Neurodegenerative processes in temporal lobe epilepsy with hippocampal sclerosis: Clinical, pathological and neuroimaging evidence

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Cognitive decline is increasingly described as a co-morbidity of temporal lobe epilepsy (TLE). Mechanisms underlying cognitive impairment are not fully understood despite examining clinical factors, such as seizure frequency, and cellular mechanisms of excitotoxicity. We review the neuropsychometry evidence for progressive cognitive decline and examine the pathology and neuroimaging evidence supporting a neurodegenerative process in hippocampal sclerosis (HS)-related TLE. Accelerated cognitive decline is described in groups of adult HS-related TLE patients. Large childhood studies show early onset of seizures result in poor development of verbal memory and a hindrance in achieving cognitive potential. We discuss HS classification according to different patterns of neuronal loss and correlation to post-temporal lobectomy cognitive outcomes in refractory TLE patients. Factors such as lateralization of HS pathology, neuronal density and sub-type have correlated with varying significance between different studies. Furthermore, alterations in neuronal maturity, regenerative capacity and aberrant connectivity appear to affect cognitive performance post-operatively suggesting a complex multifactorial process. More recent studies have identified tau pathology being present in HS-related TLE and correlated to post-operative cognitive decline in some patients. A traumatic head injury-related or novel tauopathy has been hypothesised as an underlying process. We discuss the value of prospective and cross-sectional imaging in assessing cognition and review volumetric magnetic resonance studies with progressive ipsilateral hippocampal atrophy identified to correlate with seizure frequency. Finally, we consider the use of positron emission tomography biomarkers, such as tau tracers, and connectivity studies that may examine *in vivo* pathways and further explore cognitive decline in TLE.

Abbreviations

TLE – Temporal lobe epilepsy

HS – Hippocampal sclerosis

DG – Dentate gyrus

MRI – Magnetic resonance imaging

PET – Positron emission tomography

FDG - ^{18}F-fluorodeoxyglucose

Introduction

Temporal lobe epilepsy (TLE) is the most prevalent form of chronic epilepsy with hippocampal sclerosis (HS) being the most common primary pathology, representing 36% of all focal epilepsy pathologies in a recent Europe-wide surgical series [1] . Cognitive decline is an increasingly recognised co-morbidity of TLE with higher prevalence of dementias, such as Alzheimer's disease, compared to the general population [2]. Underlying mechanisms driving cognitive decline have been investigated; Clinical factors such as seizure frequency and cellular mechanisms as excitotoxicity, though important, do not clearly correlate directly to the cognitive trajectory. This review will focus primarily on HS-related TLE which we will refer to as TLE unless specified otherwise. We will examine the evidence for ongoing cognitive impairment in TLE patients and the pathological and neuroimaging evidence suggesting a neurodegenerative process may be contributory to cognitive decline.

Does temporal lobe epilepsy cause cognitive deterioration? If so, who declines? What declines? And why?

In the Journal of Mental Science, Dr Manley described TLE as a condition '*where the mind has never been developed and we have the idiot whose course is generally cut short in early life'* or where '*some considerable amount of intelligence has been developed, but is afterwards destroyed by successive convulsive attacks'*[3].These ideas persisted well into the 20th century. As late as 1940's, in the film 'Dr Kildare's Crisis', the fictional eponymous doctor explained to a patient who he had just diagnosed with epilepsy that he faced '*a gradual disintegration of the brain, probable insanity and a wretched living death'*. This example, despite its fictional nature, reflects the view of epilepsy as a progressive condition. Modern science has identified many factors that can contribute to cognitive dysfunction in people with TLE including the underlying pathology and the impact of seizures, comorbidities and treatments [4] (Figure 1). Until recently, however, relatively little was known about the trajectory of cognitive function in people with TLE.

Cognition is not a static function, but it changes throughout the lifespan with different functions developing and declining at different rates (Figure 2)[5]. The impact of TLE on cognitive dysfunction can only really be appreciated if it is studied within this developmental framework, across the lifespan.

Helmstaedter & Elger (2009) [6] reported the results of a cross sectional design examining the verbal memory functions of over 1000 people with TLE aged between 6 and 80 years. The authors illustrated

how people who developed epilepsy in childhood demonstrated a hindrance in their development of verbal memory skills with a slower progression and premature plateau of abilities compared to healthy controls (Figure 3).

After development, verbal memory skills were not subject to an accelerated deterioration over the lifespan however the TLE group plateaued earlier and started their normal age related deterioration from a lower 'peak' performance. The TLE group reached levels of impairment much earlier in life than their healthy peers. In this study, the mean performance of TLE patients aged 50-60 years was comparable to that of the healthy control group aged around 80 years.

In a similar cross sectional design, we examined whether the same trajectories were evident in other cognitive functions in a large group of un-operated TLE patients (n=382) [7]. Consistent with Helmstatedter & Elger's study we found no evidence for accelerated cognitive decline on tests of verbal learning, visual learning, verbal and performance IQ and working memory, but the developmental hindrance identified in the previous study was evident in all cognitive domains. These findings raise two important questions: Firstly, what accounts for the developmental hindrance in a wide spectrum of cognitive functions in people who develop TLE in childhood. Secondly, whilst not evident in group studies, clinical experience tells us that a subset of people with TLE do experience accelerated cognitive decline. Who are these patients and why does this happen?

What accounts for the hindrance in cognitive development in TLE?

