A systematic review of psychiatric and psychosocial comorbidities of genetic generalised epilepsies (GGE)

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Disclosure of Conflicts of Interest

The authors declare that they have no conflict of interest

Abstract

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

Keywords: idiopathic/genetic generalized epilepsy, psychiatric comorbidity, psychopathology, psychosocial

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Introduction

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

However further synthesising the limited literature regarding psychopathology in GGE is impeded by variability in sample characteristics with regards to syndrome, age, recruitment source and by methodologies used to report psychopathological outcomes. In considering this variability between studies, this systematic review aims to: (1) summarise the literature on psychiatric and psychosocial functioning in GGE; (2) consider risk factors for psychiatric and associated outcomes in GGE; and (3) compare comorbidities in GGE with other chronic illness.

Methods

Search strategies and selection criteria

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

Study eligibility criteria comprised: (a) original research published in a peer-reviewed journal with full-text in English; (b) sample or subsample with a diagnosis of GGE (either consisting of mixed, unspecified syndromes or one of the ILAE-recognised syndromes of idiopathic generalised epilepsy (IGE)/GGE from 1989 ILAE Classification guidelines onwards: Childhood absence epilepsy [CAE], juvenile absence epilepsy [JAE], juvenile myoclonic epilepsy [JME], GGE with generalised tonic-clonic seizures only (previously known as IGE with generalised tonic-clonic seizures on awakening) [GGE-GTCS]); (c) outcomes including rates of psychiatric comorbidity, rates of psychopathological symptoms on a validated measure, mean scores on a validated measure of psychopathological symptoms or study-designed

questionnaire. Studies were ineligible if results were not presented separately for at least one GGE patient group.

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

Assessment of quality

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

Results

Study selection and characteristics

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

[Figure 1]

[Table 1]

[Table 2]

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

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

Aim 1: Psychiatric and psychosocial functioning outcomes

Psychiatric comorbidity in children with GGE

Eleven studies included children with GGE. Six samples comprised mixed syndromes (#1, 2, 8-11); four included CAE only (#3-5, 12); one included JME only (#11). Several studies were co-authored by the same team, and correspondence with the lead author confirms overlapping sampling (#2-4, 10).

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

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

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

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

Psychiatric comorbidity in adults with GGE

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

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

Personality disorder and traits

Personality disorders and traits were reported only in samples of late adolescent and adult samples. Eight studies used validated measures of personality disorders or personality traits with JME patients only. Rates of personality disorders ranged from 5% to 25% (#18, 19, 21, 22, 33), one study reporting higher rates in refractory compared to non-refractory patients (#21). One study observed a higher rate of personality disorders (23%) than mood disorders (19%: #33). A study of Egyptian males with JME (#32) reported levels of aggression, neurosis, extroversion, psychosis and 'lying', of between 0.44 and 1.37 standard deviation units above that of a healthy comparison group. Limitations of this study include unclear definition of the significance of the elevated scores and an atypical sample that excluded females.

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

A study by Karachristianou and colleagues (#23) found no significant differences on personality or psychopathology scales of the MMPI-2 between young adult JME and their healthy comparison group. The MMPI-2 is a sensitive and validated measure of

psychopathology and personality traits (Graham 2006). This was the only study to report a null finding despite the proliferation of studies regarding personality abnormalities in JME following Janz' oft cited anecdote describing careless and impulsive patients (Janz 1985).

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

Psychosocial outcomes

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

In a German sample Schneider von Podewils and colleagues observed 'major unfavourable social outcomes', such as unemployment, withdrawal from school and criminal conviction in 87.9% of those surveyed (#31). In addition, 36.2% of their sample reported unplanned pregnancies, although the 19.2% rate of induced abortions

was considered comparable to the cited rate in the general population (13.7%). The rate of unemployment in GGE was considered to be well above the population average. Another sample also from Germany was followed an average of over 40 years following diagnosis was reported to have favourable educational, occupational and social outcomes in JME, CAE and JAE groups, although healthy control comparison rates were not provided (#7).

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

Aim 2: Factors impacting on outcome

The impact of GGE syndromes

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

The proliferation of JME research may be due to greater patient availability or researcher interest, rather than clinically important differences between JME and

other GGE syndromes. Increasing evidence regarding the cognitive and psychosocial outcomes points to the similarity of JME and other GGE syndromes rather than JME being a distinct syndrome with different cognitive outcomes (Loughman et al. 2014). In the case of personality style, comparison with other syndromes is precluded by lack of studies with sufficient methodological rigour. Long-term psychosocial outcome findings also seem to support similarity across GGE syndromes (#7).

