Cognitive impairment predicts social disability in persons with epilepsy

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SUMMARY
Introduction. Cognitive dysfunction is one of the main comorbidities of epilepsy which co-exists with seizures and contributes to the adverse impact of the disease on employment, education and interpersonal relationships. A fundamental question regarding cognitive dysfunction in epilepsy goes as follows: in comparison to seizures, what role does cognitive dysfunction play in causing social disability? The purpose of this review was to evaluate our understanding of the role cognitive impairment plays in social disability in persons with epilepsy (PWE). We systematically searched the medical literature and identified studies which assessed the impact of seizures and cognitive function on some aspect of social disability in PWE.

Results and Discussion. We identified 12 studies which adequately measured all variables in non-surgical cohorts, and 9 studies of cohorts following epilepsy surgery. We found evidence from non-surgical and from surgical series that cognitive variables strongly correlate with levels of social disability.

Conclusions. We conclude that efforts to better understand the origins of cognitive dysfunction in epilepsy and subsequently at developing treatment modalities will be needed in order to reduce the degree of social disability caused by the condition.

Key words: epilepsy • cognitive impairment • social disability

INTRODUCTION
The International League Against Epilepsy (ILAE) defines epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition (Fisher et al., 2005). This encompassing definition underlines that persons with epilepsy (PWE) not only experience seizures, but also disturbances in cognitive and psychiatric function. In addition, the definition points out that PWE experience high rates of social disability as a consequence of this condition. For instance, PWE are more likely to be unemployed (Elwes et al., 1991) and are more likely to live in poverty (Callaghan et al., 1992). The World Health Organization through the International Classification of Functioning, Disabilities and Health (ICF) uses the term social disability as an umbrella term for impairments, activity limitations and participation restrictions. In PWE, the degree of social disability is likely to be related to multiple overlapping factors, such as age of epilepsy onset, epilepsy severity, concurrent cognitive and psychiatric impairment, family support, access to medical care, access to education, social attitudes, etc.

The main strategy for limiting social disability in PWE has been the pursuit of seizure control. However, in 2012 the U.S. Institute of Medicine Report on Ep-
ilepsy proposed that treatment of epilepsy should not only focus on seizures, but also on its comorbidities (England et al., 2012). Epilepsy comorbidities include a multitude of somatic, psychiatric, and cognitive disorders which co-exist with seizures and contribute to the adverse impact of the disease. Our current understanding of the full impact of epilepsy comorbidities on everyday lives of PWE is in its infancy (Berg, 2011).

Research dating back to the 1950s has firmly established that one of the main comorbidities of epilepsy is cognitive dysfunction which ranges from mild memory impairment to severe intellectual disability (Hermann and Seidenberg, 2007; Berg, 2011; Meador, 2011). The underlying causes of cognitive dysfunction in PWE are multifactorial. They include the neurological insult which caused the seizures (e.g. encephalitis, traumatic brain injury, etc.), the seizures themselves, the ongoing epileptic interictal discharges (Kleen et al., 2013), and medication side effects (Park and Kwon, 2008; Bromley et al., 2011). The physiological mechanisms of cognitive dysfunction include neuronal death (Holmes, 2005), alterations in intraneuronal synaptic transmission (Lothman et al., 1995) and synaptic reorganization (Cavazos and Cross, 2006).

A fundamental question regarding the underlying causes of social disability in PWE goes as follows: in comparison to seizures, what role does cognitive dysfunction play in causing social disability? This question is difficult to study due to the complex, multivariate, and multidirectional web of relationships between seizures and epilepsy comorbidities.

With the goal to better understand the role cognitive dysfunction plays in social disability in PWE, we searched the medical literature for studies which measured all three variables: some aspect of seizure burden (i.e. seizure frequency, seizure type, age of onset of epilepsy, duration of epilepsy), some aspect of cognitive function (i.e. full scale IQ, working memory, language function, delayed recall) and some aspect of disability (i.e. years of education, rate of unemployment, relationship status, divorce rates). We excluded studies which measured only two of the above three variables (for instance, seizure burden and social disability but not cognitive function). Furthermore, we excluded studies which measured Health Related Quality of Life (HRQOL) as the main outcome measure because our goal was to understand the impact of epilepsy on social disability, and because psychiatric factors (i.e. depression) have a significant impact on measures of quality of life (Tracy et al., 2007). In addition, we excluded studies which measured the impact of “stigma” on disability in PWE.

