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Neurobehavioural comorbidities of epilepsy: towards a network-based precision taxonomy

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Abstract

Cognitive and behavioural comorbidities are prevalent in childhood and adult epilepsies and impose a substantial human and economic burden. Over the past century, the classic approach to understanding the aetiology and course of these comorbidities has been through the prism of the medical taxonomy of epilepsy, including its causes, course, characteristics and syndromes. Although this ‘lesion model’ has long served as the organizing paradigm for the field, substantial challenges to this model have accumulated from diverse sources, including neuroimaging, neuropathology, neuropsychology and network science. Advances in patient stratification and phenotyping point towards a new taxonomy for the cognitive and behavioural comorbidities of epilepsy, which reflects the heterogeneity of their clinical presentation and raises the possibility of a precision medicine approach. As we discuss in this Review, these advances are informing the development of a revised aetiological paradigm that incorporates sophisticated neurobiological measures, genomics, comorbid disease, diversity and adversity, and resilience factors. We describe modifiable risk factors that could guide early identification, treatment and, ultimately, prevention of cognitive and broader neurobehavioural comorbidities in epilepsy and propose a roadmap to guide future research.

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Author contributions

B. H. organized the overall structure and content of the Review and the whole team wrote targeted discipline-specific sections of the paper and all reviewed and edited the ensuing versions of the manuscript and approved the final version. The various authors contributed predominantly to different sections of the manuscript, including neuropsychology (B. P. H., R. M. B., C. R. M. and A. R.), neuroimaging (C. R. M., E. K., A. R. and B. P. H.), genetics (R. M. B.), behaviour (B. P. H., R. M. B., C. R. M. and AR), networks (A. F. S. and E. K.) and conceptual models (B. P. H., R. M. B., C. R. M., A. R. and E. K.).

Competing interests

The authors declare no competing interests.

This Review offers a novel theoretical perspective on the neurobehavioural comorbidities of adult and childhood epilepsy, involving new analytical approaches, derivation of new taxonomies, and consideration of the diverse forces that influence cognition and behaviour in individuals with epilepsy.

Introduction

Epilepsy is a costly and complicated international public health problem[1,2] In addition to recurrent seizures, epilepsy is associated with abnormalities in cognition, psychiatric status and social–adaptive behaviors — complications that are referred to collectively as the neurobehavioural comorbidities of the epilepsies (BOX 1). These comorbidities represent substantial life burdens for which the aetiology and most effective treatments continue to be sought.

This Review offers a novel theoretical perspective on the neurobehavioural comorbidities of adult and childhood epilepsy, involving new analytical approaches, derivation of new taxonomies, and consideration of the diverse forces that influence cognition and behaviour in individuals with epilepsy. In several respects, this approach is consistent with the concept of precision medicine, which, according to the International Consortium for Personalized Medicine[1,3], relies on “characterization of individuals’ phenotypes and genotypes (for example, molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease or deliver timely and targeted prevention.” Precision medicine is having a substantial impact on many medical specialties[4,5], including neurology[4,5] and important subspecialty areas such as epilepsy[6–9], but has been extended minimally to the comorbidities of epilepsy[10].

We begin by reviewing the classic paradigm that has dominated neuropsychological and behavioural research in epilepsy, highlighting the many striking inconsistencies of this paradigm. Next, we discuss an emerging taxonomy that harnesses the inherent heterogeneity of the neurobehavioural comorbidities of epilepsy. Finally, we propose a reformulated paradigm that encompasses a broader range of important aetiologies of cognitive and behavioural phenotypes. We believe that this new taxonomy will accelerate efficient identification, intervention and prevention efforts for individual patients with epilepsy. Our focus is on evidence from the broad spectrum of focal (including lesional) and genetic generalized epilepsies, and we do not address the severe childhood epilepsies associated with developmental delays and markedly abnormal EEG backgrounds, such West and Lennox–Gastaut syndromes, which have been addressed elsewhere[11].

The classic paradigm

Epilepsy can be accompanied by a broad range of somatic, psychiatric and neuropsychological comorbidities, and studies to gain a better understanding of the aetiology of these comorbidities and their course across the lifespan have been ongoing for >100 years[12]. A primary focus of these studies has been the association between cognitive and behavioural complications and the fundamental medical taxonomy of epilepsy, that is,

those factors related to its aetiology, course, characteristics and treatment in young, mature and ageing patients (FIG. 1).

The classic paradigm that has driven much of the research into the neurobehavioural comorbidities of epilepsy emerged from an interest in the effects of epilepsy on cognition. Early studies identified objective cognitive impairments associated with epilepsy[13–15], initially focusing on global cognitive ability (that is, intelligence) and later exploring specific cognitive domains as the understanding of human cognition and its assessment evolved[16]. The existence of substantial heterogeneity in cognition among patients with epilepsy rapidly became evident, prompting efforts to identify clinical correlates of cognitive dysfunction, such as age of onset and seizure frequency. The earliest empirical examples of this approach date back to the 1920s[14] and persist to the present day[17,18]. Since the 1940s, efforts to characterize the relationship between disease-related factors and cognition have been reflected in narrative[19–27] as well as systematic and meta-analytic reviews[28–32]. Factors that have been linked to an increased risk of cognitive impairment include earlier age of onset, increasing duration of epilepsy, poorer seizure control, symptomatic epilepsies, number of lifetime generalized epilepsies and episodes of status epilepticus, number and type of medications, and the type, frequency and severity of EEG abnormalities. However, owing to variability in the reliability and reproducibility of the findings, these relationships have undergone continual re-evaluation.

Efforts to classify seizures according to their aetiology and underlying pathophysiology were especially influential in this research. Early attempts were limited by an imprecise understanding of the epilepsies and were driven largely by clinical theorizing (for example, ‘predisposing’ versus ‘exciting’ aetiologies)[33] but were subsequently advanced by the application of EEG and the development and evolution of the International League Against Epilepsy (ILAE) Classification of the Epilepsies[34–37]. Neuropsychological and behavioural research paralleled the evolution of this taxonomy, and efforts to link specific cognitive abnormalities with distinct epilepsy syndromes followed, aptly referred to as the ‘lesion’ or ‘localization’ model[38]. This model has provided an important organizing influence to explore the neuropsychology of epilepsy, as well as the behavioural complications associated with focal[39, 40] and generalized epilepsies[28]. Exemplars of the lesion model include memory impairment in temporal lobe epilepsy (TLE)[41], dysexecutive function in frontal lobe epilepsy (FLE)[42], disrupted attention in absence epilepsy[43], abnormalities in aspects of language in Rolandic epilepsy[44], visuoperceptual and spatial impairments in occipital epilepsy[45], and abnormal primary memory and behaviour in juvenile myoclonic epilepsy (JME)[46,47].

Challenges to the classic paradigm

Substantial challenges to the classic model have accumulated from several sources, including cognitive, neuroimaging, neuropathology and clinical research. These studies indicate that the neurobehavioural comorbidities of epilepsy are more variable and extensive than would be predicted by lesion location alone. In a prescient view, Jokeit and Schacher[48] argued that because the taxonomy of the epilepsies was constructed independently of neuropsychological concepts, specific associations between cognitive deficits and

epilepsy type and aetiology could represent exceptions rather than the rule. Furthermore, neurobehavioural comorbidities often predate seizure onset, posing an additional challenge to the classic paradigm.

Cognitive research—Neuropsychological impairments associated with epilepsy do not always respect the hypothesized boundaries of the classic lesion model. In both children[49–54] and adults[55–61] with temporal or frontal lobe epilepsies, cognitive anomalies are often more widespread and generalized than would be anticipated on the basis of the lesion location. This pattern of generalized cognitive impairment has also been observed in less well-investigated focal epilepsies involving posterior regions (occipital and/or parietal) in children[45,62,63] and adults[64]. Furthermore, meta-analyses in Rolandic epilepsy and genetic generalized epilepsies[27,31] have reported widespread cognitive abnormalities[29].

Conversely, abnormalities in specific prototypical cognitive domains have been reported across diverse epilepsy syndromes. For instance, executive dysfunction has been reported in TLE[51,65,66], FLE[54,66], JME[67], absence epilepsy[68] and Rolandic epilepsy[69,70]. Similarly, language impairments have been reported in absence epilepsy[71,72], FLE[30,52], Rolandic epilepsy[73,74] and JME[72,75,76], as well as in TLE, even when seizures arise from the non-dominant hemisphere[77,78]. Thus, empirical links between purported domain-specific cognitive impairments and specific epilepsy syndromes are more complex than predicted by the classic model.

