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Is an earlier onset of focal epilepsy associated with atypical language lateralization? A systematic review, meta-analysis and new data

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ABSTRACT

Right and bilateral language representation is common in focal epilepsy, possibly reflecting the influence of epileptogenic lesions and/or seizure activity in the left hemisphere. Atypical language lateralization is assumed to be more likely in cases of early seizure onset, due to greater language plasticity in childhood. However, evidence for this association is mixed, with most research based on small samples and heterogenous cohorts. In this preregistered meta-analysis we examined the association between age at seizure onset and fMRI-derived language lateralization in individuals with focal epilepsy. The pooled effect size demonstrated a correlation between an earlier onset and rightward language lateralization in the total sample ($r = 0.1$, $p = .005$, $k = 58$, $n = 1240$), with no difference in the correlation between age at seizure onset and language lateralization between left and right hemisphere epilepsy samples ($Q=62.03$, $p = .302$). In exploratory analyses of the individual participant data ($n = 1157$), we demonstrated strong evidence that a logarithmic model fits the data better than a linear ($BF=350$) or categorical model with 6 years of age as a cut-off ($BF=36$). These findings indicate that there is a small but significant relationship between age at seizure onset and language lateralization. The relationship was consistent with theories of language plasticity proposing an exponential decline in plasticity over early childhood. However, given that this effect was subtle and only found in larger sample sizes, an early age at seizure onset would not serve as a good indicator of atypical language lateralization on the individual patient level.

1. Introduction

Most of the general adult population is left lateralized for language (approximately 95 % of right-handers: Knecht et al., 2000; Springer et al., 1999; and 75 % of left-handers: Szaflarski et al., 2002), and left language lateralization is present from early childhood (Berl, Mayo, et al., 2014; Olulade et al., 2020). Children and adults with focal epilepsy, however, show higher rates of right and bilateral patterns of language representation compared to those seen in the general population (Berl, Zimmaro, et al., 2014; Rasmussen and Milner, 1977). This is presumed to reflect disruption of the typical trajectory of left language specialization or potential interhemispheric reorganisation of language networks from the left to the right hemisphere (as first suggested in early case series; Basser, 1962; Lenneberg, 1967; Rasmussen and Milner, 1977). Atypical language lateralization has been associated with disruption from epileptogenic lesions (Liégeois et al., 2004; Weber et al., 2006) and seizure activity (Berl et al., 2005; Branch et al., 1964; Janszky et al., 2006) in the left hemisphere.

Consistently, atypical language lateralization in focal epilepsy has also been associated with an earlier age at seizure onset in studies using

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both intracarotid amobarbital procedure (Brazdil et al., 2005) and functional magnetic resonance imaging (fMRI) (Anderson et al., 2006; Gaillard et al., 2007; Springer et al., 1999; Woermann et al., 2003). This association may be specific to those with epilepsy in the left hemisphere (Helmstaedter et al., 1997; Rey et al., 1988). Such findings fit with theories of language plasticity, which describe trajectories of increasing specialization and lateralization of language networks over childhood, accompanied by decreasing plasticity (Lenneberg, 1967; Newport et al., 2020; Olulade et al., 2020; Satz et al., 1990; Vargha-Khadem et al., 2000). Accordingly, reorganisation of language from the left to right hemisphere would be more likely when an insult is sustained at an early age and the likelihood would decrease over development

Based on early case series, Lenneberg (1967) suggested that there was a critical period for language plasticity between the ages of 2 and 14 years, and that injury after this period would be unlikely to result in atypical language lateralization. A critical or sensitive period for language reorganisation has remained a popular idea, with more recent studies in children with intractable epilepsy indicating that 6 years of age may be the potential 'boundary' before which plasticity is greater, and after which reorganisation is less likely (Saltzman-Benaiah et al., 2003). Complementary evidence comes from the stroke literature where studies have found that atypical language lateralization is associated with an earlier age at insult to the left hemisphere (Szaflarski et al., 2014). Right and bilateral language representation appear most common when the stroke occurs before the age of 2 years, or between 2 and 5 years, respectively (Lidzba et al., 2017). In contrast, others have suggested that instead of a sharp cut-off there is a gradual linear decline in the proportion of individuals with reorganisation as age at seizure onset increases (Helmstaedter et al., 1997; Springer et al., 1999), and therefore the relationship between age at seizure onset and language lateralization is linear.

