Neuropsychological Markers of Executive Function in Paediatric Epilepsies and Paediatric Epilepsy Surgery

A thesis submitted to the University of Manchester for the degree of Doctor of Clinical Psychology in the Faculty of Biology, Medicine and Health

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Word Count *(main text, excluding tables, figures, references and appendices)*

Paper 1: 11,053 *(5,189)*

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Paper 3: 6,247 *(4,648)*

Total: 27,111 *(15,185)*

Thesis Abstract

This thesis comprises three papers investigating executive function outcomes in paediatric epilepsies and paediatric epilepsy surgery: a systematic review, an empirical study and a critical appraisal.

Within the review, systematic searching techniques were used to identify all available literature exploring functional neuroimaging and neuropsychological functioning related to executive functions in children with epilepsy. Twenty-three publications were identified for inclusion in the review. All studies underwent quality assessment and results were brought together using narrative synthesis, with ongoing recommendations for clinical practice and research discussed thereafter. Overall, studies revealed evidence of disruptions to a fronto-parietal network involved in executive functions. The findings have relevance for understanding key brain regions and networks, and disruption to their development, in paediatric epilepsies.

The empirical research project took a network approach to compare fronto-parietal and temporal epilepsies on measures of executive function, including working memory, cognitive flexibility, attention and parented-rated executive function. A longitudinal, multi-centre study was conducted, using Northern Children's Epilepsy Surgery Service (NORCESS) data in children aged 6 years to 17 years 11 months, at pre- (n = 194) and post-surgery (n = 48). At baseline, children with fronto-parietal epilepsies had greater rates of working memory and cognitive flexibility difficulties than children with temporal epilepsy. Following surgery, there was evidence to suggest a stabilising of the development of executive function skills in a fronto-parietal epilepsy group, however at an individual-level outcomes were variable. The findings highlight the need for more research on the individual components of executive function and an agreement on core outcome measures for executive function in the UK.

Finally, the critical appraisal included a discussion of the strengths and limitations of the systematic review and empirical study. Reflections on process and contributions to research are discussed, in addition to the clinical implications of the findings.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

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Paper 1

Neuropsychological markers of executive function from functional neuroimaging in children with epilepsy: a systematic review

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11,053 (all text), 298 (abstract), 3,233 (tables and figures), 2,333 (references)

Manuscript prepared in line with guidance for *Epilepsia* (see Appendix A for author guidelines), with additional information provided for context.

ABSTRACT

Objective: In the typically developing brain, neuroimaging studies have highlighted neural networks that are important for executive function skills. The current review aimed to systematically evaluate studies exploring functional neuroimaging and neuropsychological functioning related to executive functions in children with epilepsy. ***Method:*** A systematic search of Embase, MEDLINE and PsycINFO databases was conducted (limited to English and studies published in or after the year 2000). Clinical studies investigating combined functional neuroimaging and executive function neuropsychological outcome data in children (0-17 years), with a disease-matched control or healthy control group, were eligible for inclusion in the review. Quality assessment appraisals were completed to highlight strengths and weaknesses of included publications. ***Results:*** Twenty-three publications were identified and a narrative synthesis was undertaken. Identified studies used functional magnetic resonance imaging (fMRI, *n* = 14), electroencephalogram (EEG, *n* = 8) and magnetoencephalogram (MEG, *n* = 1), and reported on neural correlates for working memory (*n* = 14), attention (*n* = 4), inhibitory control (*n* = 7) and cognitive flexibility (*n* = 9). The most widely studied component of paediatric executive function was working memory. Studies revealed evidence of disruptions to a fronto-parietal network involved in executive functions across a range of mixed epilepsy types. Methodological quality was variable, with 65% of studies rated as of 'fair' quality overall. No studies reported statistical power calculations, limiting conclusions that can be drawn from the findings. The review also reported some findings of disruption to temporal regions. ***Significance:*** This review was the first to systematically evaluate the literature on correlates of functional neuroimaging and neuropsychological functioning related to executive function in paediatric epilepsy. The findings have relevance for understanding disruption to key brain regions and networks which underpin executive functions. Future studies should aim to improve the methodological rigour and address highlighted methodological weaknesses.

Keywords: Paediatric epilepsy, Executive function, Functional neuroimaging.

1. INTRODUCTION

The epilepsies have been reconceptualised by the International League Against Epilepsy (ILAE) as a brain network disease (Berg et al., 2010). The new classification outlines that seizures may be focal (arising from a network in one hemisphere) or generalised (arising from or rapidly involving networks that are bilateral). The update emphasises the need to understand epilepsies as a disorder of cognition and behaviour related to changes in these networks (Wilson & Baxendale, 2014). Since it was originally theorised that epileptogenic neurons may be hyperexcited throughout a large neural network (Spencer, 2002), research has increasingly focused on looking beyond the location of seizures and at the wider network impact (Smith, 2016). Even when studies classified the epilepsy as focal, localisation-related abnormalities have been found beyond the seizure onset zone and in the contralateral hemisphere. The findings suggest widespread neuronal dysfunction and possible associated neuropsychological impairments which are broader than predicted by a single lesion or the location of seizure onset (Hu et al., 2012; Lawson et al., 2002; Widjaja et al., 2011).

Executive function difficulties have been reported in up to 50% of children with epilepsy (Cainelli et al., 2020; Høie et al., 2008; Parrish et al., 2007) and are a common feature amongst various paediatric epilepsies (for a review, see MacAllister et al., 2014). Executive functions are defined as a set of top-down cognitive processes involved in initiation, planning, goal-setting, inhibition, working memory, flexibility and emotional control (Diamond, 2013; MacAllister et al., 2014). There has been considerable debate about the structure and organisation of executive functions (Fiske & Holmboe, 2019). The authors of this review recognise the unity/diversity model which views the executive function system as composed of three core components: working memory, inhibitory control and set shifting/cognitive flexibility (Friedman & Miyake, 2017; Miyake et al., 2000). Support for the application of this model to explore executive functions using functional neuroimaging in children has been reported (McKenna et al., 2017). Within the current review, set shifting/cognitive flexibility will be referred to as cognitive flexibility in line with an overarching review of executive function (Diamond 2013). Attention has been included as a

separate construct to working memory due to differences in the two processes (Oberauer, 2019) and its prominence in paediatric epilepsy research; although it is noted that there is considerable overlap between working memory and attention (Oberauer, 2019).

There is evidence that executive function skills, including aspects of working memory and inhibitory control, start developing in early infancy and continue to develop until early adulthood (Anderson & Reidy, 2012; Diamond, 2013). Epilepsies in children can impact the developing brain given interference with the normal developmental trajectory, including the failure to develop a skill, a regression in skill, or a slower rate of development (Smith, 2010). Furthermore, there is increasing evidence that there is a bidirectional relationship in early childhood with epileptic activity having negative consequences on the development of the neuronal networks themselves and any later functions supported by these widespread networks (Anderson et al., 2018).

Neuropsychological investigations have highlighted overlapping executive function and memory difficulties between children with frontal lobe epilepsy and temporal lobe epilepsy (Smith, 2016), supporting the theory of a network disease with wide ranging atypical patterns across neural networks. More specifically, research suggests that difficulties are comparable across frontal lobe epilepsy and temporal lobe epilepsy in the domain of working memory (Kibby et al., 2019) and parent and teacher reported executive function (Campiglia et al., 2014).

Neuroimaging studies in the typically developing brain have highlighted neural networks that are involved in supporting executive function skills. Resting-state functional magnetic resonance imaging (fMRI) analyses in adults have identified connections between fronto-parietal and cingulo-opercular networks (Crittenden et al., 2016; Power et al., 2011). Engelhardt et al. (2019) used task-based fMRI data in children and found similar brain regions that were consistently engaged across executive function tasks also corresponded to networks that had been identified in adults. Findings of the association between fronto-parietal activations and executive function have been reported in a meta-analysis of functional neuroimaging findings in children (McKenna et al., 2017).

The developmental trajectories and neural substrates of executive functions have been extensively researched in recent years, spurred on by the increased use of neuroimaging techniques. In their review of the neural substrates of early executive function development, Fiske and Holmboe (2019) identified that the frontal and parietal cortices, and the connectivity between them, were key neural regions, both functionally and in facilitating the development of executive function. Furthermore, they identified that typical development of executive function requires the specialisation of brain regions involved in executive function, and also decreased activity of other regions (Karmiloff-Smith, 1996).

To date, there has been no systematic review of functional neuroimaging and executive function outcomes in paediatric epilepsies. In a targeted review of just task based-neural activation studies, Oyegbile (2019) identified evidence of functional neuroimaging differences in executive function in children with temporal lobe epilepsy (any age) compared to healthy controls (HCs), reduced activation in frontal regions and increased activation in parietal regions. This review systematically evaluated studies exploring the correlates of functional neuroimaging and executive functioning, in paediatric epilepsy groups to advance current conceptualisations of executive function in paediatric epilepsies and inform further research. The review aimed to explore whether functional neuroimaging of executive functions differs in young people with epilepsy compared to those without epilepsy. Given it was the first systematic review on this topic, an approach was taken with the aim of identifying all available studies that used any functional neuroimaging method and reported on any of the four core components of executive function (working memory, attention, inhibitory control, and cognitive flexibility).

2. METHOD

The review was PROSPERO-registered prior to commencement (ID: CRD42022350017) and was carried out according to Preferred Reporting for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021).

2.1. Search strategy and selection criteria

Embase, MEDLINE and PsycINFO databases were searched using the Ovid platform, in November 2022 and updated in February 2023, for published literature containing search terms within titles or abstracts. Search blocks related to paediatric epilepsy, executive function outcomes and functional neuroimaging outcomes. The search strategy is listed in Appendix B.

Inclusion criteria were as follows: studies in which participants were children (aged 0-17 years) with a diagnosis of epilepsy, studies which included functional neuroimaging (including brain localisation) and executive function neuropsychological outcome data (this would include assessment during neuroimaging or standard neuropsychology assessment recorded at different times to neuroimaging), studies with a disease-matched control or healthy control group and studies published in full text in English. Results were restricted to peer-reviewed studies published in or after the year 2000, given the reconceptualised view of epilepsy as a disorder of large neural networks (Spencer, 2002). Studies were excluded when localisation of function in functional neuroimaging data were not included, and when only functional neuroimaging or only neuropsychological outcome data were available.

All returned titles, abstracts and full texts were independently screened to confirm eligibility for inclusion in the review by two authors (D.R. & R.S) using the a priori selection criteria. Disagreements were discussed and if not resolved, the opinion of a third author (R.B.) or other author was sought. Data was extracted in relation to study characteristics and outcomes shown in Table 1.

2.2. Data synthesis

A degree of variability was expected in terms of neuropsychological assessment, functional neuroimaging methods, and analyses undertaken, and therefore, a narrative synthesis of the findings was undertaken (Campbell et al., 2020). Information on study characteristics and findings were extracted. The ordering of information was completed chronologically (most recent to least recent)

based on cohort. An in-text summary was used to highlight key findings. Studies were grouped for synthesis based on the reporting of functional neuroimaging data in the four components of executive function: 1) working memory, 2) attention, 3) inhibitory control, and 4) cognitive flexibility. The reporting of findings was based on clinical interpretation of reliable differences in each component between children with epilepsy and HCs. Where applicable, executive function tasks were categorised in line with Diamond's (2013) review paper. The confidence the reader could place in the findings was addressed by taking into consideration the consistency of reliable differences in each domain across studies, and the quality of evidence.

2.3. Quality appraisal and risk of bias assessment

Given the expected inclusion of studies using observational designs, the quality appraisal and assessment of risk of methodological bias was based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Institutes of Health, 2014). Two reviewers independently completed a quality assessment for all included studies (D.R. & R.S). The original study assessment tool (Appendix C) was adapted in line with the review question (Appendix D). Four domains were appraised as 'good', 'fair' or 'poor', namely 1) research question, 2) selection (including specification and recruitment of population, rate of participation, and application of inclusion and exclusion criteria), 3) design (including sample size, appropriateness of assessment, and definition and implementation of epilepsy diagnosis), and 4) outcome (including outcome measures, rate of follow-up, control of confounding variables, reporting of results). Ratings across the domains were categorised as outlined in the assessment tool in Appendix D. Overall methodological quality was also categorised as 'good' ($\geq$12), 'fair' (7-11) or 'poor' ($\leq$ 6).

3. RESULTS

Data extraction revealed a high variation of neuropsychological and functional neuroimaging outcome data collected arising from a wide range of methods and analyses. A total of 4756 results were returned across the three databases. After removing duplicates and excluding papers that did not meet criteria (see Figure 1 for PRISMA flowchart), 23 articles remained for inclusion in the review. Inter-rater reliability was analysed in SPSS version 25 (IBM Corp, 2017) and revealed a good level of agreement between reviewers ($\kappa = .987$, $p < .001$). Table 1 summarises the study characteristics and findings.

3.1. Study characteristics

All 23 publications were non-randomised cohort studies, employing prospective ($n = 22$) or retrospective ($n = 1$) dataset designs with a HC comparison group. The studies comprised 19 different cohorts that were sampled from Asia ($n = 4$), Europe ($n = 10$), and North America ($n = 5$), with outcomes available for ages ranging 6 to 17 years of age. Using cross-sectional assessments, studies used fMRI ($n = 14$), electroencephalogram (EEG) ($n = 8$) and magnetoencephalogram (MEG) ($n = 1$) and reported on neural correlates for working memory ($n = 14$), attention ($n = 4$), inhibitory control ($n = 7$) and cognitive flexibility ($n = 9$). Epilepsy type (focal or generalised) was focal ($n = 7$), mixed ($n = 11$), or not reported ($n = 10$). Epilepsy localisation/diagnosis was either frontal ($n = 4$), temporal ($n = 2$), self-limited epilepsy with centrotemporal spikes (SeLECTS, $n = 7$), mixed ($n = 7$), or not reported ($n = 3$).

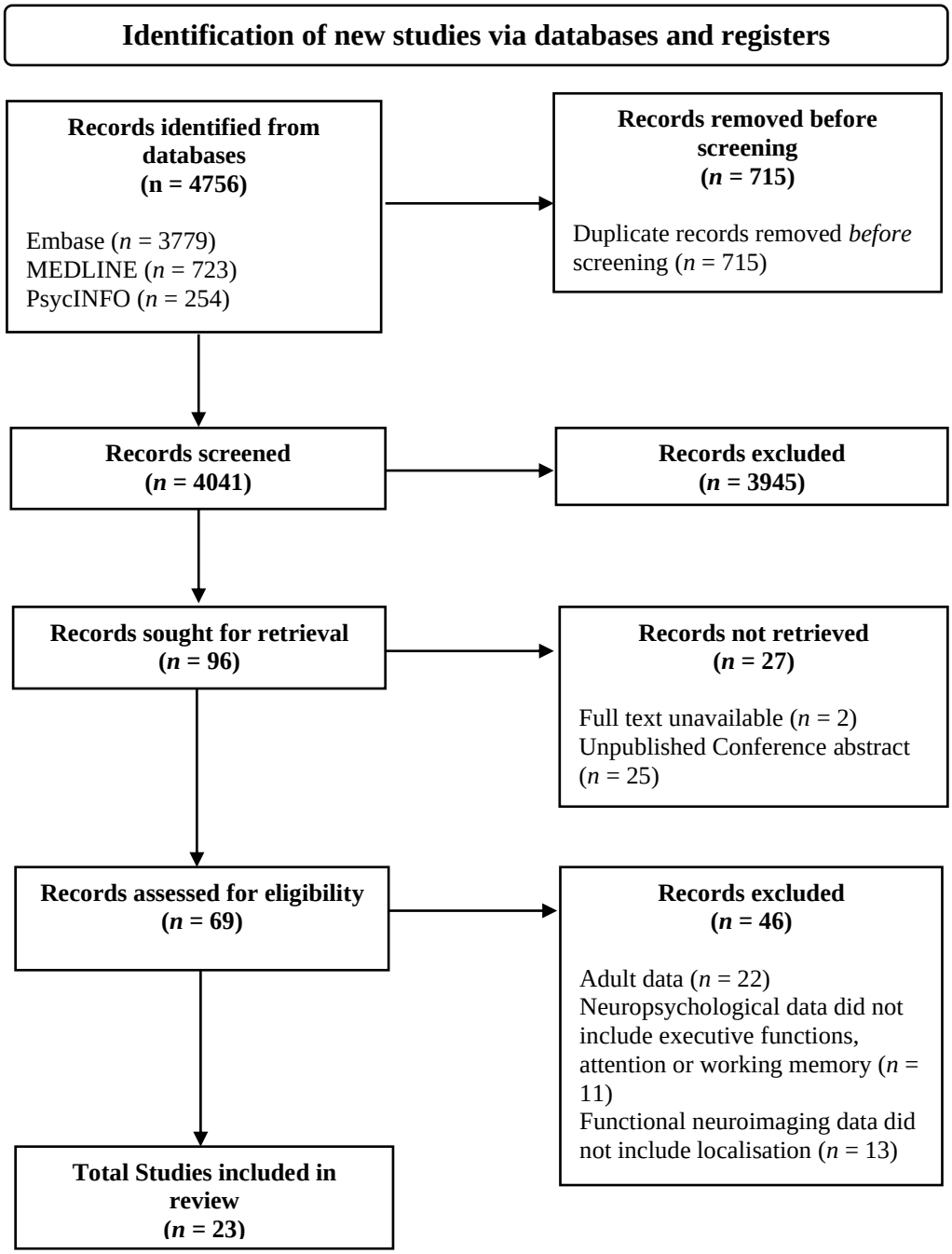

Figure 1. PRISMA flowchart

Table 1. Study characteristics and findings for all included studies

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
Scientific Institute, IRCCS ‘‘E. Medea” Duma et al. (2021)	Italy	hospital and university, multicentre	epilepsy (SeLECTS, *n*=13; SeLEAS, *n*=8), HC (*n*=32)	8.9	49%	Ethnicity: not reported; Comorbidities: Anxiety 14%	Not reported	SeLECTS 62%, SeLEAS 38%.	5.7	2.3	5%	WISC-IV, Conner’ s CPT III, Phonemic and semantic fluency	Dynamic Temporal Prediction	Cognitive flexibility	EEG, task-based analysis	During the task, the ERP between-group comparison of the anticipatory activity in the baseline condition revealed a larger CNV amplitude in the HC group compared to the epilepsy group. There was a larger negativity spreading over the frontocentral electrodes and a larger positivity expressed in a cluster of central posterior electrodes.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
Children's Hospital of Nanjing Medical University and the Nanjing Brain Hospital Wang et al. (2021)	China	hospital, multicentre	epilepsy (*n*=28), HC (*n*=14)	bilateral SeLECTS, 8.09; unilateral SeLECTS, 9.28	bilateral SeLECTS, 43%; unilateral SeLECTS, 36%	Ethnicity: not reported; Comorbidities: not reported	Not reported	SeLECTS 100%	bilateral SeLECTS 7.85; unilateral SeLECTS 9.02	bilateral SeLECTS 2.86; unilateral SeLECTS 3.14	Not reported	WISC-IV	N/A	Working memory	MEG, resting-state FC analysis	In the 8–12 Hz frequency, bands, children with bilateral SeLECTS displayed prominent involvement of the frontal cortex, relative to the controls. However, no significant correlations with WISC WMI were observed. In the unilateral SeLECTS epilepsy group, WISC WMI was negatively associated with FC path length in the 8–12-Hz band.

Cohort and study Details		Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
Cincinnati Children's Hospital Medical Center and the Pediatric Neuroimaging Research Consortium	Vannest et al. (2021)	USA	hospital, single centre	epilepsy (*n*=29), HC (*n*=20)	15.4	76%	Ethnicity: White, Hispanic 6.9%, White, Non-Hispanic 82.8%, Black, Non-Hispanic 6.9% More than once race (3.4%); Comorbidities: not reported	Focal 20.7%, Generalised 58.6%, Unclassified 20.7%	not reported	12.1	3.3	100%	BRIEF, WISC WMI, WAIS-IV WMI	N-back	Working memory	fMRI, task-based FC analysis	There were no significant differences in group activation on fMRI N-back between the epilepsy group and HCs. fMRI activation during the N-back task showed no significant relationship with neuropsychological working memory scores. There was significantly reduced FC between the left frontal operculum and anterior cingulate gyrus in the epilepsy group compared to HCs during the n-back task. There were no significant differences in fronto-parietal network connectivity between the epilepsy group and HCs.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
Gutierrez-Colina et al. (2020)	USA	hospital, single centre	epilepsy (*n*=29), HC (*n*=20)	15.4	76%	Ethnicity: White, Hispanic (6.9%); White, Non-Hispanic (82.8%); Black, Non-Hispanic (6.9%); More than once race (3.4%); Comorbidities: ADHD 17%	Focal 20.7%, Generalised 58.6%, Unclassified 20.7%	not reported	12.1	3.3	100%	BRIEF-Parent Form	N/A	Working Memory	fMRI, resting-state FC analysis	In the epilepsy group, lower connectivity between the left supramarginal/superior parietal and the right lateral cerebellum, and the left middle frontal and the left middle inferior frontal/precentral ROIs was associated with poorer BRIEF working memory ratings. In the epilepsy group, increased FC between the right middle superior frontal and the right supramarginal ROIs, and the left middle frontal and right supramarginal/superior parietal ROIs was associated with poorer BRIEF working memory ratings.
University Hospitals of Lyon Ciumas et al. (2020)	France	hospital, single centre	epilepsy (*n*=17), HC (*n*=17)	9.7	29%	Ethnicity: not reported Comorbidities: ADHD 5%	Not reported	SeLECTS 100%	7.2	2.3	47%	WISC-IV	Sternberg working memory task	Working memory	fMRI, task-based analysis	In the epilepsy group, the study found further left sided activation of the IFG and middle frontal gyrus relative to HCs. Between-group analyses showed that that HCs showed significantly greater fMRI activation than the epilepsy group for high load versus no load contrast over the left superior temporal gyrus, inferior temporal gyrus, medial frontal gyrus, middle frontal gyrus and the right IFG. No region was more activated in patients than in controls.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
National Center Hospital, National Center of Neurology and Psychiatry Ueda et al. (2020)	Japan	hospital, single centre	epilepsy (*n*=24), HC (*n*=22)	11.0	46%	Ethnicity: not reported: Comorbidities: not reported	Focal 100%	Frontal 100%	Not reported	Not reported	Not reported	SNAP-IV, RCPM test; Go no-go visual CPT	N/A	Inhibitory control; Attention	EEG, sleep FC analysis	In the epilepsy group, the gamma PLI (FC) of the interhemispheric frontal and frontoparietal pairs was positively correlated with inattention scores in the SNAP-IV as well as omission error and reaction time scores on the Go-no go CPT. The gamma PLI of the interhemispheric frontal and frontoparietal pairs was negatively correlated with commission error scores on the Go-no go CPT in the epilepsy group. There was no significant relationship between the gamma PLI of the interhemispheric frontal and frontoparietal pairs and SNAP-IV scores and Go-no go CPT scores in the HC group.