RESULTS
Our initial search identified 5,283 studies. By reviewing titles and abstracts, and removing duplicates, this search was narrowed to 298 studies. Next, we separated the studies into ones investigating the above relationships in non-surgical and surgical (i.e. post-epilepsy surgery) series. 263 studies were included in the non-surgical group. 162 studies were excluded as they measured the impact of seizures on social disability but did not measure cognitive variables. 81 studies were excluded as the main measurement was “Quality of Life” rather than measures of social disability. 8 studies were excluded as they measured “stigma caused by epilepsy”, not disability. 12 studies met the final inclusion criteria. In the surgical group, 35 studies of disability following epilepsy surgery were identified. 8 studies were...
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Figure 1. Studies which met all three aspects of seizure burden, cognitive function and some aspects of social disability.

excluded as they did not measure cognitive function. 18 studies were excluded as they measured quality of life. 9 studies met the final criteria (fig. 1).

Description of Articles
The studies which met inclusion criteria spanned the years from 1966 to 2014. The non-surgical group included 8 cross-sectional studies where a cohort of epilepsy patients is selected and characterized (e.g. patients seen in outpatient clinic), and 4 longitudinal studies where a cohort of epilepsy patients was selected and followed for a period of time (tab. 1). The surgical group included nine longitudinal studies which investigated the effect of epilepsy surgery on social disability (tab. 2).

Patient selection
In most instances, selection of patients for studies in the non-surgical group was made by selecting consecutive patients from outpatient clinics and review of medical records. Notable exceptions were population wide studies (for instance, Camfield et al. and Chin et al.) which used unique referral patterns or nationally representative birth cohorts. Selection of patients for inclusion in the surgical series included consecutive patients who received a particular surgical treatment (i.e. temporal lobectomy) during a specified period of time.

Epilepsy type
Most studies in the non-surgical series included patients with diverse types of epilepsy, either controlled on medication or medically refractory, and included idiopathic generalized epilepsy, localization related epilepsy or symptomatic generalized epilepsy. Certain studies did not provide a definitive diagnosis for type of epilepsy. One study included only patients with well controlled epilepsy, three studies included only patients with refractory epilepsy. Most studies did not distinguish between primary generalized epilepsy and localization related epilepsy (tab. 1). In the surgical group, only patients with medically refractory localization related epilepsy treated with standard temporal lobectomy or extratemporal resections were included (tab. 2).

Seizure burden
In the non-surgical group, all studies selected with the exception of Williams et al. (2001) and Dickmen and Morgan (1980) included a detailed description of seizure variables. Descriptions included age of onset of epilepsy, duration of epilepsy, frequency of seizures, seizure type (i.e. simple partial, complex partial and generalized). Williams et al. reported only on whether seizures occurred, and did not include other epilepsy variables. Dickmen and Morgan (1980) provided only
Table 1. Studies included in the review which measured three aspects of epilepsy, namely seizures, cognition and social disability