Some studies have failed to identify a significant association between age at seizure onset and language lateralization (Janszky et al., 2003, 2006; Sveller et al., 2006; You et al., 2011). Inconsistent findings may partially be driven by methodological differences between studies. Language lateralization is influenced by both the language and baseline condition used (Bradshaw, Thompson et al., 2017; Seghier, 2008). For example, rest has been shown to be a poor baseline for language tasks due to the language activation which occurs at rest (Binder et al., 2008), resulting in less robustly lateralizing activation. In addition, the regions of interest (ROI) used for the calculation of laterality indices (LI) and how this interacts with the tasks used may also influence results. Crossed lateralization, where language functions supported by frontal and temporal regions are supported by the opposite hemispheres, is more common in epilepsy than in the general population (Berl, Zimmaro, et al., 2014). In addition, Duke et al. (2012) found that temporal lobe epilepsy was associated with atypical language lateralization in temporal but not frontal ROIs, perhaps suggesting that the former may be more predisposed to reorganisation. Therefore, whether age at seizure onset is associated with language lateralization may depend on whether lateralization is measured in frontal or temporal ROI.

Given the heterogeneity of the current literature, a meta-analysis is needed to address whether there is an association between age at seizure onset and language lateralization in focal epilepsy, and whether this relationship is linear or suggests a 'sensitive period' hypothesis. To disentangle the heterogenous populations and methodologies, we examined how this association varied based on the side (left vs. right) and location (frontal vs. temporal) of epilepsy pathology, and ROI chosen (frontal vs. temporal) for LI calculation.

2. Method

2.1. Preregistration

We conducted a systematic literature search following the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Page et al., 2021). The preregistration protocol was uploaded to the Open Science Framework on 19th May 2022 before data extraction began and can be found at this link: https://tinyurl.com/bdctb3t2. The preregistration outlines the search strategy, study selection, data extraction and data synthesis processes. The completed PRISMA checklists, summary statistics for each identified study and meta-analysis script can also be found at this link.

2.2. Search and screening

We searched Embase, MEDLINE and PsycInfo databases for studies that were available online before August 14th 2024[1] using the keywords, MeSH and Embase terms in Table 1. Keywords, MeSH and Embase terms within a concept were combined with 'OR' and the different concepts were combined using 'AND'. The search terms were the same as outlined in the preregistration but with the addition of MeSH and Embase terms and the term 'Magnetic Resonance Imaging'. We carried out an additional citation search by screening all articles which cited influential studies on the topics of LI methodology (Adcock et al., 2003; Baciu et al., 2005; Holland et al., 2001; Jansen et al., 2006; Liégeois et al., 2002; Nagata et al., 2001; Seghier, 2008; Wilke and Lidzba, 2007) and early fMRI language lateralization (Hertz-Pannier et al., 1997; Springer et al., 1999).

Two independent reviewers (F.P. and L.C.) examined the identified titles, abstracts and studies based on the exclusion criteria (see Table 2). Disagreement when screening was resolved through discussion with a third reviewer (T.B.). A total of 34 articles were included in the final meta-analysis. A flow chart showing how many studies were identified and excluded at each stage is shown in Fig. 1.

2.3. Exclusion criteria

The exclusion criteria can be found in Table 2. The exclusion differed from the preregistration in two ways. First, studies were excluded if the sample size was less than or equal to three, rather than less than or equal to two, as more than three participants are required to estimate the sampling variance of the effect size for each study. Secondly, the exclusion criteria of individuals being under 18 years of age at the time of seizure onset was removed. The later exclusion criterion was originally proposed because a linear relationship was not expected between age at onset and LIs in adulthood when plasticity would be greatly reduced compared to in (early) childhood. As this exclusion criterion substantially reduced the sample size and resulted in the exclusion of several articles, it was removed, and the meta-analysis was run on individuals with an age at onset in adulthood as well as childhood. We reran the meta-analyses with the original exclusion criterion of onset < 18 years of age and the results were broadly consistent with the results

Table 1
Keywords, MeSh and Embase terms used in literature search.