There are a number of factors that can contribute to the hindrance of cognitive development in children who develop epilepsy including the underlying pathology, the physiological and psychological impact of seizures as well as the side effects of antiepileptic medications.

Common underlying epileptogenic pathologies in TLE, apart from HS, include focal malformations (in particular Focal Cortical Dysplasia) and Low Grade Epilepsy Associated Tumours (LEAT). Dysembryoplastic neuroepithelial tumours (DNET) is a main subtype of LEAT [8]. DNETs are cortically based, hypodense lesions most commonly located in the temporal lobes. They are associated with medically intractable epilepsy, usually presenting with focal seizures. DNETs were originally thought to be associated with an onset of seizures before 20 years of age [9] however subsequent studies suggest adult seizure onset in up to one in four people[10]. DNET patients with an adult onset of seizures share the same underlying pathology as those with childhood onset but their first two decades are unaffected by seizures. Thus, DNET patients provide a natural model to examine the specific influence of seizures

and their treatment on cognitive development in childhood, over and above the effects of the underlying pathology.

Baxendale *et al.* (2013) [11] examined the cognitive profiles of 56 adult DNET patients with medically intractable epilepsy. 60% of the sample had an onset of seizures prior to the age of 12 years. The childhood onset group had significantly lower scores on measures of verbal IQ, performance IQ, reading, naming and verbal memory compared to those with an onset of seizures after the age of 12 years. This study indicates that seizures and their treatment in the first twelve years of life are associated with developmental hindrance in core cognitive abilities resulting in a pattern of cognitive underfunction that remains apparent in adulthood.

The specific contribution of antiepileptic medications to cognitive dysfunction in epilepsy has been examined by the Standard And New Antiepileptic Drug (SANAD) study[12]. Taylor *et al.* (2010) compared the cognitive profiles of 155 newly diagnosed untreated epilepsy patients to healthy volunteers using comprehensive neuropsychological testing. The patients with epilepsy obtained lower scores on tests of memory and psychomotor speed. Cognitive performance was not related to the number of seizures the patient had experienced (although the variance was low given that this was a newly diagnosed group). Over half of the group had at least one score more than two standard deviations below the control mean. These findings indicate that many newly diagnosed patients are cognitively compromised prior to starting antiepileptic drug treatment.

Clinical factors associated with accelerated cognitive decline in temporal lobe epilepsy

Whilst accelerated cognitive decline is not apparent in large group studies, there are subsets of patients with epilepsy who undoubtedly demonstrate cognitive deterioration over time. In a longitudinal study, Thompson & Duncan (2005) [13] examined the cognitive trajectories of 136 patients with medically intractable epilepsy over 10 years. The sample was biased as patients were included partly on the basis of their cognitive complaints, but the authors found that cognitive decline over time was severe and widespread in this group. The strongest predictor of cognitive decline was the frequency of generalised tonic clonic seizures. Frequent complex partial seizures were associated with deteriorations in measures of memory and mental flexibility but not measures of intellect.

Whilst gradual declines in function are associated with generalised seizures, stepwise deterioration in cognitive functions have also been reported following status epilepticus [14]. Frequent drop attacks, resulting in multiple head injuries are also associated with cognitive deterioration[15]. Studies

examining repetitive mild traumatic brain injury have linked the cognitive deterioration to neurofibrillary tangles of hyperphosphorylated tau [16, 17]. Tau pathology is not just implicated in the cognitive decline seen in patients who experience drop attacks, but are beginning to be recognised in TLE groups [18]. Although cognitive decline in TLE is generally thought to be irreversible, normalisation of function can be seen in other epileptic syndromes such as patients with acquired autoimmune limbic encephalitis who respond well to immunotherapy [19, 20].

Cognitive deterioration in TLE can also be accelerated by lifestyle factors. In the general population, obesity is associated with accelerated age-related cognitive decline. Baxendale *et al.* (2015) [21] explored the relationship between obesity and cognitive underfunction in 81 people with medically intractable epilepsy. Controlling for education and socio-economic factors, they found that the obese patients had a greater degree of suboptimal processing speed and demonstrated a lower IQ measure compared to the healthy weight group. All measures of memory function were significantly correlated with BMI, with poorer scores associated with higher BMIs. The authors concluded that a small but significant proportion of the variance in memory function and intellectual underfunction in people with epilepsy was explained by BMI. It remains to be seen whether a reduction in BMI to within healthy limits is associated with improvements in cognitive function in this group.

Cognitive trajectory in post-temporal lobectomy patients is a debated topic. Several studies have found cognitive decline at one year or longer post-temporal lobectomy with age, left-sided resection and ongoing seizures identified as important factors [22, 23]. There is evidence to suggest that cognitive decline can be stopped or even reversed when seizures are controlled [24]. However, Thompson et al. (2015) examined different age groups post temporal lobectomy showing that the oldest cohort, 50 years and above, had the greatest decline in verbal memory testing and seizure freedom was not associated with memory outcomes [25]. An explanation for further cognitive decline despite removal of the epileptogenic source is an underlying pathological process that we will discuss below.