The comparison of psychosocial outcomes in different GGE syndromes is also possible in the Nova Scotia population-based study of epilepsy (studies #14, 15 and 34). This study is unique in its detailed reporting of very long-term outcomes in people with JME, GGE-GTCS and absence epilepsies (CAE and JAE), all drawn from a common population recruited at the same time – a significant strength. However in addition to a relatively small sample size (n=23, 30 and 56 in each of those studies), an important caveat on this comparative approach is that outcomes in Study #34 were published 8 years prior to the others, reflecting a shorter follow-up period (and younger sample). Nonetheless, the three studies report similar psychosocial outcomes for all subtypes of GGE patients 10-25 years following their initial diagnosis. The presence of a psychiatric disorder during the follow up period, unemployment and pregnancies 'outside of a stable relationship' occurred equally frequently across the three GGE syndromes. An exception was the rate of high school graduation, which was significantly higher in JME (87%) than in CAE/JAE (64%) and GGE-GTCS (60%), mirroring educational findings from Almane and colleagues (#7).

Relevance of epilepsy disease characteristics

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

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

The association between epilepsy history and psychiatric outcome was similarly equivocal, with some studies reporting poorer outcomes in early epilepsy diagnosis before age 5 and longer epilepsy duration (#2, 4, 26, 30), other studies reporting null findings (#12, 25, 33). Epileptiform discharges in sleep were reported, however there was insufficient power to evaluate their impact on psychopathology (#9). It is likely

that psychosocial factors such as parent-child relationship quality moderate mental health outcomes (Rodenburg et al. 2005), however such factors were not considered in any of the included studies. Additionally, the relationship between epilepsy disease characteristics and psychosocial functioning was not reported.

Aim 3: Comparisons with other chronic health conditions

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

Discussion

This review summarises the literature regarding psychiatric and psychosocial comorbidities in GGE. The results of this review suggest clinically significant psychiatric comorbidity in more than half the children and a third of all adults with GGE. This prevalence is higher than in the general population (Baumeister and Harter 2007). Higher rates of psychopathology in children compared to adults, together with the equivocal relationship between increased psychopathology and duration of

epilepsy, suggest that the risk of psychopathology in GGE may decrease across the lifespan. However the use of different instruments to measure risk across different studies is a caveat, and longitudinal research is required to further examine this possibility. The limited available evidence relating to predictors of poor outcome suggests a detrimental impact of seizure burden on psychological well-being. One possible interpretation of the findings is that initial neurobiological disruption and psychosocial adjustment to epilepsy in childhood and adolescence results in increased risk of psychological distress (manifesting as externalising or internalising disorders). Clinical expression of distress may resolve in up to half of those affected and may be linked to seizure control or spontaneous remission. A portion of the population with persisting GGE may develop psychopathology in adulthood, most commonly mood spectrum disorder.

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

Limitations of the current study

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

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

Implications for clinical practice and future research

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

Rates of psychiatric comorbidity are high in both children and adults with GGE. Further, psychosocial dysfunction several years following diagnosis of GGE also occurs more frequently than the estimated prevalence in the healthy population.

Presuming that the risk of these problems accumulates over time, data suggest that there may be a window of opportunity for intervention for these treatable conditions. These findings highlight the importance of careful, early screening so as not to overlook incipient psychopathology.

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

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

outcomes (e.g. Australia's National Assessment Program – Literacy and Numeracy, NAPLAN).

Table & Figure Captions

Figure 1: Flow diagram of study selection

Table 1: Summary of included studies

Table2: Expansion of acronyms used in Table 1

Online Resource 1: Methodologic detail of included studies

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ID #	Authors	Syndrome/s	Age (years) M (SD)	Age range (years)	N (GGE)	Interpretation and main findings
1	Almane, Jones, Jackson, Seidenberg & Hermann (2014)	GGE heterogenous; localisation-related epilepsy, healthy first degree cousins	13.3 (3.4)	8-18	61	Both epilepsy groups had higher problem scores and lower competence scores than controls.
2~	Caplan, Arbelle, Magharious, Guthrie, Komo, Shields, Chayasirisobhon & Hansen (1998)	GGE heterogeneous; partial epilepsies	10 (2.6)	5-16	40	Epilepsy diagnosis before age 5 associated with psychiatric diagnosis.
3~	Caplan, Siddarth, Gurbani, Hanson, Sankar & Shields (2005)	CAE; Complex partial seizure disorder	9.8 (2.2)	5-16	71	Higher rate of anxiety in CAE compared to CPS, and the inverse for depression. No seizure variables differentiated patients with and without psychiatric comorbidity.
4~	Caplan, Siddarth, Stahl, Lanphier, Vona, Gurbani, Koh, Sankar & Shields (2008)	CAE	9.6 (2.5)	6-11	69	CBCL elevations most common for attention and somatic complaints, followed by social and thought problems. Predictors of psychopathology: duration of illness, seizure frequency, and AED monotherapy

