Examining the Association between Depression and Seizures amongst Adults with Epilepsy: A Longitudinal Analysis.

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Abbreviations and Terminology

DSM-IV- Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

(American Psychiatric Association)

GABA- Gamma-amino butyric acid

HAD (scale) - Hospital Anxiety and Depression (scale)

ICD-10- International Classification of Diseases, 10^{th} Edition

LGCA –Latent Growth Curve analysis

PSS - perceived stress scale

QOL- Quality of Life

RMSEA- Root Mean Square of Approximation

SEM- Structural Equation Modeling

Summary

This programme of work examined the links between psychopathology and seizures for adults with epilepsy using longitudinal data from two datasets and employing state-of the-art analytic approaches to tease apart inter-relationships.

In the first study, using path analysis to examine direction of effects, a bi-directional relationship between seizure frequency and depression scores was confirmed. That is, not only did seizure frequency influence depression scores longitudinally and concurrently, but that depression scores also influenced seizure frequency equivalently.

The second study employed a latent variable structural equation modelling approach to examine moderation and mediation and prediction of change in variable scores over time. In this study although anxiety, perceived stress and depression all separately influenced changes in seizures (frequency and recency), depression mediated the relationship between both anxiety and stress with seizures.

The third study used a latent growth curve approach to focus on patterns of change within individuals. Trajectories of change in depression scores for individuals over time were examined as well as factors predicting this variation. This study found that seizure recency was a significant predictor of the individual differences in baseline depression scores as well as of the changes in depression scores over time for individuals with epilepsy.

The implications of these results are that both effective management of seizures and depression are essential for people with epilepsy. Given that the current focus of clinical management strategies for people with epilepsy is on seizure management,

this research suggests the importance of also identifying and managing depression amongst people with epilepsy. Strategies to implement this would include increased awareness of the importance of depression amongst clinical staff, improved screening for depression amongst people with epilepsy (for example by using depression screening questionnaires such as the Hospital Anxiety and Depression Scale), implementing effective treatment (such as by using antidepressants or cognitive behaviour therapy) if depression is identified.

Future aims would include confirming these findings using alternative designs, for example a randomised trial to investigate whether these links between depression and seizures arise because of a common antecedent factor or shared risk factors and examine whether other factors (such as gender) influence the relationships observed between depression and seizure outcomes.

Publications

Thapar A, Roland M, Harold G. Do depression symptoms predict seizure frequency--or vice versa? *J Psychosom Res.* 2005; **59(5)**:269-74.

Thapar A, Kerr M, Harold G. Stress, anxiety, depression, and epilepsy: Investigating the relationship between psychological factors and seizures. *Epilepsy Behav* 2009; **14(1)**:134-40.

Submitted for publication

Thapar A, Kerr M, Harold G. Investigating Individual Differences in Depression Scores Amongst People With Epilepsy: A Latent Growth Curve Analysis.

Contents

Overview of thesis

This thesis reflects the results of a programme of research on adult epilepsy. The central results of this programme of work have been published (2 papers) or have been submitted for publication (1 paper) in peer reviewed journals. These papers constitute three of the six chapters and for these chapters the material is in the published or submitted form. There will therefore be some repetition especially regarding methodology and on strengths and limitations of the work in the discussion. The other three chapters provide the background to the work, the methodology (samples, measures and analytic approach) and a general discussion which also incorporates the clinical implications of the findings and highlights ideas for future work. There is also a technical appendix which provides more details of some of the analytic strategies.

The primary objective of the programme of research presented in this thesis is to examine the interplay between depression and two seizure measures (frequency and recency) in a community based sample of adults with epilepsy. Using the attributes of a large scale, prospective, longitudinal research design, a set of interlocking studies is presented. These studies employ "state-of-the-art" data analytic approaches to examine the interplay between depression and seizure measures, and the role of other psychological factors, anxiety and perceived stress, that may explain variation in these seizure outcomes. The focus is on depression and anxiety symptoms rather than disorder in this thesis but the terms will be used interchangeably. Results are discussed throughout with a view to implications for clinical practice and for development of interventions.

This thesis is divided into six main sections.

Relevant background information on epilepsy and existing literature on depression, anxiety and stress amongst people with epilepsy is provided in the first section of this thesis. This section highlights that although depression, anxiety and stress seem to be quite common amongst people with epilepsy the exact nature of their inter-relationship as well as their relationship with seizures is not clear. This section concludes with the main aims of the thesis.

The second section of this thesis focuses on Methodology. Information is provided about the individuals who participated in the studies included in this thesis and on the measures used. The rationale for using longitudinal methodology and the evolution of statistical techniques employed in this thesis are next discussed. The importance of using appropriate statistical methods to answer particular clinical questions is highlighted.

The third to fifth sections of this thesis relate to the three individual sets of analyses from the two studies that this thesis is based on. The first two represent published, peer reviewed papers and the third a paper submitted for publication. The first of these sections examines the directionality of links between depressive symptoms and seizure frequency using path analysis. The next section of this thesis explores how anxiety, stress and depressive symptoms are inter-related in their association with seizure frequency and recency. This section introduces the concepts of moderation and mediation and of using latent variable modelling. The fifth section of this thesis is based on inter-individual differences in depression scores and individual variation

in changes to depressive symptoms over time amongst people with epilepsy. This section introduces an analytic method to examine this variation, latent growth curve modelling, and uses this method to examine whether seizure recency plays a role in explaining this individual variation in depression symptoms.

The results and implications of the above studies are discussed in the context of existing literature on this topic in the final section of the thesis. This section concludes with a summary of the main findings from this thesis.

Chapter 1:

Introduction

1.0. Introduction

Recent years have seen an explosion of interest in depression and on the links between depression and chronic diseases. Depression is responsible for the largest non-fatal disease burden in the world (Ustun et al, 2004) and has been found to have a larger impact on health than major chronic medical illnesses such as ischaemic heart disease, diabetes and osteoarthritis (Moussavi et. al., 2007). However depression often coexists with physical health problems (Moussavi et.al. 2007, Stein et.al., 2006, Farmer et.al, 2008), and in this situation, the impact on health is considerably greater than if only one problem was present (Moussavi et.al. 2007, Stein et.al., 2006, Merikangas et.al, 2007, Scott et.al, 2007).

Epilepsy is a common chronic neurological condition. The association of depression with epilepsy has been long appreciated (at least from the time of Hippocrates (Sykiotitis et.al. 2006)). Depression is at least as important a problem for people with epilepsy as it is for people with most other chronic diseases and may be commoner (Beghi et.al, 2002, Ettinger et.al, 2004, Anderson et.al, 2001). However longitudinal clinical research examining the links between depression and epilepsy has lagged behind research examining links between depression and some other chronic diseases (notably coronary heart diseases and diabetes). This situation has already led to considerable differences not only in awareness of the links between depression and chronic diseases but also in clinical management and government policies, with depression screening and management prioritised, and attracting payment for, individuals with diabetes and coronary heart disease but not for individuals with epilepsy in the new GP contract in the UK (DOH, 2006).

However despite all this interest and recognition of the importance of the links between depression and chronic medical illnesses, the nature of the association between depression and chronic medical illness is still not well established (Musselman et.al, 2003, Whooley, 2006), both in terms of direction of effects and on how these links arise. These questions can only be answered if appropriate research designs are employed. Much of the current research is based on findings from cross-sectional studies which are inappropriate to establish direction of effects or answer questions on mechanisms (Rutter et.al, 2001). There has however been an increase in longitudinal research in recent years, which is more appropriate for answering questions on causal links than cross sectional research (Rutter et.al, 2001; Susser et.al., 2006). Longitudinal research has established that for people with some chronic illnesses such as diabetes, ischaemic heart disease and asthma, depression is a risk factor for the onset (Eaton et.al, 1996, Kawakami et.al, 1999, Whooley, 2006, Jonas et.al, 1999) of these disorders. There is also some research which has found that depression predicts the severity of illness in those with current illness (Roy et.al, 2007, Jiang et.al, 2005, Mancuso et. al., 2001).

Evidence has also emerged on the role of depression as a risk factor for the onset of epilepsy (Fosgren & Nystrom, 1990; Hersdorffer et.al, 2000; Hersdorffer et.al, 2006). However there has been little longitudinal research examining mechanisms and the direction of effects between depression and seizures for those with current epilepsy. It is sometimes assumed that frequent seizures are a risk factor for depression in those with current epilepsy (Grabowska-Grzyb et.al, 2006) but the study designs employed in these studies are often inappropriate to study causation (Rutter et.al. 2001).

It is essential to establish the nature of the associations so that intervention studies and clinical management can be planned accordingly (Kraemer et.al., 2002, MRC, 2000). To establish the mechanisms by which these links between depression and chronic illnesses may occur, it is important to examine existing research on how they arise (Rozanski et.al, 1999, Whooley, 2006). There are strong conceptual grounds and increasing empirical evidence in favour of considering depression as the end result of a causal or several causal chains of events (Kraemer et al 2001, DeKloet et.al., 2005). The situation seems similar for many other chronic diseases (Kraemer et.al., 2001). The pathway for the evolution of epilepsy is not clear but it has been argued that seizures too, are end results of progressive changes to the brain with cognitive and behavioural changes preceding the onset of seizures (Noebels, 2006).

Given that depression represents one end of a causal pathway, what other factors may be involved? We know that in the general population, anxiety, stress disorders and depression are closely linked. Anxiety has been found in some studies to precede the onset of depression (Merikangas et.al, 2003) and stress (Van Praag, 2004) and stressful life events have been recognised to be risk factors for depressive illness (Kendler et.al., 2002; Kendler et.al., 2006). Recent studies have also highlighted the importance of anxiety (Rozanski et.al 1999,Scott et.al, 2007), stressors and perceived stress (Cohen et.al., 2007) as risk factors for the onset and exacerbation of chronic medical illnesses. Moreover, it has also been found that when both anxiety and depression coexist with a physical illness the effect on health is much greater than if only one of these psychological disorders is present with the physical disorder (Rozanski et.al, 1999; Scott et.al., 2007). Stress, depression and anxiety have all been linked to dysfunction of the hypothalamo-pituitary axis (HPA axis) which has been

suggested as having a role in the evolution of chronic physical illness (Rozanski et.al., 1999;Gold & Chrousos, 2002, McEwen, 2007) .

Anxiety and stress are common psychological problems amongst people with epilepsy. Anxiety has indeed been found to be the commonest psychological problem amongst people with epilepsy (Beyenburg et.al., 2005). Anxiety symptoms also seem more prevalent amongst people with epilepsy than in the general population (Jacoby et.al,1996; Mensah et.al, 2007) and high seizure frequency has been associated with high levels of anxiety (Jacoby et.al, 1996, Ridsdale et.al., 1996,Mensah et.al, 2007). Stress has been highlighted as the main perceived risk factor for precipitating a seizure by people with epilepsy (Frucht et.al, 2000). There is however only limited information, as yet, on the relationship between frequent seizures and elevated levels of stress (Haut et.al., 2007). What is yet to be established is how these different psychological factors interact with each other in their association with seizures in the "web of causation" (Susser et.al., 2006). Possible roles could be as independent risk factors, antecedent factors, mediators, causal co-partners or even confounders (Susser et.al, 2006). It is important to establish the nature of the associations, to inform the development of services for people with epilepsy. To give an example, if there is evidence that anxiety mediates the relationship between depression symptoms and seizures and moderate anxiety was found to be present then the preferred first line treatment might be Cognitive Behavioural Therapy (NICE CG22, 2004) rather than antidepressants.

Finally we also know that the onset and course of depressive symptoms vary considerably within individuals amongst the general population (Judd et.al, 1998).

Moreover, factors that affect depression symptoms in one individual may not affect others in the same way or to the same extent. There is however little information on how depression symptoms change over time for different individuals with epilepsy (intra-individual variation). Whilst we know that when we examine relationships between different individuals (inter-individual differences), seizure frequency is associated with variation in depression scores **between** individuals, we do not know what influence seizure activity has on how depression scores change over time **within** individuals (intra-individual variation). If seizure activity also explains this intra-individual variation in depression scores, this would provide very strong empirical evidence for prioritising good seizure management as a means of improving depression. However if seizures were found not to predict intra-individual variation in depression scores, then this would lead us to re-examine our approach to management; for example, either seeking other factors which do explain this intra-individual variability or simply ensuring effective depression management.

In next sections of this Chapter a brief background to the disorders and psychological factors (epilepsy, depression, anxiety and stress) considered in the thesis will be presented and the Chapter will conclude with the aims of this thesis.

1.1: Epilepsy overview

1.1.1. Introduction

Epilepsy is a common chronic neurological condition. It is best understood as a family of related conditions (sometimes called the epilepsies) which are indicated by the individual suffering seizures (Engel & Pedley, 1998). Seizures are the manifestation of the underlying paroxysmal electrical disturbance in the brain. In most cases of epilepsy the precise aetiology is unknown, although with advances in brain imaging and genetic research, abnormalities in brain structure and genetic risk factors are being increasingly reported (Duncan et.al, 2006). Epilepsy can be also classified by whether the paroxysmal disturbance only affects part of the brain ("partial" seizures) or the whole of the brain ("generalised" seizures) both at onset and subsequently. There are also distinctions made by grouping clinical characteristics with specific types of seizures, and these are termed epilepsy syndromes.

1.1.2. Prevalence of Epilepsy

Epilepsy typically follows a relapsing and remitting course (Sillanpää & Schmidt, 2006). A considerable proportion of individuals who develop epilepsy may become seizure free subsequently (50% in the study quoted above (Sillanpää & Schmidt, 2006)) and are able to discontinue their medication. This leads to the situation where although the lifetime prevalence of epilepsy is about 5%, the prevalence of active epilepsy (defined as having a diagnosis of epilepsy and either reporting a seizure in the last 5 years or being on medication for epilepsy) in adults is about 6 per 1000 individuals (Jacoby et.al, 1996, Sillanpää & Schnidt, 2006). The prevalence varies by

age with reported prevalence rates of 4.5-5/10000 in children and adolescents, 6 per 100 in adults aged 20-65 and 7 per 1000 in adults over 65 (Forsgren et.al., 2005). The prevalence of epilepsy is approximately equal in males and females but some studies have found a slight male preponderance (Forsgen et.al., 2005).

1.1.3. Seizure characteristics

To quantify the severity of epilepsy, several measures can be used. Seizure type, seizure frequency, seizure recency and seizure severity have been commonly used to describe the pattern of epilepsy in terms of impact (Baker et.al, 1998). For the purposes of simplicity, the term "seizure measures" will occasionally be used in this thesis rather than seizure recency or seizure frequency when making general statements about seizures, but should be interpreted as referring to either seizure recency or seizure frequency or both.

1.1.3.1. ***Seizure types***

A variety of terminologies have been used in the past to describe epilepsy and these were often based on clinical features rather than on pathogenesis and these led to considerable difficulties in communicating findings, clinical management and diagnosis. Considerable efforts have been made in the last few decades in standardising terminology and basing it on the pathogenesis of the disorder. This led to the International League against Epilepsy (ILAE) Classification of epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy ,1981 and Engel, 2001) which divides seizures into those with a *partial or focal* onset (initial localised activity in a part of the brain) and those with a *generalised* onset (initial widespread activity throughout the brain). This is an

important distinction as there may be therapeutic implications and also in terms of considering the impact of epilepsy, as one of the most disabling aspects of seizures is unpredictability (Schneider & Conrad, 1983; Scambler, 1989). Those individuals who have a focal onset may get a warning (an aura) whereas those with a generalised onset will not. An outline of the ILAE classification system is presented in Figure 1.1.3.1 (ILAE, 2008).

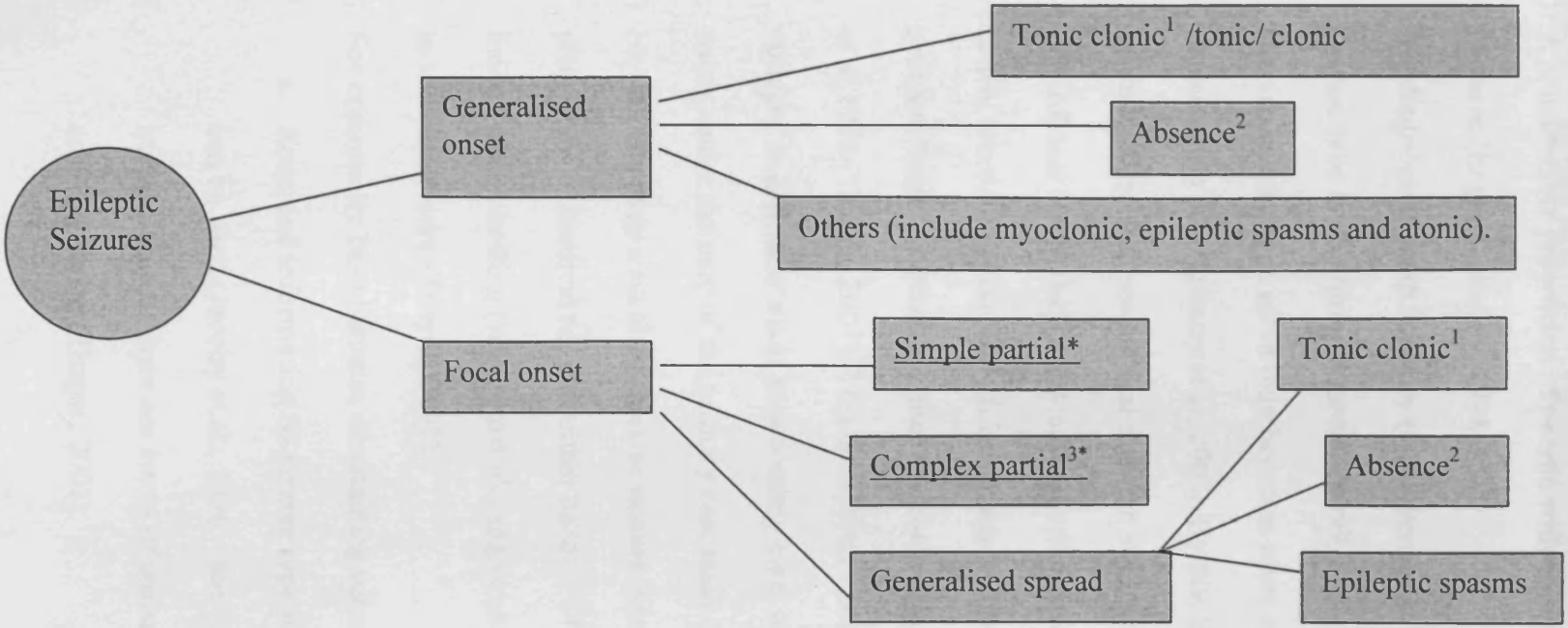


Figure 1.1.3.1
Classification of epileptic seizures (adapted from International League Against Epilepsy classification 2006 (except * based on 1986 classification)- (ILAE, 2008).
[1]Formerly known as Grand mal seizures
[2]Formerly known as Petit mal seizures
[3]Includes Temporal Lobe epilepsy

1.1.3.2. Using seizure types for research purposes

There are however considerable problems in using the above classification for research purposes in a pragmatic manner, certainly for community based samples.

1) A considerable proportion of people with epilepsy exhibit several types of seizures (Engel & Pedley, 1998).
2) Misdiagnosis of both epilepsy (Scheepers et.al, 1998, Smith et.al., 1999) and seizure type is common (Benbadis, 1999, Forsgren et.al., 2005).
3) Precise seizure type often only becomes more apparent some time after initial consultation (Chowdhury et.al, 2008). By this time the patient may no longer be under specialist review and research suggests that many GPs either feel unconfident about their knowledge of epilepsy and about initial management or feel too time pressured to fully engage in epilepsy care. This may lead to problems with misclassification or non-classification of seizure type (Thapar et.al.1998, Thapar, 2001). This is important as although the diagnosis of epilepsy is generally made in secondary care, most people with epilepsy are solely under the care of the primary care team (Thapar, 2001).
4) No definite diagnosis about precise seizure type is available in a significant proportion of medical records either because of errors of omission or of inconsistent labelling (with terms like major seizures and minor seizures used) in secondary care (Thapar, 2001).
5) For community based studies ascertaining seizure type can be difficult.
    a. Recorded information on seizure type in primary care medical records can be used (Jacoby et.al., 1996 – see Table 1.1) but often records are incomplete and there are errors of omission or of inconsistent labelling, as noted above (Thapar, 2001).

b. Patient self reports are commonly used in prevalence studies. However, as a recent systematic review highlighted, self reports generally reflect the predominant manifestation of seizures and are likely to significantly under-report partial seizures which rapidly generalise and if EEG measurements are used, the proportion of individuals who will be found to have focal onset epilepsies will increase (Forsgren et.al., 2005). However one secondary care EEG based study suggested, in contrast to the above, that patients were misdiagnosed as having partial epilepsy when in fact, using EEG recordings, they were suffering from generalised epilepsy (Benbadis, 1999).

To highlight some of these issues the results from a) a large community based study using recorded information (Jacoby, 1996) and b) the findings of a systematic review of European studies (Forsgren, 2005) are noted in Table1.1.3.2 As can be seen, there are considerable differences in prevalence rates reported, with community-based studies generally reporting the majority of seizures as generalised and hospital-based studies reporting partial seizures as being the most prevalent.

Table 1.1.3.2. Comparing information on seizure types from different types of study

a) Information on seizure type recorded in Primary Care records (Jacoby et.al, 1996)

Partial seizures only	12%
Generalised seizures only	40%
Combination partial/generalised seizures	17%
Information not recorded	31%

b) Prevalence of seizure types from a systematic review (Forsgren et.al., 2005)

Partial seizures/localisation related epilepsies	55-83%
Primary generalised seizures	6-32%
Unclassifiable seizures	8-20%

In this thesis, for the above reasons, no distinction by seizure type will be made for most analyses.

1.1.3.3. Seizure frequency

Seizure frequency is simply a measure of how often seizures occur. The importance of seizure frequency as an outcome measure amongst people with epilepsy has been highlighted (Baker et.al., 1998). This is generally a self-report measure and is based on retrospective recall over a particular time period. Daily seizure diaries represent an advance but have only generally been used in fairly small samples. Most community based studies on adults with active epilepsy have found that about half of the sample have been seizure-free in the previous year, about a quarter have had more than a

seizure a month and the remaining quarter have between a seizure a month and a seizure a year (Jacoby et.al, 1996, Thapar et.al., 2002). Most community based studies have not reported seizure frequency separately by seizure type.

1.1.3.4. Seizure recency

Another measure of seizure activity that has been used and reported on in several studies is that of seizure recency; that is, how long ago the individual had experienced the last seizure (Wagner et.al. , 1995, Cramer et.al. , 2004). Some (Mrabet et.al, 2004) but not all studies (Leidy et.al., 1999) which have used both seizure frequency and seizure recency as outcome measures have found that both are associated with Quality of Life (QOL) measures. This issue was not discussed in the review paper on outcome measurement (Baker et.al, 1998).

1.1.3.5 .Seizure severity

Seizure severity has been used to try and encapsulate how the characteristics of a particular seizure (such as predictability/warning, recovery, tongue biting, incontinence) can be used to gauge the impact of a seizure (Baker et.al, 1991). This is ascertained generally by the score on a self report scale (the Liverpool seizure severity scale (Baker et.al, 1991) is the most widely used in the UK and has been shown to have good reliability and validity). Although it has been argued that much of the variation in the impact of epilepsy rests not on number of seizures but on the severity of seizures (Baker et.al, 1998), this measure has been little used in community based studies.

1.1.4. Aetiology and seizure precipitants

1.1.4.1. Aetiology

The aetiology of seizures is often unknown (idiopathic) although vascular injury (cerebrovascular disease), tumours, congenital causes, physical trauma (birth trauma, head injuries), or biochemical trauma (e.g. alcohol abuse) play a role for seizures in some individuals. A summary of the results from a recent systematic review of European population based incidence studies on presumed causes of epilepsy is given below in Table 1.1.4.1 (Forsgren et.al, 2005).

Table 1.1.4.1. Estimated proportion (%) of presumed causes of epilepsy in population based incidence studies (Forsgren et.al., 2005)

	Range
Unknown	44-69
Vascular	14-21
Trauma	2-16
Neoplasm	6-10

Genetic factors seem to play a role in a polygenic manner (Duncan et.al., 2006, Greenberg & Pal, 2007) and seem especially important for the category termed idiopathic generalised seizures (Jallon & Latour, 2005) for which there is also a female preponderance (McHugh & Delanty, 2008) as opposed to a slight male preponderance for epilepsy overall.

1.1.4.2 Seizure precipitants

Many factors have been suggested to be seizure precipitants (lack of sleep, stress, fatigue, alcohol, flashing lights, not taking medication, depression) but these are generally on the basis of patient perceptions rather than based on prospective studies (Nakken et.al., 2005)). Stress is the most commonly cited seizure precipitant, along with sleep deprivation (Nakken et.al., 2005, Haut et.al, 2007).