Concept	Keywords	MeSH or Embase terms
Epilepsy	epilep* OR epilepsy	Medline: Epilepsy Embase: Epilepsy
Language	language OR linguistic* OR verbal OR speech	Medline: Language Embase: Language
fMRI	magnetic resonance imaging OR functional magnetic resonance imaging OR functional MRI OR fMRI	Medline: Magnetic resonance imaging Embase: Functional magnetic resonance imaging

[1] The original search was conducted on May 19th 2022 and was topped up on August 14th 2024, when additional MeSH and Embase terms were added.

Table 2
Exclusion criteria for meta-analysis.

Exclusion criteria
Article type
• No presentation of new data
• Conference abstracts
• No English translation
Participant group
• No epilepsy
• Sample size of N $\leq$ 3
Methodology
• No language task-based fMRI
• Post-operative fMRI only
• No calculation of LIs

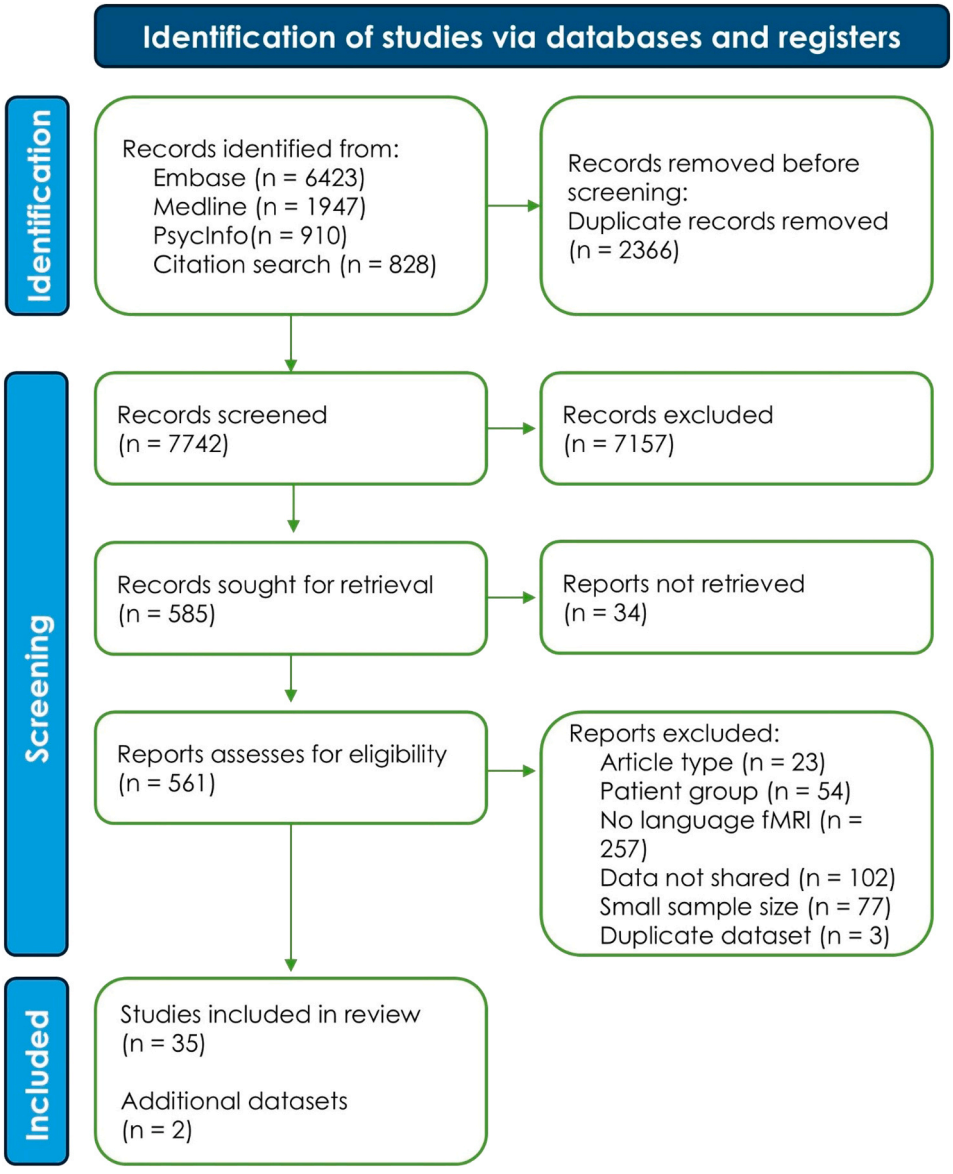

Fig. 1. Flow chart depicting the number of published reports identified by the database and citation searches and how many were excluded at each stage of the screening process.

without this exclusion criterion. This can be found in the Supplementary Materials.

2.4. Inclusion of additional samples

Retrospective data from two centers were added to the data collected as part of the meta-analysis. The addition of these two cohorts increased the sample size to 1254 participants (k = 37). 14 of these participants

were not included in the meta-analysis as they represented a sample size of 3 or less participants for the right-sided sample (Genetti et al., 2013; Herfurth et al., 2022; Hertz-Pannier et al., 1997; Koop et al., 2021; van der Kallen et al., 1998; Wilke et al., 2011). Consequently, the total sample size for meta-analysis was 1240.

2.4.1. Great Ormond Street Hospital

We included a retrospective cohort of 268 children who underwent language task-based fMRI as part of their presurgical evaluation at Great Ormond Street Hospital (GOSH) in London, UK. We screened all children who had language fMRI at GOSH from 2000 to 2022 (N = 350). Participants were excluded if fMRI was unavailable or poor quality or LI calculation failed (30), age at seizure onset was missing (16) or epilepsy was not lateralized (36). Due to the inclusion of this dataset, we excluded data from a previously published study that contained a partially overlapping sample (Pahs et al., 2013). Ethical approval was granted by the Great Ormond Street Hospital clinical audit department as a service evaluation (No. 1443, extended), according to the guidelines set by NHS Research Ethics Committee Review.