Cohort and study Details		Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
MedSTAR Georgetown University Hospital	Oyegbile et al. (2019)	USA	hospital, single centre	epilepsy (*n*=15), HC (*n*=15)	11.2	46%	Ethnicity: White (42%), Other (not reported); Comorbidities: ADHD 20%	Not reported	Temporal 100%	Not reported	3.9	87%	D-KEFS, WASI-2	N-back	Working memory	fMRI, task-based analysis	During the n-back task, the DMN demonstrated significantly reduced deactivation in the patients with epilepsy compared with HCs, specifically in the left parietal lobe and the right precuneus region. fMRI analyses reported on a combined group and did not report on differences between HC group and epilepsy for neuropsychological assessment.
	Oyegbile et al. (2018)	USA	hospital, single centre	epilepsy (*n*=15), HC (*n*=15)	11.2	46%	Ethnicity: White (42%), Other (not reported); Comorbidities: ADHD 20%	Focal 100%	Temporal 100%	Not reported	3.9	87%	D-KEFS; WASI-2, Grooved Pegboard	N-back	Working memory	fMRI, task-based analysis	Comparison of HC group and epilepsy group showed reduced activation in the left middle frontal gyrus in the epilepsy group during the task. fMRI analyses reported on a combined group and did not report on differences between HC group and epilepsy for neuropsychological assessment.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
University Hospitals KU Leuven Protopapa et al. (2016)	Belgium	hospital, single centre	epilepsy (*n*=21), HC (*n*=25)	11.4	52%	Ethnicity: not reported; Comorbidities: not reported	Generalised 57%	SeLECTS 43%, Absence 24%, generalised with tonic–clonic seizures 33%	Not reported	Not reported	86% on	N/A	Go-No go	Inhibitory control	EEG, spatio-temporal causal connectivity analysis	Differences between HCs and the epilepsy for Go networks were most profoundly seen in alpha band. The HC group showed greater network connectivity in left midline, parietooccipital, right midline and frontal brain areas. Differences between HCs and the epilepsy for No go networks were found in a large number of bands. In delta band, the HC group showed greater connectivity in right parieto-occipital and central midline brain areas. In theta band, the HC group showed greater connectivity in right parieto-occipital and left temporal-midline brain areas. In beta band, the HC group showed greater connectivity left midline brain areas. In alpha band, less widespread differences were shown, where HCs showed greater connectivity in left-midline channels, whilst the epilepsy group showed greater connectivity in left frontal areas.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
West China Hospital of Sichuan University Xiao et al. (2015)	China	hospital, single centre	epilepsy (*n*=73), HC (*n*=73)	9.7	44%	Ethnicity: not reported; Comorbidities: not reported	Not reported	SeLECTS 100%	Not reported	0.8	40% on	WISC-CR; CBCL, TMT, Boston Naming test, Verbal fluency test	N/A	Cognitive flexibility; Attention	fMRI, resting-state FC analysis	Two connected networks were identified in which all connections displayed decreased values in the epilepsy group compared to HCs. The first network was predominantly located in posterior regions (the bilateral fusiform gyrus, the left middle occipital gyrus and the right superior occipital gyrus). The second network primarily consisted of sensorimotor regions (the left SeLECTS operculum, the right supplementary motor area, the bilateral postcentral gyrus, and the bilateral paracentral lobule). There was no significant correlation between functional connectivity global network metrics and neuropsychological findings.
Hospital for Children Toronto snd the Foothills Medical Centre Ibrahim et al. (2014)	Canada	hospital, multicentre	epilepsy (*n*=26), HC (*n*=28)	13.4	Not reported	Ethnicity: not reported; Comorbidities: not reported	Focal 100%	Temporal 42%, Extratemporal 54%	Not reported	4.34	100%	WISC-IV, Working Memory Test Battery for Children	N/A	Working memory	fMRI, resting-state seed-based analysis and hierarchical clustering	Increased clustering of the DMN was associated with higher scores on neuropsychological testing for digit span. There was no significant group effect for the epilepsy vs HC groups. Decreased pathlength of the DMN was associated with higher digit span scores. No significant group effect or two-way interactions were identified. Increased centrality of the PCC was more strongly associated with forward digit span recall in HCs than children with epilepsy.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
University of Pittsburgh Medical Center Triplett et al. (2014)	USA	hospital, single centre	epilepsy (*n*=17), HC (*n*=17)	12.7	47%	Ethnicity: not reported; Comorbidities: ADHD 35%, Depression 12%	Focal 59%, Generalised 41%	SeLECTS 24%, Generalised tonic-clonic 24%, Absence 18%	9.9	2.3	100% on	N/A	Anti-saccade task	Inhibitory control	fMRI, task-based region of interest analysis	Analysis showed significant increased activation in the left posterior cingulate gyrus in the epilepsy group compared to HCs.

Cohort and study Details		Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
Maastricht University Medical Center and Epilepsy Centre Kempenhaeghe	Vaessen et al. (2014)	The Netherlands	hospital, single centre	epilepsy (*n*=35), HC (*n*=42)	11.0	not reported	Ethnicity: not reported; Comorbidities: not reported	Focal 100%	Frontal 100%	Not reported	Not reported	Not reported	Computerised visual searching task	N/A	Attention	fMRI, resting-state FC analysis	The brain was subdivided into a number of modules. No significant correlations were found between CVST score and between module FC. A trend for higher within-module FC values was observed for the cognitively impaired epilepsy group and the Entire epilepsy group compared to the HC group. No significant correlations were found between CVST score and within-module FC. Module 4 (distributed over frontal, temporal and occipital regions) showed higher within-module FC for the epilepsy group compared to the control group. A positive association between CVST score and within module FC was found for module 4 in the HC group.

Cohort and study Details		Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
	Braakman et al. (2013)	The Netherlands	hospital, single centre	epilepsy (*n*=32), HC (*n*=41)	11.3	44%	Ethnicity: not reported; Comorbidities: not reported	Focal 100%	Frontal 100%	4.9	6.1	,97%	WISC-III; Computerised visual searching task, The Stroop Colour Word Test	Sternberg working memory task	Working memory	fMRI, task-based and FC analysis	The epilepsy group showed reduced activation in several regions during the Sternberg task compared to controls. However, this was non-significant once corrected for multiple comparisons.
Specialized epilepsy referral center Kempenhaeghe	Besseling et al. (2013 a)	The Netherlands	hospital, single centre	epilepsy (*n*=23), HC (*n*=21)	11.4	30%	Ethnicity: not reported; Comorbidities: not reported	Not reported	SeLECTS 100%	7.5	Not reported	Not reported	CELF-4	Verbal fluency	Cognitive flexibility, Working memory	fMRI, task-based and resting-state FC analysis	Pooled data for the verbal fluency task showed activity in the ACC bilaterally and in the left IFG for both HCs and the epilepsy group. No significant group differences were found. Decreased connectivity in patients compared to HCs was found between the left motor ROI and the right IFG. The connectivity values were correlated with the CELF-4 working memory index.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
Besseling et al. (2013b)	The Netherlands	hospital, single centre	epilepsy (*n*=22), HC (*n*=22)	11.4	27%,	Ethnicity: not reported; Comorbidities: not reported	Not reported	SeLECTS 100%	7.5	2.4	55%	CELF-4	Verbal fluency	Cognitive flexibility	fMRI, task-based and resting-state FC analysis	ROI analysis showed left IFG activation for the verbal fluency task. There was significantly reduced connectivity between an identified SeLECTS network (covering bilateral sensorimotor areas, superior temporal areas, bilateral cerebellar, medial regions and the left IFG) and the left IFG in the epilepsy group compared to HCs. No associations were found between network connectivity and verbal fluency.
Hospital for Sick Children Toronto Widjaja et al. (2013)	Canada	hospital, single centre	epilepsy (*n*=15), HC (*n*=14)	13.9	53%	Ethnicity: not reported; Comorbidities: not reported	Focal 100%	Frontal 100%	8.2	5.5	Not reported	D-KEFS; Connor CPT II, Trail-Making tests A and B, Grooved pegboard	N/A	Cognitive flexibility; Attention	fMRI, resting-state FC analysis	There was a weak relation between reduced connectivity in the right superior frontal gyrus of the frontal network and impaired executive function. There was no significant association between regions of abnormal connectivity in DMN or attention networks with attention.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
University Hospital Basel Bechtel et al. (2012)	Switzerland, Germany	hospital, multicentre	epilepsy (n=17), ADHD only (*n*=15), HC (*n*=15)	11.5	0%	Ethnicity: not reported; Comorbidities: not reported	Focal 47%, Generalised 18%, Other 35%	Absence 12%, Frontal 18%, Parietal 6%, Temporal 6%, SeLECTS 18%, Other 41%	7.5	4.7	53%	Raven's progressive matrices	N-back	Working memory	fMRI, task-based analysis	There was increased activation in HCs compared to the unmedicated epilepsy group in the frontal lobe, parietal lobe, insula, cerebellum and cingulum. The unmedicated epilepsy group showed no increased activation compared to controls. The two most significant clusters were selected for six ROIs: left precentral (BA 6/44); left superior motor area (BA 6); right parietal supramarginal (BA 40); left parietal inferior (BA 40); right cerebellum crus; and cerebellum vermis. HCs exhibited more pronounced activation within all ROIs compared to the epilepsy group.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
University Hospitals KULeuven Myatchin & Lagae (2011)	Belgium	hospital, single centre	epilepsy (*n*=31), HC (*n*=31)	9.9	42%	Ethnicity: not reported; Comorbidities: not reported	Focal 58%, Generalised 42%	SeLECTS 26%, Temporal 10%, Frontal 19%, Absence 16%, generalized with tonic-clonic seizures 19%, juvenile myoclonic 3%, myoclonic-absence 3%, Occipital 3%	Not reported	Not reported	84%	short form of WISC-III	N-back	Working memory	EEG, ERP analysis	ERPs in the epilepsy group were consistently of higher amplitude than the ERPs of HCs across both conditions and across both n-back tasks. In the one-back task, SPM analysis showed significant differences over prefrontal and fronto-central regions. In the two-back task, SPM analysis showed significant differences over pre-frontal, fronto-central and centrotemporal electrodes regions.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
Schneider Children's Medical Center Goldberg-Stern et al. (2010)	Israel	hospital, single centre	epilepsy (*n*=36), HC (*n*=15)	9.5	Not reported	Ethnicity: not reported; Comorbidities: not reported	Not reported	SeLECTS 100%	Not reported	Not reported	0%	WISC-R; (K-ABC), Corsi's Block Tapping Test, Verbal Fluency	N/A	Cognitive flexibility; Working memory	EEG, correlation analysis	No significant difference in neuropsychological scores by EEG epileptic focus was found.
University of Turku and Turku University Central Hospital Krause et al. (2008)	Finland	not reported	epilepsy (*n*=6), HC (*n*=11)	11.3	50%	Ethnicity: not reported; Comorbidities: not reported	Focal 100%	Fronto-temporal 50%, Centro-temporal 33%, 17% Back-temporal	5.8	5.5	83%	NEPSY	Sternberg working memory task	Working memory	EEG, ERD and ERS	During the Sternberg working memory task, at the 6-8 Hz frequency band, the greatest difference in mean ERD/ERS values were in the frontal electrodes. The magnitude of the initial ERS response was lower and the magnitude of the later emerging ERD was greater in the children with epilepsy compared to HCs. This resulted in the significant interaction between time, electrode location and group. At the 8-10 Hz frequency band, the greatest difference in mean ERD/ERS values were in the frontal electrodes. The main effect for group differences was non-significant.

Cohort and study Details	Country	Setting	Sample Size	Mean Age (years)	Gender (female)	Sample Characteristics	Epilepsy Type	Epilepsy Localisation/Diagnosis	Mean Onset (years)	Mean Duration (years)	Medication Status (on)	Neuropsychological Assessments	Functional Imaging Task	Executive Function Domain Studied	Functional Imaging Method Used	Findings
C. Besta National Neurological Institute in Milan Riva et al. (2007)	Italy	hospital, single centre	epilepsy (*n*=24), HC (*n*=16)	9.4	33%	Ethnicity: not reported; Comorbidities: 0%	Not reported	SeLECTS 100%	7.0	Not reported	21% on	WISC-R; PPVT; BNT, TROG, phonemic fluency and semantic	N/A	Cognitive flexibility; Working memory	EEG, correlation analysis	Children with prominently mid-temporal spikes scored significantly lower than HCs on Digit Span and verbal fluency (phonemic). Children with right-sided mid-temporal spikes scored significantly lower than HCs on Digit Span, whereas Children with left-sided mid-temporal spikes scored significantly lower than HCs on Digit Span and verbal fluency (phonemic).
Hospital Civil de Guadalajara González-Garrido et al. (2000)	Mexico	not reported	epilepsy (*n*=58), HC (*n*=20)	10.3	48%	Ethnicity: not reported; Comorbidities: not reported	Not reported	Not reported	not reported	not reported	Not reported	N/A	go-no go CPT	Inhibitory control	EEG, task-based analysis	There were no statistically significant differences in the location of the interhemispheric discharges and errors on the task.

Anterior cingulate cortex (ACC); Battery of Neuropsychological Evaluation (BVN); Beery Buktenica Developmental Test of Visual-Motor Integration (BEERY VMI); Boston Naming Test (BNT); Brodmann's area (BA); Child Behavior Checklist (CBCL); Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-4); Contingent negative variation (CNV); Continuous Performance Test (CPT); Default mode network (DMN); Delis–Kaplan Executive Function System (D-KEFS); electroencephalogram (EEG); Event-related desynchronisation (ERD); Event-related potential (ERP); Event-related synchronisation (ERS); Functional connectivity (FC); functional magnetic resonance imaging (fMRI); Healthy control (HC); Inferior frontal gyrus (IFG); Kaufman Assessment Battery for Children (K-ABC); magnetoencephalogram (MEG); A Developmental NEuroPSYchological Assessment (NEPSY); Peabody Picture Vocabulary Test (PPVT); Phase lag index (PLI); Posterior cingulate cortex (PCC); Prefrontal cortex (PFC); Raven's Colored Progressive Matrices (RCPM) test; Regions of interests (ROI); Rey Auditory Verbal Learning Test (RAVLT); Rey-Osterrieth Complex Figure (ROCF); Self-limited epilepsy with centrotemporal spikes (SeLECTS); Self-limited epilepsy with autonomic seizures (SeLEAS); Swanson, Nolan, and Pelham Rating Scale (version IV) (SNAP-IV); Test Reception of Grammar (TROG); Trail-Making Test (TMT); *Wechsler* Abbreviated Scale of Intelligence - Second Edition (WASI-2); Wechsler Intelligence Scale for Children China-Revised (WISC-CR); Wechsler Intelligence Scale for Children-Revised (WISC-R); Wechsler Intelligence Scale for Children-Third Edition (WISC-III); Working Memory Index (WMI)

3.2. Quality appraisal and risk of bias assessment

An overview of quality appraisal outcomes is shown in Table 2. The domains of research question, selection, design and outcome were appraised as 'good', 'fair' or 'poor' based on a star rating system (see quality assessment key in Table 2). Overall methodological quality was also categorised as 'good' (≥12), 'fair' (7-11) or 'poor' (≤ 6). There was a good level of agreement between reviewers for quality assessment ratings ($\kappa = .946$, $p < .001$).

Table 2. Quality assessment ratings

Study	Imaging Method	Research question (/2 stars)	Selection (/5 stars)	Design (/3 stars)	Outcome (/6 stars)	Total (/16)
Duma et al. (2021)	EEG	**	*	*	***	**7**
Wang et al. (2021)	MEG	**	***	**	******	**13**
Vannest et al. (2021)	fMRI	**	***	**	*****	**12**
Gutierrez-Colina et al. (2020)	fMRI	**	***	**	*****	**12**
Ciumas et al. (2020)	fMRI	**	**	**	*****	**11**
Ueda et al. (2020)	EEG	**	****	**	****	**12**
Oyegbile et al. (2019)	fMRI	**	****	**	*****	**13**
Oyegbile et al. (2018)	fMRI	**	**	**	*****	**11**
Protopapa et al. (2016)	EEG	**	**	**	***	**9**
Xiao et al. (2015)	fMRI	**	**	**	****	**10**
Ibrahim et al. (2014)	fMRI	**	***	**	***	**10**
Triplett et al. (2014)	fMRI	**	****	**	*****	**13**
Vaessen et al. (2014)	fMRI	**	**	**	****	**10**
Braakman et al. (2013)	fMRI	**	**	**	*****	**11**
Besseling et al. (2013 a)	fMRI	**	**	**	**	**8**
Besseling et al. (2013 b)	fMRI	**	**	**	**	**8**
Widjaja et al. (2013)	fMRI	**	**	**	**	**8**
Bechtel et al. (2012)	fMRI	**	**	**	***	**9**
Myatchin and Lagae (2011)	EEG	**	**	**	***	**9**
Goldberg-Stern et al. (2010)	EEG	*	***	**	***	**9**
Krause et al. (2008)	EEG	**	*	*	***	**7**
Riva et al. (2007)	EEG	**	*****	**	*****	**14**
González-Garrido et al. (2000)	EEG	0	**	*	***	**6**
Quality assessment key						
Good		2 stars	4-5 stars	3 stars	5-6 stars	**≥12**
Fair		1 star	3 stars	2 stars	3-4 stars	**7-11**
Poor		0 stars	0-2 stars	0-1 stars	0-2 stars	**≤6**

fMRI = functional magnetic resonance imaging; EEG = electroencephalogram; MEG = magnetoencephalogram

Overall, methodological quality was assessed as ‘good’ (*n* = 7), ‘fair’ (*n* = 15) or ‘poor’ (*n* = 1). The study with the highest rating across all domains was conducted by Riva et al. (2007). It had good defintion of the research question, study population, study participants, epilepsy diagnosis and outcome measures, key confounding variables were controlled for, and at least 50% of eligible participants were included.

Twenty-one studies achieved a rating of ‘good’ for *research question*, meaning that the research question or objective was clearly stated. The domain in which quality was weakest was *selection.* Four studies were rated ‘good’, and thus were judged to have recruited from a non-selective population. The studies clearly specified and defined the study population, recruited subjects from the same or similar populations and specified the time period of recruitment and data collection. Few studies (*n* = 5) reported a participation rate of at least 50% of eligible persons. Inclusion and exclusion criteria was consistently reported in the majority of studies (*n* = 21). No study reported a sample size justification, power description, or variance and effect estimates which led to reduced rating in the domain of study design. Twenty studies therefore achieved a ‘fair’ rating for *design*, while three studies were rated as ‘poor’ where there was no clear definition of epilepsy diagnosis. Finally, nine studies were rated as ‘good’ for *outcome*. All studies were judged to have used outcome measures that were clearly specified, considered to be valid and reliable, and were implemented consistently across all study participants. Only five studies adjusted for four or more confounding or mediating variables.

3.3. Results of narrative synthesis

As discussed, findings were categorised according to four components of executive function: 1) working memory, 2) attention, 3) inhibitory control and 4) cognitive flexibility. Children with self-limited epilepsy with centrotemporal spikes (SeLECTS) include the former terminology of rolandic epilepsy or benign epilepsy with centrotemporal spikes (Specchio et al., 2022).

3.3.1. Working memory

The most widely studied component of executive function was working memory. Nine studies reported fMRI findings for working memory. Task-based fMRI studies revealed findings of both reduced and increased activation in the epilepsy groups compared to HCs. Oyegbile et al. (2019) ('good' methodological quality) reported evidence of increased activation in parietal regions in a temporal lobe epilepsy group. Methodological quality was rated 'fair' for all other task-based fMRI studies. Reduced activation was most widely reported in frontal regions (n = 3 studies), with this being reported across different epilepsies—in a mixed epilepsy group (Bechtel et al., 2012), a SeLECTS group (Ciumas et al., 2020) and a temporal lobe epilepsy group (Oyegbile et al., 2018). The studies also reported reduced activation in other brain regions, including in temporal regions (Ciumas et al., 2020), parietal regions, the insula, cerebellum and cingulum (Bechtel et al., 2012). In addition to reduced activation, one study also reported evidence of increased activation in frontal regions in a SeLECTS group (Ciumas et al., 2020). Braakman et al. (2013) reported reduced activation in frontal and parietal regions in a frontal lobe epilepsy group, although differences were non-significant after correcting for multiple comparisons.

Studies reporting neuropsychological assessment correlates with fMRI functional connectivity (n = 4 studies) reported differences between children with epilepsy and HCs. Both reduced and increased connectivity in different regions in the epilepsy groups was associated with poorer working memory relative to HCs (all studies rated 'good'). There was evidence of significantly reduced functional connectivity within frontal regions (Gutierrez-Colina et al., 2020; Vannest et al., 2021) and between parietal regions and the cerebellum (Gutierrez-Colina et al., 2020), in mixed epilepsy groups. Conversely, there was evidence of increased functional connectivity between frontal and parietal regions in a mixed epilepsy group (Gutierrez-Colina et al., 2020). Studies rated less favourably in relation to their methodological quality reported evidence of significantly reduced functional connectivity within parietal regions in a mixed epilepsy group

(Ibrahim et al., 2014), and reduced connectivity between motor and frontal regions within a SeLECTS group (Besseling et al., 2013a).

Four studies reported EEG findings for working memory. Consistent with fMRI findings, EEG data showed both reduced and increased activation in the epilepsy groups compared to HCs. However, 'good' quality evidence was found for temporal spikes and association with lower scores on neuropsychological assessment of working memory in a SeLECTS group (Riva et al., 2007). Methodological quality was rated 'fair' for all other EEG studies. Task-based EEG evidence reported findings in frontal regions of both lower magnitude event-related synchronisation (ERS) and greater magnitude event-related desynchronisation (ERD) (Krause et al., 2008) and also higher amplitude event-related potentials (ERP) compared to HCs (Myatchin & Lagae, 2011). These studies had included mixed epilepsy groups which might have accounted for the heterogeneity of findings. One study reported no significant difference in neuropsychological scores according to EEG recordings, however this was based on EEG epileptic focus and not task-related EEG data (Goldberg-Stern et al., 2010).

One study reported on MEG findings and working memory (Wang et al., 2021) using MEG resting-state functional connectivity analysis ('good' methodological quality). Neuropsychological assessment of working memory was negatively associated with functional connectivity overall, in a SeLECTS group.

3.3.2. Attention

FMRI findings for attention were reported in three studies. Task-based fMRI studies revealed no significant association between neuropsychological assessment of attention and between-region functional connectivity in a frontal lobe epilepsy group (Vaessen et al., 2014) and a SeLECTS group (Xiao, Li, et al., 2015), compared to HCs. However, there was evidence of an association between neuropsychological assessment of attention and increased within-region functional connectivity in frontal, temporal and occipital regions, in a frontal lobe epilepsy group (Vaessen et

al., 2014). The study was different in that it quantified the modularity of the brain prior to analyses. In contrast, reported association of between-network connectivity and neuropsychological assessment of attention were not significant (Widjaja et al., 2013). All three studies were appraised as ‘fair’ quality.

Authors reported EEG functional connectivity findings of a correlation between poorer attention scores on neuropsychological assessment of attention and increased within-region frontal functional connectivity and fronto-parietal functional connectivity in a frontal lobe epilepsy group (‘good methodological quality) (Ueda et al., 2020).

3.3.3. Inhibitory control

In an fMRI study of inhibitory control, Triplett et al. (2014) examined task-based fMRI evidence and found significant increased activation in parietal regions in a mixed epilepsy group compared to the HC group (‘good’ methodological quality).

