Master Thesis

Psychosis of Epilepsy: a Meta-analysis

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Abstract
Background The relationship between psychoses and epilepsy has been the interest of many studies. Although a large number of these studies give a prevalence rate of psychosis among epileptic patients, to our knowledge this is the first time a meta-analysis is performed on the subject. **Aims** The aim of this study is to do a meta-analysis to calculate the percentage of psychosis in epilepsy. Also, separate meta-analyses will be performed to study psychosis in primary generalizes epilepsy (PGE) and in temporal lobe epilepsy (TLE). **Methods** Databases were searched for literature that includes percentages of psychosis in epileptic patients. The meta-analysis is performed with the program Comprehensive Meta-Analysis version 2. **Results** Seventeen studies were found that met the inclusion criteria. The calculated event rate was 0.042 for overall epilepsy, 0.046 for PGE and 0.10 for the separate meta-analysis that specifically included studies of psychosis in patients with TLE. **Conclusion** As expected, the percentage of psychosis in TLE was higher than in general epilepsy patients. In conclusion, psychosis appears to be occurring twice as often in epileptic patients than in the general population. Although this is a notable increase, the association between epilepsy and psychosis is not so high as to assume a shared final common pathway.

Introduction

Since the end of the 19th century, investigators have described the simultaneous appearance of psychiatric disorders and epileptic seizures (Bruens, 1971).
The coexistence of more than one condition in the same patient is described with the term comorbidity. By studying the association of two conditions that have a higher frequency of occurring together than should be expected by statistical chance, a relationship can be discovered that suggests a common onset of disease that is not discovered with other methods of study.
The interest of this paper is the co-occurrence of psychosis in epileptic patients.
Epilepsy is a chronic brain disorder, characterized by recurrent seizures due to excessive discharge of cerebral neurons (Gastaut, 1973;Rodenburg et al., 2005) and is the most common serious neurological condition (Shorvon, 1990). Epilepsy is known to have multiple kinds of psychiatric comorbidity; for example depression and suicide are more common in epileptic patients (Bell and Sander, 2009;Modrego et al., 2002;Pompili et al., 2006;Rodenburg et al., 2005;Swinkels et al., 2005).
Psychosis is a group of psychiatric disorders and can be defined as a thought disorder that is characterized by impairment in reality testing. This can be manifested by hallucinations, delusions, formal thought disorder or catatonia. These symptoms are often accompanied by a lack of insight into the unusual or bizarre nature of the patient's behavior, as well as difficulties with social functioning (Association, 1994).
Gibbs and Gibbs (1952) were one of the first to report an increased incidence of interictal (between seizures) psychoses in patients with epilepsy (Gibbs and Gibbs, 1952). Psychosis seemed to be occurring more often together with epilepsy than was expected by chance (Slater et al., 1963). Slater et al. were the first to define schizophrenia in epilepsy as schizophrenia-

like-psychosis of epilepsy, SLPE. They thought that it was most unlikely for a person to get fairly uncommon diseases simultaneously. The combination of these two diseases should only occur in 0.004% of the population. Other studies confirmed the notion that SLPE should be distinguished from schizophrenia, especially in temporal lobe epilepsy (TLE) (Roberts et al., 1990;Sherwin, 1981;Toone et al., 1982). Later, the article by Slater and Beard 1963 received some criticism from other groups (Mace, 1993;Schmitz, 1995;Stevens, 1988).
Nevertheless, the interest in epilepsy and psychoses is still very much alive today; numerous studies were performed to study the comorbidity of these syndromes. Also countless of review articles have been written about the subject. To our knowledge, this is the first time that a meta-analysis is performed to estimate the frequency of comorbidity of epilepsy and psychoses in adults. But, one study was found that did a meta-analysis of psychopathology, not psychosis specifically, in children with epilepsy (Rodenburg et al., 2005).
The aim of this study was to compare epidemiologic studies and perform a meta-analysis to calculate the average percentage of patients with epilepsy that develop a psychosis.
After the introduction of electroencephalography several studies suggested that psychoses in epilepsy were occurring more often in complex partial seizures (Bartlet, 1957;Flor-Henry, 1972;Gibbs and Gibbs, 1952;Slater et al., 1963). Another term used for complex partial seizures is psychomotor epilepsy, but the most usual term is temporal lobe epilepsy (Hyde and Weinberger, 1997). Therefore, a separate meta-analysis was done for psychoses in temporal lobe epilepsy (TLE) to see if the percentage is higher than in general epilepsy.
A third meta-analysis is performed with studies that had percentages of psychosis in patients with primary generalized epilepsy (PGE).