2.4.2. Children's National Hospital

We also included a retrospective cohort of 175 children who underwent language task-based fMRI as part of their presurgical evaluation or a research study at the Children's National Hospital (CNH) in Washington, DC, US, from 2003 to 2023. We screened 305 children who had fMRI at CNH. Participants were excluded if fMRI was unavailable or poor quality or LI calculation failed (75), age at seizure onset was missing (5) or epilepsy was not lateralized (50). Participants were part of clinical or research protocols with different aims related to pediatric epilepsy and language development, but all were approved by the Institutional Review Board at CNH. Parents provided informed written consent and all children gave assent to participate.

2.5. Data extraction

The data extracted for each included study are summarized in Table 3. Data were extracted from included studies by F.P. and checked by L.C. Where data were not available in the main manuscript or supplementary material, the data were requested from the corresponding author. Of the included articles, two reported correlation coefficients for the correlation between age at seizure onset and language lateralization, 27 reported individual participant data in the article or supplement, and for five article the individual participant data were shared by the authors. Table 3 outlines how data were extracted for each included study. Where individual participant data were available, participants were excluded from the total sample if (1) the side of epilepsy, age at seizure onset or LIs were unavailable, or (2) if they were part of another included sample. A list of how many individuals were removed from each study and the reason for exclusion is included in Table S1.

2.6. Measures

2.6.1. Laterality indices

We measured language lateralization using LIs calculated from task-based fMRI. We used continuous LIs as the outcome measure for all analyses.