Therefore, people with TLE as a group perform more poorly than healthy controls on tests of memory and intellectual function. The diagnosis of TLE in childhood is associated with a hindrance in the development of cognitive function and a plateau in the development of cognitive function earlier than healthy controls. Underlying pathology, seizure frequency and their treatment are all thought to contribute to this developmental hindrance. There is evidence to suggest ongoing decline of cognition post-temporal lobe surgery in TLE patients however other studies suggest normalization of cognition. Group studies do not provide support for accelerated cognitive decline in TLE in adulthood as inevitable

but a subset of people with the condition do experience a progressive decline in function. Progressive decline is associated with frequent generalised convulsions, episodes of status epilepticus and the repetitive brain injuries that can be associated with frequent drop attacks and head injury. Although cause and effect is difficult to establish, these seizure variables may be biomarkers for a different or more severe condition or an underlying global pathology that may explain ongoing decline in a subset of TLE.

Temporal lobe epilepsy as a neurodegenerative disease: pathology and cognitive dysfunction

Pathological evidence of neurodegeneration in TLE is derived from study of both post-mortem and surgical specimens ; the latter, while limited in size, can offer important insight as the temporal lobe is the neuroanatomical basis of memory, a key domain of cognition. Furthermore, study of surgical patients allows the opportunity to perform ongoing clinical assessment and even prospective studies on cognition. By comparison in post-mortem studies, cognitive assessments when available are retrospective and if done in the months prior to death may include several confounding factors related to end of life circumstances.

Hippocampal sclerosis: Patterns of neuronal loss, reorganisation and memory function

Hippocampal sclerosis (HS), a term often used interchangeably with mesial temporal lobe sclerosis (MTLS), is the most common pathological finding in TLE and involves neuronal loss mainly within the hippocampus and also the amygdala and entorhinal cortex [26]. The incidence of HS in TLE varies between studies, ranging from 43% to 73% [27, 28]. Clinical evidence supports that initial precipitating injury at an early age, most commonly a prolonged febrile seizure, is involved as the initial event in many cases [29] (Figure 1).

The 2013 International League Against Epilepsy (ILAE) classification of HS provides pathological identification of three distinct subtypes aimed at providing clinical predictive value based on the patterns of neuronal loss. HS type 1 involves neuronal loss in the CA1, CA3 and CA4 region while HS type 2 involves CA1 neuronal loss only. HS type 3 describes neuronal loss restricted to CA4. Hippocampal specimens showing reactive gliosis with little/no neuronal loss are classified as "no-HS" [30]. HS sub-type has shown clinical correlation with age of precipitating injury [31], early seizure onset, longer

epilepsy duration prior to surgery [32]and also long term seizure outcome post-temporal lobectomy [33].

Temporal lobe surgery has offered a unique opportunity to correlate pathology with memory dysfunction. Earlier studies examined neuronal cell loss and neuronal density in the hippocampus in relation to cognitive testing [34-36]. More recent studies examine for HS subtype, dentate gyrus (DG) neuronal loss and gliosis as well as network reorganizational changes. This correlation aims to elucidate normal anatomical mnemonic pathways, networks and their potential disruption and reorganization in epilepsy.

HS subtypes investigated for specific memory impairments, both pre- and post-operatively, show varying results between studies. A study of 100 TLE patients post-temporal lobectomy showed preserved pre-operative declarative memory with HS type 2 (CA1 neuronal loss only) [37]. Similar findings were shown in a smaller study involving 36 patients [38]. These studies concluded that CA1 neurones were less critically involved in memory function. Another study, however, showed that that neuronal loss in all hippocampal CA regions, with the exception of CA2, correlates to memory performance [39]. Other studies indicate that involvement of the left hippocampus rather than specific sub-type or hippocampal CA region is the main factor leading to memory impairment [40]. Prada-Jardim *et al.* (2017) investigated HS pathology with MAP2 immunohistochemistry and showed that no single HS sub-type correlated significantly with pre- or post-operative memory dysfunction [41]. It is likely that interplay between several pathological factors including neuronal loss in hippocampal subfields leads to cognitive dysfunction [41]. In the dentate gyrus (DG), which harbours multipotent progenitor cells in adults [42], reduced regenerative capacity as well as DG volume loss has been linked to poor pre-operative cognitive function [37, 39, 43]. Calbindin expression within the DG granular cell layer, as a marker of granule cell maturity, has shown reduced expression in TLE that correlated with verbal memory impairment even when no HS was detected [44].

Mossy fibre pathway reorganisation, a common and early alteration in HS/TLE, leads to aberrant connectivity and can be specifically visualised with zinc labelling using Timms preparation or zinc transporter protein (ZnT3) immunohistochemistry. An intact mossy fibre pathway has been associated with preserved verbal memory [41] while anatomical preservation of CA4/3 myelinated fibers connecting to the fimbria and subiculum was associated with intact memory function [37]. Interestingly, in the rat model, altered zinc signalling in the dentate gyrus has been shown to affect object recognition memory [45]. Studies therefore demonstrated a complex interplay between several acquired

pathological processes occurring in HS-related TLE contributing to memory deficits on psychometric testing as summarised in Table 1.

There is substantial evidence, particularly from experimental models (see also the review in this issue 'Animal models of acquired injury') , that this initial acquired neuronal loss in HS is mediated by seizures or excitotoxic injury [46, 47] and evidence for progressive neuronal loss or neurodegenerative processes are not prominent at this initial stage. The additional roles of mTOR pathway activation in mossy fibre pathway reorganisation [48-50] and pro-inflammatory cytokines, such as IL-1β and NFKappaB in mediating neuronal loss (see review in this issue 'Neuroinflammation and epilepsy'), have also received recent attention [51-53] but any further effects on long term cognitive outcomes have not been well studied.