						compared with no drug treatment.
5	Conant, Wilfong, Inglese & Schwarte (2010)	CAE	8.0 (1.3)	6-11	16	CAE group showed greater levels of social dysfunction
6	Hermann, Black & Chhabria (1981)	GGE heterogeneous	10.3 (3.5)	6-16	21	No differences were found between TLE and GGE patients on the compared measures.
7	Holtkamp, Senf, Kirschbaum & Janz (2014)	JME, CAE, JAE	60.9 (13)	30-85	82	Favourable psychosocial long-term outcomes in JME, similar to outcomes of absence epilepsy group. No apparent correlation between 5 year seizure freedom and psychosocial outcomes.
8	Jones, Watson, Sheth, Caplan, Koehn, Seidenberg & Hermann (2007)	GGE heterogeneous; partial epilepsies	12.7 (3.3)	8-18	23	Higher rates of comorbidity in new onset epilepsy than controls. No significant differences were found between generalised and localisation-related idiopathic epilepsies (except higher rate of conduct diosrders in GGE).

9	Maganti, Sheth, Hermann, Weber, Gidal & Fine (2005)	GGE heterogeneous	13.36	5-18	11	3/11 patients had discharges during sleep. Trend observed between total behaviour problems scale and REM percentage. Authors postulate that discharges could disrupt quality of sleep, cause chronic poor sleep and sleep deprivation itself facilitates more discharges and seizures.
10~	Ott, Siddarth, Gurbani, Koh, Tournay, Shields & Caplan (2003)	GGE heterogeneous; partial epilepsies	9.9 (2.8)	5-16	52	Less than half of those with a psychiatric diagnosis received treatment. Despite the high rate of diagnosis, CBCL group means well below clinically significant cut-off points. GGE children with a single psychiatric diagnosis less likely to be treated than CPS children with >1 comorbidity. AED polytherapy associated with mental health treatment.
11	Plattner, Pahs, Kindler, Williams, Hall, Mayer, Steiner & Feucht (2007)	JME	18.7 (2.9)	13-20	25	JME patients showed double the rate of psychiatric symptoms of the normative sample. No specific personality type of JME found, however higher levels of 'repressive defensiveness' than age-matched norm and 'trend towards' less restraint (i.e. higher impulsivity) in JME patients.

12	Vega, Guo, Killory, Danielson, Vestal, Berman, Martin, Gonzalez, Blumenfeld & Spann (2011)	CAE	10.4 (3.4)	6-16	45	No relationship was found between disease duration, active seizures, or medication use with anxiety or depression scores.
13	Akanuma, Hara, Adachi, Hara & Koutroumanidis (2008)	GGE heterogeneous	35	18-72	157	26% comorbidity in this adult-onset GGE sample and was associated with poor seizure control.
14^	Camfield & Camfield (2009)	JME	36 (4.8)	20-30	23	There is some evidence of poor long term psychosocial outcome in JME. No association reported between seizure and social outcomes.
15^	Camfield & Camfield (2010)	GTSCO	31.9 (6.2)	21.7-47	30	75% GTCSO had 'serious social problems'. These were similar to patients with JME from our cohort except that those with GGE-GTC had greater school problems.
16	Cutting, Lauchheimer, Barr & Devinsky (2001)	GGE heterogeneous (50% JME)	n/a	n/a	42	Rates of psychiatric disorders similar to general epilepsy population, most common were depression and anxiety. Rates lower than hospital samples which typically include more intractable cases. Psychotropic medications not found to directly affect seizure control, but a trend towards poor seizure control and multiple psychotropic use. Authors thought this could

						be attributable to a more refractory condition or other reasons.
17	de Araujo Filho, Pascalicchio, Lin, Sousa, Yacubian (2006)	JME	n/a	14-39	42	GAD associated with lack of seizure control and >20 lifetime GTCS. No difference found between Valproate/Topiramate groups.
18*	de Araujo Filho, Pascalicchio, da Silva Sousa, Lin, Guilhoto & Yacubian, (2007)	JME	19.5 (2.1)	18-54	100	Psychiatric disorder significantly more prevalent in JME than HC. Higher seizure frequency and >20 lifetime GTCS associated with psychiatric disorder. Treatment with AED >2 years protective of psychiatric disorder. No association between psychiatric outcomes and duration of epilepsy, type of medication or time since medication use.
19*	de Araujo Filho, Rosa, Lin, Caboclo, Sakamoto & Yacubian (2008)	JME; TLE	24.5 (12.1)	n/a	100	No differences found in rates of psychiatric diagnoses between JME and TLE. JME was associated with anxiety disorders, while TLE was associated with psychotic disorders.