Method

Pubmed, Google scholar and the literature database Omega of the University of Utrecht were searched for literature. Search terms were “epilepsy” (or “seizures”), “psychosis”/“psychoses” (or “schizophrenia”), with in addition “comorbidity” or “epidemiology”. Also papers were found by reading review articles and searching their references. The final search was conducted on 16 September 2009.

Selection of studies

The included studies had a clear definition of epilepsy and especially psychosis, using the DSM-III or -IV or ICD-8/10 (International Classification of disease) or another well-described definition. The inclusion criteria that were used for this meta-analysis can be described as follows:

Inclusion criteria:

I well defined concept of psychosis (DSM III-IV or ICD 8-10)
II a general population of epilepsy patients is studied (not only severe cases or cases with known lesions of 1 hemisphere, outpatients are included etc.)
III psychosis was rated not only as an epileptic prodrome (premonitory symptom of disease) or solely as an ictal (during seizures) phenomenon
IV studies were published in English in peer reviewed journals

Fourteen studies met all these inclusion (Bredkjaer et al., 1998;Edeh and Toone, 1987;Filho et al., 2008;Gaitatzis et al., 2004;Gudmundsson, 1966;Gureje, 1991;Jalava and Sillanpaa, 1996;Matuja, 1990;Onuma et al., 1995;Schmitz, 1995;Sengoku et al., 1983;Standage and Fenton, 1975;Stefansson et al., 1998;van der Feltz-Cornelis et al., 2008). Other studies that were included did not have a very clear definition of psychosis and thus did not fulfill the first criterion, but they depended on the diagnostic expertise of neurologists or psychiatrists and

were overall well performed studies. Nevertheless we decided to include them (Forsgren, 1992;Krohn, 1961;Okuma and Kumashiro, 1981).
Some studies made a subdivision between schizophrenia and other psychosis and/or between organic and non-organic psychoses. Organic psychoses are psychoses that are caused by a known physical abnormality. These include alcoholic psychoses, drug psychoses, transient organic psychotic conditions and chronic organic psychotic conditions (Gaitatzis et al., 2004). Organic and non-organic psychoses were added up together when the percentages were given separately.
The study by Stefansson excluded organic psychoses but still met the inclusion criteria and was thus included anyway (Stefansson et al., 1998)
In the article of Matsuura and Trimble in 2000, Japanese studies on the subject are reviewed. Some of these studies are included (Kido and Yamaguchi, 1989;Matsuura and Trimble, 2000;Oka et al., 1983;Okuma and Kumashiro, 1981;Onuma et al., 1995), but others were only available in Japanese and for that reason excluded. This makes a total of seventeen studies, of which three were from before the year 1980.
Two studies did not meet the inclusion criteria, because these studies only had statistics on the prevalence of schizophrenia and SLPE and no other types of psychosis (Mendez et al., 1993;Qin et al., 2005). A sub-analysis was performed with these two studies to make a comparison between the percentage of schizophrenia and the percentage of psychoses in epilepsy patients.

Four of the studies above were also included in the Temporal Lobe epilepsy (TLE) sub analysis (Edeh and Toone, 1987;Gureje, 1991;Onuma et al., 1995;Standage and Fenton, 1975). Two other studies gave statistics for TLE exclusively and were thus only included in the TLE sub analysis (Currie et al., 1971;Lindsay et al., 1979;Sengoku et al., 1983). Of the seven studies included in the sub analysis, three were from before 1980 and four from after 1980.
For the third meta-analysis that studied PGE, three studies were included that were also in the first meta-analysis (Edeh and Toone, 1987;Gureje, 1991;Sengoku et al., 1983).