Neurodegenerative processes in HS

In the elderly or 'oldest old' a pattern of hippocampal sclerosis is increasingly recognised, accompanied by accumulation of neuronal TPD-43 protein and associated with dementia [54]. Although there is no evidence of TDP-43 protein accumulation in HS associated with TLE [55, 56] there is increasing interest regarding a progressive neurodegenerative process superimposed on the pre-existing sclerosed hippocampus. Neurodegeneration is mainly defined by specific neuronal accumulations or modified proteins (or defects in their degeneration and cell autophagy) with a stereotypical, sequential involvement that reflects the progressive clinical picture [57]. In focal epilepsy pathologies, including cortical malformations as focal cortical dysplasia [58, 59], neuronal tangles, tau and p62 have been demonstrated in young adults and premature activation of neurodegenerative pathways observed in glioneuronal tumours [60]. In frontal lobe epilepsy series abnormalities of neuronal autophagy and protein accumulation has been recently shown in the seizure onset zone [61]. These observations suggest enhanced susceptibility to neurodegenerative processes in focal epilepsies.

Alzheimer's disease, the most common form of dementia, has a clear epidemiological link to chronic epilepsy with a higher prevalence ratio 6.3 recorded in the UK general practice research database and a similar trend seen in cross-sectional data from Canada [62, 63] and patients with mild to moderate Alzheimer's disease have an 87-fold increased risk of epilepsy compared to age-matched controls [64]. Extracellular amyloid-β plaques are a pathological hallmark of Alzheimer's disease and considered one of its main drivers of neurodegeneration [65]. Disease models indicate amyloid-β accumulation begins

within the temporal lobe and, specifically, the hippocampus resulting in a dementing disease predominantly affecting memory during early stages [66]. A small study of eight epilepsy patients found immunoreactive amyloid-β precursor protein expressed within temporal lobectomy tissue in higher amounts than age-matched controls [67]. A larger study compared 101 temporal lobectomy specimens with 406 post-mortem controls showed age-accelerated presence of senile plaques in 10% of the epilepsy cohort [68]. This correlated to the Alzheimer's disease risk genotype ApoE ε4 [69].Tai *et al.*(2016) identified Amyloid-β plaques in 15% of cases in series of surgical specimens aged between 50 to 65 years of age but there was no relationship with cognitive outcomes post-operatively. A post-mortem series of 138 patients with chronic epilepsy identified amyloid-β plaques in 44% of the cases with no correlation to pre-mortem cognitive testing [56]. The literature suggests that amyloid-β is present in higher than expected amounts in epilepsy patients, however the clinical significance of this is unclear.

Intracytoplasmic aggregation of α-synuclein, a small protein physiologically localised within neuronal synapses, forms pathological inclusions in several neurodegenerative diseases including Parkinson's disease, dementia with Lewy bodies as well as the Lewy body variant of Alzheimer's disease [70, 71]. One study of eight TLE patients identified an upregulation of α-synuclein within the supragranular region of the DG [72]. Interestingly, status epilepticus mouse models using pilocarpine induction show an increase in Western blot analysis α-synuclein expression within dentate lysates along with several other synaptosomal proteins [73]. An investigation into 67 epilepsy patients identified higher concentrations of α-synuclein within cerebrospinal fluid and serum in patients with intractable, refractory epilepsy compared to newly diagnosed epilepsy patients [74]. These studies likely signify synaptic impairment or disruption with abberant connectivity and electrical activity of chronic seizures. No studies have examined α-synuclein pathology in relation to neuropsychometric assessment or cognitive decline in TLE.

Tau hypothesis in HS

There is a modest literature examining tau within epilepsy with more recent studies identifying a correlation with cognitive co-morbidity. The microtubule associated protein tau is a natively unfolded protein involved in several physiological roles including microtubule assembly, stabilisation and axonal transport within neuronal cells [75]. *MAPT* is found on chromosome 17 and has two haplotypes H1 and H2 [76].

Tau pathology may occur from post-translational modifications resulting, most commonly, in hyperphosphorylation of tau protein [77]. Hyperphosphorylated tau is a key component NFTs and Pick bodies which are the pathological hallmarks to a group of neurodegenerative diseases known as tauopathies classically including Pick's disease, progressive supranuclear palsy and corticobasal degeneration [78]. NFTs are also found in Alzheimer's disease as the second pathological entity driving neurodegeneration along with Amyloid-β [65]. Chronic traumatic encephalopathy (CTE) is a more recently described tauopathy resulting from concussive head injuries or other environmental causes such as repetitive blast injuries [79]. Recently, the role of tau has been investigated in Huntington's disease with hyperphosphorylated tau identified in a cohort of patients with some co-localisation with mutant huntingtin protein. A correlation was also identified between MAPT haplotypes and cognitive decline in a larger Huntington's disease cohort[80].

A post-mortem series of 138 refractory epilepsy patients showed that NFTs were detected with an age-accelerated pattern of Braak stages III/IV in the middle-age group (40 to 60 years) compared to age-matched controls [56] (Figure 5a). Interestingly, NFTs were found in both hemispheres with more tau accumulation in the hemisphere contralateral to the side with hippocampal sclerosis (Figure 5b). While this study did not identify a correlation between higher Braak stages and cognitive scores, these clinical assessments were performed over variable periods prior to death and open to several confounding factors. Of significance, however, pathological evidence of head trauma was associated with higher Braak stages (Figure 5c) which leads to the possibility that a CTE-like process of neurodegeneration. Interestingly, in an original CTE case series, one epilepsy patient was included with tau pathology and progressive neurological deterioration [81].