EEG findings for inhibitory control were reported in three studies, which provided conflicting evidence. Relative to HCs, task-based EEG findings showed increased frontal connectivity in a mixed epilepsy group (Protopapa et al., 2016) and both frontal and fronto-parietal connectivity in a frontal lobe epilepsy group (Ueda et al., 2020). Studies were rated as ‘fair’ and ‘good’, respectively. Reduced functional connectivity in frontal, parieto-occipital, and temporal regions in a mixed epilepsy group was also reported (Protopapa et al., 2016). Additionally, the third study found no statistically significant associations between inhibitory control and EEG data across all regions (Gonzalez-Garrido et al., 2000); however methodological quality was lower.

3.3.4. Cognitive flexibility

Three studies reported fMRI findings in relation to cognitive flexibility for which the methodological quality was rated as ‘fair’. Within SeLECTS groups, studies revealed no significant association between neuropsychological assessment of cognitive flexibility and task-based

activation (Besseling et al., 2013a), and no significant associations between neuropsychological assessment of cognitive flexibility and functional connectivity (Besseling et al., 2013b). Evidence of reduced connectivity in frontal regions within a frontal lobe epilepsy group was reported (Widjaja et al., 2013), however this was reported as a weak correlation and the finding was uncorrected for multiple comparisons.

Three EEG studies reported findings for cognitive flexibility. With 'good' methodological ratings, Riva et al. (2007) found evidence of an association between neuropsychological assessment of cognitive flexibility and temporal spikes in a SeLECTS group. In contrast, no difference was found between the epilepsy group and HCs in the association between neuropsychological assessment and brain activations (Goldberg-Stern et al., 2010), within another SeLECTS cohort. Finally, task-based EEG findings showed lager ERP amplitude in the healthy control group in frontal regions and reduced activity in parietal regions (Duma et al., 2021), compared to a mixed epilepsy group ('fair' methodological quality).

3. DISCUSSION

This review is the first to systematically evaluate the literature on correlates of functional neuroimaging and neuropsychological functioning related to executive function in children with epilepsy. Studies were identified across four core components of executive function—working memory, attention, inhibitory control, and attention—in relation to three methods of functional neuroimaging—EEG, fMRI and MEG. Sixteen studies revealed evidence of disruption to frontal and/or parietal regions involved in executive functions in paediatric epilepsy groups relative to healthy controls (Bechtel et al., 2012; Besseling et al., 2013a; Ciumas et al., 2020; Duma et al., 2021; Gutierrez-Colina et al., 2020; Ibrahim et al., 2014; Krause et al., 2008; Myatchin & Lagae, 2011; Oyegbile et al., 2019; Oyegbile et al., 2018; Protopapa et al., 2016; Triplett et al., 2014; Ueda et al., 2020; Vaessen et al., 2014; Vannest et al., 2021; Widjaja et al., 2013).

Studies showed both localisation-related increases and decreases in activation, and also functional connectivity increases and decreases highlighting heterogeneity across the findings. Activity in frontal and parietal regions, and connectivity between them, are important for executive function and for facilitating the development of executive function (Fiske & Holmboe, 2019). The disruption to these regions and networks in the current review may therefore indicate a lack of specialisation of brain regions involved in executive function. The findings are consistent with previous research which has associated a fronto-parietal network and executive functions within the typically developing child and adult brain (Crittenden et al., 2016; Power et al., 2011; Engelhardt et al., 2019). Support was therefore found for the executive function "fronto-parietal flexible hub" theory posited by Cole et al. (2013) and for disruption to this network in epilepsies (Berg et al., 2010; Spencer, 2002). The findings also provide functional neuroimaging evidence of how executive dysfunction occurs across the separate components of executive functions in paediatric epilepsies, in support of the unity/diversity model (Friedman & Miyake, 2017; Miyake et al., 2000).

In studies that did not report fronto-parietal disruption, one study reported a significant association between EEG temporal spikes and neuropsychological assessment of working memory (Riva et al., 2007), however it can be difficult to localise the origin of EEG spike activity and this may have involved frontal and parietal regions. One study reported a significant association between executive function and reduced overall brain connectivity (Wang et al., 2021). Two studies showed that there were activity differences in frontal and parietal regions (Braakman et al., 2013; Xiao et al., 2015) and reduced frontal and parietal connectivity (Besseling et al., 2013b) in the epilepsy groups but the results did not reach statistical significance. Other studies were limited by low methodological quality (Gonzalez-Garrido et al., 2000) and EEG being based on epileptic focus and not task-related EEG data (Goldberg-Stern et al., 2010).

Evidence of disruptions to frontal and parietal activity were most commonly reported in mixed epilepsy groups (n = 8 studies) but also for specific epilepsy types, including frontal lobe epilepsy (n = 3 studies), temporal lobe epilepsy (n = 2 studies) and SeLECTS (n = 2 study). The

findings suggest possible overlapping executive function difficulties between children with frontal lobe epilepsy and temporal lobe epilepsy, consistent with neuropsychological investigations (Smith, 2016). However, comparison between epilepsies was not examined directly and there was much variation in the reporting of findings. Furthermore, epilepsy type or diagnosis was not consistently reported, and there was a range of different measures of executive function, making it difficult to compare across epilepsy types and results on measures of neuropsychological functioning. Thus, differences in affected networks between these groups could not be reported on.

Findings in three studies identified evidence of wider network disruption related to executive functions in children with epilepsy. There was evidence of reduced activation in temporal regions (Ciumas et al., 2020) and within-region functional connectivity in temporal regions as part of a brain module (Vaessen et al., 2014). As noted above, EEG temporal spikes were also associated with working memory (Riva et al., 2007). Findings may reflect the high heterogeneity in the reported findings, given data included came from different epilepsy groups and mixed epilepsy groups and different functional neuroimaging methods. However, the frontal lobes in particular are still developing and specialising long past adolescence and into early adulthood (Otero & Barker, 2013) and findings may again indicate a lack of specialisation of brain regions involved in executive function.

The most numerous and compelling evidence of disruptions to executive function was in working memory. Working memory tasks, such as the n-back task (Gevins & Cutillo, 1993), typically involve similar task instructions and involve repetition of the same task. Thus, they are highly suitable for functional neuroimaging studies and between group analyses. Of the working memory studies included in the review, 86% reported statistically significant differences between the epilepsy group and HCs, in contrast to 50% across the other components of executive function. Furthermore, five out of the seven studies appraised as of good methodological quality assessed working memory performance (Gutierrez-Colina et al., 2020; Oyegbile et al., 2019; Riva et al., 2007; Vannest et al., 2021; Wang et al., 2021). This highlights possible methodological challenges

of conducting functional neuroimaging studies with some of the other components of executive function.

Evidence of similarities between working memory and attention were reported in four studies. Functional imaging findings revealed evidence of increased fronto-parietal connectivity in children with epilepsy, relative to HCs, for both attention (Ueda et al., 2020) and working memory (Gutierrez-Colina et al., 2020). There was also evidence of an association between neuropsychological assessment of attention and increased within-region functional connectivity in frontal regions (Vaessen et al., 2014) and increased activation in frontal regions for working memory (Ciumas et al., 2020). The findings are in support of the conceptualisation of some overlap between the components of executive function (Oberauer, 2019). However, again, this was limited by a small number of studies investigating attention.

The overall methodological quality rating for most studies was 'fair' (65%). Studies that had 'good' methodological quality ratings had clear definitions of epilepsy diagnosis, had well-defined, selected and implemented outcome measures, and controlled for four or more confounding variables. A weakness in studies included failing to adequately define the study population and not specifying the time period during which data was collected. No studies reported statistical power calculations, thus introducing the risk of Type II error in the interpretation and reporting of results. This is particularly an issue as studies in neuroimaging tend to be underpowered to detect the effect sizes that are published (Ellis, 2022). Furthermore, group analyses in epilepsy groups may be limited by large within group variations in functioning. Low statistical power therefore also limits conclusions that can be drawn from findings that did not reach clinical significance.

4.1. Clinical implications

The current review is the first to draw together evidence of disruption to a fronto-parietal network involved in executive functions in children with epilepsy. Importantly, this is found across mixed epilepsy groups and specific epilepsy types, including frontal lobe epilepsy, temporal lobe epilepsy

and SeLECTS. It suggests possible overlapping executive function difficulties between children with frontal lobe epilepsy and temporal lobe epilepsy, consistent with neuropsychological investigations (Smith, 2016). The findings have relevance for understanding key brain regions and networks, and possible disruption to their development, in paediatric epilepsies. Therefore, executive functioning difficulties should be assessed for children with all types of epilepsy and considered in clinical interventions wherever possible.

The review provides support for the utility of functional neuroimaging for furthering our understanding of paediatric epilepsies. It provided evidence of disruption to networks which support the development of key neuropsychological skills in children who experience seizures, thus offering an opportunity to increase accuracy in clinical decision making. One area of clinical utility is in paediatric epilepsy surgery where it has been shown that use of resting-state fMRI on paediatric epilepsy surgery planning led to an increase in 50% of patients becoming surgery candidates who would not have been candidates otherwise (Boerwinkle et al., 2020). Moreover, the review provides support for the utility of working memory task-based functional neuroimaging for exploring brain regions and networks involved in executive functions. These tasks involve similar task instructions and involve repetition of the same task making them highly suitable for functional neuroimaging studies and between-group analyses. High levels of heterogeneity in findings means support cannot be given for the use of other executive function domains for the delineation of key neuronal networks.

4.2. Strengths and limitations

Strengths of this review include its synthesis of a wide range of studies and rigorous two-author review of abstracts and full text papers against the inclusion criteria and methodological quality ratings. Studies included four components of executive function, all available paediatric epilepsy types and all available functional neuroimaging methods. It was conducted using a rigorous systematic search in line with current PRISMA guidelines (Page et al., 2021).

A limitation of the current review was in its inclusion of a mixed epilepsy types meaning that comparisons could not be made across different epilepsies. Given this was the first systematic review to explore functional neuroimaging and executive function outcomes in paediatric epilepsies, the decision was made to include all available epilepsy data. This provides a platform for future reviews within the field.

Only peer-reviewed studies published in English were included in this review. It is important to acknowledge the potential introduction of publication and location biases and it is possible that only studies from Europe, Australia and USA were selected. Grey literature was not included in the present review, although it is acknowledged that including grey literature can reduce publication bias, increase a reviews' comprehensiveness and foster a more balanced picture of available evidence (Paez, 2017).

It is important to note that, currently, there is no single definition of executive functioning and several models have been described (Burgess et al., 2005; Stuss et a., 2011). Within the review, the unity/diversity model (Friedman & Miyake, 2017; Miyake et al., 2000) was used to define the separate components of executive function and, where applicable, executive function tasks were categorised in line with Diamond's (2013) review paper.

4.3. Future directions

The current review highlights the potential for a greater understanding of executive dysfunction in paediatric epilepsies through more research in this area, particularly in the context of epilepsy as a brain network disease (Berg et al., 2010). Functional neuroimaging can offer greater clarity on how disruptions to brain functioning and brain development can impact the development of executive functions in children and the potential for differentiated network development in the presence of frequent seizures. It has the potential to provide clinical teams with a deeper understanding of executive functions within paediatric epilepsy populations. More studies are therefore needed in functional neuroimaging of cognitive flexibility, inhibitory control and attention in paediatric

epilepsy in order to provide greater richness to the clinical interpretation of neuropsychological assessment. Future studies should aim to improve in methodological quality by clearly defining the study population, clearly defining epilepsy diagnosis, including a power analysis and controlling for key confounding variables.

5. CONCLUSION

This review is the first to systematically evaluate the literature on correlates of functional neuroimaging and neuropsychological functioning related to executive function in children with epilepsy. Studies revealed evidence of disruptions to a fronto-parietal network involved in executive functions across a range of mixed epilepsy types and across working memory, attention, inhibitory control and cognitive flexibility. The review also reported findings of disruption to temporal regions, highlighting evidence of wider network disruption related to executive functions in children with epilepsy. These findings have relevance for understanding the key brain regions and networks, and possible disruption to their development, and the impact this has on executive functions in paediatric epilepsies. Future studies in this area should aim to improve on the methodological weaknesses of studies highlighted in the review.

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Paper 2

Comparing executive function outcomes between fronto-parietal and temporal epilepsies in paediatric epilepsy surgery

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ABSTRACT

Objective: The study aimed to address a gap in knowledge regarding executive function outcomes of children who undergo epilepsy surgery. A network approach compared executive function ability between fronto-parietal and temporal epilepsies. ***Method:*** A longitudinal, multi-centre study was conducted, using Northern Children's Epilepsy Surgery Service epilepsy surgery pathway (NORCESS) data in children aged 6 years to 17 years 11 months. Demographic and clinical data were collected from medical records. Working memory was used as a primary outcome. Exploratory outcomes were cognitive flexibility, attention and parented-rated executive function. Scores were compared between fronto-parietal and temporal epilepsies, both pre- and post-surgically. **Results:** One hundred and ninety-four children met criteria at baseline. Forty-eight (25%) children had assessment following surgery. Mean age was 11.15 (range 6-17) years. Baseline findings revealed high rates of executive difficulties. Significant group differences were found for working memory (n = 152) and cognitive flexibility (n = 109) scores. Group differences for attention and parented-rated executive function were non-significant. In linear regression analyses, daily seizures and polypharmacy were significantly associated with lower working memory scores. Post-surgical differences in working memory (n = 37) were not found between the groups, however, analyses showed a significant decline in working memory scores in the repeated baseline fronto-parietal group (n = 12). Analyses using the reliable change index showed much variation in post-surgical outcomes. Children with temporal epilepsy had higher rates of remaining at pre-surgical working memory level (83.3%) compared to fronto-parietal epilepsies (53.8%). ***Significance:*** Group differences between fronto-parietal and temporal epilepsies may be related to fronto-parietal network disruption shown to be involved in executive function. Future directions are proposed to focus on individual components of executive function as part of pre- and post-surgical neuropsychological intervention, and to increase the comparability of outcomes across the UK by agreeing core executive function outcome measures.

Keywords: Paediatric epilepsy, Paediatric epilepsy surgery, Executive function.

1. INTRODUCTION

The epilepsies are the most common long-term neurological condition of childhood and affect an estimated 112,000 children and young people, or approximately 1 in every 220 children in the UK (Bui et al., 2022; Joint Epilepsy Council, 2011). Studies have estimated that 12-37% of children become resistant to antiseizure medication (ASM) treatment (intractable epilepsy) (Berg et al., 2006; Geerts et al., 2012; Kwan & Brodie, 2000). Childhood epilepsies pose a risk to typical developmental trajectories, with risks to skill acquisition ranging from a slowed rate of development to a failure to develop (Smith, 2010). Paediatric epilepsy surgery is an established treatment option for children with medical intractable epilepsy (Duchowny, 2020; Spencer & Huh, 2008). Epilepsy surgery involves removal of the epileptogenic zone with the aim of achieving seizure-freedom and weaning off ASMs. Achieving such can lead to benefits in quality of life (Hoppe et al., 2023). The risk for cognitive impairment in children with intractable epilepsy increases with greater seizure frequency, longer duration of epilepsy, and required polypharmacy (Lah, 2004). Polypharmacy is especially detrimental in relation to executive function difficulties (Reilly et al., 2015; Witt et al., 2015).

Executive dysfunction is a highly reported neuropsychological impairment in paediatric epilepsy, with difficulties reported in up to 50% of this population (Cainelli et al., 2020; Campiglia et al., 2014; Høie et al., 2008; Modi et al., 2019; Parrish et al., 2007). Executive functions are defined as a set of top-down cognitive processes involved in initiation, planning, goal-setting, inhibition, working memory, shifting/cognitive flexibility, and emotional control (Diamond, 2013; MacAllister et al., 2014; Miyake et al., 2000). Difficulties with executive function are a common feature amongst the epilepsies, including temporal lobe epilepsy and frontal lobe epilepsy (MacAllister et al., 2014). Executive dysfunction is reported to contribute to poorer social, academic, behavioural, and quality of life outcomes in paediatric epilepsy (Austin et al., 1999; Love et al., 2016; Modi et al., 2011; Tse et al., 2007). Executive functions are therefore vital for success in all aspects of life, with some suggesting that they are more predictive of school outcomes than IQ

(Diamond & Ling, 2016). Therefore, in the context of paediatric epilepsy and surgery, executive functions remain an important target for evaluation and intervention.

Neuropsychological assessment is a core investigation in the pre-surgical planning for children with epilepsy (Anderson et al., 2018; Gonzalez & Wrennall, 2020; Jayakar et al., 2018; Smith & Berl, 2017). Long-term cognitive outcomes following surgery vary dependant on the function or skill measured, the region of the brain being resected, and any resulting disruption to functional networks (Moosa & Wyllie, 2017). Epilepsy surgery in children has the added complexity of the dynamic nature of the developing brain and its capacity for functional plasticity in younger patients (Spencer & Huh, 2008). There is evidence of a capacity for 'recovery' or 'reorganisation' of functions but windows of opportunity for these changes are limited (Anderson et al., 2011). In a long-term follow-up study (ranging 11-30 years post-surgery), 85% of children with uni-lobar epilepsy (e.g., temporal lobe epilepsy and occipital lobe epilepsy) who had undergone successful epilepsy surgery went on to finish mainstream school, and 72% subsequently had employment (Hoppe et al., 2023). It is hypothesised that the post-surgical gains in cognitive functioning may correspond to a release effect of seizure-freedom and ASM cessation on developmental trajectories (Ramantani et al., 2018).

There is limited research with regards to executive function outcomes after epilepsy surgery and outcome reporting is limited by the diffuse nature of this set of skills. Sherman et al. (2011) noted in their systematic review that all cohort sizes were too small (<20) to meet their threshold for inclusion. Six years later, a further review by Flint (2017) reported an overall decrease in the percentage of patients with an impairment in executive function in children who had undergone temporal lobe surgery from one study (Miserocchi et al., 2013), but this was not replicated by others (Williams et al., 1998). The review also reported a decline in cognitive flexibility in some participants within both frontal and temporal lobe epilepsy groups (Blanchette & Smith, 2002). In a cohort of 31 children with mixed aetiologies, Sibilia et al. (2017) found significant increases in working memory (forward digit span) one year after surgery compared to a control group. Increase

in forward digit span occurred in 2/3 patients (66.7%) who had undergone frontal lobe resections and in 4/7 patients (57.2%) following temporal lobe resections. From a large group of 306 children, Helmstaedter et al. (2020) found baseline and post-surgical executive function outcomes were not related to epilepsy location. However, the study was limited by the use of an executive function/attention composite score.

Given the inconsistencies in reported executive function outcomes following children's epilepsy surgery, the gap in knowledge remains significant. Currently, executive functions are thought to be mediated by a fronto-parietal network (Crittenden et al., 2016; Engelhardt et al., 2019; Niendam et al., 2012; Power et al., 2011). Previous cohorts publishing on executive function outcomes in paediatric epilepsies have not considered this aspect, despite evidence of disruption to a fronto-parietal network involved in executive function (Reed, 2023). The current study therefore took a network approach to examine executive function, comparing fronto-parietal and temporal epilepsies, at pre- and post-surgery. Working memory is crucial to executive functioning given it supports complex task performance, such as reasoning, comprehension and learning (Baddeley, 2010), and on this basis it was selected as the primary outcome of executive function.

The primary aim of this longitudinal study was to determine whether there were differences in working memory capacity between children with fronto-parietal epilepsies and temporal epilepsies, using a UK based cohort of children aged 6 years to 17 years 11 months seen within the Northern Children Epilepsy Surgery Service (NorCESS). The study further aimed to explore post-surgical changes in working memory when compared to pre-surgical functioning.

2. METHOD

The study was conducted in accordance with ethical approval provided by Manchester University NHS Foundation Trust and Alder Hey Children's NHS Foundation Trust for use of anonymised, routinely collected NHS data (Appendix E). This study utilised data within the NorCESS Research

Database, as part of a collaboration between the Royal Manchester Children's Hospital and Alder Hey Children's Hospital.

2.1. Design

This research comprised a longitudinal, multi-centre study that compared executive function outcomes between fronto-parietal epilepsies and temporal epilepsy. Comparisons were made between groups at baseline and post-surgically for those that went onto receive epilepsy surgery.

It was hypothesised that working memory functioning in children with fronto-parietal epilepsies would be significantly poorer at baseline (Hypothesis 1), and they would experience greater change scores following surgery (Hypothesis 2), when compared to children with temporal epilepsy. It is anticipated that changes in working memory functioning may be related to alteration in underlying fronto-parietal functional networks, which have been shown to be involved in executive function. Further neuropsychological outcomes measuring executive function were included as exploratory analyses.

2.2. Participants

The data related to patients assessed for the purposes of epilepsy surgery planning at the Royal Manchester Children's Hospital or Alder Hey Children's Hospital between April 2007 and January 2023. Among all the identified patients (see Appendix F), those with fronto-parietal epilepsies (frontal or parietal) or temporal epilepsy were eligible. Baseline inclusion criteria were: i) aged 6–17 years at the time of the assessment; ii) fluent in the English language; and iii) have a NorCESS multidisciplinary team diagnosis of frontal, parietal or temporal epilepsy. Post-surgical inclusion criteria were the same, with the addition of iv) follow-up assessment over one year following the baseline assessment. Exclusion criteria for both studies were: i) children with multi-lobar epilepsy; ii) children who did not have a well-defined aetiology of epilepsy region; or iii) children who had high levels of missing demographic and clinical data.

A power analysis (Faul et al., 2007) was conducted based on the effect size of previous investigations into working memory (Gleissner et al., 2002) to detect large effects (d = 0.5, score of >7.5) with 80% power, and an alpha set to 0.05. Pre-surgical analyses indicated that a sample of n = 64 participants per group would be required (total n = 128) using an independent mean analysis. Post-surgical analyses indicated that at a sample of n = 17 participants per group would be required (total n = 34) using a repeated measure analysis, within-between interaction F test (with 2 groups, and 2 means).

2.3. Demographic and Clinical Characteristics

The following demographic and clinical data were collected from medical records: age at assessment, sex, handedness, epilepsy lateralisation (right/left hemisphere), age at onset of epilepsy, duration of epilepsy, seizure frequency, and number of ASM's. Additional post-surgical variables were also collected: time since first assessment, time since surgery, and surgery type. Epilepsy groups were determined based on evidence of seizures being of fronto-parietal (frontal or parietal) or temporal origin. Investigations used to inform epilepsy type included neurological evaluations, video-electroencephalogram (vEEG) during wakefulness and/or sleep, magnetic resonance imaging (MRI) brain scan, and, when indicated, positron emission tomography (PET) brain scan.

2.4. Neuropsychological Outcomes

Standardised neuropsychological assessments are completed as routine for all children pre- and post- epilepsy surgery. Data on assessment outcomes related to executive function were selected in line with the research questions.

As the most consistently available data were for the Working Memory Index (WMI) of either the Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV; Wechsler, 2003), Fifth Edition (WISC-V; Wechsler et al., 2014) or Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008), the WMI was selected as the primary outcome. WMI scores are standardised

based on a normal distribution with a normative mean of 100 and standard deviation (SD) of 15. The WMI is a measure of working memory that is widely used within the field and has been validated in paediatric epilepsy patients (Sherman et al., 2012).