1.2: Depression in Epilepsy

1.2.1: Depression in the general population

1.2.1.1: Depression in the general population: Overview

Depression has been recognised as an illness from times of antiquity. Hippocrates used the term melancholia which he attributed to an excess of "black bile", one of the four humours (Glas, 2003, Sykiotitis et.al. 2006). However it has been argued that this viewpoint restricted research and treatment approaches for depression for many years as it was felt to be a temperamental attribute rather than an illness (Glas, 2003). In recent years, the importance of depression has been increasingly highlighted (Murray & Lopez, 1997, Mathers & Loncar, 2006) and the impact on health either alone or in conjunction with other chronic medical disorders has become increasingly apparent (Stein et.al, 2006, Moussavi et.al., 2007, Farmer et. al, 2008). One of the studies, a global WHO funded study, showed not only that depression had a larger impact on health than major common chronic illnesses such as angina, asthma, diabetes and osteoarthritis but that the rates of depression amongst sufferers with these conditions were greater than for the general population and also if the two conditions (depression and chronic illness) coexisted, the impact on health was significantly greater than if the individual had either problem alone (Moussavi et.al., 2007).

There are no objective biological tests for depression at the current time. The "gold standard" for diagnosing depression is using a standardised psychiatric interview but this is time and resource intensive so in many large scale research projects, depression is assessed using self rated questionnaires (such as the Hospital Anxiety and Depression scale, (HAD) (Zigmond & Snaith,, 1983), or the Center for Epidemiologic

Studies Depression (CES-D) scale (Radloff, 1977). These questionnaires are standardised and have been extensively psychometrically tested and seem reliable measures (Eaton et.al., 2007).

1.2.1.2: Depression in the general population: categories

Depression is a heterogeneous condition. Depression can either be viewed categorically ("a clinical diagnosis" using either a psychiatric interview or using questionnaire scores above a pre-determined cut-off) or dimensionally (for example using questionnaire scores).

Diagnostic classification systems for psychiatry (DSM-IV (American Psychiatric Association, 1994), ICD-10 (WHO, 2007)) view depression categorically. Categories used in the DSM-IV classification include **Major depressive disorder, dysthymia** (chronic intermittent minor depression), **cyclothymia** (mild form of bipolar disorder) and **bipolar disorder**. Major depressive disorder can be further categorised as melancholic depression, psychotic depression and atypical depression depending on the precise mix of symptoms. ICD-10 (WHO, 2007) essentially categorises depressive disorders as bipolar or unipolar; as mild, moderate or severe; as single or recurrent, with or without psychotic features and has other categories of mood disorders such as cyclothymia. The diagnostic criteria for major depressive disorder using the DSM-IV classification system are highlighted in Figure 1.2.1.1. The importance of persistence of several symptoms as well as impairment in functioning is emphasised in this classification system. This system forms the basis of psychiatric interviews and generic instruments to score and identify depression.

Figure 1.2.1.2.Major depressive disorder as defined by DSM-IV (American Psychiatric Association, 1994)

At least **5** of the following symptoms **every day for at least 2 weeks** with accompanied **impairment of functioning** and the symptoms **must include** either depressed mood and/or loss of interest.

*depressed mood

*lack of interest

*weight loss

*insomnia

*psychomotor agitation/ psychomotor retardation

*fatigue or loss of energy

*feelings of worthlessness /excessive or inappropriate guilt

*diminished ability to think or concentrate

*recurrent thoughts of death.

1.2.1.3: Depression in the general population: using a dimensional approach.

The precise utility of considering major depression as a category however has been challenged (McCullough et al, 2003, Klein et al, 2006). It has, for example, been argued that chronicity and severity of symptoms are more crucial in terms of impact than the pattern of symptoms that meet diagnostic criteria (Klein et al, 2006). Also the implications of depressive symptoms are similar to those of major depressive disorder in terms of long term outcomes (Judd et.al., 1998, Klein et.al., 2006). Finally depressive symptoms are predictive of depressive disorder (Klein et.al, 2006) and are associated with increased service use (Johnson et.al, 1992). Overall, two different

approaches have generally been adopted: 1) for epidemiological prevalence studies, diagnostic categorisation is generally used and 2) for clinical and aetiological research purposes a dimensional approach using depression symptoms has been recommended (Klein et.al, 2006).

1.2.1.4: Depression in the general population: Prevalence

There is considerable variation in estimates of the prevalence of major depressive disorder. A recent review, using pooled rates for large studies published between 1980 and 2000 which met fairly rigid inclusion and exclusion criteria, estimated that the 1 year incidence rate was 2.9%, 1 year prevalence rate was 4.1% with a lifetime prevalence rate of 6.7% (Waraich et.al., 2004). However, higher figures on prevalence were found in the results from the large National Comorbidity Study Replication sample (Kessler et.al., 2003) which had not been included in the above review. Based on responses from 9090 adults, the lifetime prevalence of Major Depressive disorder was 16.2%, with a 12-month depression prevalence rate of 6.6%. In this study, for those in the latter group (that is, those who were depressed in the last 12 months), the severity of depression, mean duration of depression and the presence of co-morbid anxiety were also determined. 10.4% of cases were classified as mild, 38.6% as moderate, 38% were severe and 12.9% were classified as very severe. The mean episode duration was 16 weeks and 67% reported co-morbid anxiety. Other studies have found different prevalence rates and rates seem to depend on the sample, type of instrument used and definition of depression. It has been noted by some researchers that the prevalence of depression is likely to be increasing (Klerman & Weissman, 1989).

1.2.2: Depression in people with epilepsy

1.2.2.1: Depression in people with epilepsy: Overview

The association between depression and epilepsy has also long been recognised and goes back to the time of Hippocrates (Robertson & Trimble, 1983). He is reported as recognising the complex nature of the relationship and stating "melancholics ordinarily become epileptics, and epileptics melancholics: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy" (quoted by Robertson & Trimble, 1983). Most studies have reported that depression rates amongst people with epilepsy are higher than those commonly reported for the general population (Jacoby et.al., 1996, Ridsdale et.al, 1996, Mensah et.al, 2006) or for those suffering from another chronic non-neurological condition (Ettinger et.al., 2004). The importance and difficulties of identifying depression amongst people with epilepsy have been highlighted (Reynolds, 2005).

1.2.2.2: Depression in people with epilepsy: clinical manifestations

It has been argued that the pattern of depressive disorder amongst people with epilepsy has been reported as being different to the pattern of depression in the general population. For example, symptoms such as irritability appear to occur more commonly amongst people with epilepsy and symptoms are often more intermittent and occur in more atypical clusters (Blumer et.al, 2004). Also groups have been described for which there is no equivalence in the general population (such as Ictal / Peri-ictal depressive symptoms (mood disturbance closely related to individual seizures) and mood symptoms related to anti-convulsant use).

1.2.2.3: Depression in people with epilepsy: Using a dimensional approach.

As for the general population depression can be viewed dimensionally as well as categorically in those with epilepsy. Research on this is however much more limited. From the preceding discussion on the different manifestations of depression amongst people with epilepsy, treating depression dimensionally may be advantageous. Many of the individuals with more atypical manifestations of depressive disorder and ictal and peri-ictal depressive disorders would not be captured using a categorical, DSM-IV diagnostic criteria based approach. The arguments for treating depression dimensionally in the general population would also hold for those with epilepsy.

1.2.2.4: Depression in people with epilepsy: Prevalence

It has been argued that the prevalence of major depression as defined by the DSM-IV classification system (American Psychiatric Association, 1994) is higher amongst people with epilepsy than in the general population (summarised in Kanner, 2003). However there are considerable differences in **reported** prevalence figures of major depressive illness. Community based studies have reported overall rates of 10-15 % ((Jacoby et al, 1996 (11%), O'Donaghue et. al, 1999 (10.3%), Gaitatzis et.al. 2004 (13.6%), Thapar et.al., 2005(11%)) whereas clinic /hospital based studies have generally reported rates of 20-50% (e.g. Grabowska-Grzypa et al., 2006. (49.2%)).

There is less research on the prevalence rates for other subtypes of depression amongst people with epilepsy. Some studies have found prevalence rates of up to 50% for the more atypical patterns of depressive symptoms (Blumer, 1997, 2004, Mendez et.al., 1986) and for dysphoric mood disturbance over the three days before a

seizure (Blanchett & Frommer, 1986). There is very little research on the prevalence of individual depression symptoms for people with epilepsy.

1.3: Anxiety amongst people with Epilepsy

1.3.1: Anxiety in the general population

1.3.1.1: Anxiety in the general population: Overview

The distinction between clinically defined anxiety disorders and everyday feelings such as fear and restlessness has been recognised for at least 2500 years but the generally accepted distinction between anxiety and depression only dates to the mid-19th Century (Glas, 2003). Anxiety disorders are the most common psychiatric disorders (Kessler et.al., 2005). Like most common chronic disorders, anxiety symptoms seem to be continuously distributed amongst the population, with most of the general population having few anxiety symptoms unless associated with specific life events or stresses and the rest of the population having a range of symptoms (Kessler et.al, 2005, Kendler et.al., 1998). There has been much less published research on the consequences of anxiety disorders than on the consequences of depressive disorders until very recently. Recent reports have found that anxiety disorders and symptoms can have important consequences on functioning and health of individuals (Kroenke et.al., 2007, Roy-Byrne et.al, 2008, Frasure-Smith et.al.,2008)

1.3.1.2: Anxiety and stress in the general population: Subtypes

Anxiety can be described by clustering symptoms into categories (such as by using the DSM-IV classification, discussed later), by severity (such as mild, moderate or severe), by aetiology (such as Post Traumatic Stress disorder) as well as by impact on functioning.

1.3.1.2.1. DSM-IV defined anxiety

DSM-IV defines 12 types of anxiety disorders. These include generalised anxiety disorder, phobias, panic disorder, post-traumatic stress disorder amongst others (APA, 1994). As an example of the type of symptoms encountered in anxiety disorders, the diagnostic criteria for Generalised Anxiety Disorder using DSM-IV are highlighted below (Table 1.3.1.2.1). In line with the DSM-IV criteria for depression it is necessary for several symptoms to be present and persistent and functioning to be impaired but for DSM-IV generalised anxiety disorder symptoms can be somewhat intermittent but over longer period and the difficulties in controlling the symptoms are emphasised.

Table 1.3.1.2.1 : The diagnostic criteria for Generalised Anxiety Disorder according to DSM-IV.

These are as follows:

1. For more than half the days in at least 6 months, the patient experiences excessive anxiety and worry about several events or activities.
2. The person has trouble controlling these feelings.
3. Associated with this anxiety and worry, the patient has 3 or more of the following symptoms, some of which are present for over half the days in the past 6 months:

*Feels restless, edgy, keyed up.

*Tires easily.

*Trouble concentrating.

*Irritability.

*Increased muscle tension.

*Trouble sleeping (initial insomnia or restless, unrefreshing sleep).

4.The symptoms cause clinically important distress or impair work, social or personal functioning.

5.The disorder is not directly caused by a general medical condition or by substance use, including medications and drugs of abuse.

6.It does not occur only during a Mood Disorder, Psychotic Disorder, Posttraumatic Stress Disorder or Pervasive Developmental Disorder.

1.3.1.3: Anxiety in the general population: A dimensional approach

It has been argued that anxiety disorders should be treated dimensionally to maximise reliability and validity and retain the categorical approach for clinical utility (Andrews et.al., 2008). A dimensional approach for both clinical and research purposes is also suggested by other types of empirical evidence. Genetic studies have found similar patterns of heritability for most of the subtypes of anxiety, and it seems to be the predisposition to any anxiety disorder that is inherited rather than the specific subtype (Smoller et.al, 2008). Research on co-morbidity for the different types of anxiety disorders found that all these disorders could be detected adequately using the same brief screening instruments (Kroenke et.al, 2007). Interestingly, distinctions between different types of anxiety disorders have only been highlighted in the more recent versions of the DSM classification (particularly in DSM-IV). In the past, DSM-II only really distinguished between anxiety neurosis and specific phobias (Cassano et.al, 2003).

1.3.1.4: Anxiety in the general population: Prevalence

Anxiety disorders are the commonest form of psychiatric disorder (Kessler et.al, 2005). Although there is some variation in reported prevalence rates of anxiety disorders, the findings from the recent National Comorbidity survey indicated a lifetime prevalence of any anxiety disorder of 28.8%,12-month prevalence rate of 18.1% for any anxiety disorder and of 5.7% for generalised anxiety disorder (Kessler et.al., 2005).

1.3.2: Anxiety amongst people with epilepsy

1.3.2.1: Anxiety amongst people with epilepsy: Overview.

The association between epilepsy and anxiety has been long recognised (the term melancholia used in Hippocratic times having an overlap with both anxiety and depression (Glas, 2003)). Anxiety disorders have been found to be more common amongst people with epilepsy than for the general population (Beyenberg et.al, 2005).

1.3.2.2: Anxiety amongst people with epilepsy : Clinical manifestations

Anxiety symptoms, like depression symptoms, can be related to epilepsy in a variety of ways (Goldstein & Harden, 2000). They can be independent of individual seizures (interictal), related closely to individual seizures (ictal or peri-ictal), as part of the more atypical depressive symptom complex described earlier or related to medication side effects(Valquez & Devinsky, 2003). The DSM-IV classification can be used to categorise inter-ictal anxiety disorders (Vazquez & Devinsky, 2003).

1.3.2.3: Anxiety amongst people with epilepsy: A dimensional approach

There has been little discussion of this topic in the epilepsy literature. The DSM-IV classification system has a category for anxiety explained by medical conditions (APA, 1993). Most reported research on anxiety amongst people with epilepsy does not use DSM-IV anxiety disorder categories and instead relies on results from self-report anxiety rating scales (Beyenburg et.al, 2005) with cut off scores on these questionnaires to define whether or not clinical anxiety is likely to be present (Jacoby et.al., 1996). The cut-off scores have generally been recommended on the basis of research in the general population, although the risks of applying these scores to people with epilepsy have been highlighted (Krishnamoorthy, 2006). There is some recent tentative neurobiological evidence to support analysing anxiety scores as a dimension. A recent study on patients with intractable temporal lobe epilepsy found post-operative anxiety scores were associated with the volume of the left hippocampal remnant after anterior temporal lobectomy. However a weakness of the study was that no pre-operative psychological assessments were carried out (Paparrigopoulos et.al., 2008).

1.3.2.4: Anxiety amongst people with epilepsy: Prevalence

The prevalence of anxiety amongst people with epilepsy in community based studies has been found to be consistently higher than in the general population. The reported prevalence rates however vary considerably (as for depression), with point prevalence rates of over 20% (20.5% (Mensah et.al., 2007), 25% (Jacoby et.al, 1996), 30.4% (Ridsdale et.al, 1996) and 39.4% (O'Donaghue et.al., 1999). Hospital based studies have found even higher rates of anxiety, with some studies reporting rates of over 50% (Beyenburg et.al., 2005).

1.4: Stress amongst people with Epilepsy

1.4.1. Stress in the general population:

1.4.1.1: Stress in the general population: Overview

Stress is a difficult concept to define (Cohen et.al.,1997) . One approach has been to emphasise the importance of homeostasis for living organisms. Using this approach stress would be any physical or psychological event (a **stressor**) which threatens this state of dynamic equilibrium (De Kloet et.al, 2005). However individuals vary greatly in their response to stressors (Cohen et.al., 2007). Another approach to stress emphasises the importance of **stress appraisal**, where it is the individual's subjective perception of stress which is important. A useful working definition which may unify some of these concepts is "(stress) is a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease" (Cohen et.al., 1997).

Disease causation and exacerbation are often linked to the presence of stress by the general population (Cohen et.al., 2007). There is mixed evidence on the impact of both stressors and stress appraisal on health. A recent commentary in the *Journal of the American Medical Association* (JAMA) highlighted the studies which had found increased risks of physical illness in those reporting stress or stressful life events (Cohen et.al, 2007). There is also some research which suggests that stress appraisal is not a risk factor for diseases such as coronary heart disease (Mcleod et.al, 2002) but the measure used to measure stress appraisal has been criticised (Hotopf, 2002, Rosch, 2002).

1.4.1.2: Stress in the general population: categories

The DSM – IV classification system has no equivalent framework to the schemata of stressors and stress appraisal outlined above and is instead based on acute symptoms after a stressor or long term problems with adjustment. The DSM-IV system lists categories for Acute Stress reactions, Adjustment Reactions (both of these are limited to 6 months after an event (stressor)) and Post Traumatic Stress disorder.

The advantages of using stress appraisal (sometimes termed perceived stress or subjective stress) have been highlighted (Cohen et al, 1997).

1.4.1.3: Stress in the general population: a dimensional approach

As discussed above, measurement of stress can be undertaken either by using questionnaires, interviews or by biological measurements (such as cortisol) (Cohen et.al, 1997). Interviews are generally recommended but questionnaires are also used and are acceptable (Cohen et.al, 1997). Questionnaires can be either used to measure exposure to stressors (using instruments such as the Holmes-Rahe social readjustment scale) or by measuring stress appraisal (such as by using the Perceived stress scale) (Cohen et.al, 1997). Both of these constructs are usually used dimensionally. Some studies have reported on prevalence figures using categories, based on cut-off scores.

1.4.1.4: Stress in the general population: prevalence

Here, the emphasis is on perceived stress not on life events, the measurement of which has been extensively discussed (Cohen et.al, 1997). The prevalence of reported stress in the general population depends on the type of measure used and the sample. In a study based on adults in Sweden which used the Perceived Stress Questionnaire, the prevalence of moderate stress was estimated to be 10.0% and the prevalence of

high stress 4%. Higher stress levels were reported by women, with the highest prevalence in the 30-34 age group (Bergdahl & Bergdahl, 2002). In a further European study using the same questionnaire, the prevalence rate of moderate stress was 14.5% and prevalence of high stress was 3.1% with highest scores in the 35-54 age group (Kocalevent et.al., 2007).

1.4.2: Stress amongst people with epilepsy

1.4.2.1: Stress amongst people with epilepsy: overview

The psychological strains of living with epilepsy were well documented in early qualitative research by Graham Scambler (Scambler, 1989) and Peter Conrad and Joseph Schneider (Schneider & Conrad, 1983). Qualitative work has continued to document the adverse life circumstances of people with epilepsy. However there has been little use of quantitative measures of stressors and stress appraisal amongst people with epilepsy. Most of the reported research has focussed on the role of stress as a seizure precipitant. Studies have supported the role of both environmental stress (i.e. life events) (Rajna & Veres, 1989) and perceived stress (Temkin & Davis, 1984, Mattson, 1991, Frucht et.al, 2000, Spector et.al, 2000, Haut et al, 2007, Nakken et al, 2005,Sperling et.al, 2008) as a seizure precipitant. However most of these studies are small and have not controlled for emotional state either as a confounder or as a moderator. The aetiology of stress in epilepsy is not precisely understood. Epilepsy leads to a variety of handicaps. Seizures can be highly embarrassing especially if coming on without warning. Seizure frequency and type are also extremely important in this regard. Idiopathic epilepsy is also common in adolescence and this is a vulnerable period in terms of self image. The social consequences of epilepsy including stigma and employment problems have been highlighted for many years

(Scambler, 1989) and social difficulties such as problems with employment and economic circumstances are still evident (Smeets et.al, 2007).

1.4.2.2: Stress amongst people with epilepsy: subtypes

There seems to have been little research looking at the relationship of specific subtypes of stress and epilepsy. There have been several studies which have found increased rates of PTSD amongst individuals with pseudo seizures. One study has found increased rates of post-traumatic stress disorder (PTSD) amongst people with intractable epilepsy as well as those with pseudo seizures (Rosenberg et.al., 2000).

1.4.2.3 : Stress amongst people with epilepsy: a dimensional approach

As discussed above there has been little quantitative research examining stress amongst people with epilepsy. Qualitative research has highlighted the individual experiences of individuals with epilepsy which would lead to the suitability of using a dimensional approach (Schneider & Conrad, 1983, Scambler, 1989).

1.4.2.4.: Stress amongst people with epilepsy: prevalence

Data on the prevalence of high levels of stress amongst people with epilepsy are not available. Qualitative work (Schneider& Conrad, 1983, Scambler, 1989) suggested that stress is a common problem amongst people with epilepsy. Quantitative work does not generally report prevalence levels of background stress but instead has examined the role of stress as a precipitant for seizures (Haut et. al. 2007).

1.5 : Aims

The overall aims of this programme of research are to systematically examine the relationship between depression and seizure measures in adults with epilepsy using data from large scale, prospective longitudinal studies and "state-of-the-art" data analytic strategies to also examine the influence of other psychological variables on two principal seizure measures.

Specific aims include:

1) To examine the nature of the relationship between depression symptom scores and seizure frequency amongst people with epilepsy by specifying and testing different theoretical explanatory models of this relationship.

2) To examine how depression, anxiety and stress act separately and in combination to influence seizures.

3) To examine the pattern and extent of individual variation in depression symptom scores amongst people with epilepsy over time.

4) To investigate whether seizure recency predicts individual variation in depressive symptoms.

5) To tailor and apply appropriate multivariate statistical analytic techniques to examine the specific relationships postulated.

Chapter 2:

Methods overview

2.1. Introduction to the datasets used: subjects and measures

Information from two community-based studies of adults with active epilepsy was used for the analyses.

2.1.1.Study 1.

2.1.1.1. Sample

The sample consisted of adults with active epilepsy who were recruited from 82 general practices in Greater Manchester and who consented to participate in an intervention study to assess the effectiveness of an epilepsy prompt and reminder card in improving quality of care (Thapar et.al, 2002). This study had taken place from 1996 to 1999. Ethical approval was obtained from the relevant local Research Ethics Committees (South Manchester, Bury and Rochdale, Salford and Trafford and Stockport).The definition of active epilepsy used was that of either a seizure recorded in the medical records in the last two years or currently on anticonvulsant medication for epilepsy with a history of epilepsy. The sample is described in further detail in Section 2.2.

2.1.1.2. Measures

All patients had been sent a battery of questionnaires for self- completion. Data were collected at two time points 1 year apart. For the purposes of the analyses contained in this thesis the following measures were used

1) *Seizure frequency.* This was a measure from the battery of questionnaires combined to form the Liverpool Quality of Life questionnaire (Baker et.al., 1993). Seizure frequency was assessed using a self-report measure rated on the

response to a question "How many epileptic attacks have you had in the past year" with the three response categories being "None", "Less than one a month" and "One or more a month". This item has been shown to have good reliability and validity (Baker et.al., 1993).

2) *Depression scores*. These were derived from the Hospital Anxiety and Depression Scale (HAD) (Zigmond & Snaith 1983). These are based on responses to seven questions pertaining to depressive symptoms and the range of possible scores on the HAD depression subscale range from 0 to 21. This measure has been shown to have good reliability and validity (Zigmond & Snaith 1983) .

2.1.2. Study 2

2.1.2.1. Sample

A cohort of adults with active epilepsy was recruited to participate in a longitudinal three-wave 15 month observational study of factors affecting the quality of life of people with epilepsy. Active epilepsy was defined as individuals with a history of epilepsy who were either on medication for their epilepsy or who had had recent seizures. Individuals identified through general practices who had taken part in previous studies in Cardiff (Mensah et.al., 2006) and Manchester (Thapar et.al., 2002) were contacted and invited to participate in the present study and 341 individuals from Cardiff and 108 individuals from Manchester agreed to participate. Ethical approval was obtained from the relevant local Research Ethics Committees (BroTaf and Salford & Trafford). A volunteer sample of people with epilepsy was also recruited through Epilepsy Action (115 individuals). Information was collected at three time

points about 5 months apart. The study took place between 2002 and 2004. This sample is described in further detail in Section 2.2.

2.1.2.2. Measures

Participants completed a comprehensive package of well-known and validated measures of physical, social and psychological health[1].

The following subset of measures was used for the analyses contained within the thesis.

1. *Anxiety* and *Depression.* The Hospital Anxiety and Depression (HAD) scale was used (Zigmond & Snaith, 1983). This is a widely used measure with good psychometric properties which has been successfully used to measure caseness for depression and anxiety in previous community based studies examining the quality of life of people with epilepsy (Jacoby et.al., 1996). It refers to how the respondent had been feeling in the previous week. Depression and anxiety scores were also categorised into "normal"(score from 0-7), "borderline " (scores 8-10) and "probable case" (scores 11 or above) (Zigmond & Snaith, 1983, Snaith, 2003).