Temporal lobe resection specimens from 47 TLE patients identified microtubule-associated proteins MAP2 and tau around the hippocampal CA regions [82]. Authors identified a possible association between increased tau expression in the CA2 region with below average verbal scores. The main cognitive finding of the study was granule cell layer dispersion correlated inversely with pre-operative verbal memory scores. More recently, Tai *et al.* (2016) examined 33 TLE patients, aged between the 50-65 years, who had undergone temporal lobectomy to treat refractory disease. Tau pathology was identified in 31 of these patients. A modified tau score (0-6) was applied showed that more tau pathology was present than expected for their age. The authors showed a significant correlation between the extent of tau pathology and decline in verbal learning, verbal recall and graded naming test scores over one year post-resection (Figure 4). Further analysis showed a similar correlation with verbal

learning decline between 3 months to one year post-resection which would account, at least in part, for the cognitive effect of surgical resection [18]. Prada-Jardim *et al.* (2017) identified more subtle hyperhosphorylated tau within the DG and subiculum in a younger series with HS which was significantly associated which nevertheless associated naming score decline one year post-operatively. These studies provide suggest a tau-related neurodegenerative process is occurring in TLE.

A further question would be the role of tau and whether the pathology seen represents another tau-related disease such as Alzheimer's disease or CTE. Tai *et al.* (2016) examined the pattern and extent of tau pathology and described ten patients having a 'Braak-like' Alzheimer's disease pattern of pathology with NFTs and neuropil threads densely located within the entorhinal and transentorhinal region. A further eight cases were described as 'CTE-like' with identification of tau within axons of the white matter, cortex, layer I or hippocampus within a distinct tract of axons. This CTE-like pattern may corroborate previous findings suggesting head injury pathology is associated with cognitive scores in the post-mortem epilepsy series [56]. Of note, however, the characteristic sulcal or peri-vascular neuronal tau pathology of CTE was not reported. In 18 cases, a novel pattern of tau pathology was described with deposition along the sub-pial region (Figure 5d), granular tau aggregates throughout the cortex (Figure 5e,f), co-localisation with mossy fibre sprouting (Figure 5g) and sparing of hippocampal CA regions (Figure 5b). This pattern appears to be unique to TLE and authors hypothesized that this reflects reorganisation of temporal lobe networks as a result of seizure activity and neuronal loss. A separate study of 19 TLE surgical specimens compared to four CTE brains highlighted the similar appearance of a sharp edge of sub-pial staining for hyperphosphorylated tau only in TLE specimens [83]. This study concluded that the appearance of tau pathology seen within CTE and TLE had some similarities however TLE specimens contained a larger proportion of the insoluble form of tau.

In summary, there is increasing evidence that tau pathology plays a role in a proportion of TLE patients. Unique patterns of tau deposition along with clinical correlation to cognitive decline have been described. Studies into amyloid-β and other neurodegenerative proteins have not shown a similar cognitive effect. It is difficult to discern from pathology studies whether hyperphosphorylated tau is causative or representative of neurodegeneration however a TLE-specific process raises the possibility for monitoring of cognitive decline using in vivo imaging and possible treatment avenues.

Temporal lobe epilepsy as a neurodegenerative disease: neuroimaging

Neuroimaging, particularly magnetic resonance imaging (MRI), has played a pivotal role in the investigation and management of drug-resistant TLE [84, 85]. Given its unmatched spatial resolution together with increasing availability of different contrasts allowing for a flexible assessment of morphology, tissue intensity, microstructure, and connectivity. As a whole-brain tool, MRI is essential not only to reveal epileptogenic lesions, but also to characterize the systemic impact of the disease [86, 87]. When performed repeatedly over time, neuroimaging can be used to visualize aging and disease-related progressive alterations with the promise of predicting who may eventually suffer from cognitive decline and a worsening of clinical symptoms.

Imaging disease progression in temporal lobe epilepsy: current evidence

The contribution of MRI to the concept of TLE as a potential neurodegenerative condition has so far been in the context of studies on disease progression, *i.e.*, the assessment of cumulative brain change. Most studies addressing progression have been based on drug-resistant TLE cohorts and employed cross-sectional designs, which correlate imaging metrics obtained from a single scan per subject to estimates of disease duration, seizure frequency, or age [88, 89]. Brain change has been so far assessed by MRI volumetric techniques, including automated/ manual volumetry of single or multiple structures, voxel-based morphometry, and more recently, surface-based measures of cortical thickness and subcortical shape. Volume-based assessments have overall suggested that ipsilateral hippocampal atrophy is greater in patients with a longer duration of epilepsy as well as more frequent seizures. Beyond the hippocampus, progressive atrophy has been documented in the amygdala and entorhinal cortex both ipsi- and contra-lateral to the seizure focus [90], thalamic divisions [91-94], and neocortical regions [92, 95-102].

Cross-sectional designs are cost-effective and logistically less complex than their longitudinal counterparts. As they do not carry the burden of repeated assessments, they may allow for inclusion of a broader range of measures and can be easily generated from the presurgical workup. Long term follow-ups may be challenged by the need for surgical treatment. An inherent limitation of cross-sectional studies is their inability to differentiate between- and within-subject effects [103, 104]. In other words, these designs compare patients with short duration to those with long duration (or those with low seizure frequency to those with frequent seizures) without directly measuring change within a given patient. Cross-sectional inference may thus be affected by age differences across cohorts with respect to precipitating factors, lifestyle, but also available treatments at a given time.