20	Ertekin, Kulaksizoglu, Ertekin, Gurses, Bebek, Gokyigit & Baykan (2009)	GGE; TLE	32.9 (10.4)	19-54	27	Psychiatric comorbidity rates were significantly higher in TLE than GGE and HC.
21	Gelisse, Genton, Thomas, Rey, Samuelian & Dravet (2001)	JME	33 (10.3)	15-70	155	Drug resistance was found in 15.5% of this sample, and was associated with much poorer psychiatric outcomes. The authors assert that the existence of psychiatric problems are a risk factor for poor seizure control, however, their analyses were not appropriate for the attribution of causality.
22*	Guaranha, de Araujo Filho, Lin, Guilhoto, Caboclo & Yacubian (2011)	JME	24.4 (7.28)	n/a	65	Patients were divided into good vs poor seizure control, and then seizure free vs ongoing from 3 year follow up results. The 'Persistent seizure' group had higher incidence of Cluster B personality disorders. Higher severity of anxiety scores associated with persistent seizures.
23	Karachristianou, Katsarou, Bostantjopoulou, Economou, Garyfallos & Delinikopoulou (2008)	JME	17.6 (2.19)	15-24	25	No irregularities in personality were found at onset or before treatment of JME. Those with higher 'psychotic tendencies' pre-treatment had more normal post-treatment EEG.

24*	Martins, Alonso, Vidal-Dourado, Carbonel, De Araujo Filho, Caboclo, Yacubia & Guilhoto (2011)	GGE; symptomatic focal epilepsy	29.7 (11.6)	n/a	39	Lower adverse events scores from AED for GGE relative to the symptomatic focal epilepsy group.
25	Mino, Kugoh, Hosokawa, Akada, Suwaki & Hosokawa (1995)	GGE; symptomatic focal epilepsy	27.0 (9.6)	n/a	25	Depressive symptomalogy significantly lower in GGE than the 3 symptomatic focal epilepsy groups and 'normal standard score'. No associations were found between depression and age, illness duration or seizure severity.
26	Moschetta, Fiore, Fuentes, Gois & Valente (2011)	JME	26.57 (8.38)	16-48	42	Novelty seeking interpreted as lower impulse control. Early epilepsy onset and frequency of myoclonic seizures were correlated with novelty seeking scores.
27	Olsson & Campenhausen (1993)	GGE heterogeneous	22.5	18-27	58	Authors reported that social isolation was occasionally due to practical issues such as lack of drivers' license, or fatigue. Even these 'benign' epilepsies such as GGE have a profound effect on patients' lives.

28	Pung & Schmitz (2006)	JME; TLE	34	15-60	20	No significant differences were found between JME and TLE on any psychopathological or psychosocial measures. Authors hypothesised circadian rhythm differences, with JME patients as 'evening types'.
29	Perini, Tosin, Carraro, Bernasconi, Canevini, Canger, Pellegrini & Testa (1996)	JME; TLE	27 (7.6)	n/a	18	TLE patients have a higher incidence of psychiatric disorder than JME, T1D, and HC. Authors suggest that TLE patients show interictal depression while JME/primary generalised patients do not. They propose that having temporal epileptogenic foci is a risk factor for the development of affective symptoms, but having generalised seizures is not.
30	Sarkis, Pietra, Cheung, Baslet & Dworetzkyl (2013)	GGE; TLE	36.9 (15.7)	n/a	19	Patients with GGE had lower depression scores on the BDI-II than patients with TLE. In the group with GGE, the BDI-II scores were inversely correlated with epilepsy duration.
31	Schneider-von Podewils, Gasse, Geithner, Wang, Bombach, Berneiser, Herzer, Kessler & Runge (2014)	JME	52.3 (12.34)	33-77	33	BDI scores above 14 predicted unemployment. Long term seizure freedom (>15 years) reduces the risk of depression. Seizure freedom and management is integrally linked to psychosocial functioning.

32	Shehata & Bateh (2009)	GGE heterogenous; idiopathic partial epilepsy	29.2 (8.6)	n/a	55	GGE status associated with depression, aggression, neuroticism, extroversion, psychotic personality and lying. Severity of epilepsy factors were correlated with psychotic personality scores.
33	Trinka, Kienpointner, Unterberger, Luef, Bauer, Doering & Doering (2006)	JME	32.4 (13.0)	15-63	43	Axis 1 rates only slightly above representative community-based samples in German-speaking countries. However personality disorders were double that of the known rates. No significant differences were found between with/without psychiatric diagnoses groups with respect to duration epilepsy, seizure freedom, seizure type, and compliance.
34^	Wirrell, Camfield, Camfield, Dooley, Gordon & Smith (1997)	CAE; JAE	23.1	18-31	56	Worse outcomes were found in absence epilepsies than in juvenile rheumatoid arthritis (specifically in the academic-personal, and behavioral categories). Only weak relationships between some epilepsy variables and psychosocial outcome.