2. *Perceived stress.* The 4 item perceived stress scale PSS (Cohen et.al., 1983) was used as a measure of stress appraisal. It referred to perceived stress levels in the past month. The 4 item scale was used to minimise respondent burden. It has been found to have acceptable psychometric properties (Cohen et.al., 1983) and has been used in previous outpatient and community studies (Farabaugh et.al., 2004).

3. *Seizure recency.* (Wagner et.al., 1995; Cramer et.al, 2004). Participants were asked how long it had had been since they had their last seizure. This measure has

[1] a full list of measures is available upon request

been used in previous studies (Cramer et.al, 2004). The responses were converted to days since last seizure and categorised. A 12 category variable was created with scores ranging from 12 (seizure in the last 24 hours) to 1 (last seizure was more than 15 years ago) with a midpoint score of 6 (last seizure was between 6 and 12 months ago), that is, with the most recent seizures having the highest scores. Categorization was used for conceptual and clinical reasons as well as to overcome problems with model convergence.

4. *Seizure frequency.* Individuals were also asked about the number of seizures they had experienced over the previous year with scores ranging from 0 (if the individual had had no seizures) to 10 (if the individual had 10 or more seizures) in the previous year.

5. *Medication compliance.* Individuals were also asked to rate how often they missed any medication for their epilepsy at the end of the study. Responses were on a 4 point Likert Scale and ranged from 1= "never" to 4= "missed doses more than once a week".

2.1.2.3. Missing values

Some individuals had missed items on particular scales. A two step approach was used in dealing with missing values. Where there was partial non completion of scales (for seizure recency and seizure frequency), regression based imputation methods for missing data were used (standard missing values procedure used in STATA Version 8) or (for depression and anxiety) if there was a single item with a missing value then imputation using mean substitution derived from the other items was undertaken. If there was more than one missing item the score was coded as missing.

List wise deletion of data was undertaken prior to the structural equation modelling analyses such that only individuals with complete information for all variables were included in all subsequent analysis.

Data transformations

The data were also transformed; anxiety and depression scores were negatively skewed so were transformed using a square root (raw score+1) transformation. Analyses were carried out on transformed data.

Chapter 2.2: Study sample

2.2.1. Study 1

At baseline the sample consisted of 1210 adults with epilepsy. Some participants did not provide complete data so numbers for different items may be less than this number. The characteristics of the sample have already been published (Thapar, 2001). Percentages are rounded to one decimal place so some cumulative percentages will not equal 100%.

Table 2.2.1. Sample characteristics :Study 1

Age (*n*=1210)	
Mean age (S.D.) (years)	49.6 (17.3)
Age group (years)	*n* (%)
20 or younger	41 (3.4)
21–40	364 (30.1)
41–60	453 (37.4)
61–80	321 (26.5)
81 or older	31 (2.6)
Sex (*n*=1209), *n* (%)	
Male	580 (48.0)
Female	629 (52.0)
Seizure type (*n*=596), *n* (%) (may have more than one seizure type—% will add up to more than 100%)	
Generalized—tonic—clonic	332 (55.7)
Partial—simple	28 (4.7)
Partial—complex	182 (30.5)
Others, including absence seizures	220 (36.9)

Table 2.2.1.(cont) :Sample characteristics :Study 1

Family history – first degree relatives with epilepsy (*n*=955), *n* (%)		
Yes	97 (10.2)	
No	858 (89.8)	
Seizure frequency	Time 1 (*n*=1197), *n* (%)	Time 2 (*n*=954), *n* (%)
No seizures in the last year	607 (50.7)	527 (55.2)
<1 Seizure/month	261 (21.8)	194 (20.3)
≥1 Seizure/month	329 (27.5)	233 (24.4)
Depression scores	Time 1 (*n*=1185), mean (S.D.)	Time 2 (*n*=959), mean (S.D.)
Total score	5.34 (3.8)	5.37 (4.0)
Categorized depression scores	Time 1, *n* (%)	Time 2, *n* (%)
"No depression" (0–7)	878 (74.1)	694 (72.4)
"Doubtful depression" (8–10)	170 (14.3)	141 (14.7)
"Definite depression" (11–21)	137 (11.6)	124 (12.9)
Marital status (n= 1204) %		
Single	25.8	
Married /living as married	56.7	
Divorced /separated	9.3	
Widowed	8.1	
Age of onset of epilepsy (n=1169) n (%)		
Aged 18 or earlier	507(38.8)	
Aged 19-60	551 (42.2)	
Aged over 60	111 (8.5)	
Claim income support (n=1134) n (%)		
Yes	251 (22.1)	
No	883 (77.9)	

2.2.2. Study 2

The numbers of participants in this study were 460.

Some participants did not provide complete data so numbers for different items may be less than this number. Most single data point information is based on baseline characteristics except data on seizure type and family history that are based on data collected at the end of the study. Percentages are rounded to one decimal place so some cumulative percentages will not equal 100%.

Table 2.2.2. Sample characteristics : Study2

Age (*n*=447)	
Mean age years (S.D.)	51.1 (17.3)
Age group (years)	*n* (%)
20 or younger	3 (0.7)
21–40	112 (26.6)
41–60	180 (42.8)
61–80	103 (24.5)
81 or older	23 (5.5)
Sex (*n*=460), *n* (%)	
Male	217 (47.2)
Female	243 (52.8)
Seizure type (*n*=344), *n* (%) (may have more than one seizure type—% will add up to more than 100%)	
Generalized—tonic—clonic	174 (50.6)
Partial—simple	65 (18.9)
Partial—complex	89 (25.9)
Others, including absence seizures	169 (29.1)
Fist degree family history (*n*=382), *n* (%)	
Yes	34 (8.9)
No	348 (91.1)

Table 2.2.2. (continued). Sample characteristics : Study 2 (continued)

Seizure frequency	Time 1 (*n*=452), *n* (%)	Time 2 (*n*=434), *n* (%)	Time 3 (n=390), n(%)
No seizures in the last year	224 (49.6)	221 (50.9)	211 (54.1)
<1 Seizure/month	113 (25.0)	97 (22.4)	86 (22.1)
≥1 Seizure/month	115 (25.4)	116 (26.7)	93 (23.8)
Depression scores	Time 1 (*n*=460), mean (S.D.)	Time 2 (*n*=435), mean (S.D.)	Time 3 (*n*=395), mean (S.D.)
Total score	4.10 (3.33)	4.42 (3.59)	4.40 (3.54)
Marital status (n= 460) n (%)			
Single	123 (26.7)		
Married /living as married	262 (57.0)		
Divorced /separated	39 (8.5)		
Widowed	36 (7.8)		
Employment status (n=447) n(%)			
Employed	181 (40.5)		
Unemployed, seeking work	15 (3.4)		
Retired from paid work	126 (28.2)		
Permanently unable to work (illness / disability)	78 (17.4)		
Other	47 (10.5)		
Claim income support (n=433) %			
Yes	14.8		
No	85.2		

As Sample 2 was recruited from three different localities (see Page 36) the characteristics of the sample recruited from each of the three localities is compared below (Table 2.2.2.1 on next page)

Table 2.2.2.1. Characteristics of individuals recruited from the three different localities (see Page 36)...

Sample characteristic	Cardiff sub-sample	Manchester sub-sample	Epilepsy Action sub-sample
% Male (n)	49.6 (133)	50.0 (46)	38.0(38)
Mean age in years (n)	52.7 (263)	53.9(87)	44.4(97)
Mean **categorised** days since last seizure* (n)	5.7(270)	6.0 (96)	7.8 (101)
% Seizure free in previous year (n)	57.4(147)	53.7 (51)	25.7(26)
% of individuals reporting complex partial seizures as one of seizure types (n)	16.6 (31)	22.9 (16)	48.3 (42)
Mean depression score (n)	4.0 (267)	4.0 (93)	4.5(100)

*defined on Pages37-8

2.2.3. Were the samples representative?

To check whether the samples being used were representative, a comparison was made of the characteristics of the respondents in these samples to the findings of another large, unrelated, community based study of adults with epilepsy (Jacoby, et al, 1996). The main comparisons are listed in Table 2.2.3 (below).

Table 2.2.3 Comparing sample characteristics in the present study to those from another well characterised community based study

Sample characteristic	Sample 1	Sample 2	Jacoby et al, 1996 study
Seizure free in previous year (%)	50.7	52	53
Tonic-clonic seizures (%)	55.7	50.6	52*
Employed (%)	N/A	41.3	44.8
Male(%)	48	47	49
Mean age (years)	49.6	51	46

*questionnaire responders

2.3. Overview of Statistical analyses

2.3.1. Background

Previous work has examined the links between psychopathology and seizures for people with epilepsy (see Chapter 1 for more details).

This existing evidence is of four principal types, namely:

1) Evidence from qualitative studies (Scambler, 1989, Schneider & Conrad, 1983). These have highlighted that people with epilepsy report a lot of difficulties with stress and mood in their day to day lives.
2) Evidence from cross-sectional surveys. These show increased prevalence rates of psychopathology amongst people with epilepsy, for example, anxiety disorders are commoner in epilepsy (Tellez-Zentano et.al., 2007).
3) Evidence from cross-sectional studies examining associations (Jacoby et. al, 1996, Ridsdale, 1996). These have found that there are associations between seizure factors and psychopathology. One example is that the frequency of seizures is associated (correlated) with higher rates of depression amongst people with epilepsy (Jacoby et. al., 1996).
4) Evidence from studies which have looked at "causal" relationships using regression. These have found that seizure factors predict psychopathology. One example is that complex partial seizures are found to predict depression scores (Grabowska-Grzyp et al., 2006).

However these previous studies leave many important questions unanswered and have several methodological limitations.

1) All the analyses to date are based on cross-sectional data. It is generally acknowledged that for observational studies which examine causes and

consequences, longitudinal data should be used (Menard, 1991, Rutter et.al., 2001, Academy of Medical Sciences, 2007). This is discussed in more detail below.

2) Several psychopathological factors have been associated with seizures (such as anxiety and depression) and these are closely inter-related and inter-relationships are likely to be complex (Susser et al, 2006). To examine complex relationships, appropriate methods have to be employed (Tabachnick & Fidell, 2001). There are several reasons why simpler techniques like multiple regression may not be appropriate:

    a) There is a need to take account of the precise relationship between psychological variables (e.g. mediation and dealing with correlated variables),

    b) the errors associated with measuring these correlated variables may themselves be correlated and

    c) there can only be one dependent variable. Statistical analytic methods which are able to deal with higher levels of complexity have to be adopted.

The data on which this thesis are based are longitudinal. Path analysis and structural equation modelling (SEM) were used for the analyses.

2.3.2. Key concepts

2.3.2.1. Longitudinal data

What are the advantages of using longitudinal data?

There are different types of longitudinal data. Where information from the same informants is collected over at least two occasions separated temporally this is termed as **panel data**. For studying causal relationships, longitudinal (panel) data rather than cross sectional data should be employed for the following reasons:

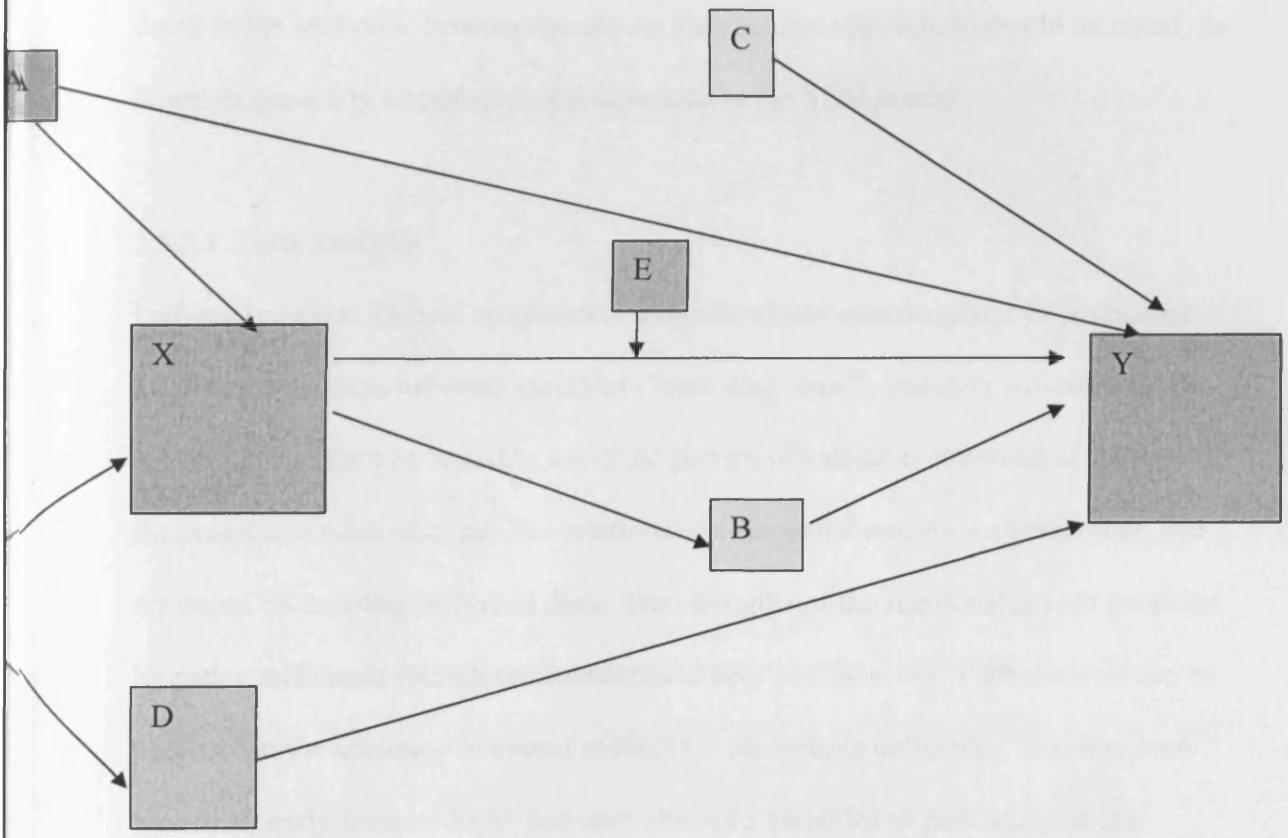
1) Temporal or causal ordering is an essential part of testing directionality of effects and hence for examining causal hypotheses. For this you generally need longitudinal data.
2) Longitudinal data allows measurement of intra-individual changes, whereas cross-sectional data only allows measurement of inter-individual differences. This is especially important if any changes over time ("developmental changes") are expected.
3) For any dynamic process, longitudinal data are necessary to estimate parameters (characteristics of population or distribution of scores) efficiently and without bias (Menard, 1991). Panel data can be used to identify and correct for residual heterogeneity.
4) Prospective panel designs are the best method for longitudinal analysis of observational data (as opposed to retrospective methods).

2.3.2.2.Examining relationships amongst causes – moderation and mediation

As highlighted above, longitudinal data are useful for studying causal relationships. However often the hypothesised cause is simply one of a range of possible risk factors impacting on the disorder and works in conjunction with other risk factors (Susser

et.al. 2006). By anticipating the roles that other factors may play in the hypothesised relationship enables data to be collected on these other factors and consequently to inform the analyses for causal explanation; that is, not only looking at the range of causes of disease but elucidating how different causes inter-relate (Susser et.al., 2006). Types of causes can be subdivided into those that are not in the hypothesised causal pathway (either as independent risk factors or confounders (associated with the postulated cause as well as the outcome but not on the causal pathway)) and that other factors are inter-related in the causal pathway either as mediators, antecedent causes or as causal partners (for which moderation is one example). This is summarised in Figure 2.3.2.2 (overleaf)

Figure 2.3.2.2: Diagrammatic representation of how an additional risk factor could impact on a postulated relationship between a risk factor X and an outcome Y (adapted from Susser et.al, 2006)



A Antecedent cause

B Mediating risk factor

C Independent risk factor

D Confounder

E Moderator

2.3.3. Evolution of the analytic approach

The analytic approach used utilises the family of techniques termed **structural equation modelling (SEM)**. For ease of understanding this will be discussed in more detail in the section following the one on path analysis (which, it should be noted, is however generally considered as a technique in the SEM family).

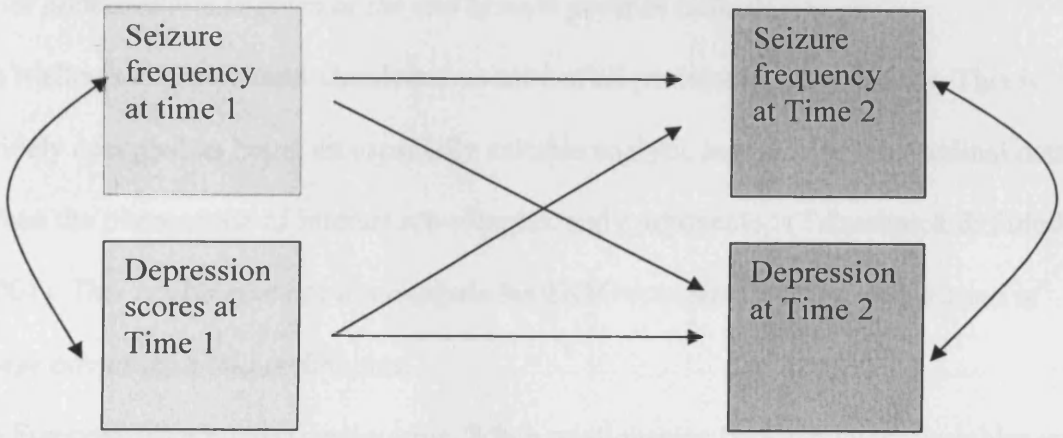
2.3.3.1. Path analysis

Path analysis is a form of multivariate analysis which uses diagrams of postulated causal relationships between variables ("path diagrams"), and data collected by the researcher can then be tested to see if the pattern of variation observed in the data fits the postulated relationships. The relationships are postulated by the researcher, and are based on existing empirical data. The strengths of the relationships are provided by path coefficients (which are standardised beta coefficients). Path analysis can be used to test the accuracy of causal models for the sample collected. This has been termed an early form of SEM and uses observed variables in path analysis (as opposed to latent variables which are used in SEM – see later). The advantages of path analysis include the following.

1) Explicit testing of collected data against postulated models encourages specific hypothesis formulation and avoids "fishing expeditions" where significant relationships are explained post-hoc and this can plague research on causation.
2) Direct and indirect effects of independent variables can be estimated.
3) There is simultaneous assessment of all relationships postulated and one can estimate direct and indirect effects on variables.
4) An estimate of how well the observed data fit the models can be made.

To highlight the application of path analysis to the examination of data, a practical example is given in the appendix (Appendix 1).

An example of the type of path model specified for the analysis is given below



Path analysis can also be applied to cross-sectional data. However only if longitudinal (panel) data are used can direction of effects be examined.

2.3.3.2. Structural equation modelling

2.3.3.2.1. What is structural equation modelling (SEM)?

SEM is a family of statistical techniques that enable the specified relationships between variables to be tested against the observed pattern of correlations and covariances between variables. Structural equation modelling represents an extension of path analysis (or alternatively path analysis represents a simple technique in the family of structural equation modelling) as it integrates factor analysis and path

analysis into a single analytic framework (Joreskog & Sorbom, 2000). Cross-lagged panel analysis is a common method for analysing data using SEM.

2.3.3.2.2. Why was SEM used?

Structural equation modelling (SEM) has some important advantages *(the comparison with path analysis is given at the end of each point in italics):*

1) It allows complete and simultaneous tests of all postulated relationships. This is widely accepted as being an especially suitable analytic method for longitudinal data when the phenomena of interest are complex and multifaceted (Tabachnick & Fidell. 2001). *This is also true of path analysis but SEM represents further elaboration of these advantages and techniques.*

2) Freedom from measurement error. When relationships between latent variables are tested, it allows the relationships to be examined free of measurement error. The error is estimated and removed and only the common variance is examined. *This represents an advance over path analysis where the measurements are assumed to be assessed without error and as some error is inevitable this reduces reliability in path analysis. For SEM, measurement error is estimated and removed from the latent variable.*

3) Flexibility. It is possible to simultaneously estimate the pattern of relations that exist between continuous and non-continuous measures when considered within the same theoretical model. In view of the combination of an ordinal variable (seizure frequency) with a continuous variable (depression) in the present study, the pre-processing package PRELIS can generate a polyserial variance-covariance (correlation) matrix that takes into account differences in the measurement properties of each measure of seizure frequency and depression at each time point *(also true of path analysis).*

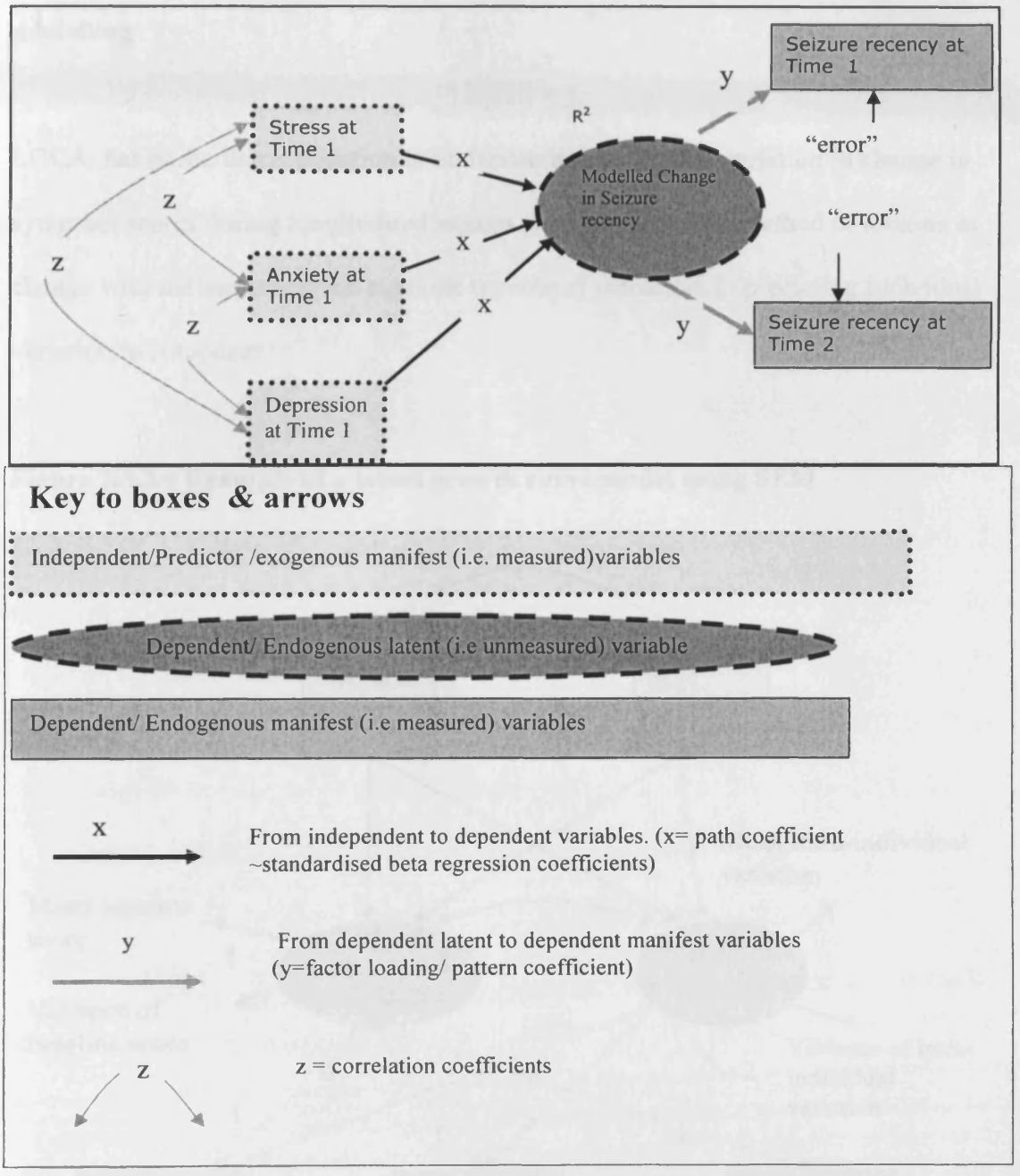
3) It facilitates formulation and testing of specific hypotheses based on empirical data. Alternative models can be tested and the provision of an estimate of model 'fit' (statistical estimate of the adequacy of a proposed theoretical model relative to the underlying pattern variance and covariance in the original data) allows testing of a postulated model against alternative models *(this is also true of path analysis)*

2.3.3.3. Random effects latent variable modelling

The example given earlier is on cross-lagged panel analysis using a path model approach. As has been discussed in the introduction, what is not clear is how other psychological variables like anxiety and stress are associated with depression in affecting seizure activity. For this to be examined we used the second dataset which had measures of stress. However there were high stability levels for seizure activity which rendered the data less suitable for cross lagged panel analysis. This triggered a search for an alternative analytic technique which could be used on two time point panel data with variables displaying high stability levels and that allowed testing for moderation and mediation. Random effects latent variable modelling (Berrington et.al., 2006), using a structural equation modelling approach with LISREL 8.50 (Joreskog & Sorbom, 2001) was decided on. In this context, the mean and variance of the latent variable represents the mean change over time of the group as a function of any given set of independent predictors (Berrington et.al., 2006; Ramos et.al., 2005), as compared to variation around the mean (as is the case in more conventional simple regression based approaches to data analysis) of a single indicator or measure of a dependent variable of interest.