In a longitudinal design, individual subjects serve as their own baseline. This is likely to result in increased sensitivity to detect subtle effects with lower sample size requirements. Compared to the large number of cross-sectional studies in TLE, longitudinal designs have been rather scarce. Several interesting case-reports have nevertheless illustrated brain change in single patients over time [105, 106]. Analyzing serial MRI data in patients from a first seizure clinic, one study reported increased ipsilateral hippocampal volume loss of around 10% over an average period of 3.5 years with more marked effects in patients with generalized seizures [107]. Another study suggested more marked volume loss in patients with recurrent seizures compared to patients with adequate seizure control, supporting a direct effect of seizures [108]. In patients with drug-resistant TLE, the few longitudinal studies performed to date sensitively detected cumulative atrophy across all lobes. Moreover, they showed additional modulation of progression by seizure estimates in some regions, supporting a more detrimental disease course in patients with frequent seizures[97, 98, 109]. A study in post-operative TLE patients, following temporal lobe resection for refractory seizures, showed shrinkage of the hippocampal volume significantly contributed to post-operative memory change [110].

A recent systematic review and meta-analysis of MRI cross-sectional and longitudinal volumetric studies of the hippocampus indicated that more severe ipsilateral atrophy occurs in patients with longer epilepsy duration and more frequent seizures [111]. Additional synthesis of whole-brain morphometric reports confirmed that changes often extend to extra-temporal and subcortical regions, collectively supporting that TLE is progressive. Of note, however, quantitative synthesis of study design variability indicated inconsistent control for chronological aging. One study separately tracked change in patients and controls[97, 98, 109], but did not directly test for progression, *i.e.*, by statistically comparing longitudinal trajectories between cohorts. Others compared aging effects between patients and controls cross-sectionally, and observed more marked effects of atrophy in the former [97, 98, 109]. Figure 6 overviews pooled longitudinal MRI evidence as well as the results of a systemic review [111] on progressive atrophy in drug-resistant TLE.

In addition to progressive grey matter atrophy, there is evidence for negative effects of hippocampal damage on limbic white matter pathways, possibly as a result of degeneration [112, 113]. Structural disconnection maylead to lasting alterations in the distribution of trophic and functional signals [114]. An important requirement for future work would be the inclusion of controlled and non-controlled patients to verify modulation of progression by both drug-dose and seizure-related factors. Some studies have suggested possible adverse effects of medication, including phenytoin and sodium valproate, on grey

matter measurements [115, 116]. Drug-related effects might be relevant to explain progressive structural damage in well-controlled patients [117]. Finally, several studies reporting temporo-limbic morphometric abnormalities in asymptomatic relatives of TLE patients [118, 119], suggest that genetic predisposition may contribute to seizure-related vulnerability and thus represent a risk factor for brain alterations.

Can Alzheimer's disease serve a model of neurodegeneration for temporal lobe epilepsy?

The understanding of disease progression in epilepsy may benefit from incorporating methods and concepts pioneered in Alzheimer's disease research. Studies in Alzheimer's disease have emphasized benefits of positron emission tomography (PET), particularly the imaging of novel tracers that more specifically tap into neurodegenerative mechanisms, including amyloid and tau pathology. Notably, *in-vivo* studies of such tracers have shown a topography of tracer uptake that may resemble histopathological Braak staging [120]. In TLE, studies have so far mainly focused on the mapping of glucose metabolism through ^{18}F-fluorodeoxyglucose (FDG) for pre-surgical diagnostic purposes [121, 122]. Few cross-sectional studies have nevertheless suggested more marked hypometabolism in patients with longer disease duration [123, 124]. A recent study examined amyloid-β burden on PET in 41 adults with childhood-onset epilepsy showing increased brain amyloid at late middle age compared to age-matched controls [125]. While this confirms, *in vivo,* a higher brain amyloid accumulation in humans with a history of epilepsy, the correlation between amyloid and cognitive decline remains unclear. By contrast, recent pathology evidence suggests an association between chronic TLE, cognitive decline and hyperphosphorylated tau [18]. By potentially providing mechanistic insights into the cascade leading from repeated seizures to neuronal loss, a taupathy may offer a framework to conceptualize progressive atrophy in TLE as a neurodegenerative process [126] and future imaging using tau PET tracers would be key in exploring this further.

In Alzheimer's disease, connectivity-based approaches have revealed high susceptibility of high-cost metabolic hubs in posterior midline parietal regions [127]. Moreover, disease spreading models have elegantly mapped the propagation of pathology along anatomical connections from the mesiotemporal disease epicenter to other limbic regions and onto neocortical areas [128]. Using similar approaches, combined with a longitudinal design as close to disease onset as possible, may unveil the sequence of events leading to the widespread nature of damage observed in chronic TLE phases [129]. Finally, dementia research has a tradition to emphasize inter-individual variability, and several models have been developed to evaluate whether subject-trajectories of multiple concomitant factors including imaging markers of structure, function at rest, vascular integrity and metabolism, blood- and cerebrospinal fluid-

derived protein levels can predict cognitive decline in patients even before the onset of clinical symptoms [130, 131].