| Author               | Epilepsy type | How was seizure burden measured? | How was cognition measured? | Which social disability was measured? | Finding                                                                 |
|----------------------|---------------|----------------------------------|-----------------------------|---------------------------------------|-------------------------------------------------------------------------|
| Dennerll et al., 1966| Refractory    | Frequency; type of seizure; age of onset; duration of epilepsy | NPT* employment            | employment                           | No difference in age of onset, duration of epilepsy, seizure type between employed and unemployed. Significant differences in full scale IQ, verbal IQ and performance IQ in employed vs. unemployed. |
| Batzel et al., 1980  | Refractory    | Type of seizure; age of onset; duration of epilepsy | NPT employment             | employment                           | Minimal effect difference on seizure variables between employed and unemployed. Strongest predictor was full scale IQ, performance IQ and years of education. |
| Dikmen et al., 1980  | Refractory    | Age of onset, and duration of epilepsy | NPT employment             | employment                           | Memory, alertness and mental flexibility correlate best with employment. |
| Camfield et al., 1993| Controlled and refractory | Frequency; type of seizure; age of onset; duration of epilepsy | Judgment of investigator employment, education, relationships | Seizure burden does not predict extent of social disability in adults. Strongest predictor of social disability in adult was the presence of learning disability as a child. |
| Kokkonen et al., 1997| Controlled and refractory | Frequency; type of seizure; age of onset; duration of epilepsy | Judgment of investigator employment, education, relationships | Seizure severity did not predict social outcomes. Borderline and low cognitive status predicts success with education, employment, cohabitation or marriage. |
| Williams et al., 2000| Controlled    | Seizure occurrence only           | NPT education, relationships | In children with history of epilepsy with normal cognitive performance and controlled seizures normal social outcomes. |
| Fastenau et al., 2004| Controlled and refractory | Frequency; type of seizure; age of onset; duration of epilepsy | NPT education             | No correlation of seizure type with education. Cognitive factors and family dynamic highly correlated. |
| Aldenkamp et al., 2005| Controlled and refractory | Frequency; type of seizure; age of onset; duration of epilepsy | NPT education             | Seizure type and seizure frequency does not predict educational impairment. Cognitive variables most important. |
| Caplan et al., 2005  | Controlled and refractory | Frequency; type of seizure; age of onset; duration of epilepsy | NPT education, relationships | Lower FSIQ, disruptive disorders, minority status and poor social communication predict social disability. Seizure variables not found to be important. |
| Wakamoto, 2000       | Controlled and refractory | Seizure occurrence, age of onset, epilepsy syndrome | Judgment of investigator employment, education, relationships | PWE and normal intelligence do not cause impairment in education and employment, but are associated with slightly lower marriage rates compared to age matched controls. PWE and mental retardation are associated with low education, employment and marriage rates. |
| Sinlapaa et al., 2010| Controlled and refractory | Epilepsy syndrome                | Judgment of investigator and partial NPT | Employment rates in patients with epilepsy correlate with measures of generalized intelligence. |
| Chin et al., 2011    | Controlled and refractory | Frequency; type of seizure; age of onset; duration of epilepsy | NPT education, relationships | Social outcome (employment, marriage, education rates) is dependent on cognitive development but is not dependent on seizure variables. |

*Neuropsychological testing.
### Table 2. Studies which assessed the impact of seizures and cognitive function on employment status following epilepsy surgery

| Author | Surgery type | Number of patients | Years of follow-up | Statistics | Finding |
|--------|--------------|--------------------|--------------------|------------|---------|
| Augustine et al., 1984 | Temporal and extratemporal | 32 | At least 2 years | Univariate | Employed and unemployed groups differed in pre-surgical performance IQ. Transition from under-employed to employed was predicted by post-surgical seizure control, and post-surgical performance IQ. Change from pre to post-operative cognitive function on employment was not assessed. |
| Sperling et al., 1995 | Temporal lobectomy | 86 | 3.5 to 8 years | Univariate | Improvement in employment following surgery was related to seizure control. Pre-operative cognitive variables did not predict post-surgical improvement in employment. |
| Lendt et al., 1997 | Temporal and extratemporal | 151 | 3 years | Preoperative MANOVA, post-operative multivariate logistic regression | Preoperative MANOVA revealed a significant effect of seizure variables but no significant effect of cognitive variables on employment. Post-surgical seizure freedom was related to change in employment status. Improvement in post-operative cognitive performance correlated with employment status; attention was found to be most predictive of employment status. |
| Reves et al., 1997 | Temporal lobectomy | 190 | 4.2 years | Multiple univariate and multivariate logistic regression | In univariate analysis, post-operative employed and unemployed groups differed in degree of seizure control, but not in FSIQ. Multivariate analysis did not reveal a significant effect of seizure variables or cognitive variables on employment. |
| Helmstaedter et al., 2003 | Temporal lobectomy | 147 | 1 year | Univariate | A significant effect of post-operative seizure control on employment and education was observed. The group with decreased memory function following surgery had a lower work and school status at follow-up. |
| Dulay et al., 2006 | Temporal lobectomy | 90 | 11.3 months | Univariate | There was no change in employment rate following epilepsy surgery. There was no significant effect of post-surgical seizure control on employment. Significant interaction between post-operative IQ and employment status. |
| Zarolli et al., 2011 | Temporal lobectomy | 369 | At least 4 years | Univariate and logistic regression | Employment rate improved following surgery and was related to seizure control. No significant effect of pre-operative IQ on change of employment status (i.e. either unemployed to employed or vice versa) following surgery. Seizure freedom following surgery was found to be best predictor of employment after surgery. |
| Andersson-Roswall et al., 2013 | Temporal lobectomy | 51 | 10 years | Univariate and logistic regression | No improvement in employment following surgery. Seizure control correlates with employment status. No effect of verbal IQ on post-operative employment. |
| Thorbecke et al., 2014 | Temporal lobectomy | 232 | 2 years | Univariate and logistic regression | Significant improvement in employment only in group who underwent vocational rehabilitation. Found significant effect of IQ on employment status prior to surgery. IQ was not found to be a predictor of post-operative employment status. |