Symbols ~^* indicate overlapping samples

Numbers have been rounded to 1 decimal place and to the

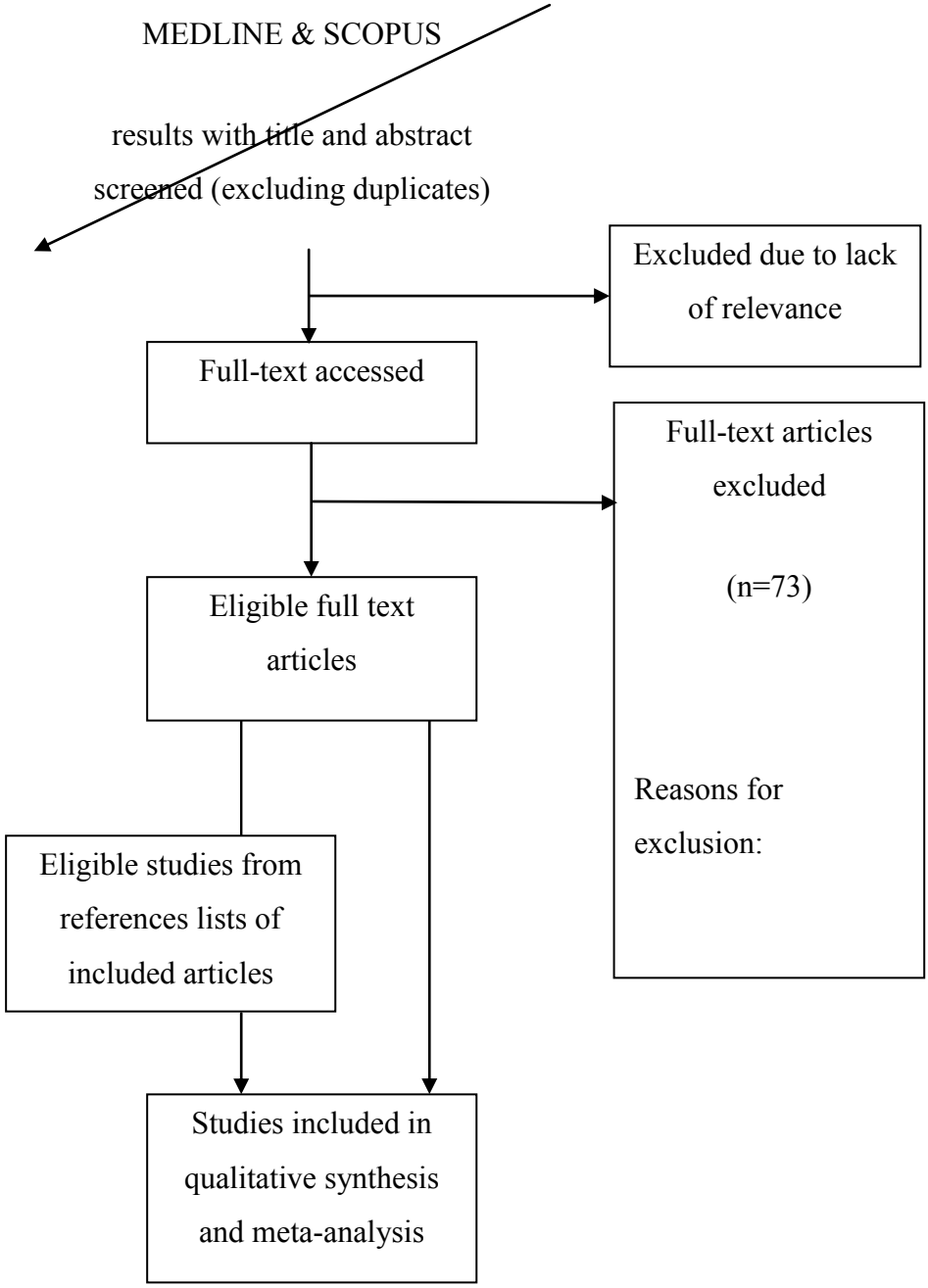
nearest whole percentage.

Acronym	Full term
BASC	Behavior Assessment System for Children
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory-II
CAE	Childhood Absence Epilepsy
CBCL	Child Behaviour Checklist
CPS	Complex Partial Seizures
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GAF	Global Assessment of Functioning scale

GTCS	Generalised Tonic Clonic Seizure
GTCSO	Genetic Generalised Epilepsy with Generalised Tonic Clonic Seizures Only
HADS	Hospital Anxiety and Depression Scale
HC	Healthy control
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
GGE	Genetic generalised epilepsy
ILAE	International Leage Against Epilepsy
JAE	Juvenile Rheumatoid Arthritis
JME	Juvenile Myoclonic Epilepsy
K-SADS	Schedule for Affective Disorders and Schizophrenia for School-Aged Children