To advance understanding of the neurodegenerative aspects of TLE, in addition to imaging markers of structure, function and connectivity, future longitudinal studies should include tau and amyloid sensitive PET tracers to shed light on *in vivo* molecular pathways. Neuroimaging should be complemented by repeated assessment of cognitive function and quality of life which will help to establish the link between brain level progression and observable clinical and cognitive outcomes. So far, despite research showing potential adverse effects of TLE on cognition over time [24, 132], only few studies have attempted to bridge neuroimaging with cognitive assessments. In this context, the inclusion of both pediatric as well as adult cohorts will be of interest, as it may clarify the interaction of brain development, disease progression, and aging. Arguably, longitudinal imaging studies in epilepsy need to be relatively well-powered, including patients at disease onset (before the diagnosis of drug-resistance is established) as well as drug-resistant patients. The adult cohort may eventually undergo temporal lobectomy and can only be enrolled for relatively short follow-up times. While the ethical constraint of timely surgery may lead to increased attrition in drug-resistant patients, access to tissue and central cerebrospinal fluid may offer unprecedented opportunities to test for specific molecular pathways implicated in disease progression. In addition, relevant neuroimaging biomarkers require validation for the study of epilepsy and neurodegenerative disorders at large. In this context, multi-site initiatives are key to establish impact collaboration, innovation, and transparency.

In summary, we have explored the cognitive co-morbidity of TLE with evidence of poor performance on several levels of cognition compared to health controls. We have reviewed the pathology evidence for a contributory neurodegenerative process superimposed on a damaged hippocampus and recent studies examining the role and vulnerability to pathological tau in these patients. A 'tauopathy' model may conceptualise neurodegenerative processes in TLE and, together with prospective neuroimaging and correlation with the cognitive phenotype, may lead to potential monitoring and treatment avenues.
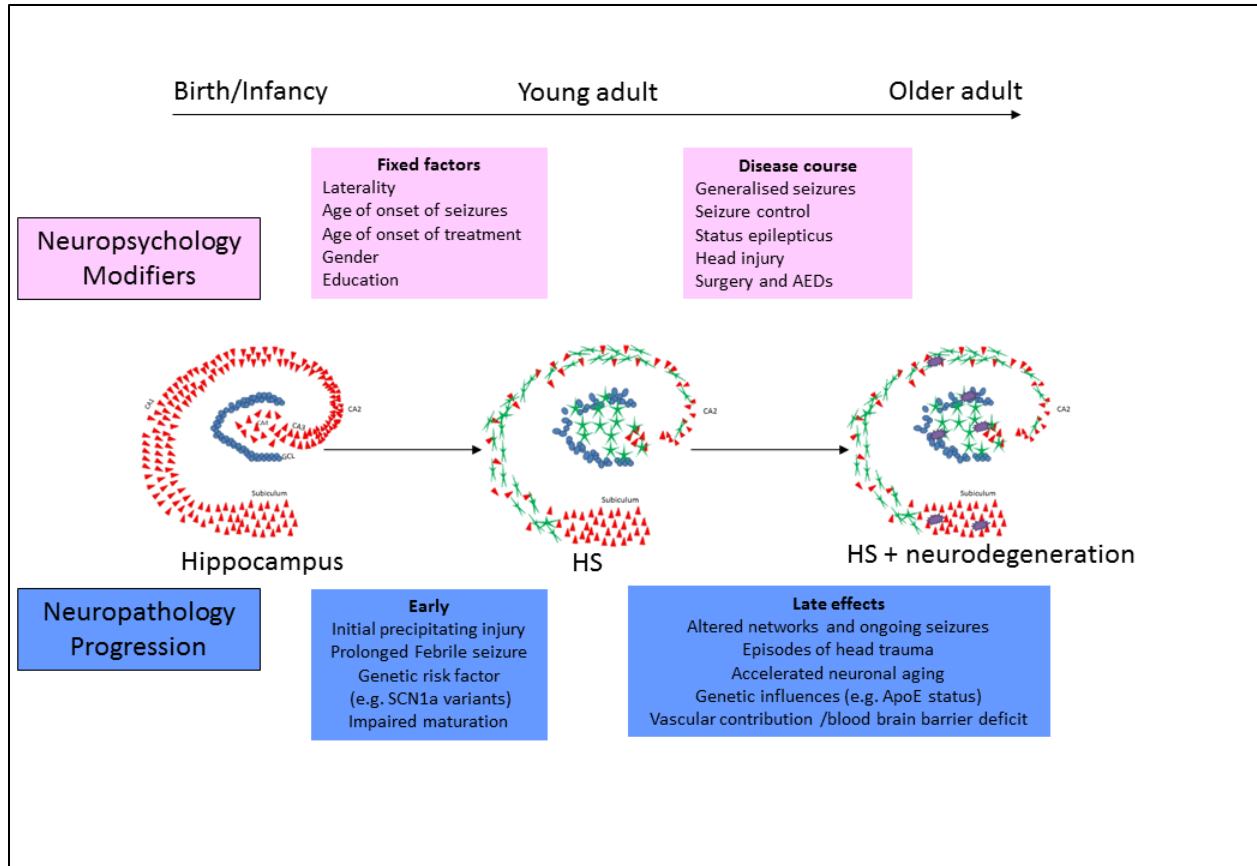
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Figure 1. Trajectory in progressive pathology changes that could occur in the course of hippocampal sclerosis (HS) and factors potentially influencing cognitive function and decline and neurodegenerative changes. .AED = anti-epilepsy drugs. Red and blue in diagrams are neurons, green for astroglia and purple for degenerative changes in neurons.