Direct multi-syndrome comparisons have demonstrated considerable overlap of cognitive abnormalities in both new-onset[72,79] and established epilepsies. For example, surprisingly few substantial differences were observed between children with Rolandic epilepsy, absence epilepsy and FLE on measures of intelligence (different on only two of 54 syndrome comparisons)[80] and memory (two of 21 syndrome comparisons)[81]. Nolan et al.[82] demonstrated reduced intellectual performance across children with diverse epilepsy syndromes, with any differences being primarily in magnitude rather than type of impairment. Similarly, memory performance was reduced across all groups of individuals with TLE, FLE or absence epilepsies[83], again varying primarily in magnitude.

Despite the clear clinical distinction between TLE and FLE, cognitive patterns can be similar in these syndromes owing to extensive frontotemporal connectivity[59–61]. For example, in TLE, the presence of executive dysfunction — a domain impairment long considered to be a hallmark of FLE — has been linked to neurobiological influences exerted directly by the frontal lobe and/or indirectly through broader network connectivity. These influences (BOX 2) have been demonstrated across metabolic (^{18}F-FDG PET)[84, 85], EEG[86], morphometric (atrophy)[87–90], diffusion-weighted imaging[91,92], resting-state[93] and task-activated functional MRI (fMRI)[94,95], and functional connectivity analyses[96]. Similarly, psychiatric complications such as depression in TLE have been linked to co-occurring frontal lobe hypometabolism[97, 98] and structural abnormalities in the frontal lobes[99,100].

We do not mean to imply that all attempts to link specific comorbidities to specific features of the lesion model have failed, but the non-supportive and contradictory findings, as reviewed above, are striking. Sophisticated methodologies such as machine learning and

other advanced analytics have been shown to discriminate both between syndromes (for example, FLE versus TLE or TLE versus Rolandic epilepsy)[66,101,102] and within syndromes (for example, left versus right TLE)[58,102–104]. Such technologies could enhance the value of syndrome or lesion approaches, but even here they are prone to inconsistent findings, and standardized measures of diagnostic accuracy will be required before they can be routinely adopted in the clinic. Despite the aid of technological innovations for improving syndrome discrimination, the fundamental heterogeneity in cognitive and behavioural presentations, within and across epilepsy syndromes and clinical seizure features, must still be considered and embraced in any competing model. In our proposed taxonomy, a lesion is but one of several neuropathological considerations for understanding cognitive comorbidities in individual patients.

Neuropathology—Histopathological and neuroimaging investigations can assist in identifying abnormalities that might explain unanticipated syndrome-specific cognitive and behavioural findings. An early study of a series of 26 autopsied patients with TLE revealed multifocal abnormalities affecting the hippocampus (85% of cases), cerebellum (46%), amygdala (42%), thalamus (34%) and cortex (23%), with only 3% of individuals showing no appreciable pathology[105]. More recent neuropathological investigations have identified distributed cortical anomalies[106], as well as the presence of neurodegenerative features and proteinopathies[107–110], in the brains of people with focal epilepsies. Among the few neuropathological studies that have been conducted in patients with primary generalized epilepsies, microdysgenesis with variable regional distribution has been reported in some[111,112] but not all[113]. In a relevant nonhuman primate (baboon) model of JME[114], untreated animals with spontaneous seizures exhibited a reduced number of cortical neurons overall, with the greatest reductions being observed in primary somatosensory and primary motor cortices and the smallest reductions in visual regions[115].

Neuroimaging—Quantitative neuroimaging studies provide perhaps the clearest understanding of why cognitive anomalies do not always adhere to the classic lesion model or follow syndrome-specific patterns. Three primary lines of evidence are problematic for the classic lesion model.

First, imaging abnormalities often extend substantially beyond the primary areas of electrophysiological abnormality. Distributed neuroimaging abnormalities in TLE include widespread volume loss[116], cortical thinning[117–119], and alterations in gyral and sulcal curvature and total cortical surface area[120,121]. In primary generalized epilepsies, a meta-analysis has revealed widespread cortical and subcortical volume loss extending beyond the thalamocortical networks that are postulated to be the primary seizure generators[122]. Similarly, distributed anomalies in white matter microstructure were reported in a meta-analysis of 1,122 healthy controls and 1,027 people with epilepsy[123]. Decreased fractional anisotropy and increased mean diffusivity were observed in commissural, association and projection white matter fibres in TLE and FLE, with less impact in generalized epilepsy.

Second, across common epilepsy syndromes, evidence is emerging that structural abnormalities are more likely to be shared than syndrome-specific, as reflected in the Enhancing NeuroImaging and Genetics through Meta-Analysis (ENIGMA-Epilepsy)

project, an international database that includes 1,727 healthy controls and 2,149 patients with common epilepsy syndromes[124]. Despite the presence of some prototypic syndrome-specific findings, such as ipsilateral hippocampal volume loss in TLE, all patient groups demonstrated reduced thalamic, hippocampal and right pallidal volumes, as well as bilateral increases in the volume of the lateral ventricles (FIG. 2a, left). In addition, widespread cortical thinning, involving the precentral, paracentral, supramarginal, precuneus and cuneus, left entorhinal and multiple prefrontal regions, was observed across all epilepsy syndromes (FIG. 2a, right)[124]. Apart from medial temporal lobe abnormalities in patients with left TLE, syndrome-specific findings were rare.

In a subsequent diffusion MRI study from ENIGMA-Epilepsy, white matter microstructural alterations were observed across all epilepsy syndromes in 36 of 38 association, commissural and projection fibres[125]. Across patient groups, reductions in fractional anisotropy and increases in mean diffusivity were greatest in the genu and body of the corpus callosum, cingulum and external capsule (FIG. 2b). Although the severity of the alterations varied across epilepsy syndromes and was most pronounced in mesial TLE[125], bilateral alterations in many anterior midline fibres were uniform across groups. These broad patterns of structural and microstructural alterations, shared across epilepsy syndromes, could help to explain the distributed nature of cognitive impairments and the variable ability to identify syndrome-specific impairments.

Last, analyses of macroscale and mesoscale connectivity patterns have demonstrated widespread network-level differences between controls and patients with either focal[126] or generalized[127,128] epilepsies. These analyses included correlation or covariance matrices derived from fMRI and single-photon emission CT[129], ^{18}F-FDG PET[130], scalp EEG and magnetoencephalography[131,132], intracranial EEG and electrocorticography[133], and structural MRI[134]. Connectivity analysis has been used to identify the epileptic network in individual patients[135,136] and to identify disease-specific patterns of abnormal connectivity at the group level. Common findings include abnormal cortical–subcortical connectivity[137–139], increased connectivity within the putative primary epileptic network[133,135,140,141] and downstream network dysfunction on a more global or multi-network scale[142,143]. Widespread downstream network abnormalities have been reported across epilepsy syndromes, including paediatric focal epilepsy[144], FLE[142], TLE[145], childhood absence epilepsy[146] and JME[128]. Taken together, these findings suggest that epilepsy can cause disruption of networks far beyond the one that is responsible for primary seizure generation.

Important questions that emerge from this research include how different imaging features (or atrophy patterns) lead to the development of cognitive impairment in epilepsy, and what factors drive these changes if they are not syndrome-specific. Some evidence suggests that in patients with drug-resistant epilepsy, early-onset seizures disrupt white matter development, especially in late-myelinating frontotemporal association tracts[147,148]. Microstructural damage to these long-range tracts could lead to impairments in attention and executive functioning as a result of cortico-cortical disconnection. Microstructural damage to short-range, U-shaped fibres directly beneath the cortex might also contribute to cognitive impairment in patients with epilepsy by disrupting communication between neighbouring

cortical regions. In addition, longitudinal studies have shown that in patients with focal epilepsy syndromes such as TLE, long disease durations can lead to widespread age-accelerated cortical thinning, thereby exacerbating global cognitive, memory, and processing speed impairments[149,150,151].

Clinical research—A range of cognitive, behavioural and brain abnormalities are known to be present in both children[152,153] and adults[154,155] at the time of diagnosis of epilepsy, long before any potential impact of recurrent seizures, psychosocial consequences or antiseizure medications is evident. Furthermore, neurobehavioural anomalies have been reported to occur well before the first recognized seizure[152,156]. These neurobehavioural comorbidities at or before epilepsy onset are inconsistent with the classic paradigm, which assumes that neurobehavioural risk accrues over the disease course, and they highlight the need to explore other potential common aetiological pathways[157], including genetic aetiologies, which are addressed below.