LAEP	Liverpool Adverse Events Profile
MMPI	Minnesota Multiphasic Personality Inventory
QoLIE-31	Quality of Life in Epilepsy-31
QoLIE-31-P	Quality of Life in Epilepsy-31 - Problems
SADS	Schedule for Affective Disorders and Schizophrenia
SCID 1	Structured Clinical Interview for the DSM-IV Axis I Disorders
SCID 2	Structured Clinical Interview for the DSM-IV Axis II Disorders
SDS	Self-rating Depressive Scale
STAI	State-Trait Anxiety Inventory
STAIX1	State and Trait Anxiety Inventory (State X1)

STAIX2	State and Trait Anxiety Inventory (State X2)
T1D	Type 1 Diabetes
TCI	Temperament and Character Inventory
TLE	Temporal Lobe Epilepsy
WAI	Weinberger Adjustment Inventory
WPSI	Washington Psychosocial Seizure Inventory
Y-BOCS	Yale–Brown Obsessive Compulsive Scale
YSR	Youth Self-Report


MEDLINE & SCOPUS
results with title and abstract screened (excluding duplicates)
Excluded due to lack of relevance
Full-text accessed
Full-text articles excluded
(n=73)
Reasons for exclusion:
Eligible full text articles
Eligible studies from references lists of included articles
Studies included in qualitative synthesis and meta-analysis

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

3~	CAE; Complex partial seizure disorder	K-SADS; CBCL; Childrens Depression Inventory; Multidimensional Anxiety Scale for Children	ILAE 1989	DSM-IV	85% anxiety disorder; 50% anxiety only; 35% anxiety with comorbid disruptive behaviour problem; 15% depression; 5% depression only; 10% depression with comorbid disruptive behaviour problem; 0% cases anxiety with comorbid depression; 0% cases anxiety with comorbid depression only; 0% cases anxiety with comorbid depression and disruptive behaviour problem.	HC - rates not presented. CPS - 51% anxiety disorder; 27% anxiety only; 24% anxiety with comorbid disruptive behaviour problem; 21.6% depression; 5.4% depression only; 16.2% depression with comorbid disruptive behaviour problem; 27% anxiety with comorbid depression; 5.4% anxiety with comorbid depression only; 21.6% anxiety with comorbid depression and disruptive behaviour problem.
4~	CAE	K-SADS; CBCL	ILAE 1989	DSM-IV; CBCL borderline-clinical cut-off	61% psychiatric diagnosis; 26% ADHD; 20% affective/anxiety disorder. Elevated CBCL subscales: 40% total problems; 36.9% internalising ; 26.2% externalising; 37.5% attention; 34.4% somatic complaints; 23.4% social problems; 20.3% thought problems; 14.1% withdrawn; 17.2% anxious/depressed;	HC - 15% psychiatric diagnosis; 6% ADHD; 7% affective/anxiety. Elevated CBCL subscales: 11.8% total problems; 15.7% internalising; 6.9% externalising; 4.9% attention; 5.9% somatic complaints; 5.9% social problems; 3.9% thought problems; 2.9% withdrawn; 7.8% anxious/depressed; 2.0% aggressive;

					9.4% aggressive; 14.1% delinquent.	6.9% delinquent.
5	CAE	CBCL (Withdrawn, Social problems, Thought problems, Somatic complaints, and Anxious/Depressed scales)	ILAE 1989 equivalent	Comparison of means	All CBCL subscale means within normal range (T: 56.8-60.3), but significant differences between CAE and HC for: attention problems, withdrawal, social problems, and thought problems subscales. No differences for somatic complaints or anxiety/depression. Effect sizes between 0.36-1.15 compared to HC.	HC - All CBCL subscale means within normal range (T: 51.1-54.9). T1D - All CBCL subscale means within normal range T1D (T: 51.1-56.4).
6	GGE heterogeneous	Child Behavior Profile (Achenbach, 1978, 1979; Achenbach and Edelbrock, 1978, 1979)	ILAE 1989 equivalent	Comparison of means (T-score: ≥60 borderline-clinical cut-off)	CBCL agression and social competence subscales within normal range (T: 57.9 and 37.0 respectively). Total Behavior Problem score T: 65.3. GGE group behaviour scores not significantly different from other epilepsy groups.	n/a

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

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

11	JME	Youth Self Report (YSR); Weinberger Adjustment Inventory (WAI)	ILAE 1989	YSR borderline-clinical cut-off, and clinical cut-off	20% in clinical range, and 12% in borderline-clinical range for internalising or externalising; 20% in clinical range, and 4% in borderline-clinical range for internalising; 4% in clinical range, and 12% in borderline-clinical range for externalising. Within internalising: 8% borderline-clinical for withdrawal; 4% borderline-clinical for somatic complaints; 8% clinical, and 4% borderline-clinical for anxiety and depression; 8% borderline-clinical for social problems; 4% borderline-clinical for thought problems. Within externalising: 4% clinical, and 8% borderline-clinical for attention problems; 4% borderline-clinical for delinquency.	n/a
12	CAE	BASC (Anxiety and Depression subscales)	ILAE 1989	1.5 SD above normative sample mean	11% clinical range anxiety; 24% clinical range depression. BASC scores: anxiety 50.7 (9.3); depression	HC - Rates not reported. BASC scores: anxiety 43.3(7.5); depression 50.4 (12.9).