Figure 2. Normal Trajectories of Cognitive Function over the Adult Span in Healthy Adults

Figure 3. The cross-sectional development of verbal learning in relation to age in controls and TLE patients.

Figure 4. Tau burden (represented by Modified Tau Score) is correlated with a decline in verbal learning scores from pre-operative and one year post-operative assessment (Spearman coefficient R=-0.66, p<0.01). Graph represents data published in [18].
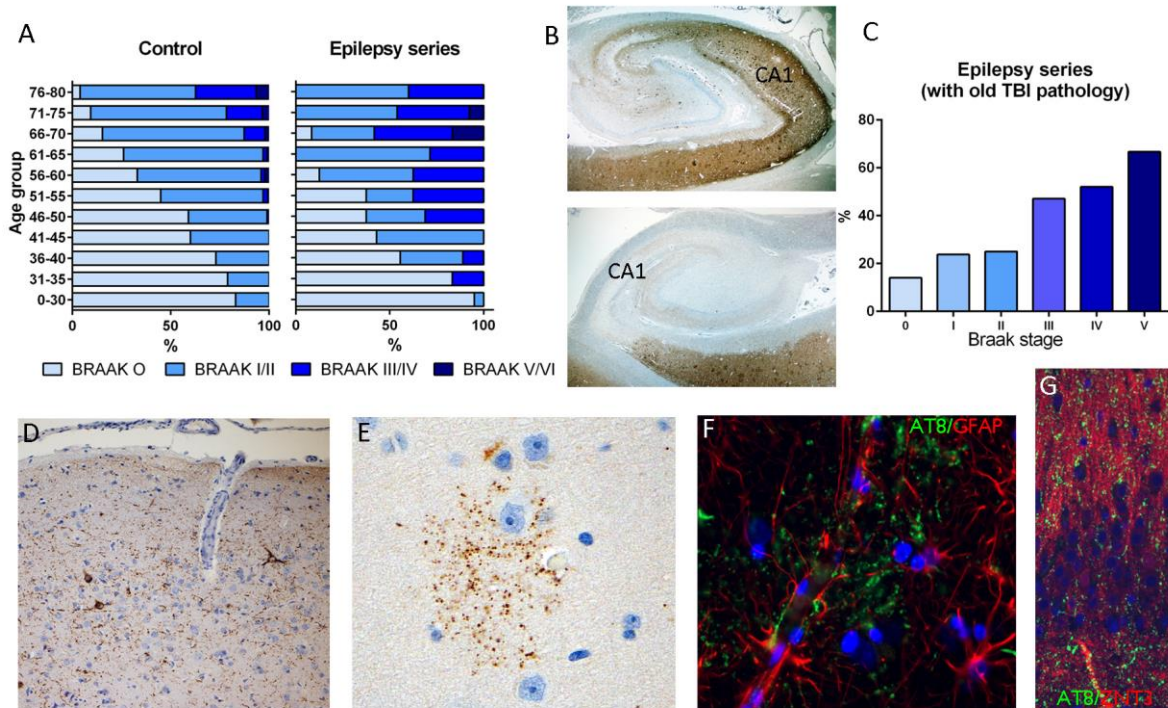
Figure 5. **Tau pathology (AT8 immunohistochemistry) patterns in Epilepsy and TLE. A-C Post mortem epilepsy series, modified from [56]. A**. Age acceleated Braak stages were noted in an epilepsy cohort, with varying epilpesy syndromes, compared to published control data ; the middle-aged group (40–65 years) showed increased representation of low (I/II) and mid (III/IV) Braak stages (P<0.01). B. In patients with unliateral hippocampal sclerosis, asymmetry in the patterns of AT8 distribution was noted with higher tau burdens in CA1 in the non-sclerotic side (top) compared to the damaged hippocampus (bottom). C. There was a significant correlation between tau burden and pathological evidence of old traumatic brain injury (TBI) with only 3 of 138 in this series having a clinical diagnosis of post-traumatic epilepsy. **D-G AT8 patterns in TLE surgical series modified from [18]. D.** Accumulation in the subpial and superficial cortical layers was a prominent finding in some cases. E. Unusual cortical perineuronal aggregates of AT8 labelling were noted ; F. Some of these appeared to be in proximity to capillarires. G. In the hippocampus overlap in the distribution of AT8 with mossy fibre sprouting as shown with zinc transporter 3 protein (ZNT3) was noted.

Figure 6. MRI studies of disease progression in drug-resistant temporal lobe epilepsy. A) Mesiotemporal (left panel) and neocortical (right panel) regions of progressive atrophy (in mm3/y) based on a longitudinal

design are mapped in blue. For each significant cluster, mixed-effects model fits illustrate the effects across different patient subgroupings (all, those with patients with hippocampal atrophy or normal hippocampal volumes at baseline). B) Meta-analytical synthesis of cumulative atrophy ipsilateral to the seizure focus as illustrated by the pooled effect size of correlation between hippocampal atrophy and duration of epilepsy (left panel). Narrative synthesis of studies assessing the whole-brain (right panel); for each study, the sample size (n) and quantitative MRI methods (AVOL = automated volumetry; MVOL = manual volumetry; CTX: cortical thickness analysis; SSA = surface-based shape mapping; VBM = voxel-based morphometry) are provided as well as the finding (blue: progressive atrophy, grey: no progression, white: progression not assessed) across the brain (MTL: mesial temporal lobe, EMTL: extra-mesial and/or lateral temporal lobe, ETL: extra-temporal lobes, SC: subcortical grey matter).

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