For this technique, measured seizure recency scores at different time points are indicators for a latent variable which will then represent "change in seizure recency score" (note this is a modelled change in score rather than a difference in raw scores) and is an estimate of true variance in seizure recency for the sample over the 5-month period considered (see Figure 1). The stability is essentially partialled out of this latent variable. Any relationship between this construct and an earlier assessed theoretical predictor (e.g., depression), represents the role of this predictor in accounting for variation or 'change' in seizure recency across the time frame considered in the study.

Figure 2.3.3.3: An example of a random effects structural equation model .

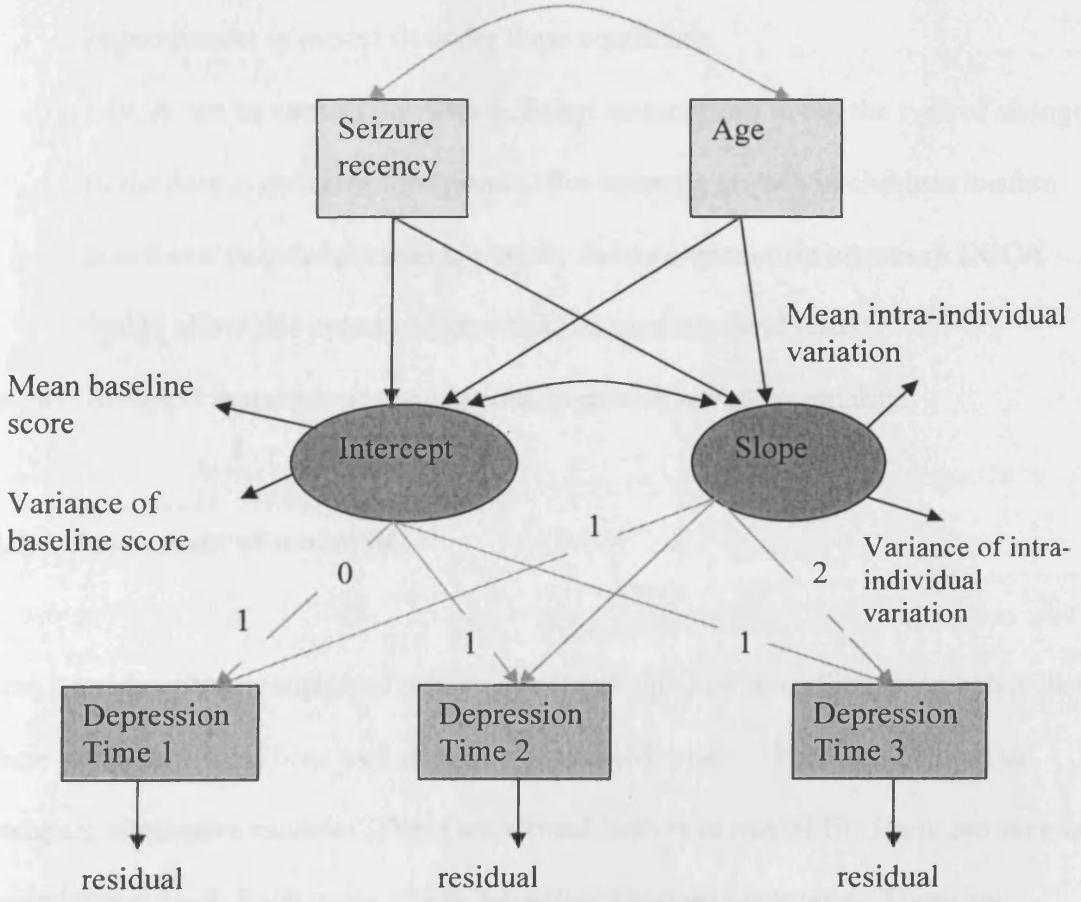


This method is very useful for examining variation in otherwise quite stable variables where there is information at two time points. If information is available from more than two time points the use of a latent growth curve model is recommended.

2.3.3.4. Latent growth curve analysis (LGCA) or Latent growth curve modelling

LGCA has particular application to understanding individual variation in change in symptom scores during longitudinal studies. This is a powerful method of looking at change with individuals as we examine the role of predictors in predicting individual variation in responses.

Figure 2.3.3.4 Example of a latent growth curve model using SEM



2.3.3.4.1: Advantages of latent growth curve modelling

1) Latent growth curve modelling allows examination of individual variation (intra-individual variation) in addition to group level variation (inter-individual variation). This gives greater insight into processes which affect individuals.
2) Although LGCA makes the same assumptions regarding structure and properties of the data as for any regression analysis the analysis can also be carried out if these properties are relaxed. In particular, models can be tested when errors at different times are allowed to be correlated and also if there is heterogeneity of variance and the model fit can be used to see if there is any improvement in model fit under these conditions.
3) LGCA can be carried out with different assumptions about the type of changes in the data at different time points. For example growth in children is often non-linear (e.g. height during puberty shows a geometric increase). LGCA would allow this pattern of growth to be modelled and tested.
4) LGCA is more robust to variations from multivariate normality.

2.3.4. Assessment of model fit

One considerable advantage of using a structural equation modelling approach is that there are measures of how well data fit a postulated model. These can be used to compare alternative models. These are termed indices of model fit. There are several main indices used. Each index has its advantages and disadvantages. These are discussed next.

Chi-squared test(χ^2 test)

This is commonly available and is easy to interpret. The aim for a "good" model is to find a non- significant chi-square test (as in this case the observed data are not significantly different from what is expected from the model). However the major disadvantage of the Chi-square test is that it is very sensitive to sample size. With large samples one can obtain high Chi-squared values (i.e. indicating a poor fit) even with trivial differences in model fit. It is also sensitive to departures from multivariate normality. It is important as it forms the basis of most of the other goodness of fit indices which however incorporate other adjustments making these less sensitive to sample size.

Root Mean Square of Approximation (RMSEA)

This has also been termed a parsimony adjusted goodness of fit index. It is a well regarded index because of several features (Kline, 2005). The first is that if there are two models with similar explanatory power for the same data, it will favour the simpler model. The second is that it does not assume a perfect fit between the data and the model. It uses the non-central chi-square distribution which rather measures the mis-specification of the proposed model (specifies a non-centrality parameter-δ). If the value of δ is zero, this is interpreted as indicating a central chi-square distribution and the null hypothesis is true. Higher values of δ indicate more misspecification of the model.

Values of RMSEA of 0 indicate a perfect fit, values less than 0.05 a good fit, less than 0.08 a reasonable fit and >0.10 a poor fit. It is recommended that the 95% confidence intervals of this parameter are used. If one is <0.05 and the other <0.10

this indicates a good fit. If any part of the confidence interval is >0.10 that indicates a poor fit.

Normed fit index (NFI) and Non-normed fit index (NNFI)

This compares the chi-square value of the estimated model to the chi-square value of a fully independent model (i.e. where there is no association postulated). The values should be in the range 0-1. Good fitting models should have a value of 0.9 or higher. Unfortunately for small samples even good fitting models (using other indices) are sometimes "rejected" using this criterion. The non-normed fit index attempts to correct for this problem but for small samples, similar problems may remain and moreover the range of values can go outside the 0-1 range.

Confirmatory fit index(CFI)

This assesses the fit of the estimated model to the independent model (i.e. where there is no association postulated) using the non-central chi-square distribution with non centrality parameters. If these are zero the fit is perfect.

The range of CFI values are between 0-1 and values greater than 0.95 indicate a good fit. The CFI is viewed by some as a good way of assessing model fit even for small samples (Tabachnick & Fidell, 2001).

Goodness of Fit Index (GFI) and Adjusted Goodness of Fit Index (AGFI)

This is an absolute fit index which can be thought of as similar to the squared multiple correlation (R^2). It estimates the proportion of variability in the sample covariance matrix (covariance found in observed data) explained by the population covariance matrix (i.e. the covariance suggested by the hypothesised model). The normal range

is zero to one, with a value of 1 showing a perfect fit (population covariance completely explained by sample covariance) and values of over 0.9 indicating a good fit. However just identified models can have values greater than 1 as can over identified models with perfect fit (Kline, 2005). The adjusted goodness of fit index developed to correct for model complexity, downwardly adjusts GFI scores with greater reduction for more complex models but scores above 1 are still an issue and computer simulation studies have shown some problems with the AGFI (Kline, 2005).

Chapter 3

Do depression symptoms predict seizure frequency- or vice versa?

Citation

Thapar A, Roland M, Harold G. Do depression symptoms predict seizure frequency-- or vice versa? *J Psychosom Res.* 2005;**59(5)**:269-74.

Abstract

Objective. To test a theoretical explanatory model of the relationship between depression symptom scores and seizure frequency in people with epilepsy.

Methods. A community based sample of adults with active epilepsy provided information on depression symptom scores and seizure frequency at two time points, one year apart.

Results. 1210 patients completed the initial questionnaire and 976 of these individuals (80.7%) completed the final questionnaire. Depression scores and seizure frequency were significant predictors of each other, both within time ($\beta = .07$, $p < .05$ and $\beta = .09$, $p < .05$), and across time ($\beta = .03$, $p < .01$ and $\beta = .07$, $p < .05$).

Conclusion. The relationship between depression symptom scores and seizure frequency in those with epilepsy is bi-directional.

3.1 Introduction

The association of increased seizure frequency with increased rates of depression is well established in cross-sectional community studies, with the assumption that it is poorly controlled epilepsy which is a major risk factor for depression in people with epilepsy in the community (Jacoby et.al., 1996, Ridsdale et.al., 1996). There is however increasing evidence from research of other chronic diseases, in particular ischaemic heart disease (Penninx et.al., 2001), diabetes (Talbot & Nouwen, 2000) and asthma (Mancuso et.al., 2001) that depression can predict the onset of physical diseases and influence outcome. Recent reviews of depression and epilepsy have also begun to suggest that the association arises as a result of bi-directional influences and have proposed a possible neurochemical basis for this relationship through specific neurotransmitter pathways (e.g. serotonin, noradrenaline, dopamine and GABA

pathways) but have lamented the overall paucity of research in this area (Kanner, 2003). To date, there have been two published studies of epilepsy that provide empirical support for the assertion that depression may precede epilepsy in adults. In these studies, depression was found to be a risk factor for the initial development of epilepsy (Forsgren & Nystrom, 1990; Hesdorffer et.al., 2000). However there is no information on whether depressive symptoms are predictive of seizure frequency for individuals with current epilepsy, that is affect the course of disorder in those with already diagnosed epilepsy. This information is important in that it has implications for the clinical management of people with epilepsy.

The aim of this study is to test a theoretical explanatory model of the relationship between depressive symptom scores and seizure frequency in people with epilepsy using a longitudinal study design.

3.2 Method

The sample included 1255 adults with active epilepsy (either a seizure recorded in the medical records in the last 2 years or currently on anticonvulsant medication for epilepsy) from a random selection of 82 general practices in Greater Manchester, U.K. who consented to participate. The sample had originally been recruited as part of a study to assess the effectiveness of an epilepsy prompt and reminder card in improving quality of care (Thapar et. al., 2002) in which there were three groups (a doctor-held card, a patient-held card and a control group; no group differences in patient rated outcome measures were found). All patients were sent questionnaires for self- completion. Seizure frequency from the Liverpool Quality of Life questionnaire (Baker et.al., 1993) and depression scores derived from the Hospital Anxiety and Depression Scale (HAD) (Zigmond & Snaith, 1983) were used in this analysis. Data

were collected at two time points 1 year apart. Seizure frequency is a self-report measure rated on the response to a question "How many epileptic attacks have you had in the past year" with the 3 response categories being "None", " Less than one a month" and "One or more a month". Total scores on the HAD depression subscale range from 0 to 21. Both measures have been shown to have good reliability and validity (Baker et.al., 1993; Zigmond & Snaith, 1983).

Statistical methods

The aim of the study was to construct a theoretical explanatory model of the relationship between depression symptom scores and seizure frequency as they relate to each other across 2 time points and test how well the underlying observed data fit this model using structural equation modeling (SEM). Structural equation modeling represents an integrative statistical technique that combines factor analytic and path analytic traditions into a single data analytic framework (Joreskog & Sorbom, 2000). SEM confers a number of advantages over more traditional approaches to the analysis of correlational data. Principal among these is the simultaneous estimation of all parameters (pathways) and the provision of an estimate of model 'fit' (statistical estimate of the adequacy of a proposed theoretical model relative to the underlying pattern variance and covariance in the original data). SEM is also a very flexible data analytic package in that it is possible to simultaneously estimate the pattern of relations that exist between continuous and non-continuous measures when considered within the same theoretical model. In view of the combination of an ordinal variable (seizure frequency) with a continuous variable (depression) in the present study, the pre-processing package PRELIS was used to generate a polyserial variance-covariance (correlation) matrix that took into account differences in the

measurement properties of each measure of seizure frequency and depression at each time point.

Cross-lagged and reciprocal models

Two sets of complimentary analyses were conducted. Firstly to assess the relationship between depression scores and seizure frequency across time, cross-lagged models were tested whereby depression scores and seizure frequency at Time 1 predicted each converse measure at Time 2, while controlling for the stability between depression scores and seizure frequency across time (see Figure 1, Page 74). Secondly to assess the relationship between seizure frequency and depression scores within time, a reciprocal effects model was tested whereby depression scores and seizure frequency rates simultaneously predicted levels of each variable at Time 2, again having controlled for the stability of depression scores and seizure frequency across time (see Figure 2, Page 74).

Assessment of model fit

The statistical adequacy of a theoretical model is determined by the relative 'fit' of that model to the underlying pattern of variances and covariance (correlations) observed in the original data. Assessment of fit is determined by the estimation of a number of goodness-of-fit criteria provided by the SEM programme LISREL. A good model would have a non significant chi-square (χ^2) value, a root mean square error of approximation (RMSEA) less than 0.05, a goodness of fit index(GFI) of $\geq$ 0.9 and an adjusted GFI of $\geq$ 0.9.

3.3 Results

Sample characteristics

1210 patients completed the initial questionnaire and 976 of these individuals (80.7%) completed the final questionnaire 1 year later. At the start of the study 11.6% of individuals had scores in the range suggestive of clinical depression and 50.7% of individuals had been seizure free over the previous year. At the end of the study 12.9% of individuals scored in the range suggestive of clinical depression and 55.2% of individuals had been seizure free in the previous year. The mean age of participants was 49.6 years and 21% of participants were over the age of 65 years. The sample characteristics are summarised in Table 1(Page 75).

Results from structural equation modelling

Figure 1(Page 74) shows the standardised path coefficients for cross-lagged tests of relations between seizure frequency and depressive symptom scores for the full sample. As expected, the stability coefficients between each measure over time were strong and significant (seizure frequency, $\beta = .87$, $p < .01$; depressive symptoms, $\beta = .71$, $p < .01$). Despite this high stability, in addition, significant paths between seizure frequency at Time 1 and depressive symptoms at Time 2 ($\beta = .07$, $p < .05$), and depressive symptoms at Time 1 and seizure frequency at Time 2 ($\beta = .03$, $p < .01$) were identified. Each measure at Time 1, therefore, significantly predicts a 'change' in the level of the other measure at Time 2, emphasising the mutual importance of these measures to each other across time. To test whether this same pattern of relations existed in the data within time, a reciprocal effects model was tested. Results presented in Figure 2 (Page 74) show that, once again, a significant reciprocal relationship exists between seizure frequency and depressive symptoms ($\beta = .09$, p

<.05) and depressive symptoms and seizure frequency (β = .07, p <.05) at Time 2, when variable levels were statistically controlled across time (seizure frequency, β = .86, p <.01; depressive symptoms, β = .70, p <.01). Because the cross-lagged model is a fully saturated model (i.e., all unknown parameters relative to degrees of freedom are estimated), this model art factually provides a perfect 'fit' to the data. The reciprocal effects model provides one degree of freedom, thereby permitting an assessment of model fit. According to statistical criteria, this model provides an excellent 'fit' to the data (χ^2_1 = 1.39, GFI = 1.0, AGFI = 0.99, RMSEA = 0.02).

It has been suggested that depression scores should be categorised into "not depressed", "doubtful depression" and "definite depression". This will result in an identical variable type (3-category variables) for both variables (depression and seizure frequency). The cross lagged and reciprocal models were re-run using categorised depression scores. The results were very similar and the same conclusions were reached i.e. seizure frequency and depressive symptoms reciprocally influence each other within and across time.

3.4 Discussion

The results of this study suggest that depressive symptom scores and seizure frequency mutually influence each other concurrently and across time, having controlled for initial symptom scores and seizure frequency in both sets of analyses. It is widely accepted that how many seizures an individual has will have psychological sequelae. The pattern of relations found in this study suggests that depression symptoms have equally important influences on future seizure frequency. There is limited research examining the relationship between depression and seizure

frequency. Most research has focused on examining the relationship of type of epilepsy to depression. Larger scale, community based research has been cross sectional and assumed a unidirectional relationship in which seizure frequency influences depression although cross-sectional designs do not allow for testing direction of influence (Jacoby et.al., 1996, Ridsdale et.al., 1996; O'Donaghue et.al., 1999). Other community-based studies of epilepsy have targeted seizure reduction as the key method for improving quality of life (Birbeck et.al., 2002). The findings of this study suggest that focusing on treating depression in people with epilepsy is as important.

To date, there has been virtually no research testing the extent to which depression affects seizures. There is limited evidence from small, uncontrolled studies, however, that antidepressant treatment of depression improves seizure control (Ojemann et.al., 1983). Existing longitudinal studies have focused on whether or not depression precedes the onset of epilepsy and found that depression may be a risk factor for epilepsy in adults (Forsgren & Nystrom, 1990; Hesdorffer et.al., 2000) and children (Hesdorffer et.al., 1998). Overall, these findings, taken together with the results from our own study highlight that it is not safe to assume that the association of epilepsy and depression arises from the unidirectional effects of seizures.

So what could account for our finding that depression scores predict seizure frequency? A neurochemical basis has been proposed based on empirical evidence (Kanner, 2003) but this is difficult to test. However psychosocial factors, such as self-efficacy and social support that are associated with chronic disease severity and depression (Amir et.al., 1999), also could be important mediating mechanisms. Other potential mediators include treatment compliance and other aspects of self-care that

are affected by depression and that may then impact on seizure control. Finally, the relationship between depression and epilepsy may be explained by a common set of aetiological factors.

The bi-directionality of the relationship between depression and other chronic illnesses has increasingly become an area of interest. For diabetes there is evidence that depressive symptoms are associated with glycaemic control (Mazze et.al., 1984), that depression precedes diabetes (Eaton et.al., 1996) and that the treatment of depression improves glycaemic control (Lustman et.al., 1998). Depressive symptoms have also been found to predict outcomes in asthma (Mancuso et.al., 2001) and heart disease (Penninx et.al., 2001). Thus, there is an increasing body of evidence implicating the importance of depression in predicting chronic disease outcomes. This has implications in terms of how chronic diseases are managed. Our results in a large sample of people with epilepsy when considered in the context of findings for other chronic diseases suggest that reducing levels of depressive symptoms may be an important component of clinical management in terms of seizure control. This now needs to be tested in a controlled intervention study. Furthermore, given that depression rates for people with epilepsy are higher than for the general population, it is important to examine whether antidepressants are under-prescribed. Antidepressant use in epilepsy may be affected by a perception amongst health professionals and patients that antidepressants worsen seizure control (although this was a risk with older antidepressants, newer antidepressants do not carry this risk).

The main strengths of this study are that a large number of representative adults with epilepsy in the community were assessed using well-validated and reliable measures and that a powerful analytic tool, structural equation modeling was used to test relationships.

There are also potential weaknesses of this study however. Firstly, not all individuals who commenced the study completed the study (19% of individuals who completed the first questionnaire did not complete the second questionnaire). Secondly, an ordinal measure of seizure frequency was used. However, polychoric correlation matrices were derived and these facilitate analysis of both continuous (depression scores) and non-continuous (seizure frequency) measures while adhering to the important assumption of multivariate normality. Thirdly, self-report measures had to be used and this could have influenced findings. However, using other informants in a large-scale community-based study was not feasible and at present little is known on the validity of information on seizure frequency and depression provided by other informants.

Two other factors which need to be taken into account are measurement time frames and the influence of seizure type. Depression and seizure frequency measures do not reflect information from exactly the same point in time (seizure frequency is measured over the past year and depression scores refer to the past week). However there is high stability of both seizure frequency and depression scores and moreover the overall effect is likely to underestimate cross-lagged and reciprocal path coefficients rather than overestimate them. Secondly, previous research has suggested that individuals with partial epilepsy are more likely to be depressed (but findings

have been mixed) (Indaco et.al., 1992). The sample size for individual seizure types was not large enough to run structural equation models for each seizure type but in a regression analysis, using seizure types as independent variables, only a history of tonic-clonic seizures significantly predicted depression scores. Moreover the closest association between seizure frequency and depression scores was found for individuals with tonic -clonic seizures (these results are available from the first author). This will be important to further investigate in future research.

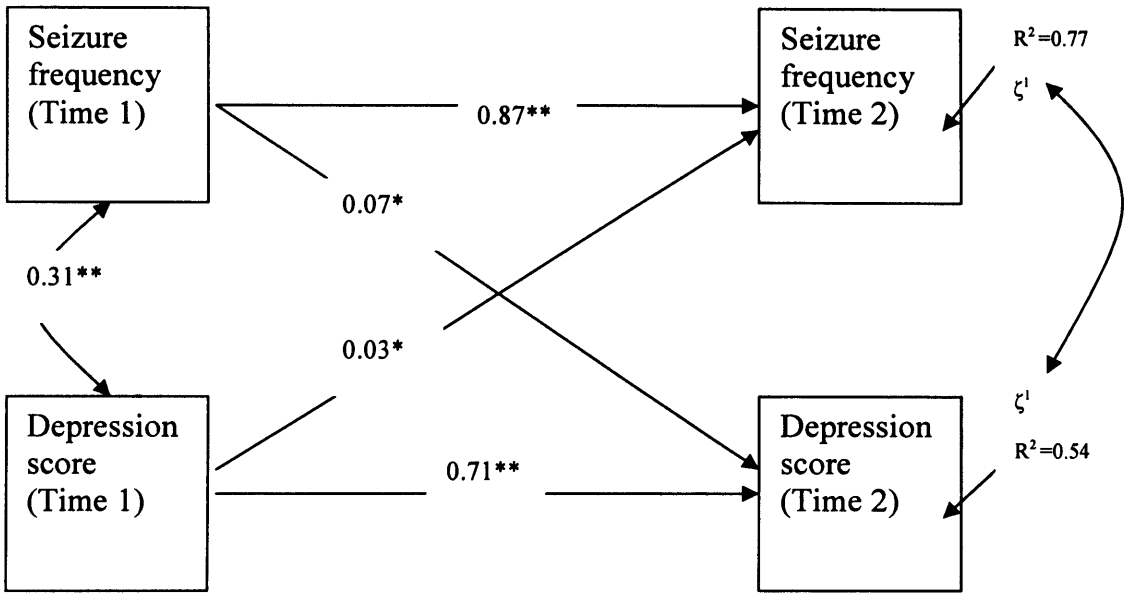
Finally, while the results in the present study suggest a statistically significant reciprocal relationship exists between seizure frequency and depressive symptoms, an important question is how clinically significant these findings are. Interpretation of the results needs some discussion of the methodology and further explanation of structural equation modeling. The results are from a study the main aim of which was to improve recording of clinical information. Depression scores and seizure frequency were not significantly altered during the course of the study. These findings are reflected in the high stability for depression scores and seizure frequency. This will result in low levels of unexplained variance in each respective dependent (endogenous) measure. Thus statistically significant cross-lagged paths will be difficult to detect, even with large sample sizes, given that relatively few individuals changed depression or seizure status spontaneously and these path coefficients will therefore necessarily be low. These path coefficients should not be equated with regression coefficients obtained by standard regression analysis. In structural equation modelling, all paths in a given model are estimated simultaneously and thus, given the stability of measures over time, there is little remaining unexplained variance and thus the magnitude of other standardised path coefficients will seem low to those more

familiar with regression coefficients. However, it is important to highlight that these pathways are accounting for a significant proportion of variance in each respective dependent (endogenous) variable over and above that accounted for the stability between measures.