					40.5 (12.9).	
13	GGE heterogeneous	n/a	ILAE 1989/2001	ICD-10	26.1% any psychiatric disorder; 13.4% mood disorder; 7.6% neurotic, stress-related, and somatoform disorders.	n/a
14^	JME	Modified version of Wirrell et al. (1997) measure	Equivalent to ILAE 1989 [myoclonic seizures and >=1 GTCS, Normal background EEG with bursts of gen'd spike and wave >= 3 Hz]	n/a	During the 20+ year follow up period: 61% had been medicated for mood disturbance at some stage. At time of follow up: 87% had graduated high school; 70% had completed additional education; 69% were employed and self sufficient (31% unemployed). Although there were no population norms for their measure, the authors noted Province unemployment to be 7% at the time of the study.	n/a

15^	GTSCO	Modified version of Wirrell et al. (1997) measure	Equivalent to ILAE 1989 [GTCS only; normal background EEG with bursts of gen'd spike and wave >2.5Hz]	n/a	27% any psychiatric diagnosis; 40% had not graduated high school; 38% pregnancy outside a stable relationship; 23% living alone; 33% unemployed; 7% criminal conviction; 55-65% reported satisfaction with their lives, friendships and social activities.	n/a
16	GGE heterogeneous (50% JME)	n/a	Equivalent to ILAE 1989	n/a	During follow up period: >30% diagnosed and treated for mental disorder; 24% medicated for depression; 17% medicated for anxiety; 2% medicated for obsessive-compulsive symptoms; 2% medicated for psychotic symptoms; 10% unemployed.	n/a

17	JME	SCID 1; SCID 2; K-SADS-PL [if aged under 18 years]	ILAE 1989	DSM-IV	62% psychiatric disorder; 24% anxiety disorder; 19% depressive disorder; 2% alcohol abuse; 9.2% personality disorder.	n/a
18*	JME	SCID 1; SCID 2; GAF	ILAE 1989	DSM-IV/DSM-III-R	49% Axis 1 disorder; 23% anxiety disorder; 19% mood disorder; 7% somatoform disorder; 3% schizophrenia; 2% alcohol abuse; 5% Axis 2 disorder; 20% mild-moderate personality disorder; GAF: 61.2 (16.0).	HC - 18% Axis 1 disorder; 8% anxiety; 6% mood; 1% schizophrenia; 3% alcohol abuse; 4% personality disorder; GAF: 84.5 (12.1).
19*	JME; TLE	SCID 1	ILAE 1989	DSM-IV	49% Axis 1 disorder; 23% anxiety disorder; 19% mood disorder; 7% somatoform disorder; 3% psychotic disorder; 5% two Axis 1 disorders; 2% alcohol abuse.	TLE - 50% Axis 1 disorder; 14.1% anxiety disorder; 25.8% mood disorder; 4.7% somatoform disorder; 15.8% psychotic disorder; 10.6% two Axis 1 disorders.
20	GGE; TLE	SCID 1; Yale–Brown Obsessive Compulsive Scale (Y-BOCS); BDI	ILAE 1989	DSM-IV; Y-BOCS Severity Scale; BDI >14	48.1% at least one Axis 1 disorder; 3.7% (1 individual) diagnosis of OCD; 11.1% (3 individuals) clinically meaningful obsessive-compulsive	HC - 16.7% at least one Axis 1 disorder; 0% diagnosis of OCD. TLE - 75.9% at least one Axis 1 disorder; 10.3% (3 individuals) diagnosis of OCD; 34.5% (10

					symptoms.	individuals) clinically meaningful obsessive-compulsive symptoms.
21	JME	n/a	ILAE 1989	DSM-IV	"Non-resistant" patients - 19% any psychiatric disorder; 10% personality disorder; 2.6% generalised anxiety disorder. "Resistant" patients - 58.3% any psychiatric disorder; 25% personality disorder; 12.5% generalised anxiety disorder.	n/a
22*	JME	SCID 1; SCID 2; K-SADS-PL [if aged under 18 years]; STAI	ILAE 1989	DSM-IV	47.6% any psychiatric disorder; 16.9% personality disorder, 16.9% generalised anxiety disorder; 12.3% mood disorder; 1.5% psychotic disorder.	n/a
23	JME	MMPI	ILAE 1989	n/a	No significant difference in subscale scores between GGE and healthy control participants.	See GGE symptom rates column.