From lesions to networks

The fundamental view of the nature of epilepsy has evolved from the conceptualization of a discrete area, the epileptogenic zone[158], to the suggestion that ‘focal epilepsy’ affects networks far beyond this zone. The latter assertion has been supported by evidence from invasive stereotactic EEG[159–161] and from connectivity analysis using scalp EEG[162,163], structural MRI[164,165] and fMRI[166,167]. Even the concept of an epileptogenic zone might be flawed, as some patients have several nodes within a broader epileptic network that are capable of independent seizure generation[168].

Neuropsychological research in the epilepsy field is also moving beyond the lesion model to focus more on disrupted networks[37,38,169–172]. Specifically advocated is a search for cognitive, behavioural and imaging phenotypes within and/or across epilepsy syndromes that are not restricted or constrained by the disease taxonomy[54,169,170,173] — an endeavour that is entirely consistent with precision medicine. However, despite the shift in the conceptualization of epilepsy, along with considerable evidence that challenges the classic lesion model, this model is likely to persist until a satisfactory alternative paradigm can be found that assimilates both contradictory and contemporary findings[174].

Moving towards a new model and taxonomy

Cognitive phenotypes—Recent research has demonstrated the utility of a phenotypic approach to the neurobehavioural comorbidities of epilepsy[93,175,176,177,178,179–181,182–189,190] and (BOX 3, Supplementary Table 1). To date, 17 taxonomic investigations have characterized phenotypes of objective or subjective cognition and, where available, their related neuroimaging correlates (Supplementary Table 1).

The landscape of cognitive phenotypes.—The studies listed in Supplementary Table 1 investigated phenotypes relating to academic skills (word reading, spelling and arithmetic)[175], objectively assessed cognition[93,176,179–182,184,187,191] and parent-reported executive function[189]. In addition, six studies characterized neuroimaging correlates

of the identified cognitive phenotypes, using structural MRI[93,177,179,180,183], diffusion MRI[180,182,183,188], activation fMRI (language)[178], resting-state fMRI[93,183] and/or advanced network analytics (for example, graph theory) on structural MRI, diffusion MRI or resting-state fMRI data[93,182,183,188,185]. These studies focused predominantly on adults with TLE[178,179,192]. Characterization of cognitive phenotypes in syndrome groups other than TLE has been undertaken, albeit on a limited scale. Among children (aged 8–18 years) with recent-onset focal or generalized epilepsies, three cognitive phenotypes were identified that cut across different epilepsy syndromes: average and comparable to controls; mild impairment across multiple cognitive domains; and impairment across all domains with severe attentional impairment[179]. Among adults with FLE, four cognitive phenotypes were identified: intact, generalized, single domain (language) impaired and multiple domain (language and executive function) impaired[186]. When children with drug-related epilepsy treated medically or surgically were followed up for 4–11 years, two prospective cognitive phenotype groups — average cognition (55% of sample) and impaired cognition (45%) — with different trajectories were identified regardless of treatment intervention (Supplementary Table 1)[190].

These findings indicate that the classic lesion-based cognitive and behavioural profiles are imprecise and fail to reflect the substantial heterogeneity in clinical presentation. Further research in a range of epilepsy syndromes will be needed to further explore the possibility of a phenotype-based profiling approach that could inform a revised taxonomy.

Phenotype distributions across investigations.—Of the cognitive phenotypes reported among adults with TLE, three are particularly prevalent (FIG. 3): an ‘intact’ or minimally impaired subgroup, largely comparable to healthy controls; a generalized impaired subgroup with abnormal scores across all administered cognitive metrics; and a subgroup[93] (or occasionally two subgroups[181]), exhibiting the expected pattern of cognitive anomalies for TLE, predominantly affecting memory, language and/or executive function (FIG. 3a)[181]. As FIG. 3b illustrates, the proportion of patients with TLE in the intact subgroup is surprisingly large, ranging from 27–54% across investigations (mean 44%). This patient group is infrequently discussed in the epilepsy literature and was arguably unanticipated among individuals with medication-resistant epilepsy presenting as surgical candidates[181,184]. The proportion with generalized cognitive impairment, another unexpected phenotype for a focal epilepsy, ranged from 15–44% (mean 29%), and the remaining individuals exhibited more focal cognitive patterns, involving reduced executive function and/or speed, and memory and/or language impairments[181,182]. A number of clinical and demographic variables have been associated with these phenotypes, albeit with some variability in findings (Supplementary Table 1).

Neuroimaging correlates of cognitive phenotypes.—Relationships have been detected between cognitive phenotypes and both the degree and distribution of neuroimaging abnormality (Supplementary Table 1). Typically, no or minimal structural, diffusion and resting-state differences are evident between minimally impaired phenotypes and control groups, whereas marked differences in these imaging measures are observed between generalized impairment phenotypes and controls[93,177,180,182]. Overall, neuroimaging

differences are more prominent and consistent when network metrics, based on diffusion MRI, resting-state fMRI or network analyses of imaging data, are examined[93,180,182,188].

Neuroimaging of cognitive phenotypes carries implications for traditional comorbidity research, in which a common approach is to administer a comprehensive cognitive battery to examine a single cognitive metric (for example, memory) in relation to clinical or imaging metrics (for example, connectivity), with little attention being paid to the impact of other co-occurring cognitive impairments. However, clear differences in white matter signatures can be appreciated when white matter network pathology is examined in patients with pure memory impaired versus mixed memory and language phenotypes (FIG. 4), highlighting the importance of distinguishing single-domain from multidomain impairments[182]. Brain network changes that give rise to multidomain impairments might not be additive and could be synergistic. Addressing how different patterns of network pathology lead to multidomain impairments is essential to understand the full cognitive burden experienced by any single patient.

Examination of global and local (temporal lobe) functional connectivity in TLE has demonstrated increased connectivity in the temporal lobe epileptogenic region that is not associated with the distribution of cognitive phenotypes[185]. Instead, global connectivity metrics — namely, clustering coefficient and rich club proportion — were predictive of the cognitive phenotype. These findings suggest that focal hyperconnectivity in the epileptogenic region contributes to the broader global network disorganization that is most closely linked to cognitive phenotypes.

Intracranial EEG provides a potential complementary technique to investigate cognitive phenotypes and cognitive processing[193], in particular, the oscillations involved in mediating the large-scale neural networks[194,195] that address cognitive adequacy in people with epilepsy. Memory deficits in TLE have been linked to pathological hippocampal oscillatory activity, with implications for alterations in large-scale neuronal synchronization[196]. Intermittent pathological high-frequency oscillations in non-lesional epilepsy have been linked to disrupted encoding of stimuli[197]. The combination of these observational approaches with parallel lines of research that use electrophysiological stimulation to identify pathological networks[198,199] or map cognitive function[200] provides potential avenues to better understand the underlying neurobiological differences that lead to distinct cognitive phenotypes. Further research is needed to explore the relationships between pathological electrophysiological activity, altered resting state metrics and disruptions to cognitive networks in epilepsy.

Approaches to cognitive phenotyping.—The cognitive phenotypes in TLE are relatively stable and reproducible, even when different methodological approaches are used for their assessment. Empirically driven methods, such as unsupervised cluster analysis, have been the most common approaches. However, diagnostic neuropsychological approaches (that is, actuarial methods), in which groups are determined on the basis of pattern of impairment (>1–2 SD below a normative sample) across cognitive domains, have also been used. A recent head-to-head comparison between cluster analysis and a diagnostic approach[187] yielded a concordance rate of 82.6% with good agreement ($\kappa = 0.716$) and,

importantly, both approaches identified the same three broad phenotypes described above. This study demonstrates the validity of a diagnostic approach to characterize phenotypic patterns of impairment at the individual patient level in a clinical setting — a crucial requirement for a precision-based therapeutic approach.

Behavioural phenotypes—BOX 3 indicates the phenotypic approaches to behavioural, developmental and psychosocial complications of the epilepsies that support broad application of this approach.