2.6.1.1. Language and baseline conditions. Where studies reported LIs for multiple language tasks, we chose to use LIs calculated using tasks which most robustly activated frontal regions (e.g., verbal fluency). Language tasks used for the LIs selected included verbal fluency (phonemic and semantic fluency, verb generation), auditory description, semantic decision, passive listening and a conjunction of multiple tasks. There was also a range of baseline conditions including active (e.g., tone discrimination, line discrimination, reverse speech) and passive ones (e.g., rest, visual fixation, white noise). Given the effect of the choice of baseline on the robustness of language lateralisation we included an unplanned exploratory subgroup analysis we examined the effect of the baseline condition on the correlation between age at seizure onset and LI by comparing studies using active versus passive baselines. The language task and baseline condition for each study are reported in Table 3.

2.6.1.2. ROI. Where studies reported LIs for multiple ROI, we chose to use LIs calculated from frontal ROIs. Frontal ROI were the most consistently reported across included studies, and have shown to be reproducible (Harrington et al., 2006) and robustly lateralizing in healthy participants (Bradshaw, Bishop et al., 2017). 15 studies reported LI calculated in both frontal and temporal ROI and could be included in the multivariate meta-analysis to examine whether ROI moderated the relationship between age at seizure onset and LI. Of these studies, 13 reported temporal LIs for same task as frontal LI, and for two they only reported temporal LIs for an alternative language task. The ROI used for each study are reported in Table 3.

2.6.2. Age at seizure onset

Studies reported 'age at seizure onset' as the age at which habitual seizures occurred. Only two studies also reported an age at first seizure and nine reported age at precipitating injury, but often for a very small number of participants. This was insufficient for meta-analysis.

2.6.3. Lateralization and localization of epilepsy pathology

We coded the lateralization and localization of epilepsy as reported in the articles or shared by study authors. For the additional UK and US samples, the side of epilepsy was coded based on the structural abnormalities from the clinical MRI reports. For all those who went on to have surgery, the side of epilepsy was consistent with the side of surgery. For scans that were reported as "MRI negative", the side of epilepsy was based on the seizure focus as reported in the clinical electroencephalography reports. Individuals were excluded if no side of epilepsy was reported or if they had a bilateral epilepsy. For the subgroup analyses we coded whether the structural abnormality involved frontal or temporal lobes only.

2.7. Analysis strategy

2.7.1. Calculation of correlation coefficients

For most of the studies we calculated the correlation between age at seizure onset and language lateralization. We calculated Pearson correlation coefficients for the correlation between LI and age at seizure onset for all relevant groups (primary analysis: left hemisphere epilepsy, right hemisphere epilepsy; subgroup analysis: left frontal epilepsy, left temporal epilepsy, active baseline studies, passive baseline studies; multivariate analysis: frontal ROI; temporal ROI).

2.7.2. Meta-analyses

All meta-analyses were conducted using the *dmetar, meta* and *metafor* packages in R (Balduzzi et al., 2019; Harrer et al., 2021; Viechtbauer, 2010). A random-effects model with a Restricted Maximum Likelihood estimator (Viechtbauer, 2005), was used to account for expected heterogeneity in effect sizes (Field, 2001; Hunter and Schmidt, 2000). Between study heterogeneity was explored by examining Cochran's Q statistic (Cochran, 1950) and the I^2 statistic (Higgins and Thompson, 2002), with I^2 values of 25 %, 50 % and 75 % indicating low, moderate and high heterogeneity, respectively. Influence analysis using the leave-one-out method was used to explore the influence of individual studies on the pooled effect sizes and between studies heterogeneity (Viechtbauer and Cheung, 2010). Publication bias was explored by visual examination of contour-enhanced funnel plots and by assessing their asymmetry using Egger's tests. If publication bias was present, the Duval and Tweedie (2000) trim-and-fill method was applied to examine

Table 3
Characteristics of studies included in meta-analysis.