A partial description of seizures. In the surgical group, most studies did not provide detailed descriptions of seizure frequency, but did provide age of epilepsy onset and type of seizure.

**Cognitive assessment**

In the non-surgical group, all studies with the exception of Camfield et al. (1993), Kokkonen et al. (1997) and Wakamoto et al. (2000) performed standard neuropsychological assessments. Testing included a wide range of both generalized (e.g. Wechsler Adult Intelligence Scale) and more domain-specific cognitive testing (e.g. Boston Naming Test). All three studies utilized only investigator judgment to assess whether each patient had normal or abnormal intelligence. All studies in the surgical group utilized standard neuropsychological testing.
Type of social disability

In the non-surgical group, academic achievement was assessed in 7 of 10 studies, employment in 6 of 10 studies, and personal relationship status was measured in 4 of 10 studies. All studies utilized either standardized scales or structured history to obtain the information. In the surgical group, the impact of seizures and cognitive factors on post-operative disability was assessed for employment in 9 studies, for educational success in 1 study, and no studies assessed seizures and cognitive influence on post-operative relationship success.

Statistical Methods

In the non-surgical group, two studies compared groups using only univariate models. This included Student t-test and chi-squared analysis to test for differences between epilepsy groups with different disability outcomes (Dennerll et al., 1966; Wakamoto et al., 2000). Most investigators utilized multivariate statistical models (i.e. multivariate regression or ANOVA) to test the relative impact of seizure burden and cognitive variables on disability (Batzel et al., 1980; Dikmen and Morgan, 1980; Camfield et al., 1993; Kokkonen et al., 1997; Williams et al., 2001; Fastenau et al., 2004; Aldenkamp et al., 2005; Caplan et al., 2005; Sillanpää and Schmidt, 2010; Chin et al., 2011). In the surgical group, univariate and multivariate statistical analysis were performed on the impact of seizure control vs. cognitive status on employment and education.

Overview of Findings

Impact of cognitive variables on social disability, non-surgical series

In the non-surgical group, the two studies which utilized univariate statistical models found no difference between groups with and without disability (employment and educational success) with regards to seizure variables. The two same studies found significantly lower cognitive scores in patients in the unemployed group or with lower educational success (Dennerll et al., 1966; Wakamoto et al., 2000). Furthermore, in the non-surgical group, all studies which utilized multivariate statistical models found that cognitive variables had a stronger impact on employment (Batzel et al., 1980; Dikmen and Morgan, 1980; Camfield et al., 1993; Kokkonen et al., 1997; Sillanpää and Schmidt, 2010; Chin et al., 2011), education (Camfield et al., 1993; Kokkonen et al., 1997; Williams et al., 2001; Fastenau et al., 2004; Aldenkamp et al., 2005; Caplan et al., 2005; Chin et al., 2011), and relationships (Camfield et al., 1993; Kokkonen et al., 1997; Chin et al., 2011) than seizure variables.