Further exploratory outcome measures were included. To assess overall parented-rated executive function in daily life, the Behavioural Rating Inventory for Executive Function First Edition (BRIEF; Gioia et al., 2000) and Second Edition (BRIEF-2; Gioia et al., 2015) data were analysed. Scores were included for the Global Executive Composite (GEC) and for individual subscale scores: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organise, Organisation of Materials and Monitor (Self-Monitor of the BRIEF-2). Scores are standardised based on a normal distribution with a normative mean of 50 and SD of 10. According to the manual (Gioia et al., 2000, 2015), a score of 1.5 SD above the normative mean indicates executive dysfunction.

To assess cognitive flexibility, the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) data were included. Scores for the Trail Making Number-letter Switching and Verbal Fluency Category Switching subtests were included. Attention was also included in the current study given its considerable overlap with working memory (Oberauer, 2019). To assess attention, the Test of Everyday Attention for Children First Edition (TEA-Ch; Manly et al., 1999) and Second Edition (TEA-Ch2; Manly et al., 2016) was reported. One subtest was included for Selective Attention (TEA-CH: Sky Search; TEA-Ch2: Hector Cancellation; or TEA-Ch2J Balloon Hunt), and one subtest was included for Sustained Attention (TEA-CH: Score; TEA-Ch2: Vigil; or TEA-Ch2J: Barking). Subtest scores from the D-KEFS and TEA-Ch/TEA-Ch2 are standardised, with scaled scores having a normative mean of 10, and SD of 3.

2.5. Procedure

Standard age-appropriate battery of assessments were completed as part of routine clinical care. All assessments were administered during a child's inpatient stay for vEEG or within an outpatient

clinic appointment. Data had been entered into the NorCESS Clinical Research Database (Research and Development office of Manchester University NHS Foundation Trust reference: Surgery_NORCESS_SE_1; Research and Development office of Alder Hey Children's NHS Foundation Trust reference: 6820) by members of the clinical team. Data was checked for completeness and accuracy, and missing values sought where possible from medical notes.

2.6. Statistical Analyses

Frequency distributions were computed for all the available categorical data. Continuous data were described by using the mean. The number of patients who were entered into the analysis for the different neuropsychological measures varied due to missing values. Normality was tested using visual inspection of histograms, review of skewness and kurtosis, and the Kolmogorov–Smirnov test for normality. Univariate analyses were performed to determine possible associations between the demographic and clinical characteristics, and the primary outcomes.

For pre-surgical analyses across all executive function outcomes, group differences between scores were tested using a t-test in normally distributed outcomes and the Mann–Whitney U test in non-normally distributed data. A continency table and a chi-square test were used to explore impairment in executive functions and any differences between the two groups. Impairment was calculated as 1 SD below the normative mean, except for the BRIEF and BRIEF-2 in which an impairment was rated as 1.5 SD above the normative mean, in line with the manual. A hierarchical multiple regression was conducted to determine the differences on the WMI between the fronto-parietal and temporal epilepsy groups, adjusting for confounding factors. Unstandardised regression coefficients (*B*) are reported. Sensitivity analysis was also conducted to compare outcomes across the three versions of the WMI (WISC-IV, WISC-V, and WAIS-IV).

For post-surgical analyses, changes in standardised scores were calculated using the reliable change index (Blampied, 2022; Jacobson & Truax, 1991). The method assesses whether a clinically significant change in scores has occurred from pre- to post-surgery and whether this change is

statistically reliable. An ANCOVA with Bonferroni correction was conducted to analyse for differences in the WMI in the interaction between epilepsy type (fronto-parietal vs temporal) and follow-up assessment type (post-surgical and repeated baseline), adjusting for confounding variables.

Scores across different editions of assessments were combined. All data analysis was performed using SPSS version 25 (IBM Corp, 2017).

3. RESULTS

3.1. Demographic and Clinical Outcomes

A total of 194 children met criteria for inclusion in the study out of a total of 284 children entered onto the database (68%). Three of those cases were excluded due to missing data (1%). The demographic and clinical data for those meeting inclusion comprised a fronto-parietal group (n=86) and temporal group (n=108) and is presented in Table 3. The groups were comparable with no detected differences between age, sex, duration of epilepsy, number of ASMs or epilepsy lateralisation. Across the whole group, the mean age was 11.15 (SD = 3.12), there were fewer female children (41.2%), mean duration of epilepsy was 6.83 years (SD = 8.69), and most children were taking a polytherapy ASM regimen (56.7%). Slightly more children had epilepsy lateralisation in the left hemisphere (53.1%). A significantly greater number of participants in the temporal group were right-handed (fronto-parietal: 60.5%; temporal: 80.6%; $\chi 2$ (3) = 13.93, p = .003). Participants in the fronto-parietal group had a significantly earlier mean age of epilepsy-onset (fronto-parietal, 4.76 years, SD = 3.80; temporal, 5.94 years, SD = 4.24; t (190) = 2.67, p = 0.46), and a higher incidence of daily seizures (fronto-parietal: 47.7%; temporal: 34.3%).

A total of 73 children (37.6%) went on to have a second assessment either after epilepsy surgery or as a second baseline later on in the epilepsy surgery pathway. The demographic and clinical data for the fronto-parietal and temporal, surgical and repeated baseline groups, are presented in Table 4. Group differences were non-significant for all variables except seizure

frequency ($\chi 2$ (12) = 35.25, p = <.001). Most children became seizure free (Outcome Classification I; Wieser et al., 2001) after surgery (post-surgical fronto-parietal: 53.3%; post-surgical temporal: 54.5%). In contrast, rates of seizure freedom in the repeated baseline groups were much lower (repeated baseline fronto-parietal: 13.3%; repeated baseline temporal: 20.0%). Type of surgery is presented in Table 5. Temporal lobectomy was the most common type of surgery (20 cases, 41.7%), followed by temporal lesionectomy (10 cases, 20.8%) frontal lesionectomy (6 cases, 12.5%), and parietal lesionectomy (2 cases, 4.2%). All remaining surgical procedures were single cases.

Table 3: First assessment: demographic and clinical variables

	Total (*n* = 194)		**Fronto-parietal (*n* = 86)**		**Temporal (*n* = 108)**		**Test of Significance**	
	Mean (SD)	Freq. (%)	Mean (SD)	Freq. (%)	Mean (SD)	Freq. (%)	Value (*df*)	*p* Value
Age (years)	11.15 (3.12)	-	10.95 (3.14)	-	11.31 (3.11)	-	*t* (192) = .80	.424
Sex (female)	-	80 (41.2)	-	34 (39.5)	-	46 (42.6)	$\chi 2$ (1) = .185	.667
Handedness (right)	-	139 (72.6)	-	52 (60.5)	-	87 (80.6)	$\chi 2$ (3) = 13.93	.003*
Age at epilepsy onset (years)	5.41 (4.08)	-	4.76 (3.80)	-	5.94 (4.24)	-	*t* (190) = 2.67	.046*
Duration of epilepsy (years)	6.83 (8.69)	-	5.57 (4.04)	-	7.04 (11.10)	-	*t* (192) = 1.54	.704
Seizure frequency:							$\chi 2$ (4) = 13.55	.009*
at least daily	-	78 (40.2)	-	41 (47.7)	-	37 (34.3)		
weekly	-	49 (25.3)	-	15 (17.4)	-	34 (31.5)		
monthly	-	26 (13.40	-	7 (8.1)	-	19 (17.6)		
less than yearly	-	19 (9.8)	-	13 (15.1)	-	6 (5.6)		
not known	-	22 (11.3)	-	10 (11.6)	-	12 (11.1)		
Antiseizure medication:							$\chi 2$ (2) = 5.93	.052
monotherapy	-	80 (41.2)	-	28 (32.6)	-	52 (48.1)		
polytherapy	-	110 (56.7)	-	57 (66.3)	-	53 (49.1)		
not known	-	4 (2.1)	-	1 (1.2)	-	3 (2.8)		
Epilepsy lateralisation:							$\chi 2$ (3) = 2.34	.508
right	-	74 (38.1)	-	29 (33.7)	-	45 (41.7)		
left	-	103 (53.1)	-	47 (54.7)	-	56 (51.9)		
bilateral	-	10 (5.2)	-	6 (7.0)	-	4 (3.7)		
uncertain	-	7 (3.6)	-	4 (4.7)	-	3 (2.8)		

*Freq. = Frequency; * = significant difference*

Table 4: Second assessment: demographic and clinical variables

	Surgical Group (*n* = 48)				Repeated Baseline Group (*n* = 25)				Test of Significance	
	Fronto-parietal (*n* = 15)		Temporal (*n* = 33)		Fronto-parietal (*n* = 15)		Temporal (*n* = 10)			
	Mean (SD)	Freq. (%)	Mean (SD)	Freq. (%)	Mean (SD)	Freq. (%)	Mean (SD)	Freq. (%)	Value (*df*)	*p* Value
Age (years)	11.27 (2.76)	-	12.52 (2.81)	-	13.07 (2.60)	-	12.10 (2.86)	-	F (1,69) = 2.42	.124
Sex (female)	-	6 (40.0)	-	15 (45.5)	-	8 (53.3)	-	2 (20.0)	$\chi 2$ (3) = 2.95	.400
Handedness (right)	-	10 (66.7)	-	28 (84.8)	-	10 (66.7)	-	7 (70.0)	$\chi 2$ (9) = 8.61	.474
Age at epilepsy onset (years)	5.26 (3.59)	-	5.08 (3.93)	-	3.81 (3.64)	-	5.35 (2.81)	-	F (1,69) = .831	.365
Duration of epilepsy (years)	13.80 (30.05)	-	7.56 (3.70)	-	9.96 (4.29)	-	7.05 (2.88)		F (1,69) = .217	.643
Time since 1st Assessment (years)	9.46 (29.06)	-	2.22 (1.25)	-	3.11 (2.19)	-	2.08 (1.82)		F (1,69) = .842	.362
Time since surgery (years)	1.20 (0.70)	-	1.27 (0.77)	-	-	-	-	-	t (46) = .28	.781
Seizure frequency:									$\chi 2$ (12) = 35.25	<.001*
At least daily	-	7 (46.7)	-	5 (15.2)	-	10 (66.7)	-	2 (20.0)		
weekly	-	0	-	4 (12.1)	-	1 (6.7)	-	5 (50.0)		
monthly	-	0	-	6 (18.2)	-	1 (6.7)	-	1 (10.0)		
seizure free	-	8 (53.3)	-	18 (54.5)	-	2 (13.3)	-	2 (20.0)		
not known		0	-	0	-	1 (6.7)	-	0		
Antiseizure medication:									$\chi 2$ (9) = 10.82	.288
no medication	-	1 (6.7)	-	3 (9.1)	-	0	-	0		
monotherapy	-	5 (33.3)	-	20 (60.6)	-	8 (53.3)	-	4 (40.0)		
polytherapy	-	9 (60.0)	-	10 (30.3)	-	6 (40.0)	-	6 (60.0)		
not known	-	0	-	0	-	1 (6.7)	-	0		
Epilepsy lateralisation:									$\chi 2$ (9) = 11.66	.233
right	-	7 (46.7)	-	12 (36.4)	-	7 (46.7)	-	4 (40.0)		
left	-	7 (46.7)	-	38 (52.1)	-	7 (46.7)	-	4 (40.0)		
bilateral	-	0	-	3 (4.1)	-	0	-	2 (20.0)		
uncertain	-	1 (6.7)	-	2 (2.7)	-	1 (6.7)	-	0		

*Freq. = Frequency; * = significant difference*

Table 5: Type of surgery

	Total (*n* = 48)	**Fronto-parietal (*n* = 15)**	**Temporal (*n* = 33)**
	Frequency (%)	Frequency (%)	Frequency (%)
Lobectomy			
Temporal	20 (41.7)	0	20 (60.6)
Frontal	3 (6.3)	3 (20.0)	0
Lesionectomy			
Temporal	10 (20.8)	0	10 (30.3)
Frontal	6 (12.5)	6 (40.0)	0
Parietal	2 (4.2)	2 (13.3)	0
Insular	1 (2.1)	1 (6.7)	0
Fronto-temporal	1 (2.1)	0	1 (3.0)
Hemispherotomy	1 (2.1)	1 (6.7)	0
Hemispherectomy	1 (2.1)	1 (6.7)	0
Resection of hypothalamic hamartoma	1 (2.1)	0	1 (3.0)
Tumour resection			
Temporo-occipital	1 (2.1)	0	1 (3.0)
Frontal	1 (2.1)	1 (6.7)	0

3.2. Neuropsychological Outcomes

3.2.1. *Pre-surgery Executive Function*

Mean scores and group differences between fronto-parietal and temporal groups are presented in Table 6 and Figures 2-4. Findings revealed high rates of executive function difficulties across the groups. Significant mean differences were found between fronto-parietal and temporal epilepsies in WMI scores (working memory) and D-KEFS Trail Making Switching scores (cognitive flexibility). Percentages of children with executive function impairment at first assessment are presented in Table 7. Consistent with group mean differences, a significantly greater proportion of children with fronto-parietal epilepsies had an impairment (1 SD below the normative mean) in WMI scores (fronto-parietal, *n* = 41, 61.2%; temporal, *n* = 36, 42.4%) and D-KEFS Trail Making Switching scores (fronto-parietal, *n* = 32, 74.4%; temporal, *n* = 28, 42.4%) (Table 7). Group differences between all other assessment scores were non-significant (see Table 6 and Table 7). However, mean scores were lower on the GEC and all subtests of the BRIEF and BRIEF-2 (parented-rated

executive function) (Figure 4). A profile chart of executive function impairment is presented in Figure 5.

Further analyses of the primary outcome measure using hierarchical multiple regression found that epilepsy type (fronto-parietal vs temporal) was significantly associated with WMI scores ($F(1,130) = 7.25$, $p = .008$; $B = -8.17$, $p = .008$). Children with fronto-parietal epilepsies had poorer working memory functioning (> 7.5 WMI points), which is considered a clinically meaningful difference. Seizure frequency (at least daily seizures vs less than yearly seizures; $B = -11.854$, $p = .017$) and number of ASMs (monotherapy vs polytherapy; $B = 10.57$, $p = <.001$) were significantly associated with WMI scores. The difference between WMI scores across the groups for those who had daily seizures versus those who had less than daily seizures was significant and clinically meaningful (daily seizures mean = 75.14, less than daily seizures mean = 86.14; $t(150) = 3.17$, $p = <.001$). Additionally, the difference between WMI scores in those in all groups who had monotherapy versus those who had polytherapy was significant and clinically meaningful (monotherapy mean = 89.75, polytherapy mean = 76.03; $t(147) = 4.81$, $p = <.001$).

A sensitivity analysis was conducted to investigate the different measurements of the WMI, due to differences in their composition (Weiss et al., 2015). Epilepsy type significantly predicted WMI scores on the WISC-V ($n = 39$) ($F(1,37) = 14.76$, $p = <.001$; $B = -19.47$, $p = <.001$) but not on the WISC-IV ($n = 85$) ($F(1,83) = .29$, $p = .589$; $B = -2.06$, $p = .589$) or WAIS-IV ($n = 8$) ($F(1,6) = .189$, $p = .679$; $B = -4.83$, $p = .679$). However, these analyses are only exploratory due to group size across the different Wechsler measures.

Table 6: Unadjusted means, standard deviations, and group differences for all executive function outcomes at first assessment

	N	Fronto-parietal	Temporal	Test of Group Difference				
		Mean (SD)	Mean (SD)	Mean diff.	Value (*df*)	*95% CI*		*p* Value
						Lower	*Upper*	
WISC-IV / WISC-V / WAIS-IV								
WMI	152	77.51 (18.92)	85.16 (17.39)	-7.65	*t* (152) = 2.61	-13.44	-1.85	.010*
BRIEF / BRIEF-2								
GEC	58	67.85 (16.40)	64.74 (15.35)	3.11	*U* = .85	-5.00	13.00	.395
Inhibit	58	66.63 (17.72)	62.81 (16.42)	3.82	*U* = .79	-4.00	14.00	.431
Shift	58	66.48 (18.42)	64.29 (15.60)	2.19	*t* (56) = .49	-6.67	11.14	.626
Emotional Control	58	67.07 (15.50)	64.45 (14.32)	2.62	*t* (56) = .67	-5.23	10.47	.506
Initiate	58	62.81 (16.23)	59.23 (13.28)	3.59	*t* (56) = .926	-4.17	11.35	.358
Working Memory	58	68.22 (16.42)	63.84 (15.07)	4.38	*t* (56) = 1.06	-3.90	12.67	.294
Plan/Organise	58	63.93 (16.74)	60.47 (13.34)	3.46	*t* (56) = .87	-4.54	11.46	.390
Org. of Materials	58	56.96 (10.64)	51.90 (10.80)	5.06	*t* (56) = 1.79	-.60	10.71	.078
Self-Monitor	58	62.15 (14.89)	59.35 (14.50)	2.79	*t* (56) = .72	-4.95	10.54	.473
D-KEFS								
Trail Making Switching	109	4.86 (3.81)	7.27 (3.55)	-	*U* = 3.15	-4.00	-1.00	.002*
Verbal Fluency Switching	102	9.07 (4.15)	8.77 (4.21)	.30	*t* (100) = .36	-1.34	1.93	.719
TEA-Ch / TEA-Ch-2								
Selective Attention	70	7.38 (3.61)	7.20 (2.83)	.18	*U* = .17	-1.00	1.00	.868
Sustained Attention	70	7.00 (3.75)	7.62 (3.62)	-.62	*U* = .69	-3.00	1.00	.491

*Mean diff. = Mean difference, * = significant difference; WMI = Working Memory Index; GEC = Global Executive Composite*

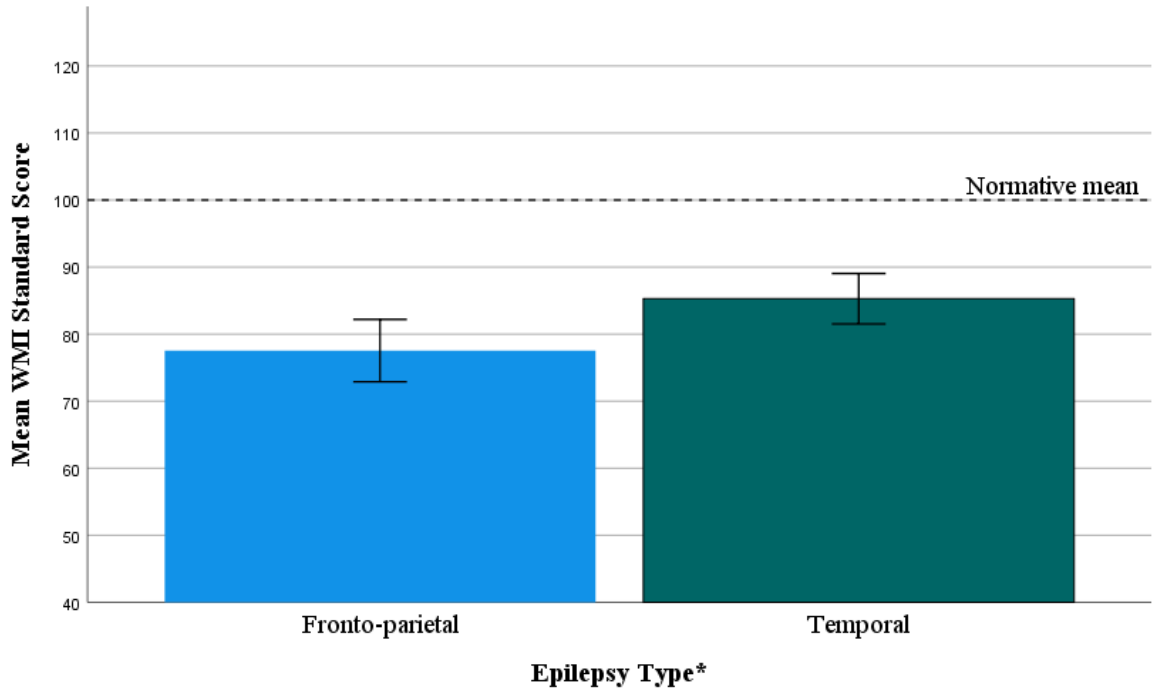

Figure 2: Mean working memory scores by epilepsy type

*WMI = Working Memory Index of WISC-IV/WISC-V/WAIS-IV; * = significant difference*

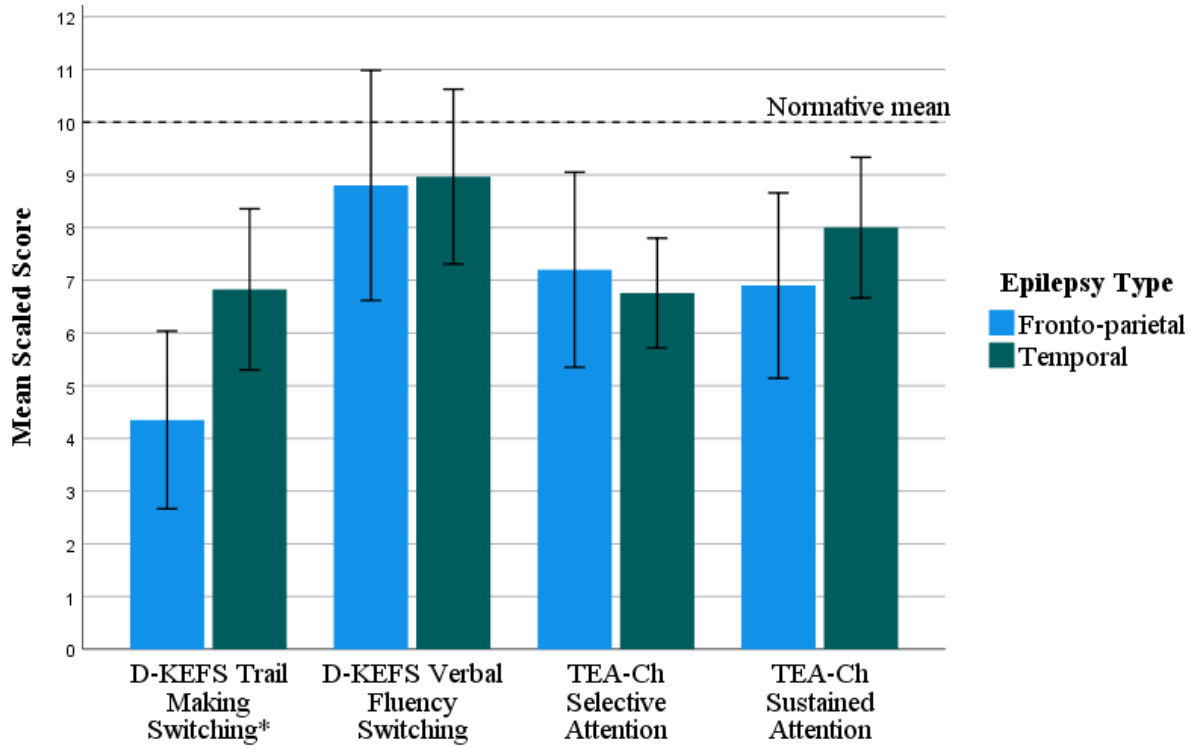

Figure 3: Mean cognitive flexibility (switching) and attention scores by epilepsy type