Study	Extraction	Participant characteristics	fMRI language task(s) and baseline condition	LI calculation method (voxel count vs magnitude, threshold)
Adcock et al. (2003)	Individual participant data from article	Left & right; TLE; mostly HS & tumors; adult sample with one pediatric case (age range: 15–54 y)	Phonemic fluency and a visual fixation baseline	Frontal ROI. Magnitude of activation in ROI
Appel et al. (2012)	Individual participant data from article	Left & right; TLE; mostly HS or MRI negative; adult sample (age range: 18–55 y)	Auditory description decision and a reverse speech baseline.	Frontal ROI. LI-toolbox: Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROIs
Arora et al. (2009)	Individual participant data from article	Left & right; mixed epilepsy locations; etiology not reported; adult and pediatric (age range: 12–51 y).	Semantic and phonemic fluency* , visual sentence comprehension, auditory sentence comprehension and a line orientation judgement baseline.	Whole brain ROI. Voxel count, threshold of $t = 2$ across ROI (chosen out of a range of thresholds as it demonstrated the greatest stability)
Audrain et al. (2018)	Individual participant data from author	Left only; TLE; etiology not specified; adult sample (age range: 23–58 y)	Conjunction of 4 language tasks (covert verb generation, sentence comprehension, category fluency, naming to description) and a visual fixation baseline.	Frontal ROI. LI-toolbox: Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROIs
Banjac et al. (2021)	Individual participant data from article	Left & right; TLE; etiology not specified; adult sample (age range: 19–54 y)	Sentence generation and a pseudoword listening baseline.	Frontal ROI. LI-toolbox: Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROIs
Banjac et al. (2022)	Individual participant data from article	Left only; TLE; etiology not specified; adult sample (age range: 23–58 y).	Sentence generation and a pseudoword listening baseline.	Frontal ROI. LI-toolbox: Voxel count/value mean LIs determined across different thresholds using bootstrapping methods in ROIs
Benjamin et al. (2017)	Individual participant data from article	Left & right; mostly TLE, 1 frontal and 1 fronto-temporal; mixed etiology; adult sample with one pediatric case (age range: 16–56 y).	Conjunction of 3 lexico-semantic tasks (object naming, word reading, naming to description) and a rest baseline.	Frontal + Temporal ROI. Voxel count, fixed threshold with a joint probability of $p < 0.001$ across ROI
Binder et al. (2010)	Individual participant data from article	Left only; TLE; etiology not specified; adult sample (age range: 21–69 y)	Semantic decision and a tone decision baseline	Frontal + temporal ROI. Voxel count, significantly activated voxels were defined as those with a task effect beta coefficient corresponding to $p < 0.001$ in ROIs
Brazdil et al. (2005)	Individual participant data from article	Left only; TLE; all HS; adult sample (age range: 19–53 y)	Phonemic fluency and a rest baseline.	Frontal ROI. Voxel count in ROI, threshold unreported
Cano-Lopez et al. (2018)	Individual participant data from author	Left & right; mostly TLE, also frontal, parietal and occipital; mixed etiology; adult sample (age range: 18–61 y)	Story comprehension and a reverse speech baseline.	Frontal + temporal ROI. LI-toolbox: Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROIs
Carpentier et al. (2001)	Individual participant data from article	Left only: mostly TLE, also frontal and temporoparietal; mixed etiology; adult sample (age range: 24–51 y)	Conjunction of tasks (syntactic and semantic judgements on auditorily and visually presentenced sentences) and tone or line baselines.	Frontal + temporal ROI. Voxel count, threshold of $t > 1.5$ in ROI
de Ribaupierre et al. (2012)	Individual participant data from article	Left only; TLE and FLE; mostly dysplasia; pediatric sample (age range: 7–15 y)	Sentence generation and a rest baseline.	Whole brain ROI. Count of voxels activated above $p < 0.05$ and $p < 0.01$ (FDR) in ROI
Everts et al. (2010)	Individual participant data from article	Left & right; frontal, temporal and other; mixed etiology; pediatric sample (age range: 7–17 y)	Phonemic fluency and a rest baseline.	Frontal ROI. LI-toolbox: Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROIs
Fernandes et al. (2006)	Individual participant data from article	Left & right; frontal, temporal and other; etiology not specified; pediatric sample (age range: 10–17 y)	Verb generation and a visual fixation baseline.	Frontal ROI. Count of voxels activated above 2.25 SD of the mean for each participant. LIs were then recomputed by using the average cross-correlation value of activated voxels (using the same 2.25 SD criteria) within the same ROI
Genetti et al. (2013)	Individual participant data from article	Left & right; mostly temporal; etiology not specified; adult and pediatric sample (age range: 11–48 y)	Auditory semantic decision task and a reverse speech baseline.	Frontal ROI. Count of voxels activated above $p < 0.05$ (FWE) in ROIs
Gross et al. (2022)	Individual participant data from author	Left TLE; mixed etiologies; adult sample (age range: 18–68 y)	Semantic decision and a tone decision baseline.	Frontal + temporal ROI. Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROIs
Herfurth et al. (2022)	Individual participant data from article	Left only; mostly temporal; mostly HS; adult sample (age range: 20–57 y)	Verb generation and a covert reading of nonsense syllable baseline.	Frontal ROI. Sum of threshold surviving t-values per left and right ROI.
Hertz-Pannier et al. (1997)	Individual participant data from article	Left & right; mostly TLE; etiology not specified; pediatric sample (age range: 8–17 y). 1 patient removed as side of epilepsy was not reported.	Phonological or semantic fluency and a rest baseline.	Frontal ROI. Count of voxels activated on a correlation coefficient map above the threshold of $r = 0.7$ in ROI
Koc et al. (2020)	Individual participant data from article	Left & right; mostly TLE; mostly HS; adult sample (age range: 18–49 y)	Verb generation and a rest baseline.	Frontal ROI. Count of voxels activated above $p < 0.05$ in ROI