Cross-lagged stability models allow examination of relations between constructs (in this paper, depression and seizure frequency) while controlling for their stability. Significant cross-lagged effects reflect the presence of a directional relationship between constructs. These cross-lagged effects are beyond that which can be accounted for by the stability of depression and seizure frequency across time and the magnitude of their association at Time 1. To examine possible bi-directional relationships between constructs within time, non-recursive or reciprocal effects models are used and are appropriate. For a bi-directional model to be identified (i.e., mathematically estimable), several conditions need to be met. The present model (see Figure 2) satisfies these conditions in that earlier measures of seizure frequency and depressive mood are predetermined variables and thereby uncorrelated with the error terms in both Time 2 equations, and both cross-lagged effects are constrained to zero. Analyzing correlational data using cross-lagged and reciprocal effects models, in the way that has been undertaken in this study, is an extremely important and robust method of investigating whether changes in one variable predict later changes in another variable and testing hypotheses representing different explanatory models of the relationships between variables. This is an essential first step prior to designing intervention studies (MRC, 2000) that can then be used to further address questions of cause and effect.

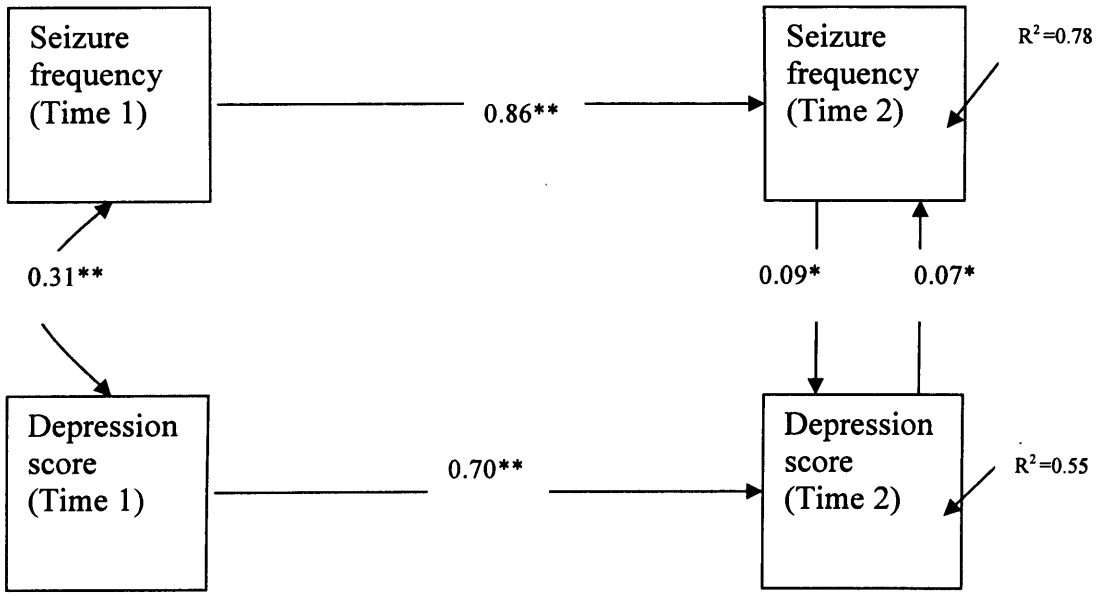
In summary, in a large, longitudinal community based study of people with epilepsy, depression symptoms were found to influence seizure frequency and vice versa, cross-sectionally and over the period of one year. This has important implications in terms of understanding the origins of the association between depression and seizure frequency and in how epilepsy is clinically managed. The results also add to the increasing literature on the important influence of depression on the onset and outcomes of chronic physical diseases.

Figure 1: Cross-lagged path model for seizure frequency and depressive symptoms



¹ ζ = error variance for this variable
* p<0.05
**p<0.01

Figure 2: Reciprocal path model for seizure frequency and depressive symptoms



* p<0.05 **p<0.01

χ^2_1=1.39, GFI= 1.11, AGFI=.99, RMSEA=0.02

Table 1 :Sample characteristics

Age (n=1210)	*Years (standard deviation)*	
Mean age	49.6 (17.3)	
Age groups (years)	*n (%)*	
20 or under	41 (3.4)	
21–30	164 (13.6)	
31–50	430 (35.5)	
51–65	321 (26.5)	
>65	254 (21.0)	
Sex (n=1209)	*n (%)*	
Male	580 (48.0)	
Female	629 (52.0)	
Seizure type (n=596)	*n (%.).May have more than one seizure type and so % will add up to more than 100%)*	
Generalized: tonic—clonic	332 (55.7)	
Partial: simple	28 (4.7)	
Partial: complex	182 (30.5)	
Others, including absence seizures	220 (36.9)	
Family history (n=955)	*n (%)*	
Yes	97 (10.2)	
No	858 (89.8)	
Seizure frequency	*Time 1 (n=1197), n (%)*	*Time 2 (n=954), n (%)*
No seizures in the last year	607 (50.7)	527 (55.2)
Less than 1 Seizure/month	261 (21.8)	194 (20.3)
One or more seizure per month	329 (27.5)	233 (24.4)
Depression scores	*Time 1 (n=1185),mean (S.D.)*	*Time 2 (n=959),mean (S.D.)*
Total score	5.34 (3.8)	5.37 (4.0)
Categorized depression scores	*Time 1, n (%)*	*Time 2, n (%)*
"No depression" (0 –7)	878 (74.1)	694 (72.4)
"Doubtful depression" (8 – 10)	170 (14.3)	141 (14.7)
"Definite depression" (11– 21)	137 (11.6)	124 (12.9)

Chapter 4

Stress, Anxiety, Depression and epilepsy: investigating the relationship between psychological factors and seizures

Citation

Thapar A, Kerr M, Harold G. Stress, anxiety, depression, and epilepsy: Investigating the relationship between psychological factors and seizures. *Epilepsy Behav* 2009;**14(1)**:134-40.

Abstract

Objective: The goal of the study described here was to examine the interrelationship between psychological factors (anxiety, stress, and depression) and seizures.

Methods: In this longitudinal cohort study, data on anxiety, depression, perceived stress, and seizure recency (time since last seizure) and frequency were collected at two time points using standard validated questionnaire measures. Empirically based models with psychological factors explaining change in (1) seizure recency and (2) seizure frequency scores across time were specified. We then tested how these psychological factors acted together in predicting seizure recency and frequency. The data were used to test whether these models were valid for the study population. Latent variable structural equation modeling was used for the analysis.

Results: Four hundred and thirty-three of the 564 individuals who initially consented to participate provided two waves of data for this analysis. Stress ($\beta = 0.25$, $p < 0.01$), anxiety ($\beta = 0.30$, $p < 0.01$), and depression ($\beta = 0.30$, $p < 0.01$) all predicted change in seizure recency. However, it was depression that mediated the relationship of both anxiety and stress with modelled change in seizure recency ($\beta = 0.19$, $p < 0.01$) and seizure frequency ($\beta = 0.30$, $p < 0.01$) over time.

Conclusion: Depression mediates the relationship between stress and anxiety and change in seizure recency and seizure frequency. These findings highlight the importance of depression management in addition to seizure management in the assessment and treatment of epilepsy in an adult population.

4.1 Introduction

Depression and epilepsy appear to be closely associated (Kanner et.al., 2005). Depression is considerably more prevalent amongst people with epilepsy as compared to the general population (Strine et.al., 2005) with people with poorly controlled epilepsy especially reporting higher rates of depression (Jacoby et.al., 1996). The nature of the association is however complex. There is some evidence that the relationship between seizure onset and depression onset is bidirectional (Kanner, 2005) with diagnosis of epilepsy acting as a risk factor for the onset of depression and depression acting as a risk factor for the onset of epilepsy (Hesdorffer et.al., 2000). There is emerging evidence that this bidirectional relationship between depression and seizures is also evident for those with current epilepsy (Thapar et.al, 2005). However other psychological problems such as anxiety (Beyenburg et.al., 2005; Mensah et.al, 2007) and stress (Frucht et.al., 2000) are also reported to be more prevalent amongst people with epilepsy but have been less studied (Beyenburg et.al, 2005). How these psychological factors act together to influence seizures is not clear.

In the general population it is well established that stress, anxiety and depression are closely linked (Hettema et.al., 2006) although for complex disorders inter-relationships are likely to be complex (Kraemer et.al., 2001). Anxiety and stress appear to precede depression (Kendler et.al, 2002; Kendler et.al, 2006). The strong links between anxiety, stress and depression are also supported by neurobiological research (De Kloet et.al, 2005; Nemeroff & Vale, 2005; Heilig, 2004) and neuro-imaging studies (Liotti et.al, 2000; Sapolsky, 2000, Shah et.al, 2002; Kalisch et.al, 2006).

Thus for people with epilepsy, anxiety and stress may also contribute to the previously observed links between depression and seizures. People with epilepsy perceive that stress is the most common precipitant for seizures (Frucht et.al., 2000) and in community studies, anxiety is the most common psychological problem amongst people with epilepsy (Beyenburg et.al., 2005). Anxiety may also be linked to poor seizure control and more recent seizures (Mensah et.al, 2007). However, although associations between these individual factors have been observed, the nature of the overall relationship between depression, stress and anxiety with seizures remains poorly understood (Haut et.al, 2007) and previous studies have been cross sectional. Longitudinal studies are important in establishing the directions of influence between different factors (Rutter, 2008).

The aims of this analysis were to test how psychological factors (depression, anxiety and stress) predict variation in 1) seizure recency and 2) seizure frequency over time.

4.2 Methodology

Sample

A cohort of adults with active epilepsy was recruited to participate in a longitudinal observational study of the physical, social and psychological health of people with epilepsy. Individuals identified through general practices who had taken part in previous studies in Cardiff (Mensah et.al, 2006) and Manchester (Thapar et.al., 2002) were contacted and invited to participate in the present study. Ethical approval was obtained from the relevant local Research Ethics Committees (BroTaf and Salford & Trafford). A volunteer sample of people with epilepsy was also recruited through

Epilepsy Action. Participants were sent questionnaires by post for self-completion and information was collected at two time points 5 months apart.

Measures

Participants completed a comprehensive package of well-known and validated measures of physical, social and psychological health.

The following subset of measures was employed in the present study:

1. *Anxiety* and *Depression.* The Hospital Anxiety and Depression (HAD) scale was used (Zigmond & Snaith, 1983). This is a widely used measure with good psychometric properties which has been successfully used to measure caseness for depression and anxiety in previous community based studies examining the quality of life of people with epilepsy (Jacoby et.al., 1996). It refers to how the respondent has been feeling in the past week.

2. *Perceived stress.* The 4 item perceived stress scale PSS (Cohen et.al., 1983) was used as a measure of stress. It refers to perceived stress levels in the past month i.e. is a measure of stress appraisal. The 4 item scale was used to minimise respondent burden. It has been found to have acceptable psychometric properties (Cohen et.al., 1983) and has been used in previous outpatient and community studies (Farabaugh et.al., 2004).

3. S*eizure recency.* (Wagner et.al., 1995; Cramer et.al, 2004). Participants were asked how long it had been since they had their last seizure. This measure has been used in previous studies (Cramer et.al, 2004). The responses were converted to days since last seizure and categorised. A 12 category variable was created with scores ranging from 12 (seizure in the last 24 hours) to 1 (last seizure was more than 15 years

ago) with a midpoint score of 6 (last seizure was between 6 and 12 months ago) i.e. with the most recent seizures having the highest scores. Categorization was used for conceptual and clinical reasons as well as to overcome problems with model convergence.

4. *Seizure frequency.* Individuals were also asked about the number of seizures they had experienced over the previous year with scores ranging from 0 (if the individual had had no seizures) to 10 (if the individual had 10 or more seizures) in the previous year.

5. *Medication compliance.* Individuals were also asked to rate how often they missed any medication for their epilepsy at the end of the study. Responses were on a 4 point Likert Scale – ranged from 1= "never" to 4= "missed doses more than once a week".

Statistical analysis

Random effects latent variable modelling (Berrington et.al., 2006), using a structural equation modelling approach with LISREL 8.50 (Joreskog & Sorbom, 2001) was used for this analysis. Structural equation modelling (SEM) was used for the analysis as it allows complete and simultaneous tests of all postulated relationships and is widely accepted as being an especially suitable analytic method for longitudinal data when the phenomena of interest are complex and multifaceted (Tabachnick & Fidell, 2001). SEM is a family of statistical techniques that enable the specified relationships between variables to be tested against the observed pattern of correlations and covariances between variables. This allows an assessment of whether or not the hypothesized relationships are valid for the study population. This approach has considerable advantages over simple regression based analysis when longitudinal data are available as it is possible to specify a latent variable model such that 'change' in

the criterion variable can be modelled as a result of one or more theoretically relevant predictors (Berrington et.al., 2006).

In this context the mean and variance of the latent variable represents the mean change over time of the group as a function of any given set of independent predictors (Berrington et.al., 2006; Ramos et.al, 2005), as compared to variation around the mean (as is the case in more conventional simple regression based approaches to data analysis) of a single indicator or measure of a dependent variable of interest. We then tested predictors firstly for modelled change in seizure recency (see Figure 1, Page 94) then for modelled change in depression scores over time.

Analyses were carried out as follows. Models were specified for 1) Depression, anxiety and stress predicting change in seizure recency 2) Depression, anxiety and stress predicting change in seizure frequency 3) Other analyses (included tests for moderation and a model predicting change in depression scores).

4.3 Results

564 individuals initially consented to participate. Of these individuals 341 were recruited from Cardiff, 108 from Manchester and 115 via Epilepsy Action. 468 individuals responded to first wave questionnaires and 443 individuals responded to second wave questionnaires.

Some individuals missed items on particular scales. A two-step approach was used to deal with missing values. First, for partially completed scales, regression-based imputation methods for missing data were used (standard missing values procedure in

STATA Version 8). Means (SD) of all variables used in this analysis for both non-imputed and imputed untransformed scores are listed in Table 1 (Page 96). Second, list wise deletion of data was undertaken prior to the structural equation modeling analyses such that only individuals with complete information for all variables were included in all subsequent analysis.

We examined whether our sample was representative in terms of epilepsy severity and socio-demographic characteristics. Our findings were comparable to findings from a large community based study of adults with epilepsy (Jacoby et. al., 1996). We also examined seizure types and anti-convulsant medication use and the effects of these parameters on depression scores. The main comparisons are listed in Table 2 (page 96). Significantly higher depression scores were reported by individuals who reported they had suffered from complex partial seizures ($F=12.78$, $p<0.01$) and myoclonic seizures ($F=6.28$, $p=0.013$) than those who reported not having these seizure types. For other seizure types there were no significant differences between those who had had and those who had not had that particular seizure type. There were no significant differences in depression scores associated with anti-convulsant medication.

One quarter of our sample suffered from seizures at least once a month. These individuals were more likely 1) to suffer from complex partial seizures; 43.6% (versus 6.5% of those who were seizure free) reported complex partial seizures were their main type of seizure (this difference was significant) and 2) to be scoring as clinically depressed (10.9% versus 4.4% of those who were seizure free).

The data were also transformed; anxiety and depression scores were negatively skewed so were transformed using a square root (raw score+1) transformation. Analyses were carried out on transformed data.

The rounded mean score for seizure recency for all three waves was 6 (6.18, 5.84, 5.96, 6= "last seizure between 6 and 12 months ago"), the modal score was 3 for all three waves ("last seizure between 5 and 10 years ago") and the median score was 6 for the first wave and 5 ("last seizure between 1 and 2 years ago") for the second wave.

There was a significant difference in terms of seizure recency between groups of individuals recruited from Cardiff, Manchester and from Epilepsy Action (Pearson χ^2 (4) = 29.95, p = <0.01). Individuals recruited from Manchester and Cardiff had a similar seizure recency (Pearson $\chi^2(2) = 1.24$, p=0.54) and these groups were combined for subsequent analyses. Individuals recruited via the British Epilepsy Association (Epilepsy Action) had significantly more severe epilepsy (i.e. a higher proportion of recent seizures) than the combined Cardiff/Manchester subgroup. To accommodate this initial heterogeneity in the sample the main analysis was performed separately for each of these two subgroups.

Generally high stability values were noted (figures in brackets represent correlation coefficients) for seizure recency (0.81), anxiety (0.81), depression (0.78), and perceived stress (0.59) between the two time points. Acceptable reliability values for all scales used in the analyses were obtained (figures in brackets represent Cronbach's

alpha values) for PSS (Time 1= 0.76 Time 2 = 0.70), depression score (Time 1 = 0.77, Time 2 = 0.81), anxiety score: (Time 1= 0.88, Time 2 = 0.87).

Depression, anxiety and stress predicting change in seizure recency

Structural equation modelling was used to test models with each of the individual psychological variables (stress, anxiety and depression) and modelled change in seizure recency score over time. All three models showed a good fit and all three psychological variables (anxiety scores (β=0.30, $p<0.01$), stress (β=0.25, $p<0.01$). and depression scores (β = 0.30, $p<0.01$)), were individually significant predictors of the latent change in seizure recency score over time.

A full model was then specified in which *stress, anxiety* and *depression* were simultaneously specified as predictors for the modelled change in seizure recency score over time (Figure 2, Page 95). When the psychological variables were analysed simultaneously, depression was the only significant predictor for modelled change in seizure recency over time. All the model fit indices indicated a good fit of the data to the model (N= 395 χ^2= 0.16; DF=2 p=0.92; RMSEA = 0.0 AGFI= 1.00; CFI =1.00 SRMR=0.0015). There was an increase in the R^2 (that is explained variance) of the modelled change in seizure recency with additional predictors. If there was only one predictor the R^2 value ranged from 0.06 (stress) to 0.09 (depression, anxiety). If stress and anxiety were predictors then the R^2 value was 0.10. With all three predictors the R^2 value was 0.12.

This model was also run for each of the two sub-groups identified earlier (as initial sample heterogeneity had been noted). Identical conclusions were reached with

similar results (i.e. only depression was a significant predictor of modelled change in seizure recency over time ($p < 0.05$ for both groups) and neither anxiety nor stress were significant predictors.

Depression, anxiety and stress predicting change in seizure frequency

The analysis was also run for the full model in which *stress, anxiety* and *depression* were specified as predictors for modelled change in seizure frequency score over time. The results confirmed the findings for recency, that is, depression mediated the relationship between anxiety and stress with change in seizure frequency over time ($t=4.65$, $p<0.01$). The model fit indices generally indicated an acceptable fit of the data to the model ($N= 386$ $\chi^2= 7.62$; $DF=2$ $p=0.02$; RMSEA = 0.085 AGFI= 0.94, CFI =1.00, SRMR=0.0072).

Other analyses

Testing for interaction effects between psychological factors

Having tested for additive effect of the psychological factors on seizure recency, we next tested for interaction effects between psychological factors. A model was specified in which *depression, stress* and *the interaction term between depression and stress* were predictors for modelled change in seizure recency over time. There was no significant effect of the interaction term on modelled change in seizure recency ($t= -1.07$, $\beta =-0.05$, p = NS). Similar results were obtained for the interaction term between anxiety and depression and for the interaction term between anxiety and stress.

Testing for the relationship between anxiety, stress and seizures

When *anxiety* and *stress* were specified as predictors for modelled change in seizure recency, only anxiety (β= 0.24, $p < 0.01$) was a significant predictor (stress $\beta = 0.10$, p= NS). The fit statistics across all models tested suggested that each model provided a good fit to the data. χ^2 ranged from 0.02- 2.3 (degrees of freedom ranged from 1 to 2).

Non-adherence with medication

We also examined non-adherence rates and tested if self –reported non-adherence was linked to seizure recency, depression, anxiety or stress. 69.7% (363) of our sample who returned questionnaires at the end of the study reported that they did not miss any medication doses. Increased perceived stress was the only factor significantly associated with higher frequency of non adherence (n=363, r=-0.108, p=0.04).

Predictors of modelled change in depression scores

Finally, given previous research suggesting the bidirectional relationship between depression and seizures, we also specified a model in which seizure recency, anxiety and stress were predictors for modelled change in depression scores over time and we found that all three variable were significant predictors of change in depression scores (anxiety scores (β=0.47, $p < 0.01$), stress (β=0.21, $p < 0.01$). and seizure recency (β = 0.12, $p < 0.01$)). There was no evidence of mediation or moderation. Fit statistics suggest that the model provided an adequate fit to the data (χ^2 (2) = 11.24, p=0.004 RMSEA = 0.11 AGFI= 0.92, CFI =0.99, SRMR=0.018).

4.4 Discussion

The aim of this paper was to gain additional insights into the mechanisms underlying the relationship between anxiety, stress and depression with seizures using the results from a longitudinal community based observational study of people with epilepsy.

Findings suggest that depression, anxiety and stress when analysed separately, predicted variation in seizure recency over time. However, depression mediated the relationship between anxiety and perceived stress with variation in seizure recency over time. Further analysis confirmed the same pattern of results for variation in seizure frequency over time. There was no evidence for any moderated relationships. Thus, depression appears to be the important pathway in linking the psychological variables we assessed to change in seizure activity.

People with epilepsy perceive stress as being the most likely trigger for a seizure (Frucht et.al., 2000). Certainly stress is implicated in increased activity in neural circuits which affect a wide range of brain regions, in regulation of neurotransmitter pathways implicated in epilepsy as well as neuroendocrine changes (Nemeroff & Vale, 2005), gene expression and structural and functional brain changes (Geuze et.al, 2005). We used a measure of stress appraisal (the 4 item perceived stress scale- PSS) for our analysis as the closest psychometrically tested variable that approximated in meaning to "stress" that had been used in other studies which had reported on the perceptions of individuals as to the trigger for their seizures. The implications of stress appraisal (using the 10 item version of the same scale) on common diseases have recently been highlighted (Cohen et.al., 2007). Our results suggested that whilst stress appraisal did seem to predict the variation in seizure recency over time, this

relationship was mediated by depression. This is in line with a classic research study in a general population sample that found negative affectivity affects the relationship between stress and health (Watson & Pennebaker, 1989) and highlights the importance of screening for depression if an individual with epilepsy reports high levels of stress. There was no evidence for stress appraisal playing a moderator role in the relationship between depression scores and variation in seizure recency over time.

The relationship between anxiety and seizures is relatively under-researched (Beyenburg et.al., 2005). There is some evidence from the general psychiatric literature that anxiety symptoms are a precursor for depression (Hettema et.al, 2006; Merikangas et.al., 2003) and share the same genetic liability (Rice et.al, 2004). In our study we found that anxiety predicted variation in seizure recency but that this relationship was mediated via depression, that is that anxiety appeared to exert risk effects through depression. The distinction between anxiety and depression is also important in terms of clinical management guidance suggesting first line psychological intervention for individuals with clinical anxiety (NICE CG22, 2004) and pharmacological (anti-depressant medication) interventions for those with clinical depression, apart from those with mild depression (NICE CG23, 2004). Our analysis also provided some evidence that anxiety partially mediates the relationship between stress and depression. The importance of identifying the exact pattern of psychopathology has been highlighted (Kraemer et.al, 2001, Kraemer et.al., 2002; Mayberg, 2007). Our findings are in line with the scientific literature on the links between stress and depression (De Kloet et.al, 2005, McEwen, 2003) which have highlighted the progressive and more severe nature of neurobiological impairment in

depression (than in stress) and the neurobiological dysfunction in epilepsy. However caution is needed with any observational study on direction of association.

Our study highlighted the importance of depression in variation in seizure recency over time but also confirmed that seizure recency can predict variation in depression scores over time. A study using a different dataset has confirmed this bi-directional relationship between depression scores and seizure frequency in those with current epilepsy (Thapar et.al, 2005). The mechanism for the effect of recent seizures on long term depression scores could either be through a direct neurobiological change (Kanner, 2005) and this would be supported by findings that depression is a risk factor for the onset of epilepsy (Hesdorffer et.al, 2000, Hesdorffer et.al., 2006). However the links between seizures and depression could also arise through other mechanisms such as life disruption or negative emotions which could manifest itself on behaviour changes such as changes in compliance with medication or by engaging in other risky behaviours such as increasing alcohol intake. Non-compliance with medication has been linked to poor seizure control (Cramer et.al, 2002) and this link may be explained by high anxiety levels (Jones et.al., 2006). The exact mechanisms underlying this relationship are unclear. Links between depression and non-compliance for other conditions such as coronary heart disease (Gehi et.al, 2005) and diabetes (Lin et.al, 2004) have been found. In our sample however there was no evidence of association of depression or anxiety scores and severity of non-compliance but individuals with higher perceived stress scores reported a higher frequency of non-compliance.