*TEA-Ch = TEA-Ch/TEA-Ch-2; * = significant difference*

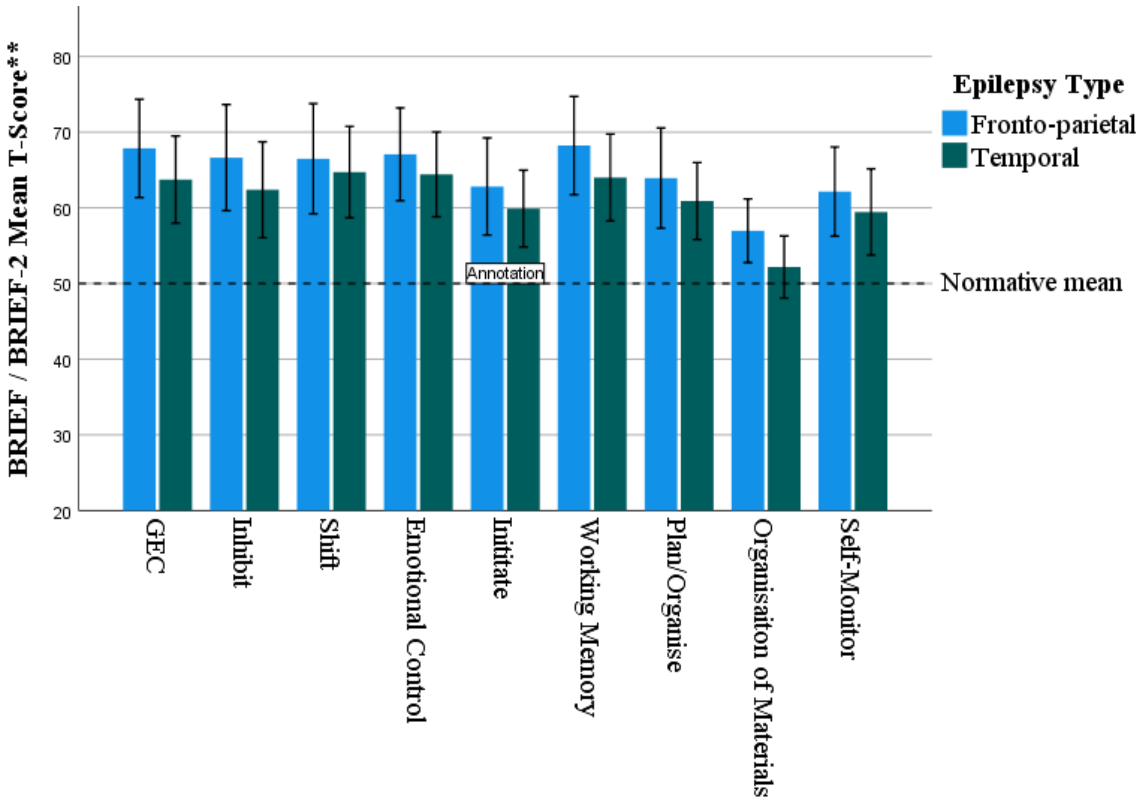

Figure 4: Mean parent-rated executive function by epilepsy type

***higher scores indicate greater executive dysfunction; GEC = Global Executive Composite*

Table 7: Percentage of children with executive function impairment at first assessment

	N	Total Impaired	Fronto-parietal Impaired	Temporal Impaired	$\chi 2$	
		Y/N (%)	Y/N (%)	Y/N (%)	Value (*df*)	*p* Value
WISC / WAIS						
WMI	152	77/75 (50.7)	41/26 (61.2)	36/49 (42.4)	5.32 (1)	.021*
BRIEF / BRIEF-2						
GEC	58	34/24 (58.6)	18/9 (66.7)	16/15 (51.6)	1.35 (1)	.246
Inhibit	58	33/25 (56.9)	17/10 (63.0)	16/15 (51.6)	.76 (1)	.384
Shift	58	32/26 (55.2)	16/11 (59.3)	16/15 (51.6)	.341 (1)	.559
Emotional Control	58	29/29 (50.0)	14/13 (51.9)	15/16 (51.7)	.069 (1)	.792
Initiate	58	24/34 (41.4)	14/13 (51.9)	10/21 (32.3)	2.28 (1)	.131
Working Memory	58	34/24 (58.6)	18/9 (66.7)	16/15 (51.6)	1.35 (1)	.246
Plan/Organise	58	24/33 (42.1)	13/14 (48.1)	11/19 (36.7)	.77 (1)	.381
Organisation of Materials	58	11/47 (19.0)	8/19 (29.6)	3/28 (9.7)	3.73 (1)	.053
Self-Monitor	58	25/33 (43.1)	14/13 (51.9)	11/20 (35.5)	1.58 (1)	.209
D-KEFS						
Trail Making Switching	109	60/49 (55.0)	32/11 (74.4)	28/38 (42.4)	10.77 (1)	.001*
Verbal Fluency Switching	102	35/67 (34.3)	14/29 (32.6)	21/38 (35.6)	.10 (1)	.750
TEA-Ch / TEA-Ch-2						
Selective Attention	70	30/40 (42.9)	12/14 (46.2)	18/26 (40.9)	.18 (1)	.668
Sustained Attention	70	38/33 (53.5)	15/11 (57.7)	23/22 (51.1)	.287 (1)	.592

*Y = impaired; N = not impaired; % = percentage impaired; * = significant difference*

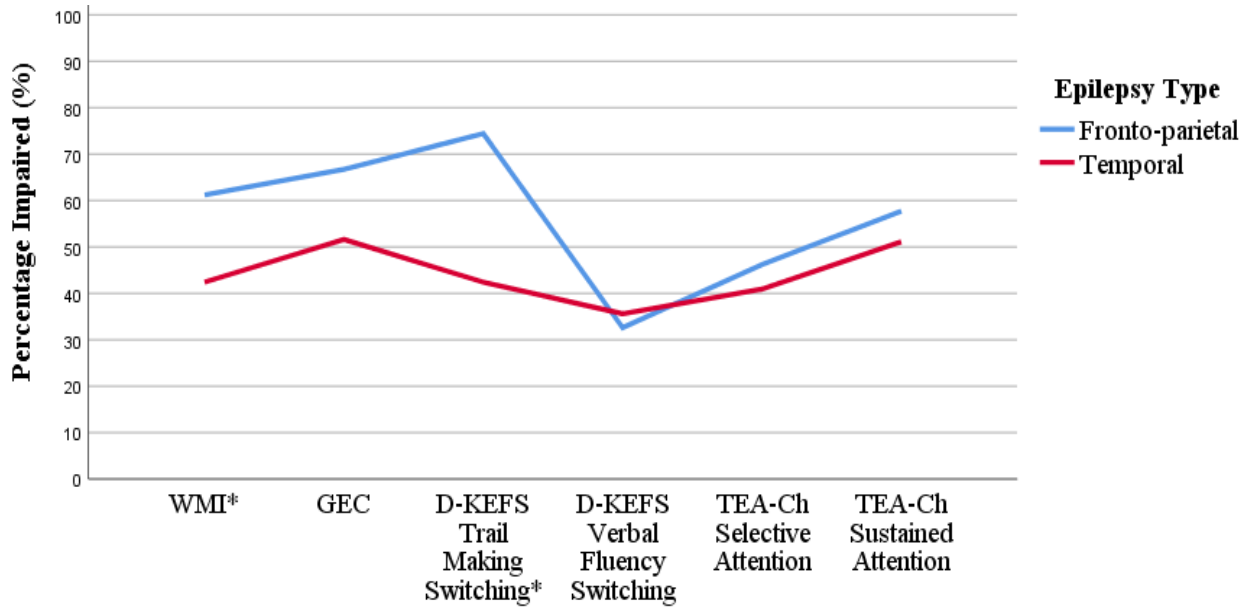

Figure 5: Executive function impairment profile by epilepsy type

*WMI = Working Memory Index of WISC-IV/WISC-V/WAIS-IV; GEC = Global Executive Composite of BRIEF/BRIEF-2; * = significant difference; impairment on GEC is calculated as 1.5 SD above the normative mean; impairment on all other assessments is calculated as 1 SD below the normative mean*

3.2.2. Post-surgery Executive Function

Analyses of an individual child's performance change between the first and second assessment was conducted using the reliable change index (Blampied, 2022; Jacobson & Truax, 1991). Significant pre-post changes in score following paediatric epilepsy surgery are presented in Table 8. A larger number of children with a temporal epilepsy remained at their presurgical WMI level (*n* = 20; 83.3%) compared with fronto-parietal epilepsies (n = 7; 53.8%). For both groups, although small, equal rates of children experienced a significant and clinically meaningful improvement or decline; however, group differences were non-significant ($\chi 2$ (2) = 3.17, *p* = .156), likely due to small cohort sizes. Three children (23.1%) in the fronto-parietal epilepsy group experienced an increase in working memory performance above that of chance, whilst three experienced a decline (23.1%), and seven stayed in the baseline range (53.8%). Within the temporal epilepsy group, two improved (8.3%), two declined (8.3%) and 20 stayed within their baseline range (83.3%).

Further analyses using an ANCOVA revealed a significant interaction between epilepsy type (fronto-parietal vs temporal) and second assessment type (post-surgical and repeated baseline) for WMI scores ($F(1,44) = 4.558$, $p = .038$), when controlling for first assessment WMI scores. The final sample size (fronto-parietal, $n = 13$; temporal, $n = 24$) fell short of the threshold identified for each group in the power analysis ($n = 17$). A significant difference in WMI scores between the first and second assessment in the repeated baseline fronto-parietal epilepsy group was observed (T1 mean = 90.75, T2 mean = 77.33; t (11) = 3.00, $p = .012$), with the mean score falling 13 points lower (see Figure 6). Caution in interpretation is advised due to the small group sizes. Differences between first and second assessment WMI scores were non-significant for all other groups.

Table 8: Post-surgical WMI significant changes in score as calculated using the reliable change index

		Fronto-parietal			Temporal			$\chi 2$	
	n	Decrease (%)	No change (%)	Increase (%)	Decrease (%)	No change (%)	Increase (%)	Value (*df*)	*p* Value
WISC / WAIS									
WMI	37	3 (23.1)	7 (53.8)	3 (23.1)	2 (8.3)	20 (83.3)	2 (8.3)	3.17 (2)	.156
BRIEF / BRIEF-2*									
GEC	10	0	5 (83.3)	1 (16.7)	2 (50.0)	1 (25.0)	1 (25.0)	4.44 (2)	.108
Inhibit	10	0	6 (100.0)	0	1 (25.0)	2 (50.0)	1 (25.0)	3.75 (2)	.153
Shift	10	0	5 (83.3)	1 (16.7)	0	4 (100.0)	0	.741 (1)	.389
Emotional Control	10	1 (16.7)	5 (83.3)	0	1 (25.0)	2 (50.0)	1 (25.0)	1.96 (2)	.375
Initiate	10	0	5 (83.3)	1 (16.7)	1 (25.0)	3 (75.0)	0	2.19 (2)	.335
Working Memory	10	2 (33.3)	4 (66.7)	0	1 (25.0)	3 (75.0)	0	0.079 (1)	.778
Plan/Organise	10	0	5 (83.3)	1 (16.7)	0	4 (100.0)	0	.74 (1)	.389
Organisation of Materials	10	1 (16.7)	5 (83.3)	0	0	3 (75.0)	1 (25.0)	2.19 (2)	.335
Self-Monitor	10	1 (16.7)	5 (83.3)	0	2 (50.0)	2 (50.0)	0	1.27 (1)	.260
D-KEFS									
Trail Making Switching	16	0	6 (100.0)	0	0	9 (90.0)	1 (10.0)	.64 (1)	.424
Verbal Fluency Switching	17	1 (16.7)	5 (83.3)	0	0	11 (100.0)	0	.16 (1)	.163
TEA-Ch / TEA-Ch-2									
Selective Attention	7	1 (100.0)	0	0	1 (16.7)	4 (66.7)	1 (16.7)	2.92 (2)	.233
Sustained Attention	11	0	3 (100.0)	0	2 (25.0)	5 (62.5)	1 (12.5)	1.55 (2)	.461

*BRIEF and BRIEF-2 scores have been reversed

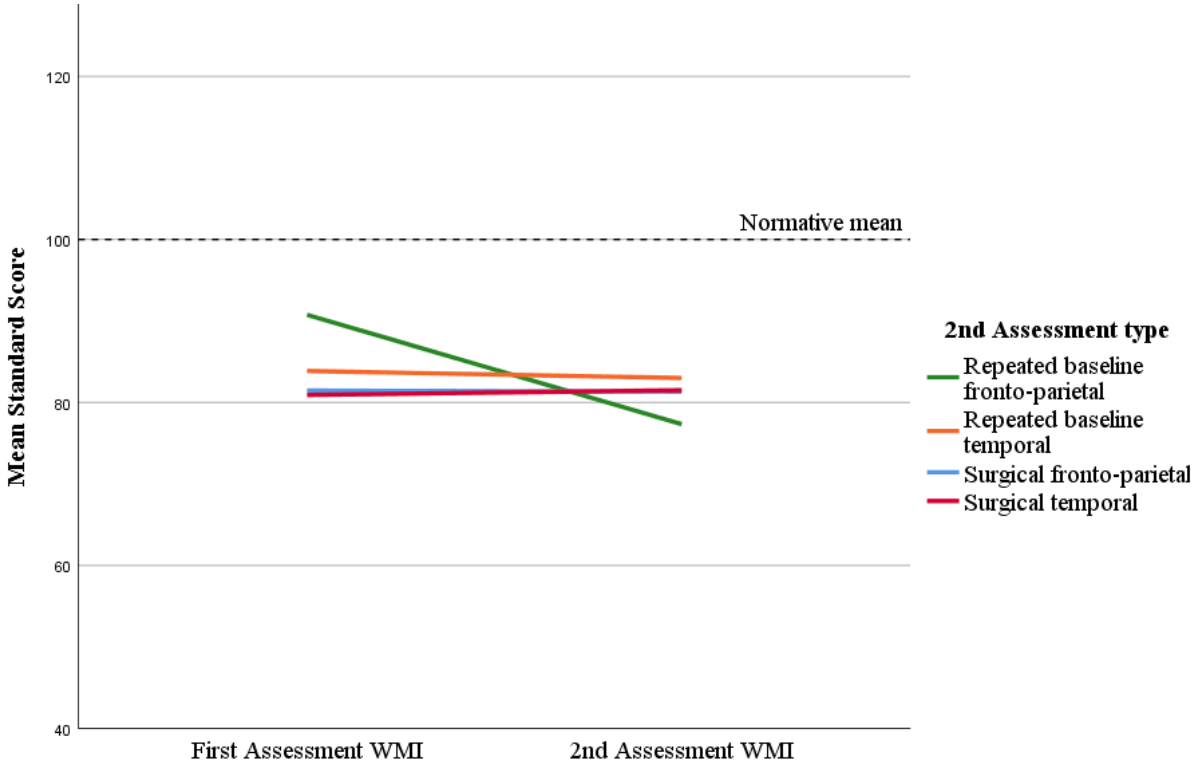

Figure 6: Change in mean WMI score from first to second assessment

WMI = Working Memory Index of WISC-IV/WISC-V/WAIS-IV; Of note, the graph is based on a small sample size.

4. DISCUSSION

The current study examined executive function abilities in children with refractory epilepsy aged 6 years to 17 years 11 months. Comparisons were made between those with fronto-parietal and temporal epilepsies, both pre- and post-surgically. Findings revealed high rates of executive difficulties across the groups in relation to working memory, cognitive flexibility, attention, and parent-rated executive function. At baseline, a different executive function profile is demonstrated between the two groups in working memory, cognitive flexibility, and parent-rated executive function. Working memory, measured by the WMI, and cognitive flexibility, assessed by the D-KEFS Trail Making Switching task, were significantly poorer in children with fronto-parietal epilepsies compared to temporal epilepsy, with a significantly greater proportion of impairment (<1 SD below the normative mean) in working memory (61% vs 42%) and cognitive flexibility (74% vs

42%). The findings therefore provided support for the hypothesised poorer working memory functioning in children with fronto-parietal epilepsies at baseline (Hypothesis 1).

The high rates of observed executive dysfunction are consistent with previous research in paediatric epilepsy (Cainelli et al., 2020; Campiglia et al., 2014; Høie et al., 2008; Modi et al., 2019; Parrish et al., 2007). Another recent study reported significantly poorer working memory in a paediatric frontal lobe epilepsy group when compared to a temporal lobe epilepsy group (Lopes-Santos et al., 2023), which is in contrast with earlier studies (Kibby et al., 2019; Longo et al., 2013). The finding of significantly poorer cognitive flexibility in children with frontal-parietal epilepsies, as assessed by the Trail Making Switching task, is inconsistent with an earlier study, although this consisted of a smaller cohort of children (Longo et al., 2013). It is also notable that a previous large-scale study (n = 306) reported no localisation-related differences in executive function, however this was based on a combined execution function/attention composite score (Helmstaedter et al., 2020). The present study therefore provided evidence of significant differences between fronto-parietal and temporal epilepsies in the largest sample that has reported on specific components of executive function at baseline, in this case working memory (n = 152) and cognitive flexibility (n = 109).

Higher rates of impairment at baseline on parent-reported executive function were found for fronto-parietal epilepsies (66.7%) compared to temporal epilepsy (51.6%) (n = 58). However, group differences were non-significant consistent with previous research comparing a frontal lobe epilepsy group and temporal lobe epilepsy group (n = 53) (Campiglia et al., 2014). Group differences for attention were also non-significant, however, rates of impairment were much more comparable between the groups for both selective attention (fronto-parietal, 46.2%; temporal 40.9%) and sustained attention (fronto-parietal, 57.7%; temporal 51.1%) (n = 70). These findings are consistent with previous research reporting comparable attention impairments in frontal and temporal lobe epilepsies (Culhane-Shelburne et al., 2002; Longo et al., 2013).

Investigations into post-surgery outcomes were limited by cohort size, as others have been (Sherman et al., 2011; Flint, 2017; Sibilia et al., 2017). Significant differences in working memory were not identified between the surgical and repeated baseline groups, and support for the hypothesised greater change in working memory scores in the fronto-parietal epilepsy group following surgery was not found (Hypothesis 2). There was however a significant interaction between epilepsy type and whether children had surgery or not. Further analyses showed a significant decline in working memory scores in the repeated baseline fronto-parietal group (n = 12), whilst all other group scores remained stable. At a group level, surgery, and higher rates of seizure freedom in children in the fronto-parietal surgical group (*n* = 8, 53.3%) compared to the fronto-parietal repeated baseline group (*n* = 2, 13.3%) likely improved working memory outcomes.

At an individual level based on the reliable change index, however, there was much variation of post-surgical outcomes. A higher percentage of children with a temporal epilepsy remained at presurgical working memory level (83.3%) than those with fronto-parietal epilepsies (53.8%). Three children with fronto-parietal epilepsies (23.1%) had a decline in working memory, three children (23.1%) had an increase, whilst others remained the same (53.8%). The variation in individual-level post-surgical outcomes likely reflects the inherent heterogeneity of epilepsies, given the numerous factors that can impact outcomes, including the age at onset of epilepsy, epilepsy duration, and the type of surgery. Higher rates (66.7%) of post-surgical increases in working memory in a frontal lobe epilepsy group were previously reported, however in a much smaller group (*n* = 3) (Sibilia et al., 2017).Whilst the current study used the reliable change index to measure significant change over time, the previous study used digit forward span and a normed score increase measure (scores 1 SD below the normative mean), and therefore a direct comparison of these studies is limited.

Daily seizures and polypharmacy were significantly associated with working memory outcomes, which corroborated previous research (Lah, 2004; Reilly et al., 2015; Witt et al., 2015), suggesting that poorer working memory in children with refractory epilepsy was associated with

these variables. Therefore, stabilising or reducing seizures on fewer ASM's or via surgical resection may improve working memory outcomes. As might be anticipated, significantly higher rates of seizure freedom were observed after surgery, when compared to repeated baseline groups. A decline in working memory in the repeated baseline fronto-parietal group compared with the post-surgical group may therefore be related to reduced seizure burden in the surgery cohort. Therefore, the continuing decline (likely a failure to develop at the same-rate as their same-aged peers) in working memory functioning in the repeated baseline group demonstrates the vulnerability of working memory over time as a result of seizures, highlighting the importance of early surgical intervention. As has been reported, post-surgical cognitive gains may correspond to a release effect of both seizure freedom and ASM cessation on developmental trajectories (Ramantani et al., 2018; Smith, 2010). The current study did not find a post-surgical association between ASM (monotherapy and polytherapy vs no medication) and executive function outcome, possibly due to the small sample size.

The findings of working memory and cognitive flexibility impairments in a fronto-parietal epilepsy group provides possible evidence of disruption to a fronto-parietal network which may be crucial for executive skills (Crittenden et al., 2016; Engelhardt et al., 2019; Niendam et al., 2012; Power et al., 2011; Reed, 2023). There is increasing acknowledgment of the parietal lobe's role in executive functions, in addition to the frontal lobe. A recent study of 217 children found that, along with frontal lobe epilepsy, a posterior cortex epilepsy (occipital, parietal, and posterior temporal lobes) group was associated with significantly poorer inhibitory control than in a temporal lobe epilepsy group (Lopes-Santos et al., 2023). Whilst inhibitory control was a component of executive function that was not explored within the current study, the corroboration of these findings suggests that this may be a line of research that warrants further exploration.

4.1. Strengths and Limitations

The study included the largest baseline and post-surgical sample size known to the authors that reported on specific components of executive function outcomes. The present findings thus highlight the importance of reporting on specific components of executive function, given the huge heterogeneity in this cognitive domain. In addition, the study addressed the lack of an adequate control group, which has been criticised in past study designs (Téllez-Zenteno et al., 2010), although it is acknowledged that the control group was limited in size (n = 25).

Sensitivity analysis revealed significant differences between WMI outcomes across the different versions of the Wechsler tests. As highlighted by Weiss et al. (2015), there are differences in the composition of the versions, particularly that the WISC-V has a visual working memory task in addition to verbal working memory tasks (Weiss et al., 2015). This is clinically significant and requires further research given the relevance to longitudinal studies which include data spanning a number of years and from multiple versions of neuropsychological tests.

This study was limited by the availability of routinely collected data. Categorisation of epilepsy groups was typically based on standard MRI and EEG clinical data, in contrast to a direct network measure of functioning (i.e., resting-state functional magnetic resonance imaging). Data also limited the inclusion of a network comparator group of temporo-insular epilepsy (see Makhalova et al., 2022), as had been originally planned. Characteristic variables such as socio-economic status and ethnicity were not available, although they may have clinical relevance and a confounding/mediating effect on outcomes. Completion rates of the various neuropsychological assessments were inconsistent thus emphasising the importance of following standardised protocols for future clinical practice.

Definitions in the literature have sought to differentiate between updating and capacity (Cowan, 2017). The current review used the WMI of the WISC-IV, WISC-V, and WAIS-IV, which involve both updating and capacity and therefore findings were not reported on for updating and capacity separately.

Post-surgical analysis was limited by a small sample size, limiting the statistical power of the post-surgical analyses. To address this, and to increase the clinical utility of the findings for patient level MDT counselling, the study used the reliable change index.

4.2. Future directions

The current findings require extension to include a larger cohort of children. Results may be refined by considering sub-types within frontal-parietal and temporal lobe epilepsies, including the age of the children and the exact surgical procedure. Furthermore, the current study emphasises the need for further research focusing on the individual components of executive function as part of pre- and post-surgical neuropsychological intervention.

