching scores had a longer duration of epilepsy and also reported high levels of cognitive problems. However, the whole sample was borderline impaired on inhibition switching. Impaired inhibition is a consistent feature in JME analysis [12, 16, 72], which suggests that this impairment may be caused by a fundamental structural or functional brain abnormality shared by all people with JME. Past studies that have assessed healthy siblings of patients with JME have also found that they perform worse than healthy unrelated controls [7]. This suggests that impaired inhibition may be genetically determined. The current thesis indicates that the common impairment in inhibition switching is exacerbated by the duration of epilepsy.

When Janz first described JME patients he described their personality as "*characterised by unsteadiness, lack of discipline, hedonism, and an indifference to their disease. ... They often appear self-assured and bragging, the girls and women coquettish and seducing, but can also act decidedly mistrusting and be timid, frightened and inhibited. ... Their mood changes rapidly and frequently. This makes their contact both charming and difficult. ... They are easy to encourage and discourage, they are gullible and unreliable."* [161]. Since, research has investigated the psychiatric co-morbidities of JME patients, and found high incidence of anxiety and personality disorders [20, 27, 28]. In support the current thesis also found high incidence of anxiety and abnormal personality traits.

Past research has investigated whether psychiatric co-morbidities are related to frontal functioning. People with extreme neuroticism and/or introversion scores demonstrated the greatest level of executive dysfunction impairment, which was not seen in any individual with unremarkable personality scores. The affective, personality, and cognitive findings indicate the sample as a whole presented with deficits in the inferior (inhibition) and medial (switching) frontal cortex. However, the results indicate a broad network failure in the frontal lobes of a high proportion of those with high neuroticism and/or introversion traits. Furthermore, people with drug-refractory JME and high anxiety scores presented with the greatest impairment in naming ability. Moreover, preliminary findings indicated that neurotic personality was associated with impaired planning ability. Thus the current thesis indicates that specific executive dysfunctions are related to maladaptive behaviour. Future research should examine whether distinct behavioural differences are a result of specific brain dysfunctions that result in the different levels of impairments found in JME.

14.1 CONCLUSIONS

This research was conducted in the context of the ReJuMEC study, which aimed to provide a comprehensive profile of drug-refractory JME. The sample as a whole presented with neuropsychological impairments previously reported in JME research, but indicated that personality traits and psychiatric symptoms were related to the greatest impairments, particularly in executive functions.

There have been previous attempts to subcategorise JME e.g. by clinical characteristics [25], however due to the multiple factors and potentially multiple behavioural patterns it may not be possible to categorise JME into neat subcategories. Nevertheless, distinct behavioural patterns may be used to identify differences in frontal structure/functioning, and ultimately in genotype.

This research has contributed to our understanding of the relationship between the abnormal personality traits and executive dysfunctions both of which have often been reported in JME research. This research has identified a possible subgroup of patients that present with a more severe type of JME, and may be distinguished by genetic stratification. Finally the current research confirms the breadth of deficits in drug-refractory JME, and highlights that it is more than just executive function difficulties that must be targeted to support individuals through education and employment.

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