In our study the same pattern was found for modelled change in seizure recency as for modelled change in seizure frequency, i.e. depression mediated the relationship between anxiety and stress and seizure activity. In the epilepsy literature the choice of outcome variables for seizure activity has been highlighted (Baker et.al., 1998). Both seizure frequency and seizure recency have been used, generally in the context of predicting quality of life (QOL). The findings have been mixed with one study reporting that seizure frequency but not seizure recency significantly predicts QOL (Leidy et.al, 1999) but another study finding that both seizure frequency and seizure recency are significant predictors of QOL (Mrabet et.al, 2004). The results of the National General Practice Study of Epilepsy found that psychosocial effects was highly significantly associated with seizure recency and total number of seizures experienced (Chaplin et.al., 2002)

Our sample was similar to that from other community based studies in terms of seizure frequency, mean age, gender and predominant seizure type (Jacoby et.al, 1996; Ettingeret.al., 2004) as well as for medication use (Goodwin et. al, 2002). In accordance with the findings of other studies higher depression scores were found amongst individuals who suffered from complex partial seizures and more frequent seizures (Jacoby et.al., 1996).

The method used for the principal statistical analysis has a strong theoretical underpinning (Berrington et.al., 2006) although it has not been as widely used as cross lagged panel models in SEM or latent growth curve analysis.

We used a variety of recruitment methods for our study. Our sample however was representative in terms of overall disease severity and socio-demographic characteristics when compared to another large community based study of adults with epilepsy (see Table 1, Page 96).

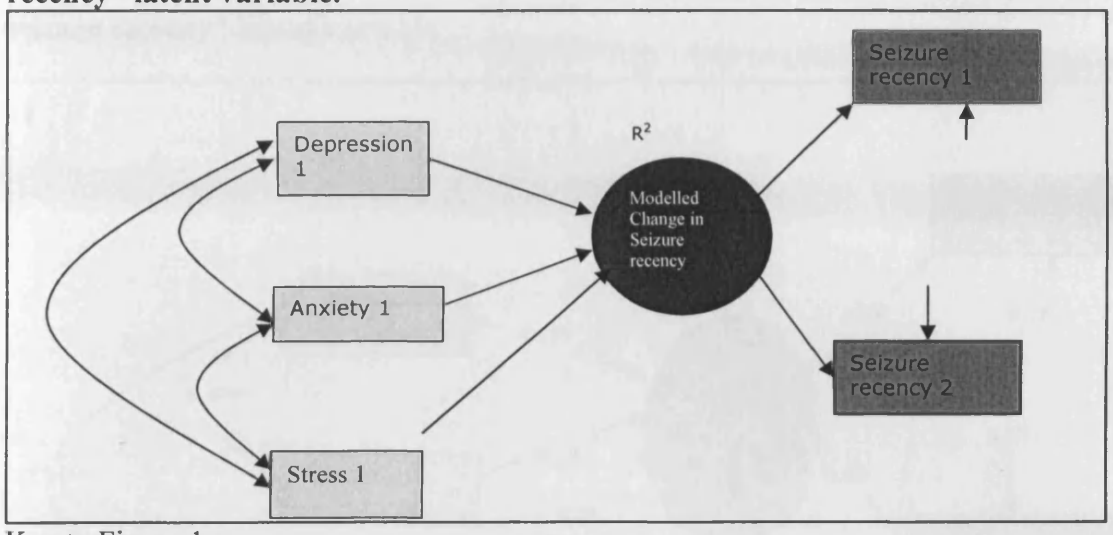
Limitations

Not all individuals completed all two waves of questionnaires and not all individuals who completed questionnaires completed all the different sections. However, more than 80% of individuals who had consented to participate and who had not died or withdrawn at the first questionnaire stage completed the second questionnaire. A further limitation is that the measures refer to different periods (PSS "past 1 month," depression "over the last week"). High stability values for the variables were noted (Table 1, Page 96), which would suggest that these results could reasonably be extrapolated outside these periods. Some individuals have infrequent seizures and many had not had a seizure over the study period. We would, however, expect this to lead to an underestimate of the effect of seizures. This study was designed to examine relatively long-term (5 months) prediction of variation in seizure recency. We are not able to extrapolate our findings to whether there are short-term effects of these variables (e.g., effects of a single episode of stress on triggering a seizure). To examine these effects, a different study design such as a daily seizure diary method would have to be employed. A further potential limitation was introduced by the fact that seizure variables are complex and heterogeneous. There are a variety of ways to capture seizure activity and impact, such as seizure frequency, seizure recency, and seizure severity, and moreover, variation is introduced by different types of seizures. We have reported results for both seizure frequency and seizure recency as outcome

variables, and the results were unchanged. There were not enough individuals for the analysis to be carried out for different seizure types.

In conclusion, although perceived stress and anxiety symptoms predict variation in seizure recency over time, this relationship is mediated by depression symptoms. It is important for health professionals to be aware of these findings and ensure that priority is given to both seizure management and depression management in the treatment of individuals with epilepsy.

Figure 1: General form of the structural equation model with "change in seizure recency" latent variable.



Key to Figure 1

Independent/Predictor /exogenous manifest (i.e. measured)variables

Dependent/Endogenous latent (i.e. unmeasured) variable

Dependent/ Endogenous manifest (i.e. measured) variables- same variables at 2 time points

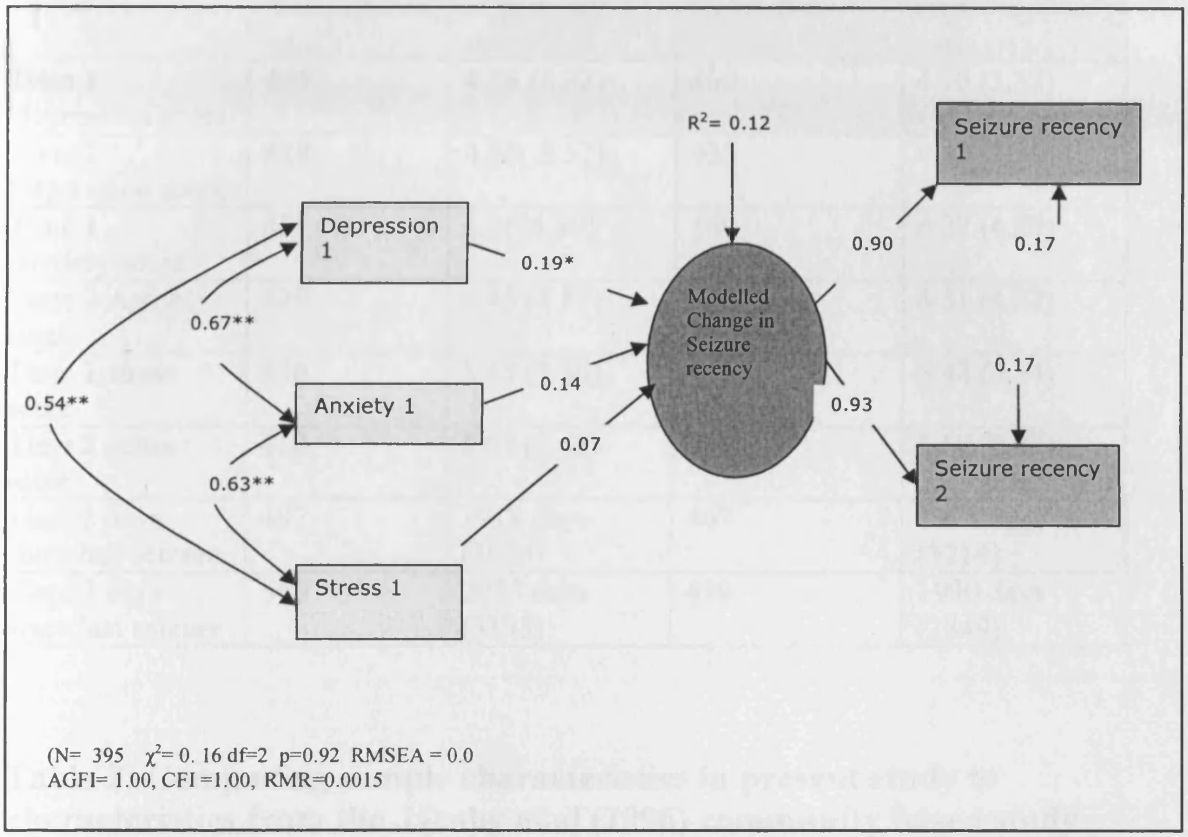
Significance of Arrows

From independent →dependent = path coefficients (=partial regression coefficients)

From dependent latent → dependent manifest = pattern coefficients (=factor loadings)

Correlation coefficients

Figure 2: Examining the effect of anxiety, stress and depression on "Change in seizure recency" latent variable



See Figure 1 and legend for Figure 1 for explanation of significance of shapes and lines.

Table 1: A comparison of the mean and standard deviation for non-imputed and imputed scores for depression, anxiety, stress & seizure recency.

Variable	*Non imputed no.*	*Non imputed mean (sd)*	*Imputed no.*	*Imputed mean (sd)*
Time 1 Depression score	445	4.09 (3.32)	460	4.10 (3.33)
Time 2 Depression score	418	4.38(3.57)	435	4.42 (3.59)
Time 1 Anxiety score	451	6.26(4.89)	460	6.27 (4.89)
Time 2 Anxiety score	429	6.45 (4.81)	435	6.51 (4.82)
Time 1 stress score	436	5.43 (3.56)	456	5.48 (3.54)
Time 2 stress score	418	5.67 (3.43)	438	5.67 (3.43)
Time 1 days since last seizure	402	1918 days (3034)	467	1971 days (3214)
Time 2 days since last seizure	340	2025 days (3133)	439	1990 days (2849)

Table 2: Comparing sample characteristics in present study to characteristics from the Jacoby et.al (1996) community based study

Sample characteristic	**Present study (n=452)**	**Jacoby et al, 1996 (n=696)**
Seizure status last year (n=452)		
Seizure free last one year	49.6%	53%
At least one seizure per year but less than one seizure per month	25%	27%
One or more seizure per month	25.4 %	20%
Seizure type (not exclusive unless specified)		
Tonic clonic seizures	50.7%	52%
Complex partial seizures	25.9%	
Only tonic-clonic seizures	30.3%	34%
Demographic characteristics		
Employed	41.3%	44.8%
Male	47%	49%
Mean age	51years	46 years
Most commonly prescribed medication(n=444)		
Sodium Valproate	29.7%	N/A
Phenytoin	29.3%	N/A
Carbamazepine	28.8%	N/A

Chapter 5

Investigating Individual Differences in Depression Scores Amongst People With Epilepsy: A Latent Growth Curve Analysis.

Submitted Paper:

Thapar A, Kerr M, Harold G. Investigating Individual Differences in Depression Scores Amongst People With Epilepsy: A Latent Growth Curve Analysis

Abstract

Background: Depression is common amongst people with epilepsy and is an important determinant of quality of life. Depression scores are associated with seizure recency for people with epilepsy when they are examined as a group. However depression scores for individuals fluctuate over time and this has not been studied for people with epilepsy. The aims of this study were to examine the pattern and extent of individual differences in depression scores both at baseline and over time and examine the role that seizure recency plays in accounting for any such observed pattern of variation.

Methods: Questionnaire data on depression symptom scores (using the Hospital Anxiety & Depression (HAD) scale) and seizure recency from a three wave prospective, longitudinal study of adults with active epilepsy were obtained. Latent growth curve analysis (LGCA) was used for the analysis.

Results: Information was available from 325 individuals who completed all three waves of the study. Significant variation in baseline depression scores and changes in individuals' depression scores over time were noted. Seizure recency significantly predicted individual heterogeneity in baseline depression scores (β=0.247, $p < 0.05$) as well as for changes in depression scores over time (β =0.037, $p<0.05$) controlling for age across all analyses.

Conclusions: For people with epilepsy, seizure recency predicts differences in depression scores between individuals as well as changes in depression scores within individuals over time. Thus seizure management is important as it influences individual trajectories of depressive symptoms amongst adults with epilepsy.

5.1 Background

Depression is an important problem for the general population (Kessler et.al., 2003). However for those individuals with chronic diseases depression has a particularly high impact (Stein et.al., 2006, Moussavi et.al., 2007). For the general population many different social, physical and psychological factors are known to affect depression (Kendler et.al., 2006) and considerable variation in depressive symptoms between individuals (inter-individual differences) has been reported (Judd et.al., 1998). However there has been much less research on differences in how depression symptoms for individuals change over time (intra-individual variation) and on how physical illness affects this variation.

People with epilepsy experience a high level of depressive symptoms (Strine et.al, 2005, Ettinger et. al., 2004, Kanner, 2003) and considerable variation in depressive symptoms between individuals has also been noted (Kanner, 2003). What is not clear is how depressive symptoms for individuals with epilepsy change over time and how this varies for different individuals (intra-individual variation). Those with more recent or more frequent seizures have been found to have higher levels of depression scores (Jacoby et.al., 1996, Cramer et.al, 2003, Thapar et.al, 2005). However there has been little research on how seizures affect intra-individual change in depressive symptoms.

Latent growth curve analysis has started to be used to study individual change in psychiatric disorders (Hertzog & Nesselroade, 2003, Lenzenweger et.al., 2004). This approach is particularly useful in the situation where longitudinal studies show there is considerable stability in symptom scores over time, but that within this overall group

stability there is considerable individual variation in symptom scores (Lenzenweger et.al., 2004). This approach has however not yet been used to study variations in psychiatric disorder amongst people with epilepsy.

The aim of this paper is to examine, for adults with epilepsy, whether significant individual differences in depression scores and the individual trajectories that these scores follow are present, and if so, to test whether seizure recency is a significant predictor of this variation.

5.2 Method

Sample

A cohort of 564 adults with active epilepsy was recruited to participate in a longitudinal three-wave observational study. Individuals identified through general practices who had taken part in previous studies in Cardiff (Mensah at.al, 2006) and Manchester (Thapar et.al., 2002) were contacted and invited to participate in the present study. Ethical approval was obtained from the relevant local Research Ethics Committees (BroTaf and Salford & Trafford). A volunteer sample of people with epilepsy was also recruited through Epilepsy Action. Information was collected at three time points 5 months apart. A description of sample characteristics is provided in Table 1 (Page 109).

Measures

Participants completed a comprehensive package of well-known and validated measures of physical, social and psychological health (Thapar et.al, 2009) with the aim of collecting information which had been identified by the scientific literature as being associated with the severity and control of seizures for people with epilepsy.

The following subsets of measures relevant to the present analysis were employed in the present study:

1. *Anxiety* and *Depression.* The Hospital Anxiety and Depression scale was used (Snaith & Zigmond, 1986). This is a widely used measure with good psychometric properties which has been successfully used in previous community based studies examining the quality of life of people with epilepsy (Jacoby et.al., 1996).

2. *Seizure recency* (Wagner et.al., 1995). Participants were asked how long it had been since they had their last seizure. This measure has been used in previous studies (Wagner et.al., 1995, Cramer et.al, 2004). The responses were converted to days since the last seizure and categorised. A 12 category variable was created with scores ranging from 12 (seizure in the last 24 hours) to 1 (last seizure was more than 15 years ago) with a midpoint score of 6 (last seizure was between 6 and 12 months ago) i.e. with the most recent seizures having the highest scores. Categorization was used for conceptual and clinical reasons as well as to overcome problems with model convergence.

Missing data

If there was partial non-completion of the item on seizure recency we used regression based imputation methods for seizure recency (Allison, 2001) using other information on seizure activity (using the missing data procedure in STATA). For depression scores if there was only one missing item, mean value imputation was used otherwise the response was coded as missing. A comparison of imputed and raw scores showed these were comparable (Thapar et.al., 2009).

Statistical analysis

In our study we used latent variable growth curve analysis (LGCA) which was based on covariance structure analysis (Willett & Sayer, 1994) utilising the software package LISREL 8.5(Joreskog & Sorbom, 2001). When three or more waves of longitudinal data are available for analysis, latent growth curve (LGC) modelling is a more powerful technique for investigating relationships within data than simple regression (Lenzenweger et.al., 2004). LGC modelling allows the investigator to not only derive an estimate of differences in depression scores between individuals (inter-individual differences), but also differences in how depression scores for individuals change over time (intra-individual variation). The principal advantage of a growth model is that information about mean change is incorporated into the modelling process, thus allowing for the inclusion of an estimate of the trajectory of intra-individual growth. This can then be used to examine the pattern of individual variation in depression scores over time (see Figure 1, Page 109 and Figure 2, Page 110) and the role of seizure recency and other theoretical predictors (e.g. age) in accounting for this pattern of variation (see Figure 3, Page 111). Further advantages of latent growth curve analysis have been summarised (Duncan & Duncan, 2004). The method adopted for this analysis was to initially specify a theoretical model (as described in Willett and Sayer, 1994) to examine the extent and pattern of baseline inter-individual differences ("intercept") and intra-individual variation ("slope") in depression scores amongst adults with epilepsy. The model was then tested using the depression scores from the three time points ("unconditional model") to examine whether there were significant inter-individual differences and intra-individual variation in depression scores and to assess how well the observed data fitted the model (using goodness of fit indices generated by the software). We then tested

whether seizure recency and age were significant predictors of this pattern of individual variation in depression scores (a "conditional" model).

5.3 Results

564 individuals initially consented to participate. Of these individuals 341 were recruited from Cardiff, 108 from Manchester and 115 via Epilepsy Action. 468 individuals responded to first wave questionnaires and 443 individuals responded to second wave questionnaires and 403 individuals responded to third wave questionnaires. The characteristics of the sample have been more completely described in a previous paper (Thapar et.al, 2009). Information from 325 individuals was available (depression score at all three time points and information on both predictors at Time 1).

On inspection of the data, considerable inter-individual differences and intra-individual variation in depression scores were apparent. To illustrate this the depression scores for the first 254 individuals are plotted at the three time points (Figure 1, Page 109). As can be seen, considerable individual differences in the pattern and extent of variation of depression scores both across and over time exist.

Unconditional mode (examining the extent and pattern of variation in depression scores)

This is illustrated in Figure 2 (Page 110). The results indicated significant individual differences in baseline depression scores (termed "intercept": mean depression score 4.19, variance 12.79; t-score 27.7, $p < 0.01$) as well as individual differences in slope trajectories of depression scores over time (slope" mean change 0.16. variance 1.01, t score 2.36, $p<0.05$). There was good fit for the linear slope model (Root Main Square

Residual (RMSEA) 0.009 (values less than 0.05 indicate a good fit), full information ML χ^2 =3.11, p=0.375 (non-significant value indicates a "good" model as this indicates that the observed data (underlying variance-covariance matrix) does not significantly differ from that expected by the proposed theoretical model).

Conditional model (examining seizure recency and age as predictors of variation in depression score)

The results are presented in Figure 3 (Page 111). Seizure recency significantly predicted both the individual variation in baseline depression scores (intercept β= 0.247, $p<0.05$) as well as individual trajectories of depression scores over time (slope β= 0.037,$p<0.05$). These scores are path coefficients and can interpreted as similar to standardised partial regression coefficients. Age did not show any significant effect on either slope or intercept.

These results indicate that seizure recency is a significant predictor of not only of depression scores over time (intercept) but of individual differences in the trajectories of these scores (slope) over time. That is, where individuals vary in the trajectory of their individual depression scores over time, they vary as a result of activity in seizure recency assessed at an earlier point in time.

5.4 Discussion

These results indicate that for adults with epilepsy followed up over a 10 month period there is significant variation between individuals in baseline depression scores as well as the individual trajectories that these scores follow over time. Seizure recency was a significant predictor of both the variation in inter-individual baseline depression scores and the intra-individual changes in depression scores over time. For this analysis we used depression scores rather than diagnoses of clinical depression. This is because there is considerable evidence that depression should be viewed as a continuum for research purposes (Judd et.al, 1998, Kessler et.al., 1997).

In this study we found that there is significant inter-individual variation in baseline depressive symptoms amongst people with epilepsy. This finding is broadly in line with the wide spectrum of depressive scores reported in other studies (Jacoby et.al, 1996), and would be compatible with indirect evidence from the epilepsy literature which suggests that whilst there is an increased prevalence of depressive illness amongst people with epilepsy (Jacoby et.al., 1996) some individuals with well controlled epilepsy have similar levels of depression to the general population (Jacoby, 1992). Indeed in our study, variation in depression scores is greater than that reported in the general population. For example, normative data from a study based on a general population sample (figures from our study in brackets) showed a mean HAD depression score of 3.68 (4.19) with a variance of 9.4 (12.8) (Crawford et.al, 2001).

The significant variation in intra-individual changes in depression scores over time (slope trajectories) has not been previously investigated or reported. Other researchers have however noted there is considerable day to day variation in depressive symptoms

in the general population (Judd et.al., 1998) and have also highlighted the impact of sub-threshold depressive symptoms (Judd et.al, 2000). There have been no equivalent studies for people with epilepsy although qualitative research suggests there is considerable variability in day to day psychological symptoms (Scambler, 1989).

Having established that there is significant individual variation in depression scores we next examined the effects of age and seizure recency in this individual variation in depression scores. We found that seizure recency but not age predicts inter-individual variation in depression scores over time. This finding is in line with other studies from the literature which have found that individuals who have more frequent seizures (Jacoby et.al, 1996, Thapar et.al., 2005, Mensah et.al, 2006) or those with more recent seizures (Cramer et.al, 2003,Thapar et.al., 2009) have higher depression scores. Conversely seizure free individuals have depression scores that approximate the depression scores from the general population (Jacoby 1992, Jacoby et.al, 1996). However previous studies have either been cross-sectional (Jacoby et.al, 1996, Cramer et.al, 2003, Mensah et.al, 2006) or if longitudinal (Thapar et.al, 2005, Thapar et.al, 2009) were "group level" analyses (that is, variation around group level scores for one variable is assessed relative to concomitant variation for a second, or further set of variables) and these include techniques such as correlation, regression, and some SEM techniques. These techniques aim to minimise the variance by the prediction rather than explain the pattern and predictors of the individual variation observed. Latent growth curve analysis facilitates such examination and is the approach taken in the present study. Moreover, it has been highlighted that this is an important distinction as group level changes can be very different from individual changes (Herzog & Nesselroade, 2003).

We also found that seizure recency predicted some of the individual changes in depression scores. This has not been examined in the past for people with epilepsy although qualitative research suggests that how long ago a seizure occurred may have affected current psychological functioning for some patients (Schneider and Conrad reported by Scambler, 1989). For individuals who have just had a myocardial infarction, emerging research suggests that there is considerable intra-individual variation in anxiety and depression scores and that severity of illness can explain part of the intra-individual variation for the sub-group of individuals who also have diabetes (Murphy et.al, 2008). Future analytic aims from the current study would be to examine specific subgroups of individuals (for example by gender) to see if these played a role in moderating the affect of seizure recency.

Seizure recency rather than seizure frequency was used as the predictor for this analysis. This distinction was made *a priori* as a previous analysis on two wave data from this dataset found similar results for seizure recency and seizure frequency as predictors of depression scores (Thapar et.al., 2009). Moreover there have been several studies which have found both seizure recency and seizure frequency have similar effects on quality of life (Mrabet et.al, 2004) and previous studies have used seizure recency in preference to seizure frequency (Cramer et.al, 2004)).

The principles and strengths of latent growth curve analysis in studying individual change have been well described (Willet & Sayer, 1994, Muthen & Curran, 1997, Wickrama et.al, 2002, Llabre et.al, 2004, Lenzenweger et.al, 2004). The present study however represents the first application of this approach to the understanding of

individual differences in depression scores among adults with epilepsy. This study adds another powerful argument for the relationship between seizures and depression scores and highlights the importance of reducing the occurrence of seizures to improve depression symptoms amongst adults with epilepsy.

The limitations of the study need to be borne in mind. As with almost all longitudinal studies there was sample attrition during the study. There was an increase in depression scores over the course of this study even though the study was an observational study which raises the possibility of selective dropout. However as can be seen from an inspection of the individual growth parameters (curves), there was wide variation in how individual scores changed over time with some scores increasing and some scores decreasing and moreover more than 80% of participants provided information on at least two data points.