Studies that were excluded for this meta-analysis did not have a clear definition of epilepsy, psychosis or studied not clearly described psychopathology (for example ‘severe mental disorder’). Modrego et al. for example studied psychopathology in chronic non-lesional epilepsy. Psychosis was not specifically mentioned and lesional epilepsy was excluded; this study was thus not of interest for this analysis (Modrego et al., 2002).
The study by Oka et al. was excluded because this study only described psychotic patients with epilepsy (Oka et al., 1983), not epilepsy patients with psychosis. Another study was excluded because it studied the schizophrenia-like state after epileptic seizures and gave no statistics about the number of epileptics with psychosis (Kido and Yamaguchi, 1989). The study of Pond and Bidwell was largely descriptive in nature and only gave statistics of psychological difficulties in epilepsy (Pond and Bidwell, 1960). The study of Small and Small was excluded because they only studied epileptic patients in a psychiatric clinic. Therefore, the study population is not representative for all epileptic patients (Small and Small, 1966). One study only gave information about the occurrence of schizophrenia and other mental health disorders, but not about the incidence of psychosis in general (Tellez-Zenteno et al., 2007). The study of Vestregaard et al. studied the risk of schizophrenia in children with febrile seizures and was therefore excluded (Vestergaard et al., 2005). Another study studied the incidence in TLE, but only in treatment-refractory patients and was therefore excluded (Umbricht et al., 1995).
Also, books that gave statistics on the incidence of psychosis among patients with epilepsy were excluded, for books are published without peer reviewing (Gibbs and Gibbs, 1952;Trimble, 1991). Table 1 gives an overview of the excluded studies.

Table 1 Excluded studies, overview of the reason for exclusion

Study	Reason for exclusion
Gibbs and Gibbs 1952	Book, no peer reviewing
Kido and Yamaguchi 1989	no statistics about the number of epileptics with psychosis
Modrego et al. 2002	Included only chronic non-lesional epilepsy
Oka et al. 1983	Included only psychotic patients with epilepsy
Pond and Bidwell 1960	Provided insufficient statistics
Small and Small 1966	Included epileptic patients in a psychiatric clinic only
Tellez-Zenteno et al 2007	No separate data for psychiatric diagnoses.
Trimble 1991	Book, no peer reviewing
Umbricht et al 1995	Included only treatment-refractory epilepsy patients
Vestergaard et al 2005	Included only children with febrile seizures

Meta-analysis

The program used for the meta-analysis is Comprehensive Meta-Analysis version 2. Table 2 gives the key characteristics of the included studies in the analysis that studied the percentage in epilepsy patients.

The sub- analysis was done with the study of Qin et al. 2005 and Mendez et al. 1993. These two studies only measured schizophrenia and SLPE, but no other types of psychosis (Mendez et al., 1993;Qin et al., 2005). Characteristics of these two studies can be seen in table 3.

Table 4 gives the key characteristics of studies that are included in the second analysis of the prevalence in a more specific type of epilepsy, temporal lobe epilepsy (TLE).

The third meta-analysis is performed with another type of epilepsy, primary generalized epilepsy (PGE). Details of the three included studies for this separate type of epilepsy can be found in table 2 (Edeh and Toone, 1987;Gureje, 1991;Sengoku et al., 1983).

Table 2, Key characteristics of the seventeen studies in alphabetic order used in the first meta-analysis. The number of epileptic patients, the number of epileptic patients that were psychotic, and the country were the study was performed are given. Also where the definition of psychosis was derived from and the settings from which subjects were found are given in the table.