A wide variety of statistical results were reported. Studies reported a correlation coefficient of neuropsychological impairment to education of \( R = 0.6 \) with no significant impact of seizure variables (Batzel et al., 1980). Furthermore, memory, alertness, and mental flexibility correlate best with employment with ANOVA F values between 9.18 and 21.52 (Dikmen and Morgan, 1980) with no significant effect of seizure variables. Relative risk of poor social maturation was highest for cognitive impairment (1.8) and history of learning disability (2.4) vs. diagnosis of epilepsy itself (0.6) (Kokkonen et al., 1997). Academic achievement correlated with measures of verbal IQ (\( R^2 = 0.62 \)) and attention (\( R^2 = 0.64 \)) while no significant impact of seizure type and duration of epilepsy were associated with differences in academic performance (Williams et al., 2001). Multiple-factor analysis found verbal/memory/executive cognitive functions most predictive of educational achievement explaining 56% of the variance with minimal influence of seizure variables (Fastenau et al., 2004). Multivariate ANOVA analysis of educational underachievement found an impact of intelligence (\( F = 10.174; p < 0.001 \)) but not seizure type (\( F = 0.665; P = 0.5 \)) (Aldenkamp et al., 2005). ANOVA analysis of factors important in academic achievement revealed a strong impact of full scale IQ (\( F = 29.93; P < 0.0001 \)) with no significant effect of seizure variables. Multivariate analysis revealed significant prediction of learning disability (\( P < 0.0001 \)) and seizure frequency (\( P = 0.03 \)) on academic achievement, unemployment, and social relationships (Camfield et al., 1993). Cognitive variables were predictive of the educational achievement (OR 1.06, 95% CI 1.06–1.07) and employment (OR 1.04, 95% 1.03–1.05) while type of epilepsy was not a good predictor (Chin et al., 2011). Lastly, multivariate analysis revealed that employment correlated with cognitive variables (normal intelligence vs. near normal intelligence OR 14.5, \( P < 0.0001 \)) but not with epilepsy type.

Impact of cognitive variables on social disability, surgical series

Seven of 9 studies included in the surgical series found significant improvement in employment following epilepsy surgery with two studies finding no change in employment status (Dulay et al., 2006; Andersson-Roswall et al., 2013). All 7 studies which found a significant improvement in employment rates, following epi-
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Epilepsy surgery, found seizure control to have the strongest correlation. Two studies reported significant correlation between lower pre-operative cognitive scores and pre-operative employment rate (Augustine et al., 1984; Thorbecke et al., 2014). This is consistent with the non-surgical literature as described above. The impact of pre-surgical cognitive variables on post-operative employment rate was reported by various investigators but the findings are inconclusive with most investigators reporting no correlation (Augustine et al., 1984; Sperling et al., 1995; Reeves et al., 1997; Zarroli et al., 2011; Andersson-Roswall et al., 2013; Thorbecke et al., 2014), and some reporting a correlation (Lendt et al., 1997; Helmstaedter et al., 2003; Dulay et al., 2006).

Cognitive domains which predict disability

In the non-surgical series, measures of generalized intellectual functioning and history of learning disability correlated with employment (Dennerll et al., 1966; Batzel et al., 1980; Dikmen and Morgan, 1980; Camfield et al., 1993; Williams et al., 2001), education (Camfield et al., 1993; Aldenkamp et al., 2005), and social relationships (Camfield et al., 1993; Caplan et al., 2005; Chin et al., 2011). Rates of unemployment also correlate well with measures of memory, alertness, and mental flexibility (Dikmen and Morgan, 1980). Furthermore, levels of unemployment correlate with cognitive measures of social competence, social adaptive abilities, Social Presence Scale and the Capacity for Social Status Scale (Dennerll et al., 1966; Batzel et al., 1980). In addition, levels of attention, working memory, and psychomotor speed correlated with educational success (Williams et al., 2001; Fastenau et al., 2004). Lastly, rates of social isolation correlated with social competence scores (Caplan et al., 2005).

In the surgical series, Augustine et al. (1984) found a significant difference in post-surgical employed vs. unemployed groups in performance IQ with no difference in verbal IQ. Lendt et al. (1997) found that change from preoperative unemployed to post-operative employed was predicted by good cognitive outcome of surgery, with attention being a predictor of this change. In addition, Helmstaedter et al. (2003) found that lower memory scores following surgery correlated with lower school performance.