Conclusion

The results of our study indicate that individuals with epilepsy vary from each other in their depression scores and in how their individual depression scores change over time. Some of this variation can be predicted by how long ago the last seizure was. This has important implications for the delivery of treatment and for understanding the source of depression amongst people with epilepsy

Figure 1: Examining Individual trajectories of depression scores for the first 254 participants

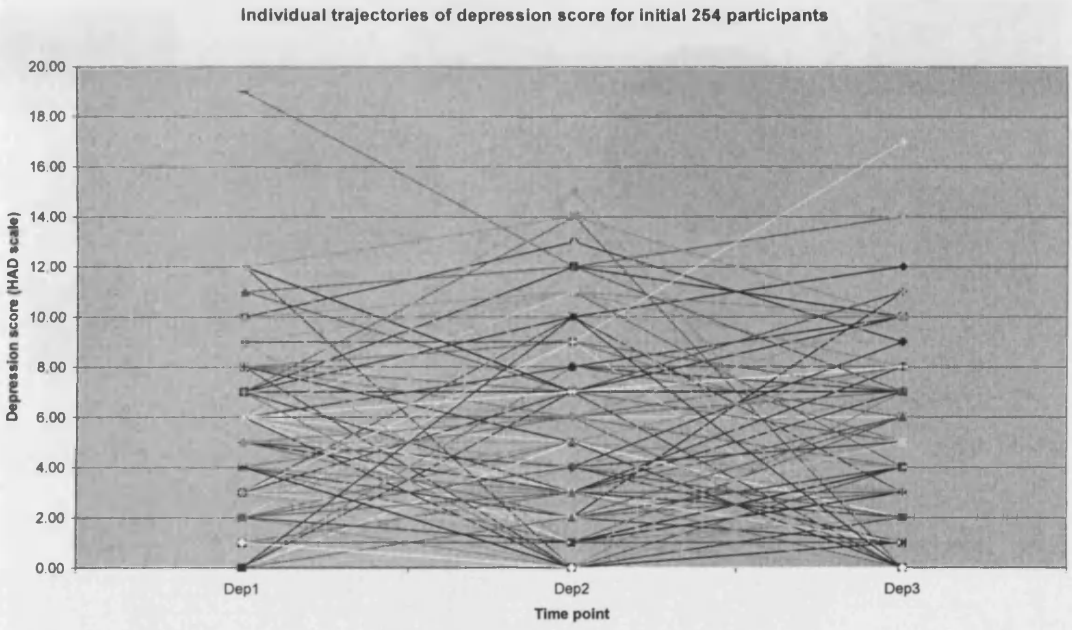
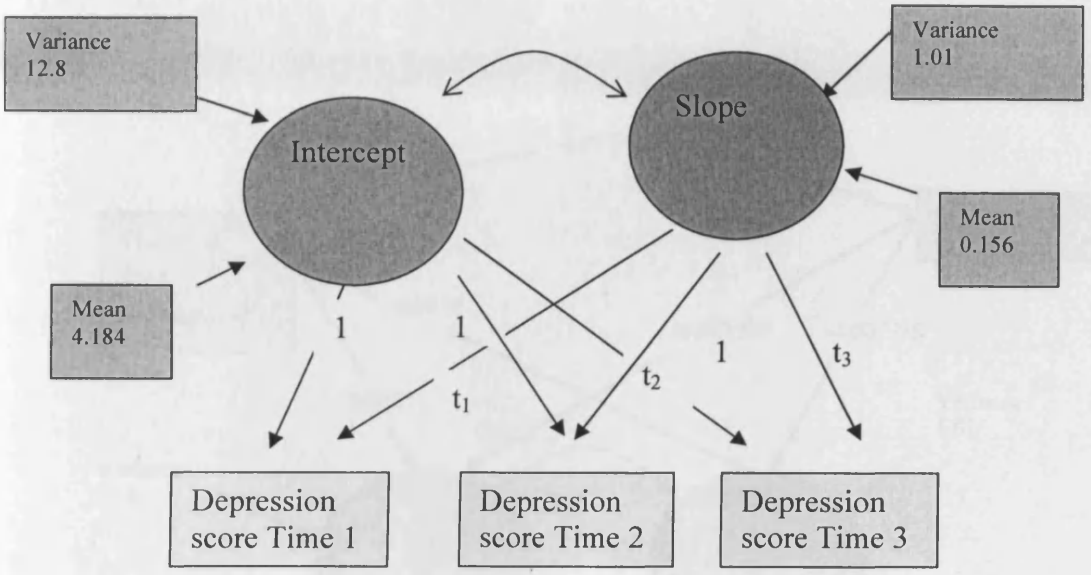


Table 1 Comparing characteristics of responders for the three waves of data

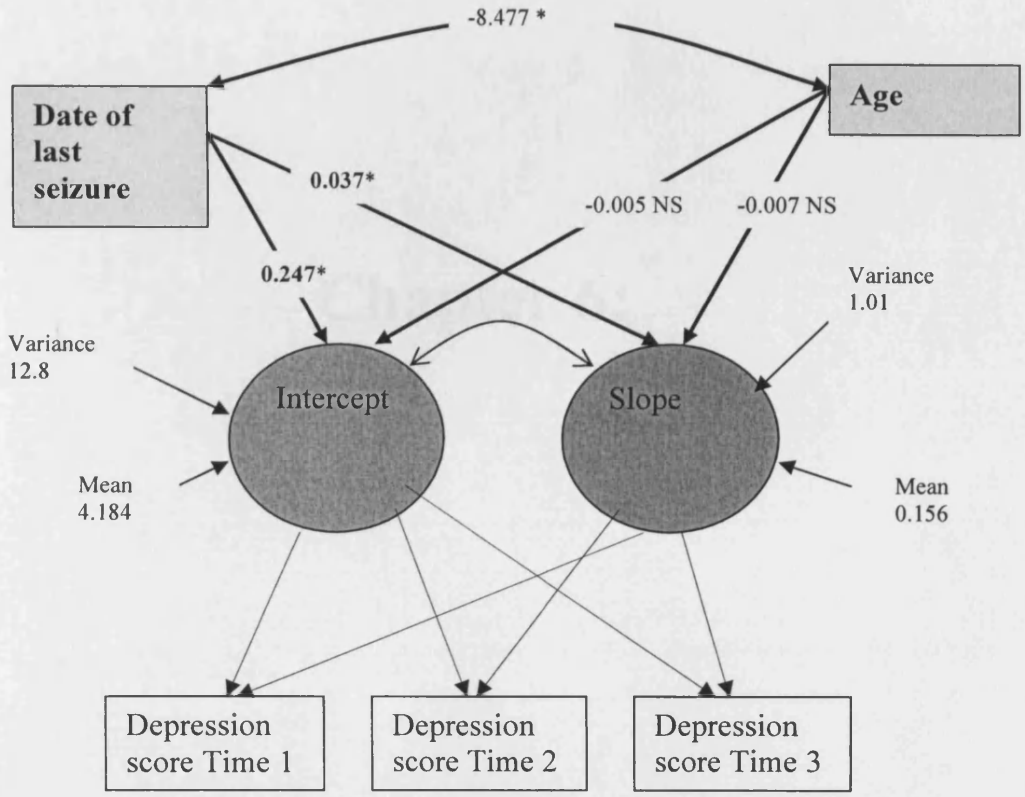
Characteristic	Time 1	Time 2	Time 3
Mean age: Years (SD)	51.2 (17.3) (n=447)	51.9 (17.1) (n=421)	52.4 (16.4) (n=386)
Gender: % male	47.2 (n=460)	47.1 (n=435)	46.3 (n=400)
On income support : (%)	14.8 (n=433)	15.0 (n=420)	15.0 (n=367)
One or more seizures a month (%)	25.4 (n=452)	26.7 (n=436)	23.8 (n=390)

Figure 2: Unconditional latent variable growth curve model (n=325)



RMSEA =0.008
ML χ^2= 3.110 (p=0.375)

Figure 3: Conditional latent variable growth curve model showing the relationships between age and seizure recency on depression score slope and intercept



RMSEA =0.008
ML χ^2= 3.110 (p=0.375)

*** p<0.05**

Chapter 6:

Discussion

6.1 Main findings

In this programme of study the overall aims were to disentangle the relationships between psychological factors and seizures. The specific aims were:

1) To examine the nature of the relationship between depression symptom scores and seizure frequency amongst people with epilepsy by specifying and testing different theoretical explanatory models of this relationship.
2) To examine how depression, anxiety and stress act separately and in combination to influence seizures.
3) To examine the pattern and extent of individual variation in depression symptom scores amongst people with epilepsy over time.
4) Investigate whether seizure recency predicts individual variation in depressive symptoms.
5) Learn appropriate multivariate statistical analytic techniques to be able to examine these relationships.

A summary of the findings with respect to the main aims will first be presented.

1) What is the nature of the relationship between depression symptom scores and seizure frequency?

A bidirectional relationship was found between depression scores and seizure frequency for adults with active epilepsy. Depression scores significantly predicted both future and concurrent seizure frequency and seizure frequency significantly predicted both future and concurrent depression scores. This was controlling for the association between seizure frequency and depressive scores at baseline and all relationships were analysed simultaneously.

2) How depression, anxiety and stress act separately and in combination to influence seizures.

When analysed separately, anxiety scores, perceived stress and depression scores predicted future seizure recency. Depression however mediated the relationship between anxiety and stress with seizure recency, that is, the effects of anxiety and stress on seizure recency could be explained by their concurrent relationship with depression scores. There was no evidence of a moderator relationship, that is, none of these psychological factors significantly influenced the relationship between another psychological factor and seizure recency. Exactly the same pattern of results was obtained when seizure frequency was considered as an outcome variable.

3) To examine the pattern and extent of individual variation in depression symptom scores amongst people with epilepsy over time.

Significant differences in baseline depression scores between individuals (inter-individual differences) were found. There was also significant variation in how depression scores for different individuals changed over time (intra-individual variation). Although the inter-individual differences in depression scores amongst people with epilepsy have been appreciated for some time, intra-individual variation in depression scores has not previously been documented for adults with epilepsy.

4) Investigate whether seizure recency predicts individual variation in depressive symptoms.

Seizure recency was found to be a significant predictor of both sources of individual variation (inter-individual differences and intra-individual variation) in depression scores amongst people with epilepsy controlling for age in all analyses.

5) Learn appropriate multivariate statistical analytic techniques to be able to examine these relationships.

In this project, path analysis, latent variable modelling and latent growth curve analysis were used for the analysis of longitudinal data after appropriate training. These techniques are all part of the structural equation modelling family of techniques. The analytic methods were tailored to the data, information available and objectives of the analyses. The value of a prospective longitudinal design was realised and yielded useful information. Structural equation modelling techniques were useful tools for the analyses as they were versatile and flexible and the approach of specifying theoretical models and testing against empirical data was attractive. Path analysis using cross lagged and reciprocal models offered a relatively simple technique which allowed an examination of direction of effects between seizures and depression. Random effects latent variable modelling was found to be suitable to test models for two wave data when outcome variables had relatively high stability and where the aim was to explore inter-relationships and to test for moderation and mediation. Latent growth curve analysis was a powerful technique for examining individual variation in symptom scores (both inter-individual differences and intra-individual variation) and examining the effects of predictors on this variation.

6.2. Implications of this work for knowledge about relationships between psychological factors and physical illness

6.2.1. Direction of associations between depression and seizures

A bi-directional relationship between seizure frequency and depression scores was found. This advances current knowledge on the links between seizures and depression

as previous studies have shown an association, but, being cross-sectional, do not allow any definitive conclusions to be reached regarding causation (Rutter et.al., 2001, Susser et.al, 2006). Over the last few years there has been more interest in the relationship between seizure activity and depression and longitudinal study designs, often in the context of an intervention, have been used. However uncertainty has remained about the nature of the association because of confounders or because of concerns about generalisability of findings. Devinsky et.al (2005) found that after epilepsy surgery, depression scores in seizure free patients were lower than in those patients who continued to have seizures. However in a review of this study, Schachter (2008) suggest that alleviation of depression and anxiety in this study could also arise through removal of affected limbic areas, less fear of seizures, improved sense of control and stopping anticonvulsant medication. This sample consists of patients selected for epilepsy surgery, so results may not be representative. In another study, the MeSS study, Jacoby et al (2007) reported at two year follow up that there were lower rates of depression amongst those patients who became seizure free compared to those patients who continued to have seizures. However, in this study those patients who were on anticonvulsants were also more likely to be depressed. Given the pattern of adverse effects from anticonvulsants (Ketter et.al., 1999), the lower rates of depression in the seizure free group could relate either to less seizures or less use of anticonvulsants and indeed, once the models in the MESS study were adjusted for anticonvulsant status, depression effects for seizure status became insignificant. Marson et.al. (2007) examined the relative effectiveness of different anticonvulsants for the treatment of partial seizures and found that for those patients who achieved a remission of seizures, depression scores were lower. It is not clear however whether this finding would apply to those with generalised seizures.

6.2.2. The role of stress and in worsening seizure control.

Stress has been highlighted as a major risk factor for worsening of seizures by patient surveys. Psychological factors are known to be highly correlated (Susser et.al. 2006) and inter-relationships between seizure activity and stress and anxiety have been proposed (Frucht et.al, 2000, Beyenburg et.al, 2005). Plausible mechanisms accounting for a link have also been suggested. The current study has found that both anxiety and stress exert their effects on seizure activity through depression symptoms. This clarifies the precise interrelationships between anxiety, stress and seizures (Haut et.al, 2007) and is in line with other studies on the general population which have found the importance of negative affectivity on the relationship between stress and health (Watson & Pennebaker, 1989). However this topic has not been much studied for chronic illnesses. Anxiety and stress were also not found to act as moderators for the relationship of depression scores with seizure activity.

6.2.3. The course of depression amongst individuals with epilepsy

Differences in depression scores between individuals with epilepsy have been long appreciated. The current study adds to this finding by demonstrating that there are significant fluctuations in depression scores over time for individuals with epilepsy. This is in line with findings on depression scores in the general population (Judd et. al., 1998). This is important to demonstrate as it was entirely plausible that chronic illness may be exerting effects which would have altered the pattern of fluctuation of depression scores particularly as high stability values were obtained for depression scores over time.

6.2.4. The role of seizures on individual changes to depression scores.

The association of seizure activity and depression scores have been long appreciated. The current study builds on these observations by demonstrating that seizure recency is a significant predictor of individual fluctuation in depression scores. This finding considerably strengthens the argument that seizures do have an effect on depression scores.

6.3. Clinical implications

6.3.1. Depression amongst people with epilepsy

Depression rates are elevated amongst people with epilepsy. It has been argued that depressive symptoms may be viewed as a natural consequence of living with an unpredictable chronic illness. It has also been noted that managing depression amongst people with epilepsy can be viewed as difficult (all antidepressants generate automatic warnings on prescribing systems that they may exacerbate epilepsy) and many GPs express reservations about their knowledge and skills in managing people with epilepsy (Thapar et.al, 1998, Thapar et.al, 2002). This can lead to the situation, which has been found, of suboptimal treatment of depression amongst people with epilepsy (Kanner et.al., 2000). The findings of the current study highlight the importance of treating depression amongst people with epilepsy. However for implementation of improved depression management in the clinical setting a systematic strategy is likely to be necessary. Some general practitioners are not confident about their knowledge of epilepsy (Thapar et.al., 1998) and as it would seem likely this will extend to psychological issues related to epilepsy (although there

is a paucity of research which has examined this issue). Moreover it has also been argued that many neurologists either are not aware of the importance of depression or do not view depression management as a required part of epilepsy management (Kanner, 2005c). An important first stage would therefore be to increase awareness amongst clinical staff of the importance and implications of depression amongst people with epilepsy and the relevance of depression management to good seizure control. There should then be improved screening for depression amongst people with epilepsy (for example by using either a generic depression screening questionnaires such as the Hospital Anxiety and Depression Scale or the newer more epilepsy specific Neurological Disorders Depression Inventory for Epilepsy (Gillam et. al, 2006)). Finally if depression is identified it would be important to implement effective treatment of depression (such as by using antidepressants or cognitive behaviour therapy). The safety of newer antidepressants (such as the SSRIs) for the treatment of depression for individuals with epilepsy has been established (Kanner et.al., 2000) and guidelines for antidepressant treatment of epilepsy are available (Schmitz, 2002). Finally, policy initiatives such as including depression screening for people with epilepsy in the General Practice Quality and Outcomes framework may be very valuable for ensuring depression management for people with epilepsy in primary care is targeted as a priority area.

6.3.2 Managing Stress and anxiety amongst people with epilepsy

Stress is viewed as the commonest precipitant of seizures by people with epilepsy (Nakken et.al, 2005). However stress is a common experience (Cohen et.al, 1997). The current study showed that depression mediates the relationship between stress and

anxiety and seizures. These findings suggest that if an individual with epilepsy is found to be stressed (or anxious), depression should be screened for and treated to avoid effects on seizures. The clinical implications of this are considerable. The results suggest that detecting and treating depression should be prioritised above stress or anxiety management in epilepsy care. There are differences in the management of anxiety and depression (NICE, 2004a, NICE, 2004b). This distinction is also important give the limitations on time and resources both in primary and secondary care. Stress may however play however other roles in epilepsy, such as acute stress acting as a trigger for individual seizures or as an antecedent factor for depression and seizures. These could be examined in future work using a different study design.

6.3.3. Seizure management

There have been several studies which have highlighted that depression amongst people with epilepsy is the main factor involved in determining the quality of life of people with epilepsy (Loring et.al, 2004, Tracy et.al, 2007), which may have had the effect of indirectly marginalising the importance of good seizure management. The current study has provided strong evidence for the importance of also obtaining optimal seizure control for people with epilepsy.

6.3.4. Individual variation in depression scores

It was found in the current project that although there were relatively small changes in mean depression scores over the course of the study, considerable differences in individual depression score trajectories were evident when plotted graphically and this variation was significant when analysed statistically. This finding would suggest that individually tailored approaches to depression management based on following up

patients may be important (some clinical software programmes have the ability to graphically display scores from psychiatric rating scales). However which pattern of fluctuation is most likely to respond to interventions is not clear at the present time.

6.3.5. Statistical versus clinical significance

One issue that is often raised is the issue of statistical versus clinical significance. Many of the results presented show relationships that are statistically significant but with small coefficients, so the issue of clinical significance arises. As has been noted earlier there is no consensus at the present time as to what represents a clinically significant change in depression score and seizure frequency. However some guides as to significance can be proposed. One guide would be by looking at the proportion of variance in the endogenous variable explained by the model proposed (R^2). In the first study the R^2 for depression at Time 2 was 0.54 and for seizures at Time 2 was 0.77. This would mean that 54% of the variance in the depression scores at Time 2 could be explained and 77% of the variance in the seizure frequency scores at Time 2 could be explained and most of the variation is explained by Time 1 scores of the same variable. The R^2 for change in seizure frequency or recency may in contrast seem very low. However as there are no prior seizure frequency or recency scores, this result suggests that 12% of the inter-individual variation in seizure recency is due to psychological factors which is similar to that found in the cross lagged model. Psychological factors were found to explain 9% of the variance in the quality of life of people with epilepsy in another study (Suurmeijer et.al.,2001). Moreover, it has been argued that simply using the percentage of explained variance can underestimate the effect of systematic factors on processes (Abelson, 1985)

6.4 Implications for analyses

The programme of study utilised different analytic methods for different study aims. This approach also yielded some insights into how further work should be carried out.

6.4.1.Having longitudinal data is much more useful than cross sectional data

Having longitudinal data offers the possibility that one can make causal inferences about the variables in question, whereas cross sectional data do not.

6.4.2. Having more than one measure of a construct is useful

Latent variables can be defined on the basis of two (preferably three) measured variables that tap the same construct. In the second study, a latent variable was defined based on seizure recency scores from two time points. This allows the "error variance" to be partialled out of the latent variable which improves the predictive power of the variable (Loehlin, 1998).

6.4.3. Having three or more waves of data is much more useful than having two wave data

There are several advantages to having three or more waves of data. Having information at three or more time points enable non-linear patterns of change over time of variable scores to be identified. Two wave data analysis assumes a linear pattern in the change of scores of variables. Many processes result in non-linear changes (Hayes et.al., 2007). Moreover having three time point data allows techniques like latent growth curve analysis to be used for analysis which allows information on individual fluctuations in symptom scores to be used for prediction purposes which provides more powerful evidence on the importance of predictors than group based

approaches. Multiple regression and path analysis are sometimes termed group level approaches as the aim is to minimise individual differences whereas latent growth curve analysis utilises the individual variation in scores and allows factors to be specified in the model which explain the causes of this individual variation (sometimes also termed variance based approaches).

6.4.4. Structural equation modelling approaches are under-used in clinical research

Structural equation modelling approaches are rarely used in clinical research which emphasises simpler regression based approaches. One major advantage of structural equation modelling for clinical research is that models (scenarios) are hypothesised on the basis of existing empirical evidence and can be tested against observed data. SEM has been criticised as claims have been made about causality on the basis of a good model fit whereas other models may have fit the (correlational) data equally well. However if the fact that there is often more than one plausible explanation for any situation arising is appreciated and competing models are specified, this apparent weakness can become a strength as these models can then be compared on the basis of goodness of fit indices.

6.4.5. Dimensional measures offer advantages in research settings

A dimensional approach to depression (as well as anxiety and stress) was adopted throughout this programme of work. Using dimensional measures offers advantages for data analysis (Tabachnick & Fidell, 2001) and is also in line with recommendations that depression is best treated dimensionally for research purposes (Andrews et.al., 2008) and that that there is no clear cut off in terms of impact of

depression symptom scores on outcomes (Kessler et.al., 1997). This issue has also been discussed in the subsections of the depression, anxiety and stress sections of the Background.

6. 5. Strengths and limitations

6.5.1.Strengths

6.5.1.1 Sample Both studies used data from community based samples of adults with active epilepsy. A relatively large number of adults with epilepsy agreed to participate and although not all individuals completed all three waves of questionnaires and not all individuals who completed questionnaires completed all the different sections, more than 80% of individuals who had consented to participate and had not died or withdrawn at the first questionnaire stage completed at least two questionnaires. In addition, the disease characteristics (such as severity and seizure type) and socio-demographic characteristics (age, gender, employment) of the samples recruited were comparable to the sample characteristics from other large community based studies of adults with epilepsy from different geographical areas. Sample heterogeneity was however noted for the second study sample. This probably arose because a variety of recruitment strategies were used. Higher seizure frequency and different seizure subtype profile in the sample recruited from the epilepsy charity was found. Separate analyses were carried out for each of the two subgroups. Interestingly, despite these considerable differences in the sample, identical results were found. This replication of results indicated the findings are more robust (Susser et.al., 2006).

6.5.1.2. Measures: The measures used to measure anxiety and depression (the HAD scale), stress (the Perceived stress scale) and seizure frequency are all well established, psychometrically tested measures which have been widely used in community based studies. Although psychiatric interviews are the gold standard for diagnosis it has been argued that questionnaire ratings show high concordance with interview findings and are more pragmatic for longitudinal studies on large community based samples (Kroenke et.al, 2001).

6.5.2. Limitations

6.5.2.1. Sample Not all individuals who commenced the study completed the study (19% of individuals who completed the first questionnaire did not complete the second questionnaire). Self-report measures were used to derive information and this could have influenced findings. It has been argued that information from other informants should also be used to increase the validity of information. However, using other informants in a large-scale community-based study was not feasible and at present little is known on the validity of information on seizure frequency and depression provided by other informants.

6.5.2.2. Measures An ordinal measure of seizure frequency was used. Polychoric correlation matrices were derived and these facilitate analysis of both continuous (depression scores) and non-continuous (seizure frequency) measures while adhering to the important assumption of multivariate normality. It is possible however that using an ordinal measure for seizure frequency and a continuous measure of depression scores could result in less power to detect a difference in terms of

influence of the ordinal variable (Pickles, personal communication), the fact that bidirectional effects were demonstrated would suggest this would not have influenced the overall conclusion.

6.5.2.3. Measurement time frames

The measures do not reflect information from exactly the same period in time (seizure frequency is measured over the past year, seizure recency is the time since the last seizure, depression scores and anxiety scores refer to symptoms in the past week and perceived stress scores ask about perceptions over the last month). However there are high stability levels for all these variables. Moreover the overall effect is likely to underestimate coefficients rather than overestimate them.

6.5.2.4. Seizure type.

Previous research has suggested that individuals with partial epilepsy are more likely to be depressed but findings have been mixed (Indaco et.al, 1992). In the first dataset, which used recorded information on seizure type, it was found that the sample size for individual seizure types was not large enough to test structural equation models for each seizure type but in a regression analysis, using seizure types as independent variables, only a history of tonic-clonic seizures significantly predicted depression scores. We also examined the association between seizure type and depression using data from the second dataset. Individuals who self-reported a history of complex partial seizures were more likely to be depressed. It has been noted that complex partial seizures are prone to being under-recognised and it is possible that self-reports may provide a more accurate estimate of whether or not an individual had complex

partial seizures than recorded information which may only record the initial seizure type. This will be important to further investigate in future research.