Study	N epileptic patients	N cases with psychosis	Country	Definition psychosis	Setting
Bredkjaer et al. 1998	67.226	256	Denmark	ICD-8	National patient registers
Edeh and Toone 1987	88	4	England	ICD-9	14 general practitioners
Feltz- Cornelis et al. 2006	901	49	Netherlands	ICD-10	tertiary care epilepsy clinic and outpatient ward
Filho et al. 2008	270	51	Brazil	DSM-IV	outpatient clinic of a tertiary center
Forsgren 1992	713	15	Sweden	Colleagues, not checked	medical register
Gaitatsis 2004	5834	525	United Kingdom	ICD-9	Registers general practices
Gureje 1991	204	22	Nigeria	ICD-9	neurological out-patient clinic
Gudmundsson 1966	987	71	Iceland	Special questionnaire	all physicians in the country
Krohn 1961	908	16	Norway	Mental states fairly well known	District doctors (practically everyone)
Matuja 1988	230	10	Tanzania	Definition in article	neurology clinic
Okuma and Kumashiro 1981	1661	90	Japan	Psychotic disturbance	20 institutions, outpatients
Onuma et al. 1995	1285	124	Japan	Definition in article	adult epilepsy clinic
Schmitz and Wolf 1995	697	28	Germany	Definition in article	epilepsy outpatient clinic
Sengoku et al. 1983	879	39	Japan	Definition in article	outpatients at the National Epilepsy Center
Standage and Fenton 1975	27	3	England	Screening questions	neurology clinic + outpatient clinic
Stefansson et al. 1998	241	15	Iceland	ICD-9	people receiving disability benefits
Jalava and Sillanpää 1996	94	3	Finland	ICD-9	long-term followed patient cohort with epilepsy

Table 3, Key characteristics of the two studies in alphabetic order used in the sub- analysis. The number of epileptic patients, the number of epileptic patients that had SLPE, and the country were the study was performed are given. Also where the definition of psychosis was derived from and the settings from which subjects were found are given in the table.

Mendez et al. 1993	1611	149	United States	ICD-9, DSM-II-R	neurology clinic, epileptic outpatients
Qin et al. 2005	34494	795	Denmark	ICD8/ICD-10	Danish longitudinal registers

Table 4, Key characteristics of the studies (in alphabetic order) used in the sub meta-analysis with TLE patients. The number of epileptic patients, the number of epileptic patients that were psychotic, and the country were the study was performed are given. Also the definitions of psychosis that were used and the settings from which subjects were found are given in the table.

Study	N TLE patients	N cases with psychosis	Country	Definition psychosis	Setting
Currie et al. 1971	666	12	England	Schizophrenic illnesses	hospital diagnostic index, files of the neurological departments and the index of the EEG department of London hospital
Edeh and Toone 1987	25	2	England	ICD-9	14 general practitioners
Gureje 1991	82	15	Nigeria	ICD-9	neurological out-patient clinic
Lindsay et al. 1987	87	9	United Kingdom	1964 codings	100 children who had suffered limbic seizures
Onuma et al. 1995	124	68	Japan	Definition in article	adult epilepsy clinic
Sengoku et al. 1983	879	39	Japan	Definition in article	outpatients at the National Epilepsy Center
Standage and Fenton 1975	19	1	England	Screening questions	neurology clinic

Results

When including every study that had statistics on the frequency of psychoses in epilepsy, the event rate calculated with this meta-analysis was 0.042. This can be seen in figure 1.

The study of Onuma et al. 1995 is one of the outliers with a percentage of 9.6% epileptic patients having comorbid psychosis (Onuma et al., 1995). The study of Filho et al. was the largest outlier with a prevalence rate of 18.8% (Filho et al., 2008).

Two studies reported the prevalence of schizophrenia-like psychosis, which is a more narrow definition than psychosis (Mendez et al., 1993;Qin et al., 2005). The sub-analysis with only these two studies gave an event rate of 0.028 (figure 2).

The second meta-analysis was performed for the sub class of epilepsy, TLE. The event rate of psychoses occurring in epileptic patients was 0.010 (figure 3).

The calculated event rate for the third meta-analysis for patients with PGE was 0.046 (figure 4).