(*continued on next page*)

Table 3 (*continued*)

Study	Extraction	Participant characteristics	fMRI language task(s) and baseline condition	LI calculation method (voxel count vs magnitude, threshold)
Kokkinos and Seimenis (2024)	Individual participant data from author	Left & right; TLE; some HS; adult and pediatric sample (age range: 11–52 y)	Sentence generation* and reading comprehension† and visual exploration baselines. Listening comprehension and a reverse speech baseline.	Frontal ROI. Count of voxels activated in the BOLD maximum (area of highest statistical change with effect) in ROIs.
Koop et al. (2021)	Individual participant data from article	Left only; location and etiology not specified; pediatric sample (range unknown, mean = 13 y)	Conjunction of different language tasks based on age, including: rhyming and a line orientation baseline, sentence completion and a gibberish speech baseline, auditory response naming and a reverse speech baseline, antonym generation and word generation with a visual fixation baseline.	Frontal + temporal ROI. Count of voxels activated above $p < 0.001$ in ROIs
Miro et al. (2014)	Correlation coefficient from article	Left only; TLE; all HS; adult sample (range unknown, LH group mean = 41 y, RH group mean = 45 y)	Passive sentence listening and a rest baseline.	Frontal + temporal ROI. Count of voxels activated above $p < 0.05$ (FDR) in ROI
Norrelgen et al. (2015)	Individual participant data from article	Left & right; TLE and some frontal and multifocal; mixed etiology; pediatric sample with two adults (age range: 8–18 y).	Verb generation* and a word repetition baseline. Story listening and a reverse speech baseline.	Frontal ROI. Count of voxels activated above $p < 0.001$ in ROIs
Okahara et al. (2024)	Individual participant data from article	Left & right; TLE; etiology not specified; mostly adult sample with 2 children (age range: 14–62 y)	Passive listening and a reverse speech baseline.	Temporal ROI. Count of voxels activated with an extent threshold of > 10 voxels.
Sabbah et al. (2003)	Individual participant data from article	Left & right: mostly TLE; mixed etiology; adult and pediatric sample (age range: 9–48 y)	Semantic fluency and a rest baseline.	Whole brain ROI. Count of voxels activated above $p < 0.0001$ in ROI
Stasenko et al. (2022)	Individual participant data from article	Left & right: TLE; mostly HS; adult sample (age range: 22–49 y)	Semantic judgement and presentation of alphabet-like stimuli as a baseline.	Frontal + temporal ROI. Count of voxels activated above $p < 0.01$ in ROI
Sveller et al. (2006)	Correlation coefficient from article	Left TLE; mixed etiology; adult sample (range unknown, mean = 32 y)	Verb generation and a visual fixation baseline.	Frontal + temporal ROI. Count of voxels activated above $p < 0.001$ in ROI
Szaflarski et al. (2008)	Individual participant data from article	Left & right; mostly TLE; mostly HS; adult sample with one child (age range: 17–53 y).	Verb generation* and a finger tapping baseline. Semantic decision and a tone decision baseline.	Frontal + temporal ROI. Count of voxels with z-scores ≥ 2.58 in ROI
Thivard et al. (2005)	Individual participant data from article	Left & right; TLE: mostly HS; adult sample (age range: 18–55 y)	Semantic fluency* and a rest baseline. Story listening and a reverse speech baseline.	Frontal ROI. Count of voxels activated above $p < 0.05$ (FWE) in ROIs