24*	GGE; symptomatic focal epilepsy	Liverpool Adverse Events Profile (LAEP) [Brazilian version]; HADS [Brazilian version]; QoLIE-31 [Brazilian version]	ILAE 1989	LAEP score range 0-100, >45 considered 'toxicity' from AEDs.	Reported LAEP scores: Sleepiness 47.0 (42.38), Memory problems 41.9 (43.07). HADS and QoLIE not reported.	Reported LAEP scores: Sleepiness 60.1 (41.19), Memory problems 56.3 (43.69).
25	GGE; symptomatic focal epilepsy	BDI; Self-rating Depressive Scale (SDS); Washington Psychosocial Seizure Inventory (WPSI)	n/a	n/a	BDI: 4.3 (5.9); SDS: 32.9 (7.9); WPSI: 4.6 (8.5).	Simple focal epilepsy - BDI: 13.3 (9.8); SDS: 40.3 (8.6); WIP: 6.9 (7.2). CPS - BDI: 10.2 (7.6); SDS: 37.8 (7.8); WIP: 17.6 (14.9). Secondary generalised epilepsy - BDI: 10.3 (9.1); SDS: 37.4 (12.0); WIP: 7.1 (9.2).
26	JME	BDI [Brazilian version]; STAI [Brazilian version]; Temperament and Character Inventory	ILAE 1989	Comparison of means	No rates or scores reported for BDI or STAI; depression, state anxiety, and trait anxiety scores significantly higher in JME than HC; with BDI and STAI as covariates, TCI scales Novelty Seeking and Harm Avoidance higher	See GGE symptom rates column.

		(TCI)			in JME than HC.	
27	GGE heterogeneous	Study-designed interview regarding impact of epilepsy; standard Social Status questionnaires from Swedish SCB census	ILAE 1985/1991	Qualitative descriptions of outcomes	34.5% no close friend; 15.5% saw friends once a month or less often; 64.1% rarely met co-workers outside their jobs; 22.4% never participated in sports or other physical activities; 17.2% had sleeping problems.	7.9% no close friend; 5.8% saw friends once a month or less often; 40.6% rarely met co-workers outside their jobs; 12.4% never participated in sports or other physical activities; 7.7% had sleeping problems.
28	JME; TLE	Social Stress and Support Inverview (Jenkins et al., 1981); BDI; NEO Five-Factor Inventory; Bear Fedio Questionnaire; Morning type/Evening type Questionnaire	n/a	n/a	No rates or scores reported.	n/a
29	JME; TLE	SADS; BDI;	ILAE 1989	DSM-III-R; comparison of	22.2% psychiatric disorder; BDI and STAI results unclear, but anxiety was	T1D - 10% psychiatric disorder. TLE - 80% psychiatric disorder; BDI

		STAIX1; STAIX2		means	higher in JME than in an unspecified control group.	and STAI results unclear, but TLE scores higher than all other groups.
30	GGE; TLE	BDI-II; QOLIE-31	n/a	Comparison of means	BDI-II: 8.3 (8.3) ; QOLIE-31 54.3 (18.3).	TLE - BDI-II: 15.5 (10.2); QOLIE-31: 47.8 (20.7).
31	JME	BDI; QOLIE-31-P	n/a	Comparison of means	QOLIE-31: 68.2 (15.89); BDI scores not reported.	n/a
32	GGE heterogenous; idiopathic partial epilepsy	BDI [Arabic version]; Aggressive Behavior Scale; Eysenck Personality Inventory	ILAE 1991	Not reported [however, Arabic version of BDI >16 indcates clinically significant depression (Fawzi, 2012)]	BDI: 17.5 (12.35).	HC - BDI: 8.59 (8.10). Idiopathic partial epilepsy - BDI: 20.81 (9.60)
33	JME	SCID 1; SCID 2	ILAE 1989	DSM-IV	At time of study: 35% any psychiatric diagnosis; 19% Axis 1 disorder; 23% personality disorder. In their lifetime: 47% any psychiatric diagnosis; 30% Axis 1 disorder; 26% personality	n/a

					disorder.	
34^	CAE; JAE	Study-designed psychosocial interview (educational attainment, behaviour, pregnancy, relationships, substance use, self-reported psychiatric difficulties, employment and financial security).	ILAE 1989 equivalent	n/a	25% described themselves as loners; 16% continued to have emotional difficulties at follow up; 50% completing higher education were employed in their field of study; compared with JRA, absence epilepsy reported poorer relationships with siblings, had fewer regular social outings, worked for fewer months of the year, were more likely to have an unskilled job, were less often employed in upper management or professional positions, and more frequently reported poor job satisfaction.	JRA - 11% described themselves as loners; 7% continued to have emotional difficulties at follow up; 86% completing higher education were employed in their field of study.

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