Supplementary Table 1 | Cognitive phenotype investigations in epilepsy

Investigation	Dependent variable(s)	Participants	Cluster method*	Cognitive phenotypes	Imaging metrics included?	Phenotype predictors+‡	Phenotype predictors–‡
Paradiso et al. (1994)[1]	3 academic measures (read, spell, arithmetic)	117 TLE	Empirical	6 academic achievement clusters	No	Gender, specific cognitive tests	Age, age at onset, laterality
Hermann et al. (2007)[2§]	7 cognitive domains	96 TLE, 82 HC	Empirical	3 cognitive clusters	Yes: cerebral, lobar, and hippocampal volumes (grey, white, CSF)	Older age, longer epilepsy duration, no. of medications, neuroimaging metrics	Gender, onset age, education, seizure frequency, laterality, aetiology
Dabbs et al. (2009)[3§]	7 cognitive domains	55 TLE, 53 HC	Empirical	3	Yes: cortical thickness; corpus callosum, subcortical and cerebellar volumes	Distributed regional cortical thickness and volumes of hippocampus, thalamus, basal ganglia, cerebellum and corpus callosum	NA
Berl et al. (2014)[4]	fMRI language activation	220 FE, 118 HC	Empirical	2, 4, and 9 cluster solutions	Yes: fMRI language activation patterns	Atypical handedness, early age of onset, abnormal MRI (especially vascular)	Age, gender, IQ, laterality or lobe of onset
Hermann et al. (2016)[5]	5 cognitive domains	138 CWE, 95 HC	Empirical	3 cognitive clusters	Yes: cortical thickness and subcortical and cerebellar volumes	Provision of early developmental services, parental IQ, neuroimaging metrics (cerebellum and subcortical structures)	Gender, parental education, epilepsy syndrome, onset age birth weight

Rodriguez-Cruces et al. (2018)[6‖]	10 indices from memory and intelligence tests	26 TLE, 24 HC	Empirical	3 cognitive clusters	Yes: diffusion MRI	Hippocampal volume, integrity of white matter tracts, education, age of onset	Laterality of TLE, number of meds, seizure frequency
Elverman et al. (2019)[7]	7 cognitive domains	185 TLE	Empirical	4 cognitive clusters	No	Lateralization, seizure frequency, age of recurrent seizure onset, Wada language lateralization	Age at onset, epilepsy duration, no. of medications, sex, race, MTS, SE episodes; no. of seizure types, lifetime GTC
Reyes et al. (2019)[8]	Language (n=3) and memory (n=3) tests	70 TLE, 46 HC	Actuarial	4 cognitive clusters	Yes: diffusion MRI (superficial white matter, fibre tract) and related network analyses	Age of onset, integrity of distributed white matter tracts and regional patterns of integrity and superficial white matter	Age, education, sex, handedness, epilepsy duration, no. of meds, MTS, seizure frequency, laterality
Kaestner at al. (2019)[9]	Language (n=3) tests, fMRI language activation	85 TLE, 47 HC	Actuarial	2 language clusters (impaired/ nonimpaired)	Yes: structure (cortical thickness), diffusion MRI, fMRI	fMRI language activation patterns, DTI tractography, WM fibre tracts	Age, education, gender, handedness, seizure frequency (partial and GTC), no. of ASMs, MTS, nonverbal IQ, laterality, language laterality
Reyes et al. (2020)[10]	Language, verbal	407 TLE, 151 HC	Empirical	3 cognitive clusters	No	Education, onset, age, duration	Laterality

	memory, executive, processing speed		Actuarial	3 cognitive clusters	No	Education, onset age, MTS	Age, duration, sex, handedness, laterality
Rodriguez-Cruces et al. (2020)[11‖]	9 cognitive indices	34 TLE, 25 HC	Empirical	3 cognitive clusters	Yes: diffusion MRI, cortical thickness, hippocampal volume	Specific features of network graphs (degree centrality, path length, cluster coefficient), MTS, education	Gender, age, age of onset, duration, ASM number
Modi et al. (2019)[12]	8 executive function scales (BRIEF)	237 CWE	Empirical	4 executive function clusters	No	Associations with patient and parental reported HRQoL scales as well as emotional and behavioral function scales	Recent seizures (prior 3 months), epilepsy syndrome, aetiology, chronicity
Hermann et al. (2020)[13¶]	6 cognitive domains	111 TLE, 82 HC	Empirical	3 cognitive clusters	Yes: cortical thickness and volume and subcortical and cerebellar volumes, rs-fMRI	Patient and parental education, racial diversity, lifetime SGS, age of medication onset, MTS, cerebellar atrophy, rs-fMRI connectivity	Gender, laterality, duration, no. of medications, cortical thickness or volume
Baxendale & Thompson (2020)[14]	4 cognitive domains	242 TLE	Actuarial	4 cognitive clusters	No	Age, age at onset, depression, anxiety, postoperative visual memory	Laterality of TLE, sex, pathology, postoperative verbal memory
Struck et al. (2021)[15¶]	16 cognitive tests	111 TLE, 55 HC	Empirical	3 cognitive clusters	Yes	Graph theory metrics of global clustering coefficient and rich club proportion	Right and left temporal lobe connectivity ratios for degree and closeness
Arrotta et al. (2021)[16]	5 cognitive domains	106 FLE	Actuarial	4 cognitive clusters	Yes	Age, education, age of onset	Sex, handedness,

							duration, laterality
Puka & Smith (2021)[17]	15 cognitive metrics	93 youth with drug-resistant epilepsy	Empirical	2 prospective cognitive clusters	No	Baseline cognitive status, age, no. of ASMs, seizure freedom	Treated or not treated with surgery

*Cluster method: determined by cluster analyses (empirical) or actuarial method.
‡Phenotype predictors: variables associated with (+) or not associated with (–) cluster membership.
§,‖,¶Investigations indicated by identical symbols represent linked studies.

Abbreviations: ASM, antiseizure medications; BRIEF, Behavior Rating Inventory of Executive Function; CSF, cerebrospinal fluid; CWE, children with epilepsy; DTI, diffusion tensor imaging; FE, focal epilepsy; fMRI, functional MRI; GTC, generalized tonic–clonic seizures; HC, healthy controls; HRQoL, health-related quality of life; IQ, intelligence quotient; MTS, mesial temporal sclerosis; NA, not applicable; no., number, rs-fMRI, resting-state fMRI; SE, status epilepticus; SGS, secondarily generalized seizures; TLE, temporal lobe epilepsy; WM, white matter.

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Supplementary Figure 1 | Pathways between epilepsy, genomics and neurobehavioural comorbidities