In order to increase the comparability of outcomes across the UK, core outcome measures should be agreed between centres and adhered to closely. Data should also be shared nationally, which would permit higher quality evidence so that clinicians, young people, and their families may make better informed decisions about proceeding to surgery and likely post-operative outcomes (Flint et al., 2017). A collaborative network of paediatric neuropsychologists across the USA has already been formed (Berl et al., 2023) and this could be replicated in the UK. This would facilitate appropriately designed, prospective, multicentre studies, with adequate follow-up for long-term outcomes to be measured (see McIntosh et al., 2023, for 20-year post-surgical follow-up of seizure outcomes). Standardised assessment of functioning and blinding to surgical status would provide a more rigorous view of the longer-term effects on executive functions from surgery in the frontal-parietal networks in the paediatric years.

4.3. Clinical Implications

The findings have helped to establish a dataset to be used for the future research, with the recommendation that clinical practice is standardised, and routine data utilised, as recommended by Berl et al. (2023). The findings also emphasise the importance of early surgical intervention in

children (Perry et al., 2022) given the longer-term impact of daily seizures and polypharmacy on the development of executive functions.

The current paper provides a profile relating to fronto-parietal epilepsies and provides support for a network approach to patient level MDT counselling for understanding neuropsychological profiles ahead of paediatric epilepsy surgery. More specifically, the present findings suggest that investigation of disruption to a fronto-parietal network may be warranted in some cases where executive function is impaired.

5. CONCLUSION

This study took a novel network approach to report on executive function impairments across working memory, cognitive flexibility, attention, and parented-rated executive function in a fronto-parietal epilepsy group. It included the largest baseline and post-surgical sample size known to the authors that reported on specific components of executive function outcomes in children with epilepsy. At baseline, children with fronto-parietal epilepsies have greater rates of working memory and cognitive flexibility difficulties than children with temporal epilepsy. Following surgery, there was evidence to suggest a stabilising of the development of executive function skills in a fronto-parietal epilepsy group, however at an individual-level outcomes were variable. The proposed directions for future research should be undertaken to address the need for more work focusing on the individual components of executive function as part of pre- and post-surgical neuropsychological intervention. An increase in the comparability of outcomes across the UK could be achieved by agreeing core outcome measures for executive function.

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Paper 3

Critical Appraisal

Word count: 4,648 (main text)

6,247 (all text), 1,599 (references)

Introduction

This paper comprises an overview and critical evaluation of the work undertaken as part of the present thesis. An examination of the systematic review and empirical study is firstly presented, with attention to the rationale for decisions made regarding methodology and the impact of these decisions on the overall quality of the work undertaken. Reflections on the process of undertaking research in this area are discussed throughout. Consideration is then given to the wider implications of our findings and their relevance within and beyond clinical psychology.

1. Paper 1: Systematic review

1.1. Topic Choice

During my time as an Assistant Psychologist, I worked within the Neuropsychology Team at the Royal Manchester Children's Hospital and attended Northern Children's Epilepsy Surgery Service (NORCESS) multidisciplinary (MDT) meetings. I was also approaching the role having previously obtained a Brain Imaging MSc. I gained experience of MDT working including with paediatric neurologists, paediatric neurosurgeons, clinical neurophysiologists, neuroradiologists, paediatric neuropsychologists, child psychiatrists, and epilepsy nurses. The integration of findings was an integral part of the pre-surgical evaluation process and vital for robust decision-making around surgical planning. I was interested in how combined neuropsychological and neuroimaging findings are interpreted when formulating, making recommendations and writing neuropsychological reports.

Executive function has been an area of research in paediatric epilepsy that has been lacking and research in the domains of memory and language have been much more robust. This is despite evidence of executive function difficulties being associated with poorer social, academic, behavioural and quality of life outcomes in paediatric epilepsy (Austin et al., 1999; Love et al.,

2016; Modi et al., 2011; Tse et al., 2007), highlighting the importance of targeting executive functions in neuropsychological work.

Functional neuroimaging has become an important tool for the understanding of paediatric epilepsy, particularly because epilepsy is now understood as a brain network disease (Berg et al., 2010). Within NORCESS, long term video electroencephalogram (EEG) or video telemetry is an essential functional neuroimaging method that is routinely part of the pre-surgical evaluation (Pressler et al., 2017). In contrast, functional magnetic resonance imaging (fMRI) is much less commonly used and typically only when lateralisation of function is not clear, for example, in the mapping of language and memory functioning (Collinge et al., 2017). Despite this, fMRI has been advocated as a reliable method for assessing large-scale brain networks in children (Thomason et al., 2011). A review of the literature revealed that no systematic reviews had been conducted which explored executive function outcomes in paediatric epilepsy using functional neuroimaging analyses, from the angle of investigating the neuronal underpinnings of executive functioning networks in paediatric epilepsies. When meeting with a number of clinicians in the planning phase of work, there was enthusiasm for research in this area to inform clinical practice.

Scoping searches conducted in line with relevant guidance (Liberati et al., 2009; Munn et al., 2018) revealed much heterogeneity in studies. There were a limited number of studies that used the same neuropsychological measures of executive function or the same functional imaging technique. A decision was therefore made to take a broad approach to the systematic review by combining any measures of executive function and functional neuroimaging methods, so long as the methodology revealed associations between these outcomes.

1.2. Searching the literature and extracting the data

In conducting the systematic review, I adhered to the Preferred Reporting for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021). These principles aim to promote transparency and consistency amongst systematic reviews. When developing the search strategy,

consideration was given to select terms which captured all available literature whilst omitting irrelevant research (Liberati et al., 2009). Given limited systematic reviews in this area, search terms were devised from terms within the literature for executive function and functional neuroimaging methods to encompass key components of the review question. Three search blocks were devised, encompassing key components of the review question.

Given the systematic review was novel, guidance was sought from supervisors and previous relevant reviews within the field of paediatric epilepsy (Flint et al., 2017; Menlove & Reilly, 2015; Verche et al., 2018) regarding the selection of appropriate databases that would best represent the different scientific disciplines of relevance to the review question. Preliminary searches were conducted in April 2022 using the Ovid platform for three databases (Embase, MEDLINE and PsycINFO databases) as well as the CINAHL and Web of Science databases. The CINAHL and Web of Science databases did not return any additional contributions to the records and were therefore excluded from the final search strategy. The decision to select the most relevant databases was taken in the interests of presenting the optimal combination of databases (Rice et al., 2016) and to allow consistency in the search strategy by using the Ovid platform.

1.3. Inclusion and exclusion criteria

Studies were excluded based on study design, when localisation of function in functional neuroimaging data were not included, and when only functional neuroimaging or only neuropsychological outcome data were available. The rationale for this was in keeping with the study aims of reviewing evidence that was clinically applicable within a neuropsychological context. In conducting the review, it became clear there was research that reported combined structural imaging and executive function findings that were excluded. These studies would be relevant to the topic area and could be the focus of a future systematic review.

Only studies published in English were included in the review. The potential introduction of publication and location biases were highlighted in the paper. Unpublished data were also excluded

from the study, in lieu of any further restrictions based on quality. It is important to be aware of the issue of bias in the publication of positive results in full text publications. These issues are well documented within clinical research and these factors can be amplified within systematic reviews (Knobloch et al., 2011).

1.4. Quality assessment

When selecting an appropriate quality assessment tool, an important consideration was the novelty of this research base in comprising studies that were observational and non-randomised in nature, and that spanned both neuropsychological assessment and functional neuroimaging findings. Notably, there is no standardised protocol for assessing the methodological and reporting quality of neuroimaging studies. It was therefore challenging to find a tool that appropriately appraised the type of study returned from preliminary searches when designing the review. A general criticism of existing tools available is also that they tend to be highly subjective which can lead to inconsistencies in quality appraisals and the conclusions of the narrative synthesis overall (Mallen et al., 2006).

Three tools were trialled. The current review opted to use the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Institutes of Health, 2014) for quality appraisal and assessment of risk of methodological bias (Appendix C). Consideration was also given to the Newcastle Ottawa Scale (Wells et al., 2000) and the ROBINS-I assessment tool (Sterne et al., 2016). The tool was adapted in line with the review question (Appendix D). Original items 6, 8, 10 and 12 were removed, the wording of some items was modified and a new item was added regarding the reporting of results.

Consideration of key covarying factors were part of the standard tool but required operationalising. Classifying the covarying factors that would be ‘key’ for the purposes of passing this quality appraisal criterion was given careful consideration by the review team, with reference to existing literature on influencers on neuropsychological outcomes in paediatric epilepsy. Research

clearly indicated severity of seizures, socioeconomic status, and number of antiepileptic medications as having the strongest effect on child outcomes and so these were integrated into the tool. To ensure fairness and consistency, all items and criteria were agreed in advance of undertaking any quality assessments.

A scoring key was developed in order to translate scores to a quality rating (Appendix D). The finalised tool was piloted between two reviewers, with decisions made independently thereafter. One hundred percent of included papers were independently quality assessed by two members of the review team, with levels of inter-rater reliability ($\kappa = .987$, $p < .001$) indicating that a consistent and methodological approach had been achieved.

1.5. Data synthesis

Preliminary searches revealed that a degree of variability was expected in terms of neuropsychological assessment and functional neuroimaging methods and analyses and, therefore, a narrative synthesis of the findings was undertaken (see Campbell et al., 2020).

Combing across different functional neuroimaging methods meant that a narrative synthesis was challenging. Furthermore, it was important to consider the target audience given functional neuroimaging data can be highly technical and could require a high level of expertise. To balance this, the focus was always brought back to the purpose of the review which was to support to knowledge base in clinical practice and provide future directions.

The majority of studies included neuropsychological findings beyond executive functions. The decision was made to report all neuropsychological assessments completed within Table 1 as that was relevant for the quality assessment and to give a summary of the study design. Subsequently, only executive function outcomes were reported on in the “findings” column of the table and in the narrative synthesis. Given the limits placed on word count within published research papers, the reporting of specific executive function outcomes was consequently limited, at times.

The narrative synthesis grouped for synthesis based on the reporting of functional neuroimaging data in the four components of executive function: 1) working memory, 2) attention, 3) inhibitory control and 4) cognitive flexibility based on existing models and discussion around the composition of executive functions (Miyake et al., 2000; Oberauer, 2019). However, it was evident when conducting the review that there was variability in the reporting of the four components and functional neuroimaging tasks could be described as involving a number of the components. For example, the Go-No go task in Protopapa et al.'s (2016) study was described as a working memory task, however, it could be argued that this involves inhibitory control and attention. To standardise the reporting of tasks, executive function tasks were categorised in line with Diamond's (2013) review paper. However, this issue highlights that a lack of consensus of the categorisation of executive function tasks limits the comparability of findings between studies.

1.6. Reflections

Despite the above limitations, the review was the first to systematically evaluate the literature on correlates of functional neuroimaging and neuropsychological functioning related to executive function in children with epilepsy. It makes an original contribution to the literature by bringing together evidence of executive function network disruption. The review therefore provides a platform for future research in this area and highlights the importance of the functional neuroimaging for understanding executive function impairment in paediatric epilepsy.

There was considerable variability in the reporting of functional neuroimaging findings which became apparent during the conducting of the review and made the narrative synthesis challenging. For example, issues exist around low statistical power in common sample sizes (n = 20-30) (Cremers et al., 2017) and proportional thresholding (van den Heuvel et al., 2017) and these issues are not always discussed when reporting findings. The lack of standardised protocols for assessing the methodological and reporting quality of neuroimaging studies is a limitation of the review, and other reviews in this area and likely impacts on the usefulness of the data produced.

Reflecting back on the process of conducting a systematic review in this field, I believe it was an ambitious topic to take on given it involved a lot of neuroscientific language and methodology. I am however proud of addressing a gap in the literature that had important clinical relevance and highlighted some key future directions, in particular highlighting a need for higher methodological quality.

2. Paper 2: Empirical study

2.1. Topic Choice

The Royal Manchester Children's Hospital is part of NORCESS—one of four national centres commissioned in 2012 by NHS England to offer epilepsy surgery to children. Large numbers of children had been on the NORCESS pathway since the NORCESS epilepsy surgery database was started in April 2007 and no research had been conducted using this routinely collected data. There was therefore a clinical need to utilise this clinical data and arguably an ethical obligation to use the available data to inform future treatment decision making to enhance the care of children and their families. When it was suggested that research using the database could be an area to consider, I was keen to develop a research project that would utilise the large dataset to inform professionals and families as part of the NORCESS presurgical pathway.

When discussing the research project with supervisors, it became clear that entry into the NORCESS epilepsy surgery database had been inconsistent and vast amounts of data—neuropsychological, demographic and clinical data—were missing. This meant a considerable research project would need to be undertaken which seemed suitable for doctoral level. During the period of this project, I undertook a clinical research placement with the NORCESS team to allow me to work with the clinicians.

A review of the literature highlighted that there is limited research with regards to executive function in paediatric epilepsy surgery and outcome reporting is limited by the diffuse nature of this set of skills. The largest study of children (n = 308) was conducted in Germany by Helmstaedter et

al (2020) and involved pre-surgical and post-surgical outcomes. However, the study used an executive function/attention composite score, therefore being limited to overall functioning and not exploring specific components of executive function. There had been no such studies in the UK, which makes me proud to have co-produced the first.

Despite limited research in executive function in paediatric epilepsy, the wide-ranging impact of executive function difficulties have been reported. In a review of what is known about attention and executive functions, MacAllister et al., (2014) highlight the importance of these skills and that children with executive function deficits often struggle academically, socially, and functionally. The authors note that, for example, children with poor inhibitory control often present as hyperactive and impulsive at home and in the classroom. Whilst children with limited working memory capacity have difficulties keeping track of task steps and struggle to complete tasks independently. More broadly, children with executive function deficits frequently struggle with planning and organising of tasks and have difficulties in managing their time. Thus, highlighting the importance of targeting executive functions in neuropsychological work.

2.2. Designing the study

When devising the study, foremost considerations centred on addressing the research question (British Psychological Society, 2021), using a design and method that were feasible as a doctoral project. The design of the project aimed to address gaps in the literature for more detailed pre- and post-surgical executive function outcomes. The study was designed with a focus on providing useful clinical findings that would benefit professionals and families of children in patient level MDT counselling ahead of epilepsy surgery, but within the time and financial constraints of the doctorate of Clinical Psychology course. This was guided by the principle of promoting and protecting the interests of service users and carers (Health & Care Professions Council, 2016).

The study design was informed by patient and public involvement. Findings from an existing survey conducted within the NorCESS community as part of a research grant application

were used. Feedback shared from eight families of children on the epilepsy surgery pathway found that more in-depth information on neuropsychological functioning would have been helpful. The study design and presenting of findings were therefore guided by a need to present data in a way that would be clinically useful, easy to convey and could inform families on the epilepsy surgery pathway about executive function difficulties and executive function outcomes after surgery. A unique contribution to literature was therefore identified with regards to the reporting of individual test scores and their related components of executive function, in contrast to an executive function composite score. This approach increased the generalisability of the results for clinical practice.

NORCESS is a collaboration between Alder Hey Children's NHS Foundation Trust and Manchester University NHS Foundation Trust (Pressler et al., 2017). The designing of the study therefore involved presenting a proposed study design to a NORCESS clinical research group which is an MDT taken from members of the wider clinical NORCESS Team. The process of presenting provided an opportunity to discuss ideas with neuropsychology colleagues in Alder Hey. It was a valuable part of the process to pool expertise and to explore potential study designs and directions. As a research group, there was a discussion around completing a long-term follow-up (i.e., 3-5 years post-surgery). However, considering the high levels of missing data from the NORCESS research database, it was agreed that the project should focus on bringing the existing available data up to date. Thus, utilising the available routinely collected data and providing a baseline for future longer-term follow-ups. An additional factor in this decision-making process was that the project was planned and conducted whilst the effects of COVID were still very present, and there were concerns around the feasibility of a long-term follow-up study for a doctoral project, given it would likely require home visits.

When planning this study discussion was also held around the appropriate age range for children to be included in the study. In line with previous research, an age range of 6-17 years was agreed in line with previous research (Helmstaedter et al., 2020). The Working Memory Index (WMI) of either the WISC-IV (Wechsler, 2003), WISC-V (Wechsler et al., 2014) or WAIS-IV

(Wechsler, 2008) was used as a primary outcome measure. To address differences in their composition (Weiss et al., 2015), a sensitivity analysis was planned to investigate the different measurements of WMI and findings were discussed.

The study design initially involved having a network comparator for the fronto-parietal epilepsy group. It was planned that temporo-insular epilepsy (see Makhalova et al., 2022) would be the comparator group for fronto-parietal epilepsy group. Unfortunately, the study was limited by the availability of clinical data for insular epilepsy cases (due to the challenges in recognising and diagnosing it) and a comparator was only able to be based on a single lobe of onset, namely temporal epilepsy.

2.3. Research database

The National Health Service (NHS) allows the utilisation of anonymised patient data with NHS Trust level approval to improve the decision making and care of patients (NHS Health Research Authority, 2022). This is in line with a need to find a balance between facilitating important research and protecting the confidentiality of patients when conducting research using routinely collected data (Foster & Young, 2012). Ethical approval for access to participant data, for the collection of routine clinical data (Appendix G) and for the use of this routinely collected clinical data to be included in the thesis and future publications (Appendix E) was therefore gained from the Service Director, from NORCESS and from both NHS Trust Research and Development Departments. The study was undertaken in line with guiding ethical principles (British Psychological Society, 2021). The routinely collected clinical data is de-identified, merged across the two hospitals and held in an anonymous approved database for research. High standards of confidentiality were maintained, and data was only accessed from secure access points. With technological advances the use of routine health data is growing (Cook & Collins, 2015), both in the UK and internationally.

As highlighted above, data entry into the NORCESS epilepsy surgery database had been inconsistent and there were vast amounts of missing data that had to be inputted. Working together with a fellow doctoral student, the steps for the work on the database included reviewing NORCESS MDT PowerPoint summary slides and clinic letters to ascertain demographic and clinical characteristics. Data were then coded according to agreed categories. Neuropsychological assessment scores were entered from past records. The time required for this data entry, an estimated 100 hours, went far beyond what was expected at the beginning of the project.

After updating the records based on available data, it was clear that there were limitations in the reporting of demographic and clinical variables. Cross-cultural tests and normative data are currently lacking in the field of neuropsychology, and have been identified as a priority for future developments (Franzen et al., 2021). Data regarding ethnicity were not available in the current study which limited the ability to control for related confounding effects, given the limitations of existing neuropsychology tests.

There were large inconsistencies in the completion rate of particular neuropsychological tests. For example, low completion rates of the Behavioural Rating Inventory for Executive Function First Edition (BRIEF; Gioia et al., 2000) and Second Edition (BRIEF-2; Gioia et al., 2015) (pre-surgical completion rate, 30%; post-surgical completion rate, 21%) meant that the Global Executive Composite (GEC) was not used as the primary outcome measure, as had initially been planned. The Working Memory Index (WMI) of the WISC-IV (Wechsler, 2003), WISC-V (Wechsler et al., 2014) or WAIS-IV (Wechsler, 2008) was subsequently used as the primary outcome measure, given rates of completion were much higher (pre-surgical, 78%; post-surgical, 77%).

The completeness of routine health record or clinical data is a challenge to this methodological approach. Whilst large samples are available in a more cost effective manner, such an approach arguably lacks the rigour of a blinded, standardised to protocol set of investigations. Given the data in the study comes from a single location, this provides the opportunity to directly

feed back to the team about data completeness, should they wish to continue to produce competitive research using their data.

Attempts were made to include an executive function composite as an additional step of analyses, in line with previous research (Helmstaedter et al., 2020). However, this led to losing more participants due to the variability in subtests completed and, considering this and the limited clinical utility, individual test scores were presented only.

2.4. Analyses and presentation of findings

Consistent with the aims and design, the analyses were conducted and presented in a way that aimed to make the findings accessible to both clinicians and families. Importantly, data were reported on a group level and individual level. It has been highlighted that adding individual-level analyses can make findings more clinically meaningful as they can offer greater detail in findings (Blampied, 2022; Sherman et al., 2011). Such data can also reflect the individual variability which is inherent within epilpesy and post-surgical outcomes for chilren with epilepsy. You cannot reliably counsel a young person on their risk of memory decline utilising risk ratios, but percentages of whose executive functioning improved, whose stayed the same, and who had a decline are far more useful. Group level analyses was therefore conducted to directly test the study hypotheses of group differences between fronto-parietal and temporal epilepsy, both pre-surgically and post-surgically, but percentages of impaired functioning pre-operatively and of those who experienced a significant change following surgery were additionally presented. Pre-surgical analyses also included analyses of impairment in executive function pre-surgically on a case-by-case basis. Post-surgical analyses included analyses using the reliable change index (Blampied, 2022), to calculate pre-post change for each child.

The presentation of data was challenging given that outcomes were in three different formats (standard scores, scaled scores and T-scores) meaning that combined graphical presentation of these formats was not possible. This was discussed in the research team and different formats

were presented separately, in keeping with clinical practice and how data is presented within the NORCESS MDT meetings.

2.5. Reflections

Involvement in the research has made me reflect on the important role of neuropsychologists, who are well placed to provide an opinion regarding the risks and benefits of surgery that integrates a range of medical, developmental, cognitive and behavioural variables (Morrison et al., 2018; Wilson et al., 2015). Furthermore, I became aware of the scarcity of findings in this topic area which places limitations on what advice can be offered regarding executive function outcomes in paediatric epilepsy surgery. It is therefore particularly surprising to learn that there is no funding for post-surgical assessments within NORCESS neuropsychology provision and assessments are limited to being offered due to clinical need and when existing resources allow. This is undoubtably a factor in the limited number of post-surgical assessments completed.

With regards to inconsistent and missing data entry into the NORCESS research database, I have reflected on the challenges of conducting research when working within the NHS. I experienced first-hand the range of challenges facing clinicians aiming to conduct research as part of their NHS roles including: lack of protected time or resources, research not being prioritised, limited specific clinical-academic roles and career structures within the NHS, and an impact on personal time (Chatburn, 2023). Furthermore, my involvement in this research project undoubtedly has implications for my own clinical practice. In particular, it has emphasised the importance of standardised neuropsychological assessments protocols given that routinely collected clinical data can have implications for future assessments and interventions.

I feel a great sense of achievement at having entered the field of paediatric neuropsychology as an assistant psychologist and to now have gone on to contribute towards the evidence base within the field of paediatric epilepsy surgery.

3. Implications

The key clinical and academic implications of the research were addressed in the review and empirical papers. Further considerations are discussed herein.

3.1. Clinical implications and future research

The current empirical paper has provided a baseline for future long-term follow-up studies with this UK cohort. These would be great value to families of children with epilepsy, providing a longer-term prognosis as well as more optimised pre-surgical planning.

The review and empirical papers provide evidence for a network approach to executive function impairment in paediatric epilepsy. Whilst a network approach is well established in the epilepsy literature and functional neuroimaging literature, this has not yet translated into the reporting of clinical data in research. In taking this approach, findings reported executive function impairments across working memory, cognitive flexibility and attention present in a fronto-parietal epilepsy group. It is hoped that this may be a platform for future research in executive function impairment in paediatric epilepsy as well as guiding discussion around such impairments in patient level MDT counselling ahead of epilepsy surgery.