6.6. Future work

6.6.1. Confirm the bi-directional relationship between depression and seizure frequency and elucidate the reason for this association

A bi-directional relationship between depression scores and seizure frequency was demonstrated but this is generally felt to be inadequate in providing robust evidence of causality (Rutter et.al, 2001). Moreover the mechanism by which this association arises needs to be elucidated; for example is this behavioural and/or neurobiological? To test for causality it is recommended that either a natural experiment or a randomised controlled trial design should be adopted (Rutter et.al, 2001). However before these can be set up, an appreciation of threats to the usefulness of findings from controlled trials and natural experiments is needed. For controlled trials threats to usefulness include sample selection, generalisibility of findings, inappropriate outcomes selected, inadequate length of follow up and sample size issues (either inadequate power to detect differences or too large to ensure standardised interventions/ contexts). Some of these reasons may be relevant in interpreting the results of recent well-designed and resourced trials on treating depression in individuals with chronic illnesses which have generally not been able to demonstrate significant benefit in terms of improved physical disease outcomes (Glassman et.al, 2002, van Melle et.al, 2007). Natural experiments are a promising alternative but are dependent on appropriate circumstances arising.

6.6.2. Examine whether there is a common antecedent factor which would explain the pattern of results between depression and seizures

For this there is a need to identify the processes by which depression and seizures have evolved. One possible strategy would be to design a prospective longitudinal study of individuals before they develop either depression or seizures and follow them up until they develop these outcomes. This could be either based on a general population sample or a high-risk sample (for example if there is a family history of epilepsy). There are existing cohort studies (e.g. the ALSPAC study) which are following up a cohort of children from birth. Provided appropriate data have been collected, the results from this study could be used to study this process.

6.6.3. Psychological variables and their effects on seizure occurrence

Given that anxiety and stress predict changes to seizure frequency and recency and that this mediated by depression, it would be important to examine whether the same pattern of inter-relationships apply when the effects of these psychological variables on the occurrence of individual seizures is considered. This would involve using diary designs and appropriate analytic techniques such as survival curve analysis. The relationship between fear of seizures, psychological factors and seizure outcomes also seems to be a promising area of research.

6.6.4. Examine relationships between psychological variables and seizure measures for complex partial seizures.

Those individuals who suffered from complex partial seizures were found to have more frequent seizures and significantly higher depression scores than individuals who had other seizure types in the second sample (Page 83). It has been suggested

that the organic basis of the relationship between complex partial seizures and depression may be different than that for other forms of epilepsy (Kanner, 2005(b)). It would be important to examine whether the models specified in the current study also apply to those individuals with complex partial seizures.

6.6.5. Depression symptoms

It was found there was significant individual variation in depression scores over time amongst the sample of individuals with epilepsy and that some of this variation could be explained by seizure recency. However depression scores are an aggregation of scores derived from several different symptoms. It was highlighted by one of the anonymous reviewers for one of the papers that it would be important to examine the effects of epilepsy on repeated measures of minor psychiatric symptoms. This is particularly important as some of the psychiatric symptoms included in common generic depression scales can also arise as iatrogenic side effects of anti-convulsant drugs and compliance can be variable. It has also been highlighted that some symptoms tend to have low variability over time and other show a more fluctuant course (Quinn & Martin, 1999).

6.6.6. Effect of gender on these relationships

Epilepsy is an unusual chronic illness in that there is an equal prevalence of depression amongst males and females (Mensah et.al, 2006). It is possible the processes which influence depression are different in males and females with epilepsy than those in the general population. Thus it will be important in the future to separately examine depression amongst men and women with epilepsy and examine the role of predictors such as seizures.

In summary, this work has shown the links between depression and seizures and provided empirical evidence to underpin the importance of effective seizure management and depression management for people with epilepsy and highlighted the future work that needs to be done.

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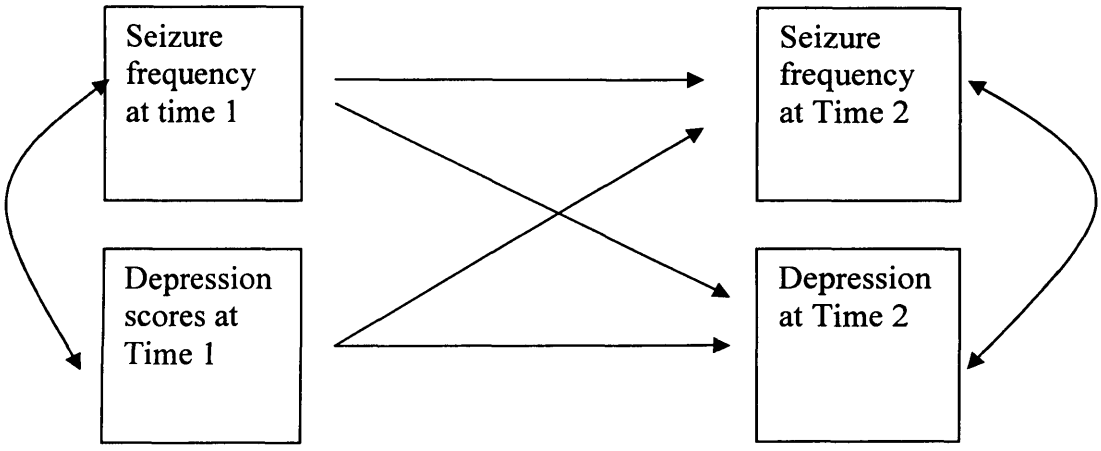
Appendices

Appendix 1

Sequence of analysis (Path model)

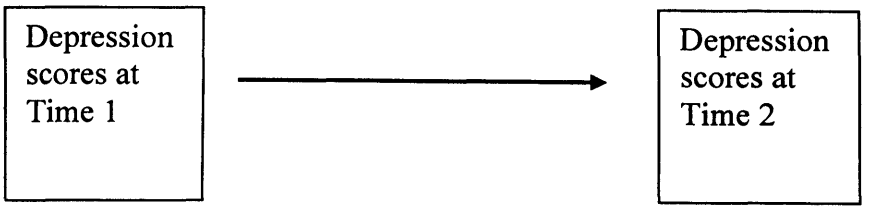
Cross lagged panel analysis).

An example of a cross lagged panel analysis model using path analysis is given below We are looking a two time points (Time 1 and Time 2) and two variables (seizure frequency and depression).

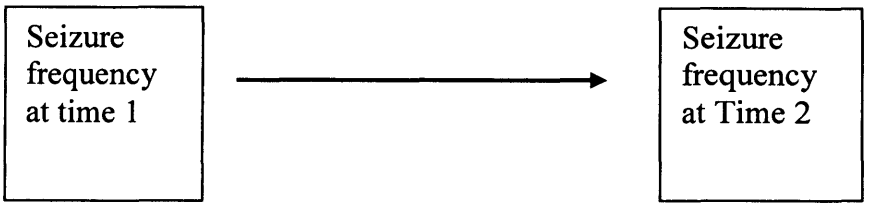


To illustrate how this was arrived at this will be broken down into steps.

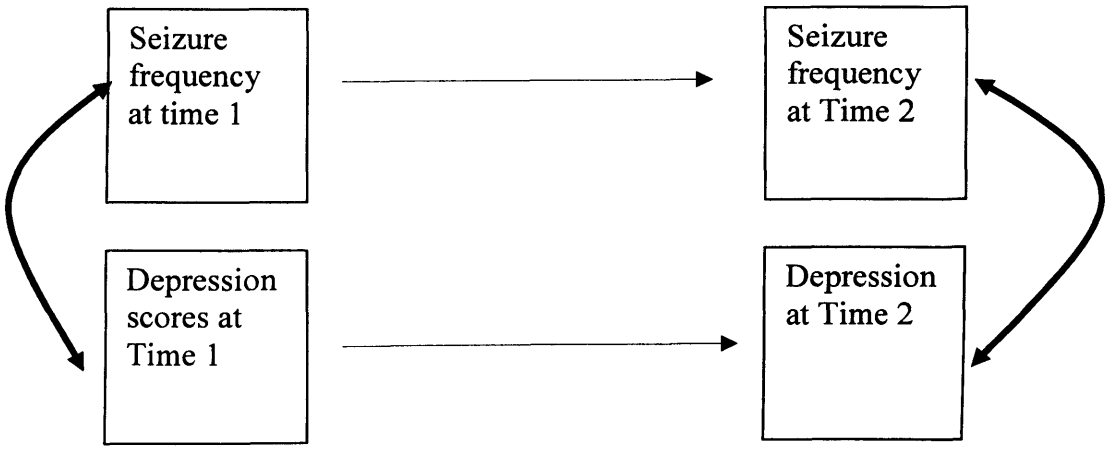
1) We know from the literature that depression symptoms are quite persistent although severity does fluctuate (Judd et.al.1999). Therefore a major determinant of depression scores at Time 2 will be depression scores at Time 1. Using the convention for path analysis, boxes represent the fact that the variables are measured and the arrows represent paths (relationships) that are equivalent to standardised regression coefficients this can be represented by (see overleaf):.



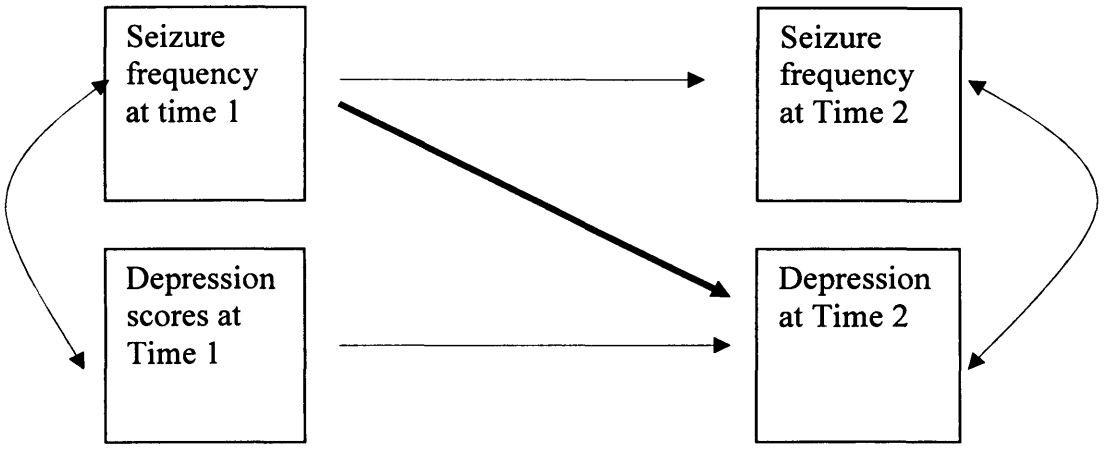
2) It is also clear that seizure frequency is also quite stable for many individuals (Thapar et. al, 2005). Thus again a major determinant of Seizures at Time 2 will be seizures at Time 1. This can be represented by:



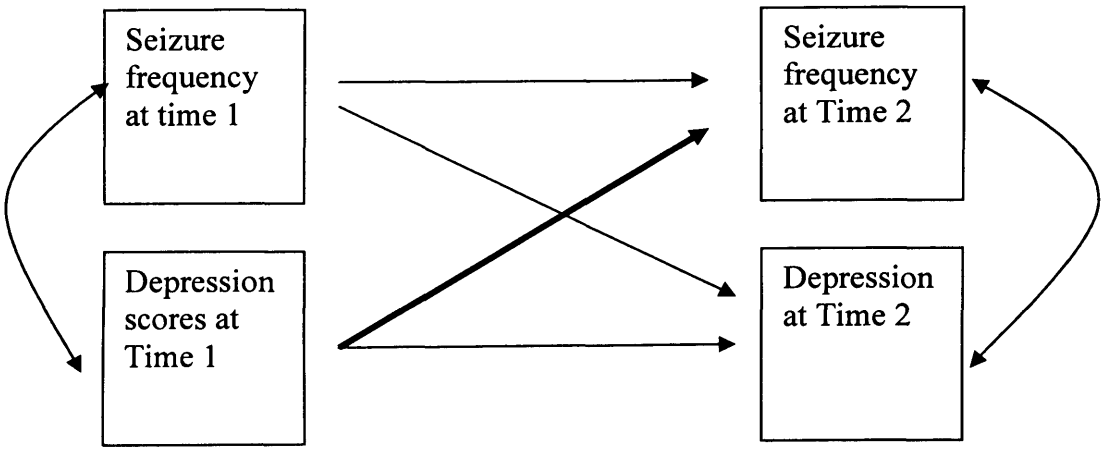
3) Several research studies have highlighted that there is an association of seizure frequency with concurrent depressive symptoms. The existing diagrams can be modified to now be represented as below (the curved arrows represent association with no implicit statement regarding causation.)



4) Seizure frequency has been found to be a predictor for depression scores (Thapar,2001). When this pathway is added to the previous model the figure below is arrived at:



5) Finally what we are particularly interested in is whether depression symptoms at Time 1 predict seizure frequency at Time 2, taking all these other relationships into consideration . This can be represented as



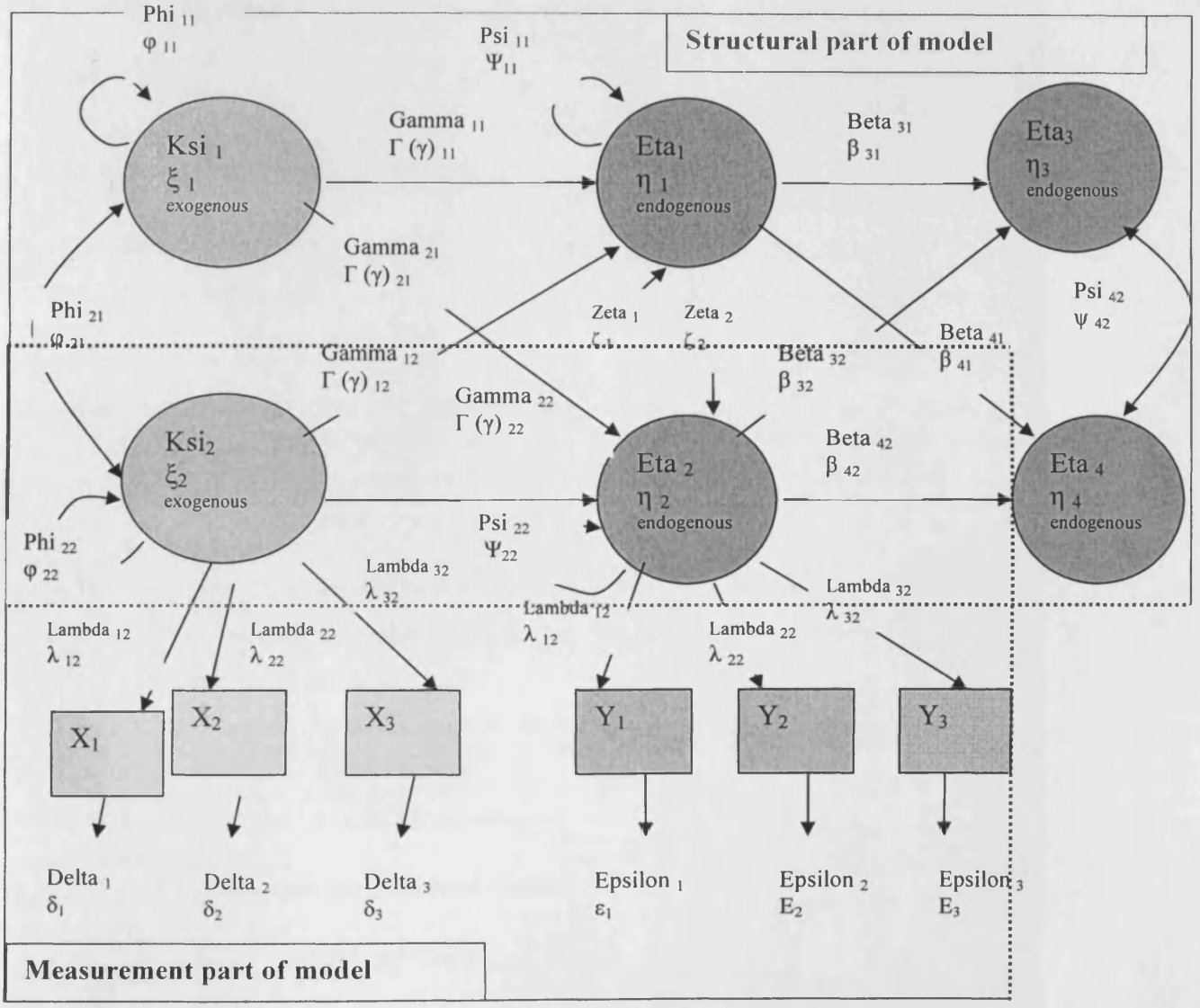
This is the cross-lagged panel analysis detailed at the start of this section.

Appendix 2

Structural equation modelling: Underlying model and specifications

A diagrammatic explanation of a type of model used in SEM is provided in figure 2.2

The underlying matrix for LISREL can be defined using the figure below:



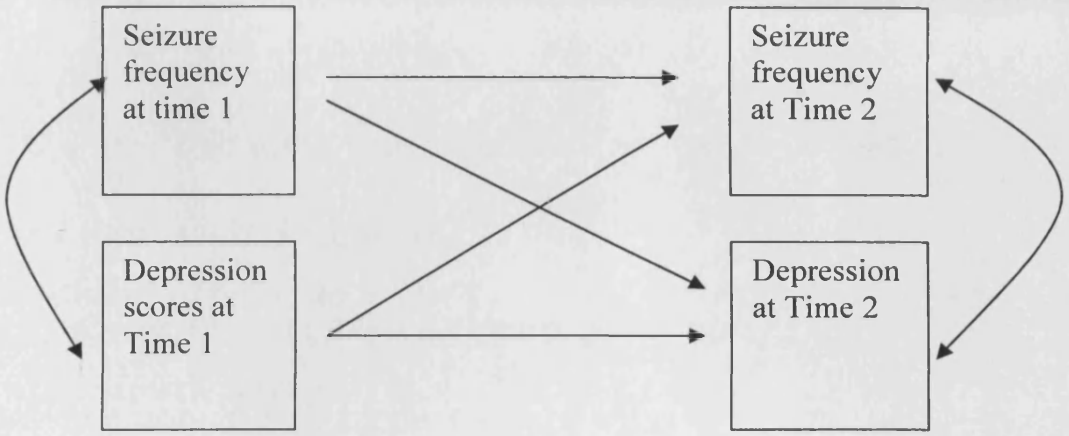
x= measured exogenous variables, ξ (ksi)= latent exogenous variables, y=measured endogenous variables, η (eta)= latent exogenous variable, λ (lambda)= path from measured variables to measured variables, γ (gamma) =path from exogenous to endogenous variables, β (beta) path from one endogenous variable to another, φ (phi) correlations between exogenous variables, ψ (psi) = correlations between endogenous variables, δ (delta) errors associated with measured exogenous variables and ε (epsilon) errors associated with measured endogenous variables, ζ(zeta) error associated with latent endogenous variables.

Once the theoretical model has been defined (e.g. Figure 2.2) we can use the previous diagram to specify the model for the analysis. For the cross lagged model we highlighted earlier this would be specified as in the Figure on the next page (underlined text explains specification):

```
Cross lagged appraisals test                    Line 1: Title for records
DA NI=4 NO=905 MA=CM                            Line 2: No of indicators, number of
                                                 Subjects, Matrix type (CM=correlation
                                                  matrix)
LABELS
2 3 4 5                                         Line 3-4: Which of the variables in the
                                                data file selected
CM
1.000 0.306 1.000 0.877 0.299 1.000
0.287 0.730 0.333 1.000                         Line 5-6:correlations between variables
ME
0.000 5.215 0.000 5.291                         Line 6-7: means of the variables
SD
1.000 3.779 1.000 3.989                         Line 8-9 : standard deviation of the
                                                 variables
SE
4 5 2 3/                                        Line 10-11: sequence of analysis
                                                (endogenous→exogenous)
MO NX=2 NK=2 TD=FU,FI LX=SY,FI PH=SY,FI NY=2 NE=2 TE=FU,FI LY=SY,FI PS=SY,FI
Line 12: number of measured exogenous variables(x), number of latent exogenous
variables (ksi), properties of matrices applied to exogenous matrices (Lambda X
(measured→latent) and error (theta delta); SY=system, FU= full, FI= fixed), number of
measured endogenous variables, number of latent endogenous variables, properties of
matrices applied to endogenous variables (Lambda Y(measured → latent) and error
(theta epsilon))
GA=FU,FI BE=FU,FI
Line 13: Properties of Gamma and beta matrices
ST 1 LX 1 1 LX 2 2
Line 14: Starting values for exogenous variables and sequence of analysis
FR PH 1 1 PH 2 2 PH 2 1
Line 15: which exogenous paths to free)
ST 1 LY 1 1 LY 2 2
Line 16: Starting values for endogenous variables and sequence of analysis
FR PS 1 1 PS 2 2 PS 2 1
Line 17 :which endogenous paths to free
FR GA 1 1 GA 2 2 GA 1 2 GA 2 1
Line 18: sequence of analysis of gamma matrices
LK
FIT1 MOOD1
Line 19: labels to be used for exogenous variables
LE
FIT2 MOOD2
Line 20: labels to be used for endogenous variables
PATH DIAGRAM
OU TV SC EF AD=OFF
Line 20-21: Output options
```

In this model as no latent variables are being specified on Line 12 the number of x variables = number of ksi variables and y variables = and number of eta variables and

on Line 14 and 16 the specification indicates the one:one mapping of the measured to the latent variable for both the exogenous and the endogenous variables.



Underlying algebra

The basic equation for the **structural** part of the model is :

$$\eta = \beta\eta + \Gamma\xi + \zeta$$

$\boldsymbol{\beta\eta}$ (effects of endogenous variables on themselves)

$\boldsymbol{\Gamma\xi}$ (effects of exogenous variables on endogenous variables)

ζ (error in endogenous variable)

$\boldsymbol{\Gamma}$ (gamma) and $\boldsymbol{\beta}$ (beta) are path coefficients and the other terms are latent variables

Latent variable modelling

This would be specified as :

```
Ajay Model anxiety stress depression fits full sample

DA NI=5 NO=386 MA=CM
LA
ANX1 STRESS1 DEP1 FITS1 FITS2

KM
1.00 0.632  1.00 0.656 .526 1.00 .259 .237 .293 1.00 .263 .232 .291
.839 1.00
ME
2.523 5.377 1.123 0.000 0.000
SD
0.934 3.567 0.781 1.000 1.000
MO NY=5 NE=4 LY=SY,FI TE=SY,FI PS=SY,FI BE=SY,FI
LE
anxiety stress depress fits
ST 1 ly 1 1 ly 2 2 ly 3 3 ly 4 4
FR LY 5 4
FR TE 4 4 TE 5 5
FR PS 1 1 PS 2 2 PS 3 3 PS 4 4 PS 2 1 PS 3 2 PS 3 1
FR BE 4 1 BE 4 2 BE 4 3
Path Diagram
OU TV SC SV EF AD=OFF
```

Notes.

1)This model is specified as an endogenous variable model so there are no terms referring to the exogenous side of the model (i.e. no x terms, ksi , phi or theta delta matrices specified). This is not a problem as long as the pattern of relationships in the diagram is maintained. This is indeed a strength of SEM, that the endogenous variable in one analysis can become the exogenous variable in another analysis.

2) The fact that a latent variable is included can be noted by NY>NE, a lambda Y matrix being included and from the specifications on the PS and BE matrix and the inclusion and freeing of (i.e. asking for estimations of) the TE matrices (error)

Latent Growth Curve modelling

The specification for this model using LISREL is:

```
DA Ng=1 NI=6 No=325
RA FI=E:\newbasicgrowth201006predictors.pr2      RA: Case by case raw data
LA
 'dep1' 'dep2' 'dep3' 'fits1' 'severity' 'age'
Se
1 2 3 4 6/
Model ny=3 Ty=ze  Ne=2 Te=sy,fi Nx=2 Tx=Fr Nk=2 Td=ze  ph=sy,fr al=fr
be=ze Ga=Fu,Fi ps=sy,fr                          AL matrix: intercept term
LK
'last fit' 'age'
Ma Lx
1 0
0 1
Fr Ga(1,1) ga(1,2) Ga(2,1) Ga(2,2)
 Le
 Int Slp
 va 1 ly (1,1) ly(2,1) ly(3,1)
 va 0 ly(1,2)
 va 1 ly(2,2)
 va 2 ly(3,2)
 fr te(1,1) te(2,2) te(3,3)
 Path Diagram
 Ou nd=3
```

Notes: In this model

1) Raw data are being used from an SPSS file imported into LISREL.
2) The SE command indicates which variables are to be used in the analysis
3) New matrices are used – the AL matrix which is used for the intercept
4) There are two aspects of the script used for the analysis
    a. in the first part (the structural model) the Gamma matrix is used to test the effect of predictors on the latent variables for intercept and slope
    b. in the second part the latent variables for intercept and slope are defined (by the measurements of depression at the three time points= equivalent to the measurement model).