Depressive symptoms.—In a 2016 study[171], Rayner et al. performed cluster analysis of nine depressive symptoms (as recognized by the Diagnostic and Statistical Manual of Mental Disorders) in adult patients with focal epilepsies (n = 91) and controls (n = 77). This analysis identified three phenotypes and associated features: a ‘cognitive’ depression phenotype (17% of epilepsy participants) characterized by self-critical thoughts and dysphoria with associated memory deficit; a ‘somatic’ depression phenotype (7%), characterized by vegetative symptoms and anhedonia, with greater anxiety compared with the other phenotype and controls; and a non-depressed epilepsy phenotype (76%).

Developmental trajectories.—In a study published in 2012, Wilson et al.[201] examined prospective developmental trajectories — operationally defined academic achievement, occupational achievement, peer social competence, relationship status and independence — in patients with childhood-onset TLE (n = 54). Three cluster trajectories were identified: normal development (52% of participants); altered and achieving some but not all developmental tasks (37%); and delayed and achieving few developmental tasks (11%). The normal group outperformed the altered and delayed groups across a range of cognitive measures, and additional analyses demonstrated that the phenotypes were independently related to chronicity of seizures, cognitive status, surgically remediable epilepsy and gender.

Child behavioural problems.—Assessment of children with new-onset epilepsies (n = 183) and normally developing controls (n = 107), using the Child Behavior Checklist, identified three behavioural phenotypes: a ‘normal’ group that was comparable to controls across all behaviour problem scales (67% of participants); a subset with abnormal scores across all scales (22%); and a specific non-externalizing behaviour disorder group (11%)[192]. The phenotypes correlated with diverse cognitive, familial, developmental and neuroimaging (cortical thickness) factors.

Adult behavioural problems.—In a study published in 2021, adults with TLE (n = 96) and healthy controls (n = 82) were assessed with the Symptom Checklist 90-Revised (SCL-90-R) and unsupervised machine-learning techniques were used to identify latent TLE groups[186]. As a group, the patients with TLE patients exhibited significantly higher (more abnormal) scores across all nine SCL-90-R scales compared with controls. However, cluster analysis identified three latent groups: unimpaired with no scale elevations compared with controls (Cluster 1, 42% of the patients with TLE); mild-to-moderate symptomatology characterized by significant elevations across several SCL-90-R scales compared with controls (Cluster 2, 35%); and marked symptomatology with significant elevations across all scales compared with controls and the other TLE phenotype groups (Cluster 3, 23%).

Significant associations were observed between cluster membership and demographic (education), clinical epilepsy (perceived seizure severity and bitemporal lobe seizure onset), and neuropsychological status (intelligence, memory and executive function), but structural neuroimaging correlates were minimal. Concurrent validity of the behavioural phenotype grouping was demonstrated through association with psychiatric (current and lifetime-to-date DSM IV Axis 1 disorders and current treatment) and quality-of-life variables.

Psychosocial profiles.—To study psychosocial profiles, Josephson et al.[10] examined patient-reported outcome data from 462 individuals with epilepsy. Cluster analysis revealed three groups, who were deemed to have high (46% of participants), intermediate (33%) or low (21%) psychosocial health. The clusters were differentiated by the degree of seizure control, need for partially or completely subsidized income support, inability to drive, and history of a psychiatric disorder.

Health-related quality of life.—Sajobi et al. (2017)[202] assessed and tracked health-related quality of life (HRQoL) for 2 years in 373 children with newly diagnosed epilepsy. Multi-trajectory modelling characterized three longitudinal HRQoL trajectory groups: high HRQoL (44.7% of participants), intermediate HRQoL (37.0%) and low HRQoL (18.3%). Predictors of HRQoL trajectories included less severe epilepsy, absence of cognitive and behavioural problems, lower parental depression scores, better family functioning and fewer family demands. Additional longitudinal (2-year) investigations of young people (aged 2–12 years at study entry) with new-onset epilepsies have similarly identified a spectrum of HRQoL trajectories[203,204], ranging from individuals with stable, intact and even superior HRQoL to individuals at increased risk and concern for poor HRQoL.

Summary.—Although attempts to identify broadly defined behavioural phenotypes are progressing, they are complicated by the need for more diversity in the comorbidities addressed and the dependent measures utilized compared with the cognitive studies. Therefore, we do not yet have broad taxonomic agreement or the ability to identify the phenotypic status of individual patients. However, these investigations have been more inclusive than the cognitive studies with regard to representation of diverse focal and generalized syndromes among children and adults (Supplementary Table 1).

Broadening the scope of risk and resilience factors—An unfortunate byproduct of the classic paradigm has been the underappreciation of potentially relevant risk and resilience factors for cognitive and behavioural comorbidities in epilepsy. This situation is not unique to epilepsy: a bibliometric analysis of trends in the precision medicine literature revealed that of 5,552 articles published from 2012 to 2018, mostly in medical specialty journals (particularly oncology), only 1.6% included terms related to social and environmental determinants of health, health disparities or health equities in their abstract and/or title[5]. Most articles used definitions of precision medicine related to tailored, individualized or personalized treatment and genetics and/or biology, with less than one-third including environment and lifestyle.

A precision approach requires an alternative framework for the cognitive and behavioural risk and resilience factors in epilepsy (FIG. 5) that more broadly addresses the aetiology of

common comorbidities and targets potential treatments and prevention efforts. Conventional risks, including the epilepsy itself and neuroimaging abnormalities, as well as ever-present concerns regarding medication effects[205,206], will remain embedded in this framework. In addition, incorporation of other factors related to cognition and behaviour, such as genomic, medical, social and lifestyle factors, will offer a more comprehensive and contemporary approach.

Genomic risk.—Identification of genomic risk and resilience factors for neurobehavioural comorbidities in epilepsy is essential to a precision medicine approach. However, although genomic research related to the development of epilepsy and related neuropathologies has burgeoned in recent years[207–211], research into the role of genomic factors in neurobehavioural comorbidities of epilepsy is still in its infancy[212]. Most neurobehavioural studies to date have been conducted in genetic epilepsy syndromes, such as tuberous sclerosis complex or Dravet syndrome[212]. Genomic contributions to comorbidities in non-syndromic, idiopathic epilepsies are largely unexplored and might have their own genetic causes or shared genetic risk factors with epilepsy (Supplementary Figure 1). Environmental factors (the exposome) are also likely to have an important role and to interact with genomic factors to influence cognitive and behavioural phenotypes. The genetic liability model for common diseases posits that the additive effects of many genetic and environmental factors contribute to an individual's liability to develop a disease or disorder, and this model is also likely to apply to common comorbidities including memory impairment and depression[213,214].

An emerging literature examining cognitive, behavioural and imaging abnormalities in unaffected family members (in particular, siblings or parents) of patients with epilepsy has raised interest in the potential genetic contributions to the neurobehavioural comorbidities of epilepsy. These far-ranging findings include effects on cortical and subcortical structures, including hippocampal and white matter volumes in relatives of individuals with TLE syndromes[215–219]; cognition, imaging and cortical excitability in relatives of individuals with JME[220–226]; reading problems, difficulties with speech sound discrimination and cognitive dysfunction in relatives of individuals with Rolandic epilepsy[227–229]; and behavioural problems in relatives of children with epilepsy[230,231].

Cognition and behaviour are affected to varying degrees in epilepsy, even among patients with the same type of epilepsy and pathological substrate (for example, mesial TLE with hippocampal sclerosis)[176]. Genomic factors are likely to account for some of this variability or to serve as key modifiers in epilepsy comorbidities, and might provide important insights to aid the future development of therapeutic approaches for these conditions. The studies to date (TABLE 1) have focused largely on genetic variants and have identified associations with memory impairment[232–235], executive dysfunction[236,237], working memory impairment[236], slowed processing speed[234], depression[238] and anxiety[238], among other comorbidities. The potential role of epigenomic, transcriptomic and proteomic changes in epilepsy comorbidities is now beginning to be explored in humans[239–241], and we recently identified >1,000 transcripts that were differentially expressed between TLE patients with and without memory impairment[242]. This study revealed overrepresentation of genes in pathways pertaining to brain-related neurological dysfunction and neurodegenerative

diseases, such as apolipoprotein E (*APOE*), amyloid precursor protein (*APP*), microtubule-associated protein tau (*MAPT*) and serine/threonine-protein kinase PINK1, mitochondrial (*PINK1*). Importantly, several microRNAs were also differentially expressed and were predicted to target a large subset of the identified transcripts, suggesting such upstream processes could serve as biomarkers and potential treatment targets for memory impairment in TLE[242].