The review paper highlighted the need for a standardised protocol for assessing the methodological and reporting quality of neuroimaging studies. The development of such a quality assessment tool is important for systematic review papers and one tailored to studies with neuropsychological outcomes is likely the optimal way forward.

The study presents routinely collected data. Whilst a benefit of this approach is that it is low in cost, a clear need for greater consistency in the completion and reporting of neuropsychological assessments was highlighted. One of the actions arising from the research is to develop and implement a Standard Operating Procedure for data entry into the NORCESS research database. Additionally, the study highlights the need for consideration of blinded standardised

neuropsychological assessments in the form of funded standardised trials across countries (see Bromley et al., 2016), to increase the reliability and comparability of findings.

3.2. Dissemination

The researcher plans to disseminate findings at a range of levels. Findings will be presented to the NORCESS Annual Review Meeting in June 2023 which will be attended by over 30 clinicians across both Children's Hospitals. The findings will be shared with the Epilepsy Service User Group and relevant third sector organisations (e.g., Epilepsy Society UK, Epilepsy Action UK) with plain language summaries. Findings will be disseminated at relevant conferences and amongst the UK paediatric epilepsy special interest groups. Both the systematic review and empirical papers would be submitted for publication within Epilepsia. This journal has a high impact factor rating and has a varied readership of relevant healthcare professionals including neurologists, clinical neuropsychologists, and specialist epilepsy nurses. As such, the journal was selected with the rationale that findings would be disseminated to a large number of researchers and healthcare professionals in the field, in turn influencing both research and practice. In adopting this dissemination strategy, we believe that the utility and benefits of the proposed research will be realised for all key stakeholders.

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Appendix A:

Author guidelines for Epilepsia

Epilepsia, **XX**(X):XXXX–XXXX, 2022
Wiley Periodicals, Inc.

Epilepsia
The Journal of the International League Against Epilepsy

INSTRUCTIONS *for* AUTHORS

Epilepsia is the official journal of the **International League Against Epilepsy (ILAE)**. The Journal publishes original articles on all aspects of epilepsy, clinical and experimental, especially of an International importance. Manuscripts should be the work of the author(s), must not have been previously published elsewhere, and must not be under consideration by another journal.

If you have a question not addressed in these pages then contact the journal at epilepsia@epilepsia.com.

EDITORIAL POLICIES

(1) The Editors-in-Chief of *Epilepsia* invite manuscripts in all areas of epilepsy-related research, especially if useful for an international audience. Manuscript submission is free. As a general guide, manuscripts will be considered for publication if they contribute significant new findings to the field. The primary aim of *Epilepsia* is to publish innovative and high quality papers that provide clinical and/or basic science insights.

The Editors will make an initial evaluation of all manuscripts to determine whether they are appropriate for the Journal (editorial review). Reports are unlikely to be accepted for publication if they are not based in sound science and/or they provide only incremental knowledge of limited general usefulness. To assist authors in deciding whether to submit a manuscript to *Epilepsia*, we provide the following commonly encountered examples of reports which we are unlikely to publish:

(a) Papers that describe clinical features or epidemiology in a given region of the world that do not provide new insights into epilepsy not already published;
(b) Correlative studies where the sample size is too low to provide statistically sound findings;
(c) Genetic association studies in which the association has already been confirmed;
(d) Investigatory articles describing the application of a new technical variation which is not likely to have clinical utility or impact;
(e) Correlative clinical studies, which are conceived without clear hypotheses and the results of which are of little clinical utility;
(f) Basic research studies that are not grounded in epilepsy relevant hypotheses;
(g) Single group, before-after evaluations of therapeutic interventions and programs that do not include a control group;
(h) Small case series which largely replicate what is already known;
(i) Case reports (highly unlikely to be accepted unless they provide novel findings of theoretical or clinical importance).

Epilepsia will accept, review, and publish studies with negative results, provided that appropriate controls have been used, the study is adequately powered, and the results are important and or useful to others in the research community.

(2) Manuscripts describing original research, and passing the initial editorial screen, will be subject to external peer review. Acceptance of these manuscripts is never guaranteed. At least two reviews are generally obtained for these submissions; additional reviews maybe sought at the discretion of the Editors. Appeals of rejection decisions will be considered by the Editors-in-Chief; decisions of the Editors-in-Chief are final.

(3) In the cover letter, authors should indicate that the material described in the manuscript is the work of the author(s), has not been previously published, except in abstract form, and that it is not simultaneously under consideration by any other journal.

(4) As a condition of publication, *Epilepsia* requires authors to transfer copyright to the ILAE. Authors will be asked to login into Author Services and complete the appropriate license agreement via Wiley Author Licensing Service.

(5) *Epilepsia* complies with recommendations of the International Committee of Medical Journal Editors (http://www.icmje.org). Authors are required to include a statement at the end of their manuscript affirming that the work described is consistent with the Journal's guidelines for ethical publication (see below). *Epilepsia* is a member of the Committee on Publication Ethics (COPE), and we adhere to its principles (http://publicationethics.org/).

(6) Data reporting should follow appropriate checklists and guidelines (e.g., STROBE for observational trials; CONSORT for clinical trials), and other checklists should be consulted for other reports including diagnostic accuracy (STARD) or meta-analyses (PRISMA). A completed checklist should be submitted with their protocols as a supporting document. Checklists can be downloaded from the following: STROBE – http://strobe-statement.org
CONSORT – http://www.consort-statement.org/consort-statement/
STARD – http://www.stard-statement.org/
PRIMSA – http://www.prisma-statement.org/

(7) For animal experiments, the authors need to state that the experiments have been performed in accordance with all applicable national and/or international guidelines/laws. The authors should also provide their allowance number for performing animal experiments when available and should add a statement indicating that the principles out-lined in the ARRIVE guidelines and the Basel declaration (http://www.basel.declaration.org) including the 3R con-cept have been considered when planning the experiments.

(8) Authors are also required to provide full disclosure of any conflict of interest as a part of the submitted manuscript (see Disclosure of Conflicts of Interest in the Manuscript Format section under Manuscript Preparation). Manuscripts that do not conform to these guidelines will not be considered for publication. Discovery of or failure to comply will result in rejection of the manuscript, retraction of the published article, and/or a ban on future submissions by the author(s).

(9) In submitting a manuscript, the submitting/corresponding author must acknowledge that: a) all co-authors have been substantively involved in the study and/or the preparation of the manuscript; b) no undisclosed groups or persons have had a primary role in the study and/or in manuscript preparation (i.e., there are no "ghost-writers"); and c) all co-authors have seen and approved the submit-ted version of the paper and accept responsibility for its content. The Editors reserve the right to require authors to submit their original data for comparison with the manu-script's illustrations, tables, and results.

(10) Sometimes editors make mistakes. If an author believes an editor has made a decision in error we welcome an appeal. Please contact the editor and in your appeal letter, clearly state why you think the decision is a mistake and set out specific responses to any comments related to the rejection. An appeal does not guarantee a re-review.

TYPES OF MANUSCRIPTS

The following types of material may be considered for publication:

(1) Peer-reviewed papers (to be submitted by upload-ing online via Scholar One Manuscript Central http://mc.manuscriptcentral.com/Epilepsia)

a. Critical reviews and commentaries. The Edi-tors-in-Chief encourage submission of reviews and commentaries on topical and controversial issues. Authors planning/proposing such papers should consult with the Editors-in-Chief before submitting the manu-scripts. Authors can also approach one of *Epilepsia*'s Associate Editors about possible reviews. While there are no strict length limits on this type of paper, manu-scripts generally should be around 4000 words and no longer than 6000 words, with no more than 5 to 7 figures/tables (combined). Longer manuscripts will be considered at the discretion of the Editors-in-Chief.

b. Full-length original research articles. These arti-cles should be limited in length to 4000 words and no more than 6 figures and tables. Additional figures and tables can be submitted as online only Supporting In-formation (which will be linked to the online version of the published article). Authors should aim for pre-senting material clearly and completely, in the most concise and direct form possible; the Introduction should be brief (typically less than 600 words), and the Discussion should be restricted to issues directly rel-evant to the Results (typically less than 1500 words).

c. Brief communications. These articles including short studies, small series, case reports, etc. should describe previously unpublished material, including original research and/or clinical observations. The papers are limited generally to 1800 words (excluding the summary), 15 references, and no more than 2 figures and tables (combined). Please note that the Editors may use their discretion to request that brief communications be shortened to a length that they feel is appropriate.

Brief Communications may be published online only (not in the print version of the journal) depending on their impact. They will appear in a specific issue in the electronic (online) version, and will be identified and described (Short Summary) in the Table of Con-tents of the printed version of that issue. The online versions will be dealt with by PubMed/Medline and other indexing/citation systems, exactly the same way as print articles; they will be referenced by their DOI number and date of online publication (which will continue to be approximately 35 working days following acceptance).

(2) Editorially-reviewed material (to be submitted by email to the Editors-in-Chief at epilepsia@epilepsia.com, except letters and commentaries which should be submitted online at http://mc.manuscriptcentral.com/Epilepsia)

Other contributions that do not report original research will be published at the discretion of the Editors-in-Chief, with only editorial review. Such material in-cludes: workshop reports and conference summaries, obituaries, letters/commentary to the Editors (500 word limit, and only exceptionally figures or tables), special (brief) reports from ILAE Commissions or other working groups, and announcements. Such material will usually be published in **Gray Matters**.

(3) Supplements (to be submitted as directed by the Editors-in-Chief)

Supplements, including meeting abstracts, will be published only after advance arrangements are made with the Editors-in-Chief. Guidelines for preparing supplements are given below. Proposal for, and questions about supplements should be directed to one of the Editors-in-Chief (epilepsia@epilepsia.com). Such proposals must be explicitly approved by the Editors-in-Chief, who will also confirm the page rate charge for the proposed supplement.

(4) Special reports In some cases, special reports from ILAE Commissions or other broadly constituted working groups will be published after peer review. The corresponding author of such papers should confer with the Editors-in-Chief to determine if the full manuscript will be peer-reviewed, or whether only a short version will be considered for publication in *Epilepsia*'s Gray Matters (see below).

MANUSCRIPT PREPARATION

General Style Guidelines

Manuscripts are to be submitted (and will be pub-lished) in English. Writers not fluent in English should seek assistance to ensure proper grammar and syntax, and to help generate a manuscript organization that facilitates reader understanding. Authors for whom English is a second language may choose to have their manuscript professionally edited before submission, to improve the English. A list of independent suppli-ers of editing services can be found at http://author services.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee accept-ance or preference for publication. The Editors will not re-write papers submitted in unacceptable English, and will return such manuscripts for revision before sending them out for review.

Use international non-proprietary (generic) names when referring to drugs; avoid proprietary (brand) names. All acronyms should be spelled out at first mention. Spell out numbers below 10 and all numbers that are used to begin a sentence; use Arabic numerals for numbers above 10 and for units of measure. Manuscript text should be double spaced with at least 1 inch margin on all sides using 12 fonts. Word limits for each type of submission will generally be enforced unless there are good reasons not to do so. If manuscripts exceed these guidelines, authors should submit a covering letter explaining why the additional length is necessary.

Authors are encouraged to use the most recent terminology of seizure and epilepsy classification of the ILAE (Berg et al., 2010). Studies involving treatments should adhere to ILAE's classification of medically refractory epilepsy (Kwan et al., 2011).

Manuscript Format

a. Critical Reviews and Invited Commentaries

- **Title Page** (see Full-Length Original Research below)
- **Summary and Key Words**

  Reviews and commentaries should generally begin with a summary (less than 300 words) of the content. The summary (structured) should provide the reader with the main points of the paper, and be divided into Objec-tive, Methods, Results, and Significance. The Summary should be followed by a list of 3–6 Key Words; please provide Key Words that will assist in the indexing of your article (i.e., make it easy for individuals who are searching PubMed to find your paper). Do not use words already incorporated into your title (those words are picked up automatically by the indexing service).

- **Body of review**

  There is no designated structure for the body of Reviews or Commentaries. Authors are encouraged, however, to use sub-headings to separate major sections and to facilitate clarity.

  Tables, figures, figure legends, references, acknowledgements, statement of compliance with the Journal's guidelines for ethical standards in publishing, disclosure of conflicts of interest, and Supplementary material – as for *Full-Length Original Research* (see below).

b. Full-Length Original Research, Special Reports, and Brief Communications

- **Title Page**

  Include the following information: Full title of the manuscript which generally should be as concise and precise as possible; authors' names (first and last names, middle initial when commonly used by that author); institutional affiliation for each author (use superscripted numbers after each author's name, and a corresponding superscripted number before each institutional affiliation); contact information for the corresponding author (name, address, telephone number, fax number, e-mail address); running title (no more than 40 characters and spaces in length);

Key Words for use by abstracting services (same as following summary); number of text pages; number of words; number of figures; number of tables.

‰ **Summary and Key Words**

Provide a summary of no more than 300 words (200 words for Brief Communications). The summary of Full-Length Original Research reports should consist of four sections, labeled: Objective; Methods; Results; Significance. This structured summary should con-cisely and specifically describe why and how the study was performed, the essential results, and what the authors conclude from the results. To promote brevity, authors may use phrases rather than com-plete sentences. The summary for Special Reports, Invited Commentaries, and Brief Communications is not structured, but should cover the same topics as the structured summary. The summary (structured or unstructured) should be followed by 3–6 Key Words (see above). A second short summary (less than 100 words) is required for Brief Communications that can be used in the print issue Table of Contents. Submit the second short summary as a Supporting Document.

‰ **Introduction**

State the objectives of the study clearly and concisely, and provide a context for the study by referring judi-ciously to previous work in the area. Do not attempt to present a comprehensive review of the field. Provide a statement about the significance of this research for understanding and/or treating epilepsy.

‰ **Methods**

Describe the research methods in sufficient detail that the work can be duplicated; alternatively, give references (if they are readily accessible) to previous comprehensive descriptions. Identify the statistical procedures that were used and the rationale for choosing a particular method, especially if it is not standard.

Reports of experimental studies on humans must ex-plicitly certify that the research received prior approval by the appropriate institutional review body and that informed consent was obtained from each volunteer or patient. Studies involving animals must include an explicit statement that animal care and use conformed to institutional policies and guidelines. When animals are subjected to invasive procedures, details must be pro-vided regarding the steps taken to eliminate/minimize pain and suffering, including the specific anesthetics, an-algesics, or other drugs used for that purpose (amounts, mode of delivery, frequency of administration).

If extensive descriptions of methods are needed, provide basic information within the text and submit supplementary information for online Supporting Information.

‰ **Results**

Results should be reported fully and concisely, in a logical order. Do not repeat methodological details from the Methods section. Where possible, use figures and/or tables to present the data in a clear and concise format. Do not repeat data in the text that are given in a table, but refer to the table. Provide textual explana-tions for all figures, with clear reference to the figure(s) under discussion. Descriptive information provided in figure legends need not be repeated in the text; use the text, however, to describe key features of the figures. When appropriate, give sample numbers, the range and standard deviation (or mean error) of measurements, and significance values for compared populations.

‰ **Discussion**

Provide an interpretation of the results and assess their significance in relation to previous work in the field. Do not repeat the results. Do not engage in general dis-cussion beyond the scope of the experimental results. Conclusions should be supported by the data obtained in the reported study; avoid speculation not warranted by experimental results, and label speculation clearly. Discuss the significance of the data for understanding and/or treating epilepsy.

‰ **Statistical Methods**

The following guidelines assume familiarity with com-mon statistical terminology and methods. We recom-mend that authors consult a biostatistician during the planning stages of their study, with further consulta-tions during the analytical and interpretational stages.

1. Analysis guidelines:

- Use robust analytic methods when data are skewed.
- Use Kaplan Meier methods, Cox Proportional Hazards, and mixed models analyses for longi-tudinal data.
- Account properly for statistical outliers.
- Use exact methods as much as possible in analy-ses of categorical data.
- Use appropriate correction procedures to account for multiple comparisons, and conduct post-hoc comparisons with statistically appropriate methods.

2. Presentation guidelines:

- Report means accompanied by standard devia-tions; standard errors should not be used.
- Present results with only as much precision as is appropriate.
- Present confidence intervals, whenever possible, including in figures.
- Describe quantity of missingness and methods used for handling such missingness.

- In general, present two-sided p-values. P-values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places, and those smaller than 0.001 should be reported as p<0.001.
- In reporting clinical trials, include a flow diagram, a completed trial checklist, and trial registration information. The CONSORT flow diagram and checklist are recommended (http://www.consort-statement.org/).

‰ **Acknowledgements**

Acknowledge sources of support (grants from government agencies, private foundations, etc.); including funds obtained from private industry. Also acknowledge (consistent with requirements of courtesy and disclosure) participation of contributors to the study who are not included in the author list.

‰ **Disclosure of Conflicts of Interest**

In addition, each author should provide full disclo-sure of any conflicts of interest. One of the following sentences must be included at the end of the paper: either "Author A has received support from, and/or has served as a paid consultant for .... Author B has received support from .... The remaining authors have no conflicts of interest." Or "None of the authors has any conflict of interest to disclose." Note: Disclosure is needed for financial income/payment from commercial sources, the interests of which are relevant to this research activity. Please identify sources from which financial assistance/income was obtained during the period of the research activity and generation of the current report. Grants from government and/ or private agencies should be identified in the Acknowledgements section. All papers must include the following statement to indicate that the authors have read the Journal's position on issues involved in ethical publication (see below) and affirm that their report is consistent with those guidelines: "We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines."

‰ **References**

Authors are responsible for the accuracy of their references. References should follow a modified Vancouver style format. Citation of references in the text should be in superscript numbers (including those in figure legends and tables). Cite the end references in numerical order. The first three authors should be listed and followed by et al. Use journals' PubMed abbreviations in the reference list at the end of the paper (as opposed to the journals' names being written out in full).

Number of references is limited to the following:
Full Length Original Research – 40
Brief communications – 15
Reviews – 80
Special Reports – 80

Sample References:

Journal article

Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51: 676–685.

Journal article published electronically ahead of print version

Faure JB, Akimana G, Carneiro JE, et al. A comprehensive behavioral evaluation in the lithium-pilocarpine model in rats: Effects of carisbamate administration during status epilepticus. *Epilepsia* Epub 2013 May 11.

Journal article In Press

Battino D, Tomson T, Bonizzoni E,et. al. Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry. *Epilepsia* (in press 2013)

Letter

Marucci, G. Commentary on the new ILAE classifica-tion system for focal cortical dysplasias. *Epilepsia* 2012; 1:219–220. Letter

Published Abstract

Noe, K, Drazkowski, J. Safety of Long-Term Video EEG Monitoring. *Epilepsia* 2008; 59 (Suppl. 7):1.125. Abstract

Book

Shorvon, S. Handbook of the treatment of epilepsy. Oxford: Blackwell Publishing; 2005

Chapter in a Book

Fraser RT, Gumnit RJ, Thorbecke R, et al. Psychosocial rehabilitation: A pre- and postoperative perspective. In Engel J (Ed) Surgical treatment of the epilepsies. 2nd Ed. New York: Raven, 1993:669–667

Online

Russo CA, Elixhauser A. Hospitalizations for Epilepsy and Convulsions, 2005: Statistical Brief #46. Available at:http://www.hcup-us.ahrq.gov/reports/statbriefs/sb46.jsp. Accessed February 12, 2011.

‰ **Figure legends**

Number each legend sequentially to conform to the figure number (e.g., Figure1, Figure 2...). The legend should provide a brief description of the figure, with explanation of all symbols and abbreviations. Writ-ten permission to use non-original material must be

obtained (from the original authors (where possible) and publishers) by the authors. Credit for previously published material (author(s), date, journal/book title, and publisher) must be included in the legend.

Tables

Tables should be formatted as the authors wish the ta-ble to appear in print. Present all tables together at the end of the manuscript, with each table on a separate manuscript page. Each table should be given a number and a descriptive title. Provide notes and explanations of abbreviations below the table, and provide clear headings for each column and row. Do not dupli-cate data given in the text and/or in figures. Writ-ten permission to use non-original material must be obtained (from the original authors (where possible) and publishers) by the authors. Credit for previously-published material (author(s), date, journal/book title, and publisher) must be included in the table notes.

Figures

All figures should be prepared with care and profes-sionalism. Submissions that do not comply with the following formatting requirements will be returned for correction and re-submission. Figures should be sub-mitted as TIFF files in the size expected for final pub-lication–approximately 3 inches for half column and 6 to 7 inches for double columns. Submit black and white figures with a minimum of 300 dpi (MRI scans) and for line drawings or figures that included imbedded text (bar graphs with numbers) at least 600 dpi. Com-plex figures (including photographs, micrographs, and MR-related images), either in color, in half-tones, or in black and white, should also be submitted in TIF format with a resolution of at least 600 dpi. We rec-ommend saving the TIF files with LZW compression (an option when you 'save as' in packages like Pho-toshop), which will make the files smaller and quicker to upload without reducing the resolution/quality. Save each TIF file with a name that includes the first author's last name and the figure number as referenced in the text (e.g., Smith-fig1.tif). Provide clear labels on the ordinate and abscissa. Figures with more than one part should be combined by the authors in the cor-rect orientation and labeled with A, B, C etc. When relevant, include calibration information. Scale bars should be applied to photomicrographs of histology and relevant figures. Label figures using Calibri font and be sure that all labels are large enough to be clear-ly legible. The maximum size of any figure is 17 × 22.5 cm and 40 megapixels; the total number of pixels for each figure (i.e., height × width) must be less than 40 megapixels otherwise the image will not convert to PDF for review. There is no charge for color figures. We strongly encourage authors to generate figures in color (to enhance clarity of presentation and aesthetic appeal), using the following color palette:

Color	CMYK Definition	RGB Definition
Yellow	0/11/65/0	255/222/117
Orange	0/58/100/8	227/124/29
Red	0/100/60/37	163/1/52
Green	27/0/95/55	103/119/24
Green-blue	100/0/28/65	0/83/94
Blue	100/46/0/0	0/118/192

Photographs or videos of patients should not reveal patient identity; masking eyes and/or other identifiers is compulsory unless the eyes are essential to the meaning of the photograph or video. In addition, such photographs and videos must be accompanied by a letter saying that signed consent forms authorizing publication have been obtained for all identifiable patients, and that the consents will be maintained by the author for seven years or until the patient reaches 21 years of age, which-ever is longer. Do not send *Epilepsia* the consent forms; U.S. Federal privacy rules prohibit sending signed con-sent forms to *Epilepsia* or Wiley-Blackwell Publishing without written permission from the patient to do so.

Supporting Information

Supporting information, to be published online only, can be submitted for review. Such material may include: additional figures, large tables, videos, etc. that can-not be accommodated within the normal printed space allocation for an article – but provide important com-plementary information for the reader. As determined by the reviewers and Editors, supporting information will be posted on the Wiley Online Library *Epilepsia* server and directly integrated into the full-text HTML article. Explicit reference to the supporting informa-tion in the main body of the text of the article is recom-mended, and the material must be captioned at the foot of the text, below the reference list. Supporting infor-mation will be published as submitted and will not be corrected or checked for scientific content, typographi-cal errors or functionality. Although hosted on Wiley Online Library, the responsibility for scientific accu-racy and file functionality remains entirely with the authors. A disclaimer will be displayed to this effect with any supporting information published.