DISCUSSION

Epilepsy is a complex neurocognitive disorder with many factors contributing to the overall degree of social disability, including seizures, cognitive dysfunction, psychiatric dysfunction and others. We reviewed the literature with a goal to better understand the impact of cognitive dysfunction on employment, education, and relationships of PWE. Although the relationship between cognitive impairment and epilepsy is well established, the relative impact of cognitive dysfunction on social disability is not well understood.

In our review of non-surgical series, all six studies which measured rates of unemployment found that the rate correlated better with cognitive variables than with seizure variables. Furthermore, all seven studies which measured educational achievement reported that it correlates better with cognitive variables than with seizure variables. Lastly, all four studies which measured relationship status found that cognitive variables correlate better with rates of divorce than with seizure variables.

In the surgical series, cognitive factors were generally found to correlate well with employment status prior to epilepsy surgery. Unfortunately, none of the surgical series assessed the relative effect of seizure vs. cognitive variables on pre-surgical social disability. In post-surgical analysis, all nine studies found a strong correlation between improvements in employment rates and seizure control. Two of nine studies found that cognitive variables also impact transition from pre-surgical unemployed status to post-surgical employed status, while seven found that cognitive factors are not important. A single study found significant correlation between cognitive outcome and educational achievement following surgery.

The findings from the review of the non-surgical series provide ample evidence that both in patients with medically controlled and medically refractory epilepsy, the degree of social disability correlates highly with cognitive function and to a smaller extent with the degree of seizure burden. The finding from surgical series provide evidence that cognitive function has a significant effect on levels of pre-surgical employment, however correlate rather poorly with transition from unemployed to employed status following epilepsy surgery where seizure burden variables dominate. This effect of cognitive function on pre-surgical employment rates is consistent with that found in non-surgical series as discussed above. Furthermore, the lack of effect on post-operative employment is not surprising given that epilepsy surgery generally has a limited impact on cognition.

In addition to correlating with many generalized
cognitive measures, the degree of social disability correlates with certain domain-specific measures. Not surprisingly, these include many measures of frontal lobe function, such as mental flexibility (Dikmen and Morgan, 1980), working memory, psychomotor speed (Williams et al., 2001; Fastenau et al., 2004), and attention (Lendt et al., 1997). Furthermore, several authors report correlation between employment success and rates of marriage/social isolation and variety of social cognitive measures (Dennerll et al., 1966; Batzel et al., 1980; Caplan et al., 2005). These findings add validity to the emerging field of social cognition which proposes that a specific set of cognitive skills (i.e. theory of mind, emotional regulation, etc.) is important in social interaction and dysfunction of which may lead to social disability (Walpole et al., 2008; Broicher et al., 2012). Lastly, the finding of Augustine et al. (1984) that performance IQ correlates better with employment then verbal IQ is surprising, but adds validity to non-verbal IQ measures.

There are many limitations to the conclusions reached in this review. Firstly, we report here only the correlation between cognitive measures, measures of seizure burden and social disability. Strong causative inferences should not be drawn from this data. Therefore, no statements can be made on the direction of influence between cognition, seizures and social disability; only that a relationship exists. In addition, we treat cognitive function, seizures and social disability as independent variables whereas a more complex inter-related model would be more reflective of the real life of PWE. For instance, the impact of seizures on breaks in education, and subsequently leading to unemployment cannot be considered but is likely to be a real factor. Secondly, there are many other variables which likely contribute to disability in PWE, including psychiatric disturbances, degree of social acceptance (i.e. stigma of epilepsy) and the degree of family support. We did not consider these variables. Thirdly, the populations of patients in these studies are generally from academic medical centers and therefore tend to be less representative of the population as a whole, although it is comforting that population wide studies reviewed in this review have similar conclusions (i.e. Camfield et al., 1993).

CONCLUSIONS
Cognitive dysfunction is strongly related to degree of social disability in PWE. Efforts to better understand the origins of cognitive dysfunction in epilepsy and subsequently at developing treatment modalities will be needed in order to reduce the degree of social disability in the condition.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

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