Although much work remains to be done, a great deal has already been learned about the potential genetic contributions to epilepsy comorbidities through research on epilepsy syndromes associated with single-gene mutations[243]. Furthermore, animal studies and human research in epilepsy and other CNS disorders have highlighted the utility of genomic strategies in elucidating the biological underpinnings of common comorbidities associated with these conditions. We believe that incorporation of such methods into neuropsychological research in epilepsy will be essential to understand the observed phenotypic variability and to develop a precision medicine approach to the neuropsychology of epilepsy.

Social and psychological risk.—Epilepsy in adults is known to be more prevalent in lower (disadvantaged) socioeconomic groups, and is independent of social drift[244] and other established risk factors, such as head injury and stroke[245]. Population-based investigations have demonstrated that adults with epilepsy have an increased likelihood of living in households with the lowest annual incomes[246]. These individuals are also sevenfold more likely to report experiencing discrimination due to health problems and have greater odds of experiencing domestic violence and sexual abuse compared with the general population[247].

Although disadvantage, food insecurity, reduced personal safety and other hardships, including stigma and discrimination, are well known and documented in adults and children with epilepsy[248–250], their relationship to neurobehavioural comorbidities has been vastly understudied, with just a few reports demonstrating their relevance to behaviour[251], cognition[252, 253] and quality of life[254]. In the Epilepsy Connectome Project, variables reflective of disadvantage, such as lower parental education, increased parental unemployment and increased racial diversity, were associated with the cognitive phenotypes and their underlying biological alterations (for example, anomalies on resting-state fMRI), underscoring the utility of a more comprehensive approach[93]. These risk factors can also have clinical consequences. The use of epilepsy treatments such as surgery is disproportionately low among ethnic minorities in the USA — a phenomenon that has been attributed to a host of factors, including access to care, fear, education, mistrust in the health-care system and physician bias[255]. Furthermore, epilepsy mortality rates are higher among non-Hispanic Black patients than in their non-Hispanic white counterparts[256]. Lack of access to specialized epilepsy care leads to poorer seizure control, which could exacerbate related issues, including cognitive impairment, psychiatric and behavioural comorbidities, and poor quality of life.

Direct and easily accessible markers of neighbourhood adversity[257] are available that can inform the social determinants of health[258]. In the USA, the Neighborhood Adversity Index, an indicator of socioeconomic status disadvantage within a given region, has demonstrated

applicability to brain disorders including Alzheimer disease[259], in which disadvantage has been shown to be linked to imaging abnormalities (decreased hippocampal and cortical volumes)[260] and underlying neuropathology[261]. This type of approach could also be informative for epilepsy.

Medical risk.—Given the prevalence and co-occurrence of somatic comorbidities in people with epilepsy[262,263], interest in their relationships with cognitive and behavioural phenotypes is expected to grow. Direct characterization of comorbid disease and specific metabolic, vascular, inflammatory, immunological and other risks to cognition and behaviour in epilepsy is underway. The available evidence indicates that many medical risk factors, including obesity, diabetes and inflammatory markers, are overrepresented among individuals with epilepsy are and related to cognition[264–267]. Other important factors, such as atherosclerosis[268], are widely documented in population-based epilepsy research, but have yet to be examined in relation to brain neuroimaging metrics, behaviour and cognition in people with epilepsy.

Resilience and reserve.—The identification of resilience factors — especially those that are modifiable — is crucial for epilepsy intervention and prevention efforts. These factors are of intense interest in other fields, such as ageing and preclinical and clinical neurodegenerative disorders[269–271], and are of particular relevance in epilepsy in light of growing concern about brain and cognitive ageing processes in epilepsy[150,272,273]. Problematic lifestyle practices that have been documented in individuals with epilepsy include decreased physical fitness, activity and mental activities, smoking and social isolation[246,274–276]. Interventions targeted at improving health and lifestyle practices in patients with epilepsy have yet to be widely implemented in clinical practice. However, improvements in mood[277], memory[278] and executive function[279] were reported in initial exercise intervention trials, and alterations in resting-state functional connectivity were linked to cognitive improvement[278].

Resilience factors, which have been shown to be important in other areas of inquiry[280], have not been extensively studied in epilepsy to date. However, consistent with the wider literature, protective effects of higher global ability level (intelligence)[281,282], bilingualism[283] and years of education[56,284–286] on neurobehavioural status have been reported in people with epilepsy. These studies were all cross-sectional in nature, and a causal modelling approach will be needed to explore the roles of these factors in shaping cognitive and behavioural phenotypes. As noted above, certain genotypes have been linked to cognitive functioning in people with epilepsy (TABLE 1). However, genetic research in epilepsy comorbidities is in its infancy, and much work remains to be done to identify the factors that are most important for cognitive and behavioural resilience.

Self-efficacy beliefs lead to better adoption of the health habits and coping skills that are needed to manage chronic conditions such as epilepsy. In the context of epilepsy, self-management approaches have tended to focus on medication management rather than broader lifestyle modifications that are intended to improve overall health[287,288]. Self-management behaviours can be improved via interventions such as education, focused interventions and psychosocial therapy (for example, cognitive behavioural therapy[289]).

However, many epilepsy self-management studies have excluded patients with cognitive impairment[289]. Furthermore, low health literacy and comorbid mental illnesses such as depression reduce the effectiveness of self-management interventions. The phenotypic approach that we advocate could enable self-management training to be tailored to the patient's level of cognitive functioning and health-care literacy while also addressing mood-related issues such as depression and anxiety. Importantly, this proposed approach might help clinicians to implement individualized health-enhancing lifestyle behaviours that address health-related risk factors such as hypertension, obesity and diabetes, which are overrepresented among people with epilepsy.

Applications and benefits of the proposed paradigm—By placing the focus on the individual patient, a proposed new paradigm (FIG. 5) has direct clinical utility. Identification of a patient's phenotype, as determined by empirical or actuarial methods, places them in a clinically meaningful category. A broader consideration of potential risk factors for neurobehavioural comorbidities could inform improvements to routine patient assessment and history taking. Validation of factors that predict adverse phenotype membership would lead to a better understanding of modifiable and non-modifiable treatment targets and, importantly, their relative predictive power, which would indicate where the most clinical impact might result. More generally, application of this paradigm would accelerate a better understanding of the relative predictive power of classic epilepsy-related versus non-epilepsy-related risk factors.

The relationship of phenotypes to longer-term cognitive and behavioural outcomes would yield valuable prognostic information to guide timely interventions in people with epilepsy. For example, factors that are likely to be linked to the generalized cognitive impairment phenotype include long-duration epilepsy (non-modifiable), elevated vascular risk (possibly modifiable), untreated depression and sleep apnoea (modifiable), and older age (non-modifiable). Understanding how this combination of risk factors manifests at the individual level in the phenotype of interest could help guide behavioural interventions and predict the risk of future decline or improvement (see ref.[290] for a precision-based case example). However, a realistic view of the strengths and limitations of an approach of this type deserves careful consideration for future clinical and research efforts, as reviewed previously[9].

Conclusions

In this Review, we have proposed a 'next-generation' precision approach to the neurobehavioural comorbidities of epilepsy, which offers to advance our understanding by identifying phenotypes that are applicable to individual patients, along with their correlates, course and, ultimately, their underlying genotypes. This revised paradigm embraces findings that are problematic for the classic model while retaining components of that model, including neuroimaging findings, which are consistent with the network view of epilepsy and now, as we have shown in this article, its comorbidities. This revised model integrates established aetiologies but expands them considerably with new directions for clinical research designed to improve patient care and quality of life, enhance biomarker discovery and inspire possible therapeutic strategies, with a focus on modifiable lifestyle factors. This

phenotypic approach has the potential to alter the perspective of epilepsy from a condition characterized as ‘debilitating’ to one reflecting its actual underlying heterogeneity, whereby substantial proportions of adults and children with epilepsy demonstrate intact cognition, behaviour and quality of life. This change of emphasis should help us to focus on those most in need, moving to a multidimensional approach to care that will be crucial for improving neurobehavioural outcomes and quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- The cognitive and behavioural complications of the epilepsies have traditionally been examined in relation to the core characteristics of the disorder, such as the epilepsy syndrome, its aetiology, the frequency and severity of seizures, and treatments.
- This ‘lesion model’ has been the predominant paradigm for over 100 years; however, substantial evidence of patient heterogeneity from cognitive, behavioural, neuroimaging, neuropathological, network science and clinical studies is inconsistent with this model.
- A precision approach to epilepsy neurobehavioural comorbidities requires an understanding of this natural heterogeneity, which could be aided by a new taxonomy based on cognitive and behavioural phenotyping.
- This Review surveys the literature that has identified cognitive and behavioural phenotypes in children and adults with epilepsy and provides a synopsis of the evolving taxonomy.
- A new and expanded paradigm is proposed, which includes sophisticated neurobiological measures, genomics, comorbid medical disease, diversity and adversity, and resilience factors.