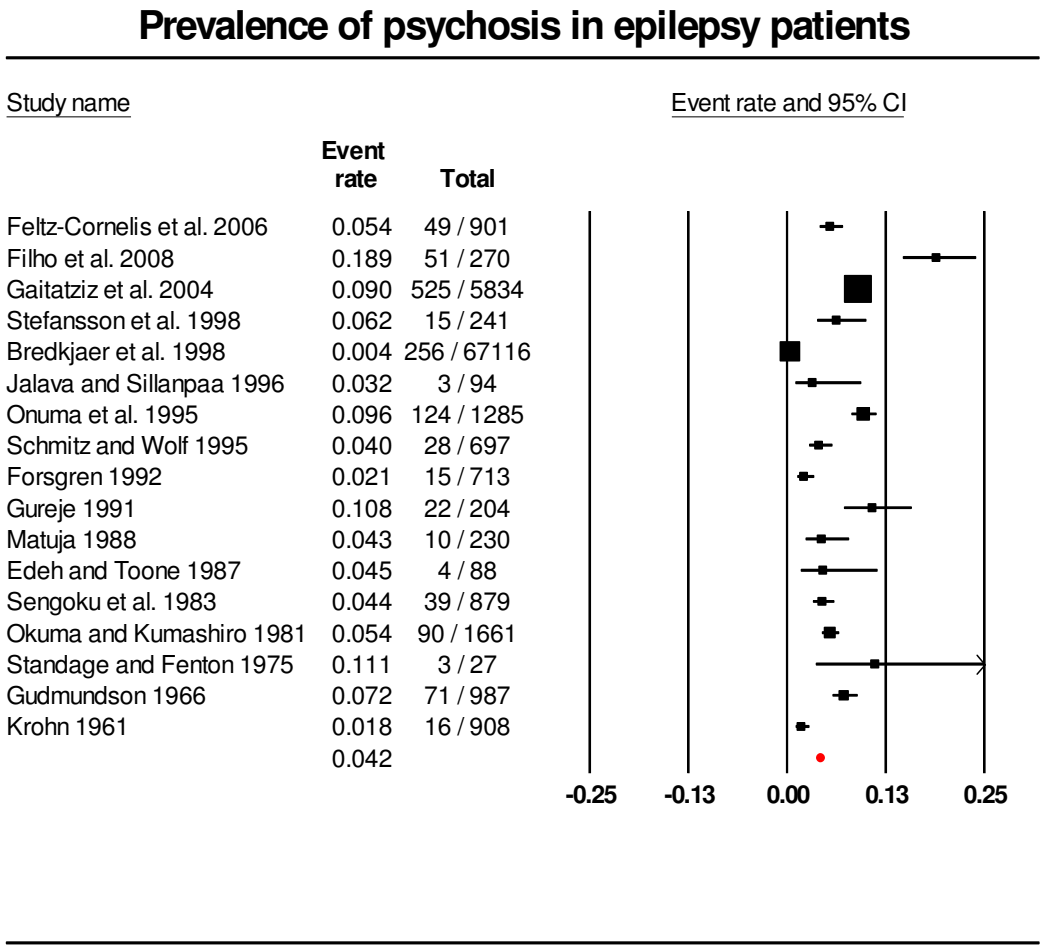

Figure 1. First meta-analysis. Event rates of psychosis in epilepsy.

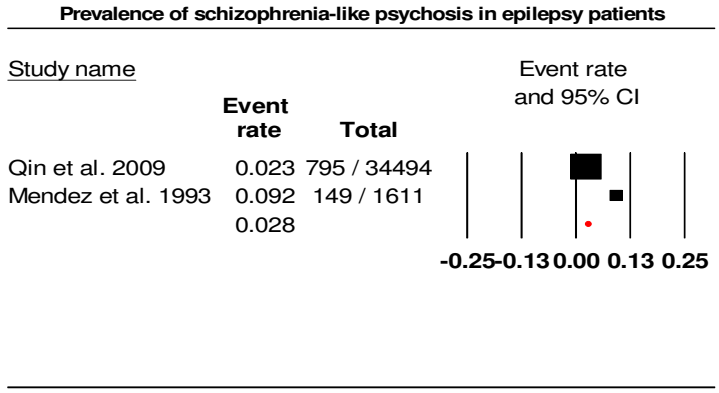

Figure 2. Sub meta-analysis. Event rates of schizophrenia-like psychosis in epilepsy patients.