Supporting Information files should be accompanied by detailed information (if relevant) about what they are and how they were created (e.g., a native data-set from a specific piece of apparatus). Acceptable formats for supporting information include:

General – Standard MS Office format (Word, Excel, PowerPoint, Project, Access, etc.); PDF

Graphics – GIF; TIF (or TIFF); EPS; PNG; JPG (or JPEG); BMP; PS (postscript); embedded graphics (e.g. a GIF pasted into a Word file) are also acceptable.

Video–QuickTime; MPEG; AVI. All video clips must be created with commonly-used codecs, and the codec used should be noted in the supplementary material leg-end. Video files should be tested for playback before submission, preferably on computers not used for its creation, to check for any compatibility issues. Video clips are likely to be large; try to limit their size to less than 10 MB.

c. Gray Matters

‰ **Title**

Letters, workshop reports, etc. should be given a brief title. Letters should start with the opening *To the Editors:*

‰ **Authors and affiliations**

Provide authors' names (first and last names, middle initial when commonly used by that author); institu-tional affiliation for each author (use superscripted numbers after each author's name, and a corresponding superscripted number for each institutional affiliation); e-mail contact address for the corresponding author.

‰ **Body of submission**

Letters and commentaries should be restricted to 500 words or less, unless otherwise allowed by the Editors. Figures and tables will be included only in exceptional cases. Gray Matters will not be used to publish case reports. Tables, figures, figure legends, references, acknowledgements, disclosure of conflicts of inter-est, and Supporting Information – as for *Full Length Original Research* (see above).

(3) Details of Preparation

Detailed instructions for all aspects of electronic man-uscript submission (including useful information on image files) is available on the *Epilepsia* Scholar One Manuscripts website (http://mc.manuscriptcentral.com/Epilepsia); please click 'Get Help Now' at the top right-hand corner of the homepage; then click on the link 'Author and Reviewer Guides'.

a. Text

Manuscripts should be prepared using a word process-ing program. Save text and tables as a Microsoft Word document. Place the lead author's name and the page number in the upper right hand corner of each page. Begin numbering with the Title Page as #1, and number pages consecutively including references, figure legends, and tables. Text (including acknowl-edgements, disclosure statement, and figure legends) and references should be double-spaced, and be com-posed in 12 point font (preferably Times New Ro-man). When generating a revised manuscript, identify the altered portions of the manuscript with highlighted text, underlined, colored or bold font to indicate where changes to the original version of the text have been made.

b. Tables, Figures, and Supporting Information

See above.

MANUSCRIPT SUBMISSION

(1) Online submission via Manuscript

Central Manuscripts should be submitted via the Jour-nal's website on Scholar One Manuscripts at http://mc.manuscriptcentral.com/Epilepsia. Instructions at the site will guide the author through the submission process. Separate files should be submitted for: Cover letter to editors, manuscript text, tables, each figure, supplemental material, permissions to use previously-published material, patient consent declaration.

(2) Cover letter

All manuscripts should be submitted with a cover let-ter, addressed to the Editors-in-Chief, which explains why the manuscript should be published in *Epilepsia*. In particular, authors should identify novel findings, innovative approaches, and important insights that would make the manuscript of particular value to the broad readership of *Epilepsia*.

(3) Text, table and figure files

All files should be given a label that includes the first author's last name and the nature of the file (e.g., Smith-manuscripttext.doc; Smith-Fig1.tif).

(4) Other materials/forms

At the time of submission, all other materials (e.g., per-mission forms, supplemental material, patient consent) must be uploaded onto Manuscript Central, faxed to the editorial office (Fax: +1-702-548-0706) or emailed to epilepsia@epilepsia.com.

(5) Questions/Contacts

Questions and request for assistance should be ad-dressed to the Journal at epilepsia@epilepsia.com. The Managing Editor, Ms. Laurie Beninsig will in most cases be able to provide direction, or will contact the Editors-in-Chief for further assistance.

MANUSCRIPT PUBLICATION

(1) Once accepted for publication, authors are required to provide a portrait color photograph of the first au-thor (1.25 inches × 1.25 inches, 300 dpi light colored background) along with a one sentence line describing who they are (limited to 100 characters with spaces) to be included in the title page, findings presented as a

figure for presentation on the ILAE website and to be used in promotion of the article.

(2) The Editors may approach authors to provide one or two of their figures as possible cover material for the printed journal. These figures will need to be large enough and with the appropriate dpi.

(3) Online tracking of your article

Online production tracking of your article is available through Blackwell's Author Services. Author Services enables authors to track their article – once it has been accepted – through the production process to publica-tion online and in print. Authors can check the status of their articles online and choose to receive auto-mated e-mails at key stages of production. The cor-responding author will receive an e-mail with a unique link that enables him/her to register and have the ar-ticle automatically added to the system. To facilitate this service, please ensure that you provide a complete e-mail address when submitting the manuscript. Visit http://authorservices.wiley.com/bauthor/ for more de-tails on online production tracking and for other pub-lication resources (including FAQs and tips on article preparation, submission and more).

(4) Proofs

Proofs are sent electronically in PDF format, and must be returned within 48 hours of receipt. ***Late returns of proofs will cause substantial delay in article publica-tion. It is the corresponding author's responsibility to see that the proof is accurately checked and cor-rected, and to return the proofs promptly to avoid publication delays.*** Please check the spelling of coauthors' names, text, tables, legends, and references carefully. It is the authors' responsibility to make sure that the information is accurate. Indicate corrections either using the PDF editor function or with clear hard-copy indications which should be faxed to +1508-586-4024. The proof corrections stage is not the time for fine-tuning language or making any other substantive changes. Confine corrections to errors in printing; authors may be charged for major author-initiated changes.

(5) Early View

The publication-ready PDF of an article will be published initially online. Early View publication will precede print publication by a variable time period. The online publication date will be considered the official publication date. Early View published material will be indexed by PubMed, and can be cited by DOI number. In general, manuscripts will be published on Early View within 35 working days of the publisher's receipt of the complete accepted manuscript (including CAF and permission forms).

(6) Print issue publication

Publication of an article in a print issue will typically occur after Early View publication. Print issue articles carry their electronic publication date.

(7) Public access of accepted/published articles

Prior to acceptance, articles may be shared (print or electronic copies) with colleagues; at this time the article may be posted on the author's personal website, on his/her employer's website, and/or on free public servers in the author's subject area – with the acknowl-edgement that the article has been submitted to *Epilepsia*. After an article has been accepted, authors may share print or electronic copies of the article (accepted and revised to address peer review) with col-leagues, and may use the material in personal compilations, other publications of his/her own work, and for educational/research purposes. Articles published in *Epilepsia* are freely accessible to the public via the Wiley Online Library website – one year after publication. *Epilepsia* will automatically upload NIH-supported studies to PubMed Central after a 12 month moratorium (provided the appropriate funding acknowledgement has been provided). Similarly, at this time authors may post an electronic version of the article on their own personal websites, on their employer's website/repository, and on free public servers in the relevant subject area. Electronic versions of the accepted (or published) article must include a link to the published version of the article, together with the following text: "The definitive version is available at http://www3.interscience.wiley.com/journal/117957420/home." Authors can also choose to make their articles open access and available free for all readers through the payment of an author fee. This facility allows authors to fulfill the requirements for studies supported by agencies requiring open access before 12 months for full details visit http://authorservices.wiley.com/bauthor/onlineopen.asp

(8) Reprints

An order form for reprints will be included with the electronic transmission of initial proofs. For pricing of quantities in excess of 500 copies, please contact Brooke Maynard at Wiley-Blackwell Publishing (bmaynard@wiley.com).

SUPPLEMENT PUBLICATION

(1) Policy

A decision to publish a supplement is based on the topic, Guest Editor, proposed table of contents and contributing authors, and availability of necessary

funding. Supplement topics must be of importance to *Epilepsia* readers, and supplements will be published only if there is scientific or educational rationale for combining papers on a given theme within one publi-cation. The number and quality of the articles must be sufficient to constitute a body of important informa-tion. Each supplement will have a Guest Editor who is an expert on the theme of the supplement. The Guest Editor is responsible for compiling articles and assist-ing with the editorial process, and is responsible for the overall quality and integrity of the supplement. The publication of a supplement usually incurs charg-es, payable to Wiley-Blackwell Publishing.

(2) Publishing guidelines

Articles in a supplement are subject to the same copy-right regulations and ethical publishing guidelines that apply to articles published in regular issues of *Epilep-sia*. All supplement articles are peer-reviewed; the first level of review is carried out by the Guest Editor and his/her designates, and the second level of review is overseen by the Editors-in-Chief.

(3) Online-only and print supplements

Abstract supplements, from meetings or congresses sponsored by the ILAE or its chapters, will generally be published online only. Longer articles will be published in print supplements (these articles will also appear on-line). Print supplements may be generated from pro-ceedings of symposia organized by an independent body of professionals in which the funding organization does not have a controlling voice on scientific content. The Guest Editor and/or organizers of such symposia should be members of ILAE chapters. Supplements from other sources including invited supplements initiated by the Editors-in-Chief will also are considered.

(4) Supplement content

The content of supplements must not be biased in the interest of any sponsor. *Epilepsia* does not per-mit presentations that extol a commercial product, and supplements should not be perceived as endors-ing a particular product. Publication of supplements does not constitute product or sponsor endorsement by *Epilepsia* or ILAE. In most cases, supplements should not focus on a single product; however, when a new product is introduced, a single product focus will be considered by the Editors-in-Chief. In all cases, the content of a supplement must be determined by a body of professionals working independently of the spon-sor. The Guest Editor is charged with assuring that the material presented in the supplement is not biased toward the interests of the product manufacturer.

(5) Supplement sponsorship

Most supplements require external sponsorship. When a supplement proposal is presented to the Editors-in-Chief, they will fix appropriate fees. Supplement costs may be negotiated with the Editors-in-Chief and the publisher's supplement representative. The Editors-in-Chief may choose to publish a supplement of particular academic and clinical value without external sponsorship.

(6) Instructions for submitting supplements

Agreement to publish a supplement must be obtained from the Editors-in-Chief prior to submission. Pro-posals for supplements should be submitted to the Editors-in-Chief (epilepsia@epilepsia.com) well in ad-vance of desired publication date, so that the proposal can be evaluated and discussed. Timing is especially critical if the supplement is linked to a symposium or congress, since rapid publication is often important to assure that the information is current. The proposals should identify the Guest Editor and, include a list of topics and potential authors. The proposal should in-clude an estimate of supplement length so that the Edi-tors-in-Chief can provide reasonable information about the cost of publication. The cost of any supplement, and related financial issues, should be discussed with Chris Breslin at Wiley-Blackwell Publishing (cbreslin@ wiley.com). Collection of manuscripts, as well as ini-tial editing and reviewing should be carried out by the Guest Editor on a schedule predetermined in discussion with the Editors-in-Chief. The Guest Editor is responsi-ble for timely submission of articles, and should expect to assist the Editors-in-Chief in collecting final revised manuscripts (including any required permissions).

(7) Format of supplement articles

In general, articles should follow the format described above for Critical Reviews (in regular issues of the Journal). Contact the Editors-in-Chief for additional information and special instructions.

Epilepsia's POSITION ON ISSUES INVOLVED IN ETHICAL PUBLICATION

(1) Authorship/Credit

Epilepsia follows the guidelines of the International Committee of Medical Journal Editors regarding criteria for authorship (http://www.icmje.org/). The author list should include those who have made substantial intellectual/conceptual contributions to the work. Such contributions should include participation in: (a) experimental design, data acquisition, and analysis and interpretation of data;

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Epilepsia's POSITION ON ISSUES INVOLVED IN ETHICAL PUBLICATION (CONT.)

(b) drafting and/or critically revising the article with respect to intellectual content; and (c) final approval of the manuscript version to be published. We strongly discourage the inclusion of "honorary" authors (individuals who are listed as authors but have not contributed to the work/manuscript – e.g., heads of departments) and "ghost" authorship (individuals who have substantively contributed to the work and/or manuscript but are not listed as authors or contributors). In cases where writing support is necessary, the writer(s) should be acknowledged in the Acknowledgements section, and the source of funding for writing support should be provided under Disclosure of Conflicts of Interest. The corresponding/submitting author must, when submitting a manuscript, give assur-ance that all authors have read and approved the submitted manuscript. The corresponding/submit-ting author should also give assurance that all authors have seen and approved the final (accepted) manuscript, and that the manuscript includes all conflict of interest declarations. All individuals who have contributed to the work but do not meet criteria for authorship should be cited in the Acknowledgement section.

(2) Funding

Sources of funding (for the research, data analy-sis, and manuscript generation) should always be disclosed in the Acknowledgements section. Sources may include government funding agencies, institutions and departments, private industry, and charitable organizations and foundations. Funding for all authors should be acknowledged.

(3) Procedures involving Human and Animal Subjects

The authors should include within the manuscript an explicit statement indicating that the submit-ted study was approved by the relevant research ethics committee or institutional review board (IRB).When the study involves human partici-pants (including material from human subjects), authors should also provide assurance that appro-priate consent was obtained. When studies involve animal subjects, authors should provide methodo-logical details about steps taken to minimize pain/ discomfort. Such papers must contain a statement that affirms that the experimental protocols were approved by the institutional animal care and use committee (IACUC).

(4) Confidentiality

In all cases, information and images derived from individual patients must be presented with assurance of appropriate consent and with details removed that might reveal identity of the individual.

(5) Disclosure

All authors are required to disclose associations which might affect their ability to present and/ or interpret data objectively, particularly financial ties to funding sources for the work under review (e.g., membership on corporate scientific boards, stock ownership, consultant arrangements, patent ownership or application, etc.). Disclosure of such associations for the Editorial personnel of *Epilepsia* (Editors-in-Chief, Associate Editors, Editorial Board members) will be published each year. Reviewers will also be asked to affirm that they have no conflict of interest when critiquing a manuscript.

(6) Research Misconduct (Data Fabrication/ Falsification)

Epilepsia will attempt to ensure that any allegations of misconduct are properly investigated. In the case of any allegations, authors will be given a right to respond. While the Journal is limited in its ability to investigate misconduct, we will seek COPE's advice and alert appropriate bodies and encourage them to investigate.

(7) Plagiarism, Duplication, and Redundant Publication

Epilepsia requires that work submitted for publication is the authors' own work and has not been misappropriated. When previously published material is used, appropriate credit must be given and written permission obtained (for use of copyrighted material). *Epilepsia* also explicitly discourages duplication of published material and redundant publication.

(8) Corrections of Erroneous Information

Authors are expected to proof-read their articles carefully before returning page proofs for publication. They should make needed corrections at this time. We recognize that it is only human to err occasionally, and the Journal is committed to correcting mistakes when those errors affect the interpretation of data or information presented in an article.
(Continued on next page)

Epilepsia's POSITION ON ISSUES INVOLVED IN ETHICAL PUBLICATION (CONT.)

Such corrections will be published in the form of an Erratum, and linked to the original article electronically. Errors that result from author oversight in the proofing process, and that do not affect data interpretation, will not be corrected.

(9) Peer Review

Epilepsia is committed to a peer-review system that is fair to the author and enhances the value of the articles published in the Journal. In order to encour-age qualified reviewers too offer their time and efforts to the Journal, reviewer identity is kept confidential. Reviewers are chosen for their expertise in the field; conflicts of interest are avoided whenever the Editors are aware of such issues, and reviewers are asked to affirm that they have no conflicts of interest in reviewing a given *Epilepsia* manuscript. Authors are encouraged to identify specific individuals who, they believe, cannot provide unbiased review. While the Editors-in-Chief reserve the right to make the final decision to accept or reject an article, appeals will be seriously considered. Address appeals to the Editors-in-Chief, who will examine the reviews and the author responses, consult the relevant Associate Editor, and seek additional reviewer input if deemed necessary.

Appendix B:

Search strategy used in Ovid for Embase, MEDLINE and PsycINFO databases

#	Query
1.	epilepsy.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
2.	child.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
3.	p*ediatric.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
4.	adolescent.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
5.	attention.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
6.	working memory.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
7.	executive function*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
8.	inhibit*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
9.	disinhibition.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
10.	neuropsychol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
11.	cogni*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
12.	flexibility.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
13.	regulat*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
14.	impulsiv*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
15.	switching.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
16.	fluency.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
17.	shifting.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
18.	functional imaging.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
19.	functional magnetic resonance imaging.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
20.	electroencephalogram.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
21.	magnetoencephalogram.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
22.	positron emission tomography.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
23.	connectivity.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn,

	dm, dv, dq]
24.	resting-state network*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf, tn, dm, dv, dq]
25.	2 or 3 or 4
26.	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
27.	18 or 19 or 20 or 21 or 22 or 23 or 24
28.	1 and 25 and 26 and 27

Appendix C:

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

(National Institutes of Health, 2014)

Criteria	**Judgement (Yes / No / CD, cannot determine; NA, not applicable; NR, not reported)**
1. Was the research question or objective in this paper clearly stated?	
2. Was the study population clearly specified and defined?	
3. Was the participation rate of eligible persons at least 50%?	
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	
5. Was a sample size justification, power description, or variance and effect estimates provided?	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
10. Was the exposure(s) assessed more than once over time?	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	
12. Were the outcome assessors blinded to the exposure status of participants?	
13. Was loss to follow-up after baseline 20% or less?	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	

*CD, cannot determine; NA, not applicable; NR, not reported

Appendix D:

Adapted Study Quality Assessment Tool

Criteria	Judgement
Research Question (2/2=good; 1/2=fair; 0/2=poor)	
1. Was the research question or objective in this paper clearly stated?	2 – clearly stated 1 – partially stated 0 – cannot determine; not applicable; not reported
Selection (4-5/5=good; 3/5=fair; 0-2/5=poor)	
2. Was the study population clearly specified and defined?	2 – clearly defined 1 – partially defined 0 – cannot determine; not applicable; not reported
3. Was the participation rate of eligible persons at least 50%?	1 – yes 0 – no; cannot determine; not applicable; not reported
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	1 – yes 0 – no, cannot determine; not applicable; not reported
5. Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	1 – yes 0 – no, cannot determine; not applicable; not reported
Design (3/3=good; 2/3=fair; 0-1/3=poor)	
6. Was a sample size justification, power description, or variance and effect estimates provided?	1 – yes 0 – no; cannot determine; not applicable; not reported
7. Was the participant's age appropriate at the time of assessment so that one could reasonably expect to see an association between epilepsy diagnosis and outcome if it existed?	1 – yes 0 – no; cannot determine; not applicable; not reported
8. Was epilepsy diagnosis clearly defined and implemented consistently across all study participants?	1 – yes 0 – no; cannot determine; not applicable; not reported
Outcome (5-6/6=good; 3-4/6=fair; 0-2/6=poor)	
9. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1 – yes 0 – no, cannot determine; not applicable; not reported
10. Was loss to follow-up after baseline 20% or less?	1 – yes 0 – no; cannot determine; not applicable; not reported
11. Were key potential confounding variables controlled for? (confounding variables: age, gender, race, age of onset, epilepsy type, severity of seizures, socioeconomic status, parental IQ, mean number of antiepileptic	2 – 4+ confounding variables 1 – 2+ confounding variables (must include age and gender) 0 – cannot determine; not applicable; not reported, did not

medications)	include age and gender
12. Were the results of all analyses reported on?	2 – yes 1 – minor omissions 0 – major omissions, cannot determine; not applicable

Appendix E:

Ethical approval provided by Manchester University NHS Foundation Trust and Alder Hey Children's NHS Foundation Trust

Northern Children's Epilepsy Surgery Service (NORCESS)
c/o Ann Prior, Department of Radiology
Royal Manchester Children's Hospital
Oxford Road
Manchester
M13 9WL

2nd March 2023

Dear Daniel Reed and Robyn Smith,

Re: Northern Children's Epilepsy Surgery Service (NORCESS) Research Database

I am writing as the Clinical Lead for NORCESS to thank you both for your time and hard work on bringing the neuropsychological aspects of this initiative together.

Now the database is complete we reviewed the included data at the annual NORCESS clinical meeting and I am very happy to inform you that both the process and the extend of data included, was thought appropriate by all stakeholders. We are therefore happy for you to include this data in your respective thesis submissions.

The use of this routinely collected clinical data is approved by the R&D office of **Manchester University NHS Foundation Trust** (ref: Surgery_NORCESS_SE_1) and that of **Alder Hey Children's NHS Foundation Trust** (ref: 6820). This approval includes the submission of your thesis and also in regards to peer reviewed publications of the data.

Please ensure to acknowledge the NORCESS clinical pathway and NHS Teams in your write up. I would also ask that you also liaise with me prior to any scientific publication, to ensure the correct team members are recognised for their contribution to this work. Of course in addition, if you require any help in regards to scientific writeup or manuscript proofing etc. I would be very happy to help.

Finally I very much look forwards to hearing your presentations at the NORCESS Away Day in June.

Prof Stavros Stivaros
Professor of Paediatric Neuroradiology

Clinical Director for NORCESS, Royal Manchester Children's Hospital.

Director of Imaging, Division of Informatics, University of Manchester.

Appendix F:

Demographic and clinical variables for all identified patients

	N	Mean	SD
Total participants	284	-	-
Sex:			
female	123 (43.3%)	-	-
male	161 (56.7%)	-	-
Age (years/range)	-	11.03	3.24
Handedness:			
right	200 (70.4%)	-	-
left	59 (20.8%)	-	-
ambidextrous	5 (1.8%)	-	-
not known	20 (7.0%)	-	-
Age at epilepsy onset (years)	-	5.29	3.98
Duration of epilepsy (years)	-	7.66	11.79
Seizure frequency:			
At least daily	119 (41.9%)	-	-
weekly	63 (22.2%)	-	-
monthly	41 (14.4%)	-	-
less than yearly	26 (9.2%)	-	-
not known	35 (12.3%)	-	-
Antiseizure medication:			
no medication	8 (2.8%%)	-	-
monotherapy	101 (35.6%)	-	-
polytherapy	175 (61.6%)	-	-
Epilepsy Localisation:			
Frontal	71 (25%)	-	-
Parietal	14 (4.9%)	-	-
Temporal	108 (38%)	-	-
Occipital	15 (5.3%)	-	-
Multi-lobar	22 (7.7%)	-	-
Uncertain	54 (19%)	-	-
Epilepsy lateralisation:			
right	92 (32.4%)		
left	132 (46.5%)		
bilateral	19 (6.7 %)		
uncertain	41 (14.4%)		

Appendix G:

Approval for involvement with routinely collected data provided by Manchester and Salford CAMHS Clinical Service Unit

NHS
Manchester University
NHS Foundation Trust

Royal Manchester Children's Hospital
Harrington Building
Oxford Road
Manchester
M13 9WL

7/5/2021

Private & Confidential

To whom it may concern

Dear Sirs,

- Re: Daniel Reed – Trainee Clinical Psychologist, Paediatric epilepsy surgery: comparing executive functioning outcomes in fronto-parietal and temporo-insular epilepsy
- Robyn Smith - Trainee Clinical Psychologist, Long term neuropsychological outcomes of memory functioning following paediatric epilepsy surgery

I am the Director for CAMHS at Manchester Foundation NHS trust. I am aware of these forthcoming research projects and am happy to approve access to participant data and for the trainee's involvement in the collection of routine clinical data required for their respective research projects. I understand the projects will have full University and Trust ethical approval.

Yours faithfully

Director, CAMHS CSU