Box 1 |

Neurobehavioural comorbidities of epilepsy

Cognition

Higher neuropsychological abilities assessed by objective tests involving intelligence, academic skills, language, visuoperceptual–spatial, memory, executive, attention–working memory and sensorimotor functions.

Emotional–behavioural

Diverse aspects of behaviour, personality and psychiatric status assessed by standardized patient or proxy-completed questionnaires or structured psychiatric interviews, including evaluation of depression, anxiety, neurodevelopmental disorders (for example, autism spectrum disorder, attention-deficit/hyperactivity disorder and specific learning disabilities) and social cognition.

Social–adaptive

Performance in diverse areas of functional status (for example, social cognition) assessed by structured assessment audit of day-to-day abilities including employment, independent living, social network, marital status and quality of life.

Box 2 |

Executive dysfunction and network changes in TLE

Executive dysfunction in temporal lobe epilepsy (TLE), as identified through neuropsychological assessment, has been related to abnormal findings in frontal, frontostriatal and midline parietal networks. The diverse sets of findings supporting this perspective are listed below.

EEG

- Increased rate of interictal epileptiform discharges to the frontal lobe[86].

Metabolism

- ^{18}F-FDG PET hypometabolism extending to the prefrontal lobe[85].

Brain volume and diffusion

- Caudate atrophy and disrupted frontostriatal networks[88,91].
- Atrophy of prefrontal cortex and thalamus[87,90].
- Decreased frontotemporal and thalmofrontal fibre tract integrity[93,291].
- Extratemporal white matter pathology (corpus callosum volume[89].
- Abnormal restriction spectrum imaging of the inferior frontostriatal tract[91].
- Abnormal uncinate fasciculus ipsilateral to side of seizure onset[292].

Altered activation patterns

- Underactivation of the executive control network on task-activated fMRI[94].
- Decreased functional MRI (fMRI) task-related deactivation of the default mode network[95].

Altered resting-state connectivity

- Decreased functional connectivity between executive control and default mode networks[96].
- Altered frontotemporal lobe and thalamofrontal connectivity on resting-state fMRI[93,291].

Box 3 |

Phenotypic investigations of neurobehavioral status in epilepsy

This box lists the range of cognitive and behavioral phenotype investigations that have been conducted in paediatric and adult epilepsy cohorts (see Supplementary Table 1 for details).

Cognitive phenotypes

- Academic achievement in temporal lobe epilepsy[175].
- Neuropsychological and imaging status in temporal lobe epilepsy[93,176,177,180,181,182,183,184,185,187,188].
- Neuropsychological status in frontal lobe epilepsy[186].
- Patterns of activation on language task-based functional MRI in children with focal epilepsy[178]
- Neuropsychological status in children with diverse epilepsy syndromes[179].
- Parent-rated executive function[189].

Behavioural phenotypes

- Depressive symptoms[171].
- Developmental trajectories[201].
- Parent reports of child behavioural problems[192].
- Psychopathology in adults with epilepsy[293].
- Psychosocial health profiles[10].
- Health-related quality of life[202,203,204].

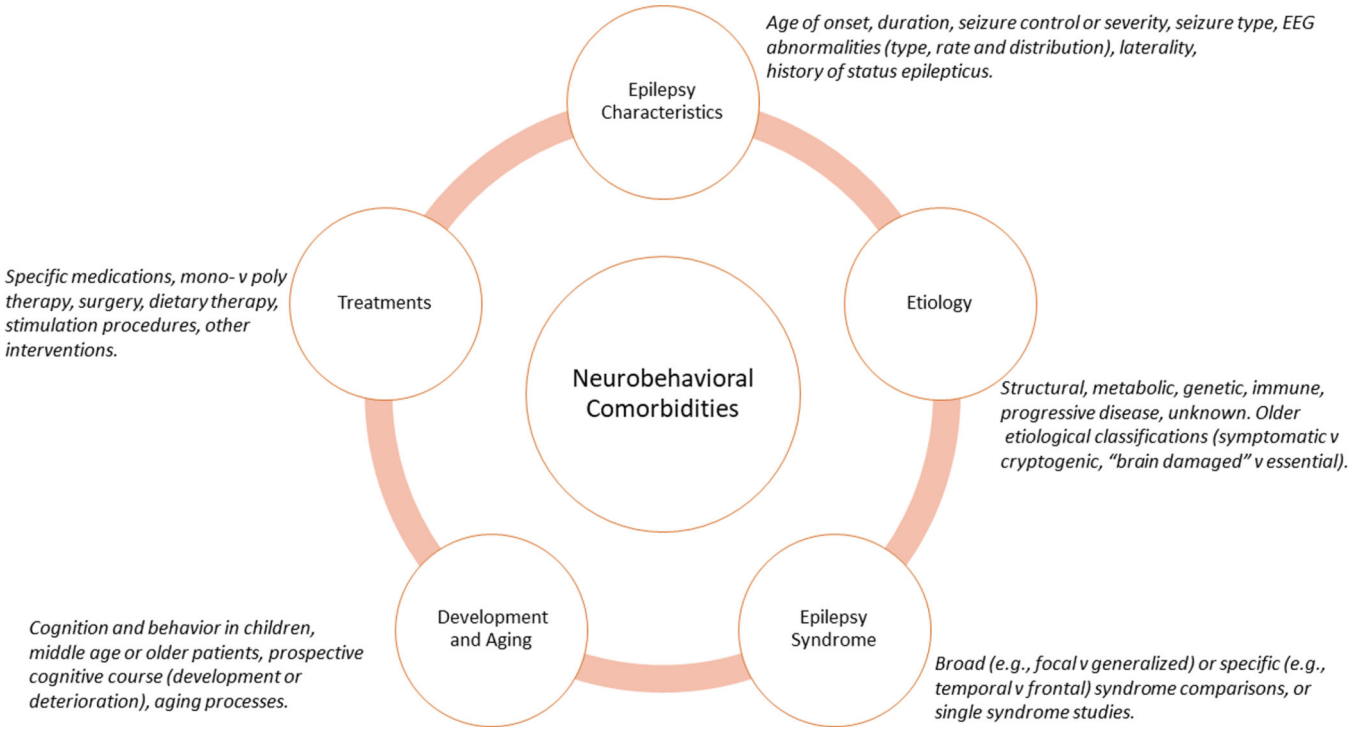

Fig. 1 |.

The classic paradigm of neurobehavioural comorbidities of epilepsy. The outer ring depicts five major factors (and associated exemplars) that have long been considered, alone or in combination, to exert direct and/or indirect influences on the causes and course of neurobehavioural comorbidities in epilepsy.