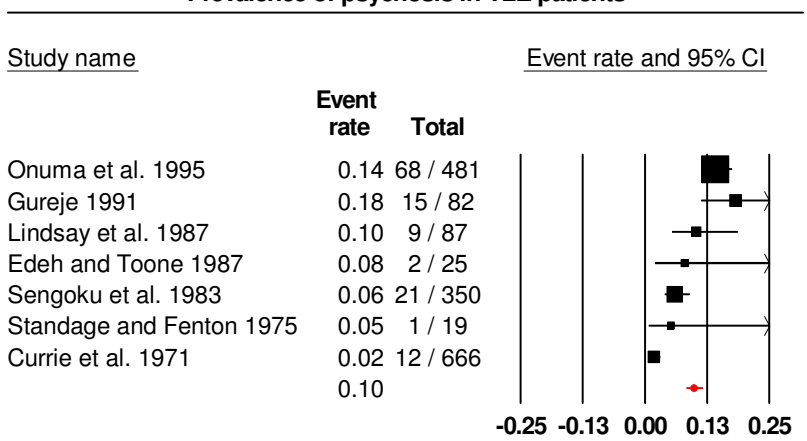

Figure 3. Second meta-analysis. Event rates of psychosis in temporal lobe epilepsy (TLE).

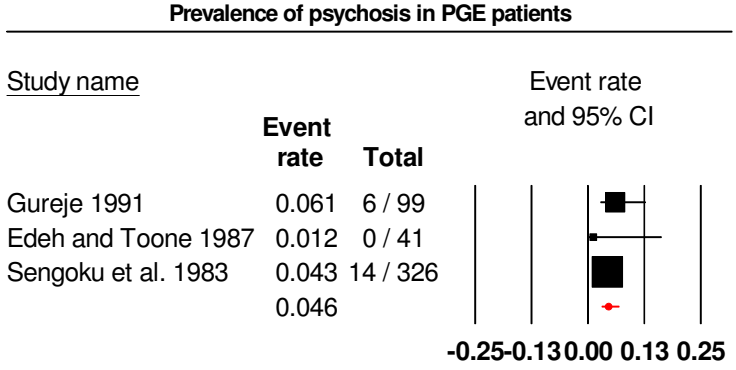

Figure 4. Third meta-analysis. Event rates of psychosis in primary generalized epilepsy (PGE).

Discussion

In the general population psychoses affect around 2% of the people, 1% gets schizophrenia. The risk of psychoses is greater for men than for women (Kirkbride et al., 2006;McGrath et al., 2008;Robins et al., 1984).

Only two studies included in the meta-analysis compared the percentage of psychoses in epilepsy patients with the percentage of psychoses in controls. In the study of Jalava and Sillanpaa, none of the 100 employee controls had psychosis. In the study of Mendez et al. schizophrenia was seen in 1.06% of the migraine patient controls (Jalava and Sillanpaa, 1996;Mendez et al., 1993).

According to these meta-analyses, 4.2% of all epileptic patients and 10% of TLE patients will be diagnosed with a form of psychosis. Thus, in temporal lobe epilepsy more psychosis occurs compared to general epilepsy.

The difference between the overall meta-analysis (4.2%) and the sub-analysis of PGE (4.6%) is minimal, suggesting that patients with PGE do not have a higher risk of psychosis than other epilepsy patients.

As expected, the percentage of the analysis with studies that included SLPE patients only was lower (2.8%) than the percentage of the meta-analysis when every type of psychosis was included (4.2%). The study of Qin et al. (2005) was a well performed study and was therefore included in a sub analysis. This study had a very large cohort size of 2.27 million people, of whom 34.494 were epileptic, and thus had a large influence on the event rate of this sub analysis. In this study, the percentages of epilepsies with schizophrenia (8%) and schizophrenia-like psychosis of epilepsy (1.5%) are given. The prevalence of general psychosis in epileptic patients is not included in the report; therefore the 2.2% is most likely an underestimation of the percentage of psychotic epileptics. In addition to this study, the study by Mendez et al. was included in the sub-analysis because this study also included schizophrenia (and SLPE) only (Mendez et al., 1993;Qin et al., 2005). The percentage of schizophrenia in epilepsy patients calculated in the sub-analysis (2.8%) is about half of the percentage of overall psychoses in epilepsy (4.2%), therefore schizophrenia accounts for about 50% and thus is probably the most prevalent type of psychosis in epilepsy patients.

The event rates found in this meta-analysis are not very high compared to some older studies. The comorbidity of epilepsy and psychosis is not as common as was thought in the studies by Curry et al. (1971), Gibbs and Gibbs (1952) and others that showed an incidence of up to 12% of psychoses in epilepsy patients (Currie et al., 1971;Gibbs and Gibbs, 1952).