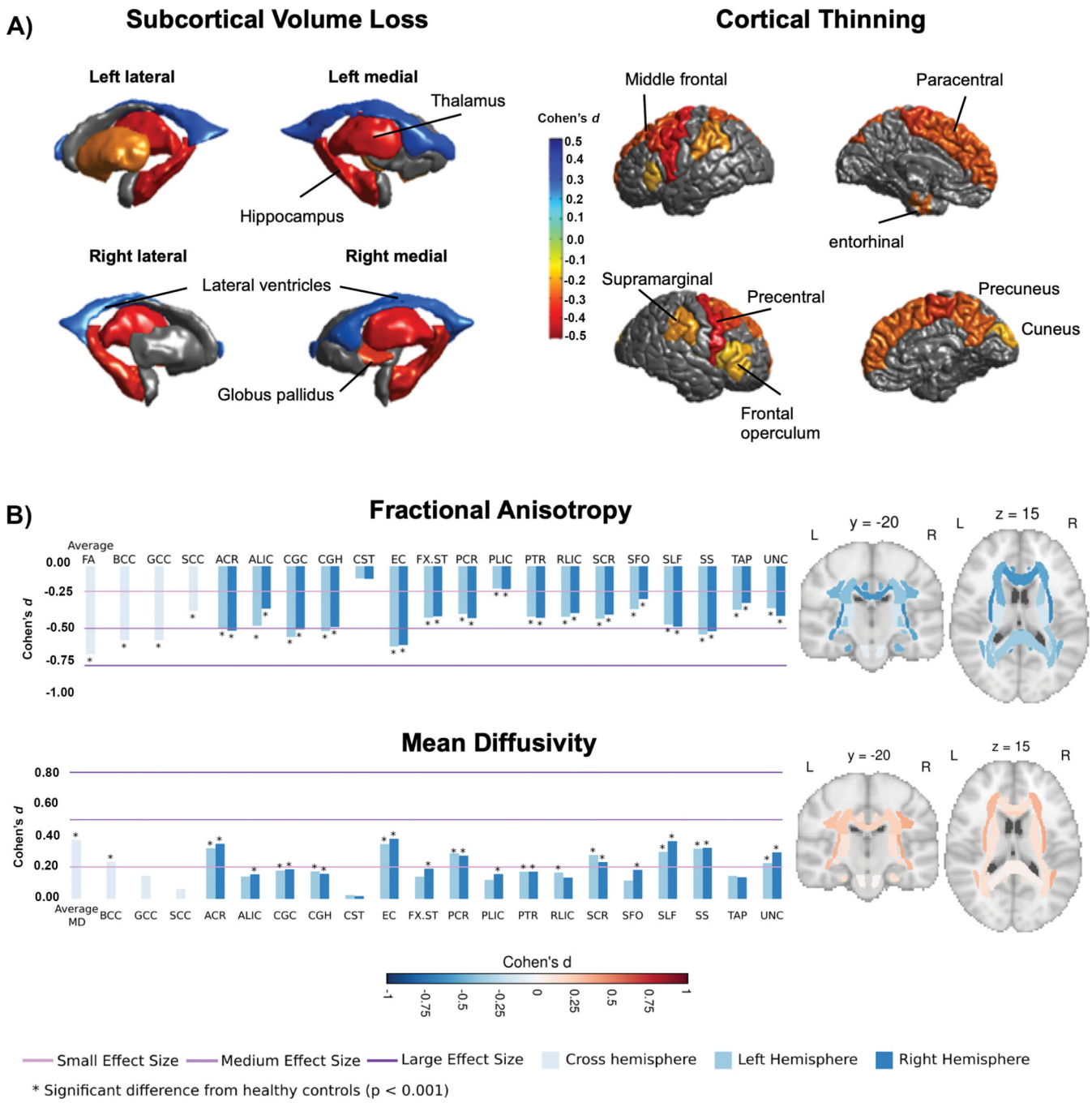

Fig. 2 |.

Subcortical, cortical and diffusion findings in ENIGMA-Epilepsy. **a** | Subcortical volume (left) and cortical thickness (right) abnormalities shared across all epilepsy syndromes in the ENIGMA-Epilepsy meta-analysis[124]. Coloured bar represents Cohen's *d* effect size estimates for case–control differences in each subcortical or cortical region. Red and yellow shading depicts regions with greater volume loss or thinning in patients relative to controls, whereas blue shading represents regions with higher volume relative to controls. Patients with epilepsy had lower volumes of the bilateral thalami and hippocampi and right pallidum

relative to controls, and increased volume of the lateral ventricles. The patients also showed cortical thinning in the precentral and paracentral gyri bilaterally and in the left prefrontal, superior parietal and cuneus. **b** | White matter microstructural differences across 38 fibre tracts for the 'all epilepsies' cohort compared with controls[125]. All values represent Cohen's *d* effect size estimates for differences in fractional anisotropy and mean diffusivity between each patient group and healthy controls. Positive effect sizes reflect diffusion values greater than controls and negative effect sizes represent values lower than controls. The y and z values represent the slice number for the coronal and axial planes, respectively. Across all epilepsies, the greatest effects on fractional anisotropy were observed in the body and genu of the corpus callosum, external capsule, cingulum and corona radiata. The greatest effects on mean diffusivity were observed in the external capsule, anterior corona radiata and superior longitudinal fasciculus. Part a reprinted with permission from ref.[124]. Part b adapted with permission from ref.[125].

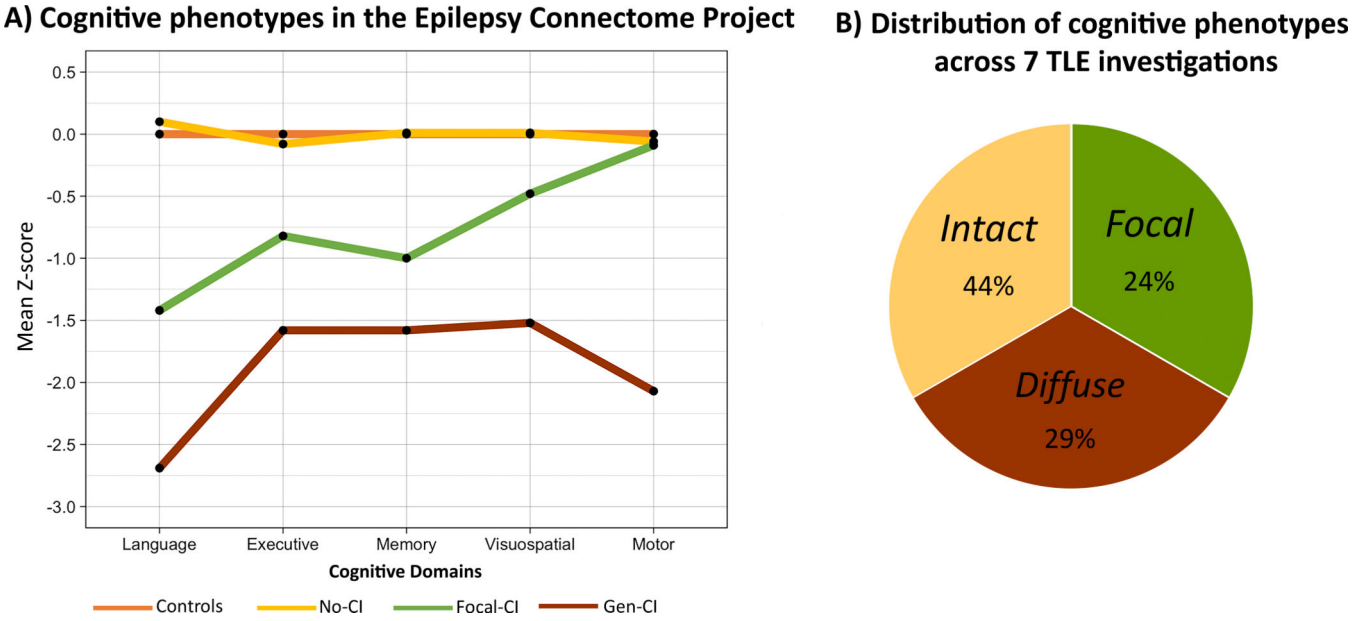

Fig. 3 |.

Cognitive phenotypes and their distribution. **a** | The Epilepsy Connectome Project identified three cognitive phenotypes in patients with temporal lobe epilepsy (TLE): intact or minimally impaired, comparable to healthy controls; generalized impairment, with abnormal scores across all administered cognitive metrics; and focal impairment, predominantly affecting memory, language and/or executive function[93]. The z-scores represent performance of the epilepsy groups compared with controls, with negative values indicating worse performance. **b** | Distribution of cognitive phenotypes across seven investigations in individuals with TLE[93,176,180,181,182,184,187].