The large difference in event rates can be explained by the fact that most studies, especially the older ones, show a lack of uniformity in the psychiatric assessment. Psychoses are not categorically described; there is for example a difference between confusional postictal psychosis, postictal manic psyschosis and interictal schizophreniform psychosis. Also the term psychopathology is used in the literature, but this term can refer to various types of psychiatric problems. It is not always clear which types of psychoses are included or which diagnostic criteria are used in the study (Mendez et al., 1993;Sachdev, 1998;Swinkels et al., 2005).

Also, seizure disorder and epilepsy are terms that are used interchangeable in the literature (Hyde and Weinberger, 1997). Nowadays it is more common to describe the precise methodology and use the DSM-IV or ICD-10 to define psychosis. Still, it remains a challenge to attain standardisation in the methodologies and thus to make a good comparison between studies.

The prevalence rates in the selected studies for this meta-analysis varied between 0.3% (Bredkjaer et al., 1998) and 18.8% (Filho et al., 2008) because methods, definitions and patient populations differed between studies (Devinsky, 2003;Krishnamoorthy, 2001). A possible explanation may be that different methods were used to define and asses psychosis across

studies (Cascella et al., 2009). The study of Gudmundson for example depends on the definition of epilepsy made by general practitioners from Iceland, although when in doubt the patients were telephoned to get extra information. Most of the epileptic patients were then visited by Gudmundsson and asked to fill in a questionnaire (Gudmundsson, 1966). The definition of psychoses was rather wide, a questionnaire was used for diagnosis, and the percentage could thus be an overestimation (Schmitz, 1995;Tellez-Zenteno et al., 2007). The study of Krohn et al. does not have a clear definition either, saying that the "mental states are fairly well-known". Also, patients who had had earlier psychotic episodes but had recovered were included (Krohn, 1961).
Moreover, the study types differed; studies that investigated the comorbidity of patients in a psychiatric clinic or hospital and excluded outpatients have an arguably unrepresentative patient population and could be overestimating the percentage of psychosis. Therefore we tried to include only those studies that had a representative sample of epilepsy patients.
In the study of Onuma et al. 1995, the patient population was derived from an adult epilepsy clinic and the authors themselves thought that the prevalence rate (0.096) was this high because the clinic was psychiatrically oriented. This could have had a small increasing effect on the calculated event rate (Onuma et al., 1995).
The meta-analysis is internationally well represented, including studies from Afrika, Europe, Amerika, Brazil and Japan. So this meta-analysis fairly represents the worldwide incidence of psychosis in epilepsy.
Gibbs and Gibbs 1952 suggested that schizophrenia and epilepsy might share a common pathology of the temporal lobe and Slater et al. 1963 suggested that schizophrenia in epilepsy should be separately classified as SLPE (Gibbs and Gibbs, 1952;Slater et al., 1963). Psychosis appears to be occurring twice as often in epileptic patients as in the general population. The prevalence of 4.2% is less than was suggested by older studies that had percentages of over 10%. The enhanced risk on psychosis in epileptics can be caused by a partly shared pathofysiology of both syndromes. But, one could argue that a brain with epileptic lesions is already messed up and is therefore already more vulnerable to other brain diseases. The brain damage in these patients can be the underlying cause of both epilepsy and psychosis. There is not enough evidence to suggest a genetically common onset, the aetiology of psychosis in epilepsy is probably dependent on multiple factors, just like psychosis itself (Toone, 2000).

Conclusion

Psychoses are more common in epileptic patients (4.2%) than in the general population (2%); the incidence is thus at least twice as much. The percentage of schizophrenia in epilepsy patients was 2.8%, thus schizophrenia is probably the most dominant type of psychoses in epilepsy patients.
As was expected from the literature, psychotic episodes occur more often in patients with temporal lobe epilepsy (10%) than in patients with other types of epilepsy (4.2%) or primary generalized epilepsy (4.6%). TLE seems to be a risk factor for psychosis. The difference between PGE and epilepsy in general is minimal, making it not likely that PGE patients have a higher risk of psychosis than other epilepsy patients.
Although the event rate of psychoses in epileptic patients is a notable increase, the association between epilepsy and psychosis is not so high as to immediately assume a shared final common pathway.

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