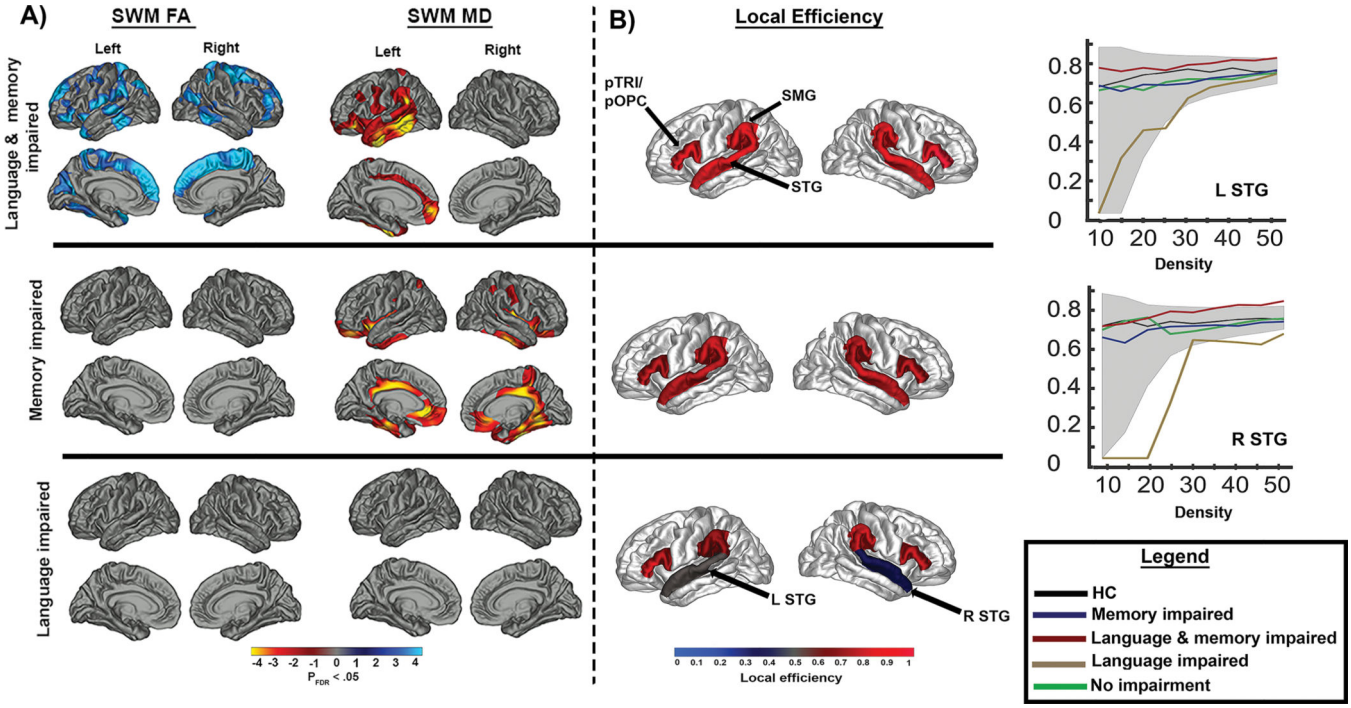

Fig. 4 |.

Diffusion and network findings across discrete cognitive phenotypes of TLE. **a** | Differences in superficial white matter (SWM) fractional anisotropy and mean diffusivity across cognitive phenotypes in individuals with temporal lobe epilepsy (TLE) relative to healthy controls. Blue and cyan represent lower values and red and yellow represent higher values than controls. **b** | Local efficiency differences between healthy controls and each cognitive phenotype within perisylvian regions (depicted in red), including the pars triangularis (pTRI)/pars opercularis (pOPC), superior temporal gyrus (STG) and supramarginal gyrus (SMG). Significant differences between patients with TLE and healthy controls are depicted in grey and blue. The line graphs demonstrate differences in local efficiency within the left and right STG between healthy controls and each cognitive phenotype across different network densities. Shaded areas represent the upper and lower boundaries of local efficiency for healthy controls. In both panels, patients with single-domain memory or language impairments demonstrate findings distinct from patients with multiple domain impairments. Patients with both language and memory impairment showed widespread SWM abnormalities, whereas patients with memory impairments alone showed SWM abnormalities predominantly in the bilateral temporal lobes and cingulum. Patients with language impairments alone showed distinct abnormalities in perisylvian network structure that were not apparent at the regional SWM level. Adapted with permission from ref.[182].

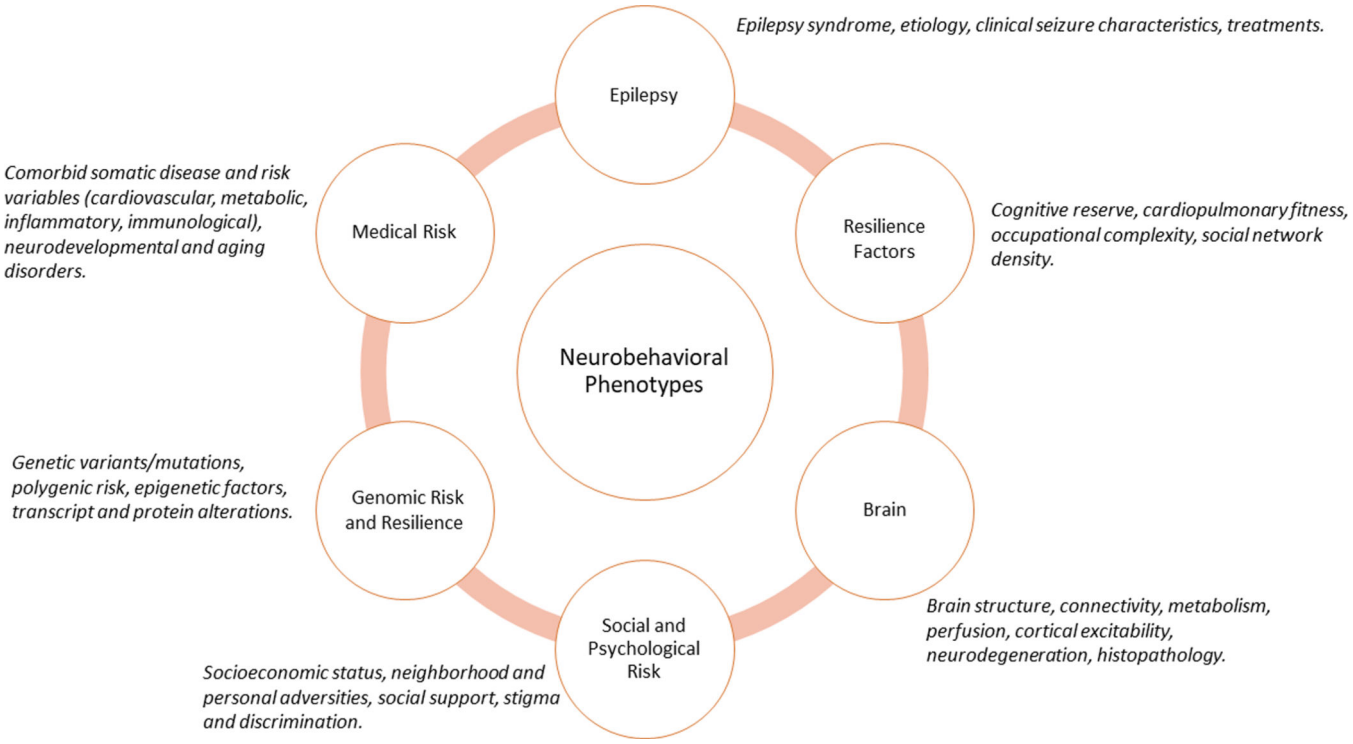

Fig. 5 |.

A next-generation paradigm for neurobehavioural phenotypes of epilepsy. The outer ring depicts six major factors (and associated exemplars) that alone or in combination are proposed to exert direct and/or indirect influences on the causes and course of neurobehavioural phenotypes in epilepsy.

Table 1 |

Genetic factors associated with neurobehavioural comorbidities in epilepsy

Comorbidity	Gene (polymorphism)	Cohort
Memory impairment	*APOE* (rs7412, rs429358)	Temporal lobe epilepsy[232,233]
	BDNF (rs6265)	Mesial temporal lobe epilepsy[235]
	BDNF (rs1491850, rs2030324, rs11030094, rs12273363)	Newly diagnosed epilepsy[234]
	REST (rs1105434, rs2227902)	Newly diagnosed epilepsy[234]
Executive dysfunction	*BDNF* (rs6265)	Temporal lobe epilepsy[234]
	COMT (rs4680)	Temporal lobe epilepsy and paediatric epilepsy (mixed types)[236]
	MTHFR (rs1801133)	Paediatric epilepsy (mixed types)[236]
Impaired working memory	*MTHFR* (rs1801133)	Paediatric epilepsy (mixed types)[236]
	COMT (rs4680)	Paediatric epilepsy (mixed types)[236]
Reduced processing speed	*REST* (rs3796529)	Newly diagnosed epilepsy[234]
Depression	*BDNF* (rs6265)	Refractory epilepsy[238]
Anxiety	*COMT* (rs4680)	Refractory epilepsy[238]

APOE, apolipoprotein E; *BDNF*, brain-derived neurotrophic factor; *COMT*, catechol-*O*-methyltransferase; *MTHFR*, methylenetetrahydrofolate reductase; *REST*, RE1-silencing transcription factor.