Tivarus et al. (2012)	Individual participant data from article	Left only; mostly TLE; mostly HS; adult sample (age range: 39–69 y)	Conjunction of four language tasks (verb generation and a visual fixation baseline, semantic decision and a tone decision baseline, definition naming and a synthetic sound judgement baseline, passive sentence reading and a presentation of a sentence made up of alphabet-like stimuli as a baseline)	Frontal + temporal ROI. Count of voxels with z-scores ≥ 2.3 in ROI
Trimmel et al. (2019)	Individual participant data from author	Left & right; TLE; etiology not specified; adult sample (age range: 19–58 y)	Phonemic fluency* and auditory naming† and a visual fixation baseline.	Frontal ROI. Count of voxels activated above $p < 0.05$ (FWE) in ROIs
van der Kallen et al., (1998)	Individual participant data from article	Left; mostly temporal; etiology not specified; adult sample (age range: 26–49 y)	Phonemic fluency and a rest baseline.	Whole brain ROI. Count of voxels activated above $p < 0.0001$ in ROI.
Voets et al. (2006)	Individual participant data from article	Left only; TLE; mostly HS; mostly adult sample (age range: 15–53 y)	Phonemic fluency and visual fixation baseline.	Frontal ROI. Activation change in voxels with maximum activation ROI
Wilke et al. (2011)	Individual participant data from author	Left & right; FLE and TLE; mixed etiology; pediatric sample with 2 adults (age range: 5–18 y)	Expressive letter task* and abstract image judgement baseline and receptive beep-stories task and tone listening baseline.	Frontal ROI. LI toolbox: Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROIs
Yuan et al. (2006)	Individual participant data from article	Left & right; mixed location and etiology, many MRI negative; pediatric sample with 2 adults (age range: 8–19 y).	Verb generation and a finger tapping baseline.	Frontal ROI. Count of voxels activated above threshold calculated from the mean value of the t-statistics for all voxels within ROI
CNH sample	Additional sample	Left & right; mixed location and etiology including MRI negative; mostly pediatric sample with 17 adults (age range: 5–23 y)	Auditory description decision and reverse speech/tone detection baseline.	Frontal ROI. LI-toolbox: Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROIs
GOSH sample	Additional sample	Left & right; mixed location and etiology; pediatric sample with 1 adult (age range: 4–19 y)	Verb generation and white noise baseline.	Frontal ROI. LI-toolbox: Voxel count/value, mean LIs determined across different thresholds using bootstrapping methods in ROI

fMRI = functional magnetic resonance imaging; FDR = false discovery rate; FWE = family wise error; CNH = Children's National Medical Centre; GOSH = Great Ormond Street Hospital; HS = hippocampal sclerosis; LI = laterality index; ROI = region of interest; TLE = temporal lobe epilepsy.

* Indicates the language task used if multiple were reported. † Indicates the language task used for the temporal LI if different from the task used for the frontal LI.

the pooled effect size after adjusting for publication bias. Studies were identified as outliers if there was no overlap between the 95 % confidence intervals of that study and the 95 % confidence intervals of the pooled effect size. The meta-analysis was rerun with these outliers removed

2.7.3. Unplanned exploratory analyses of individual participant data

Due to the unexpected volume of individual participant data available (n = 1157), additional exploratory analyses were conducted which were not reported in the preregistration. We used multilevel models to examine whether language lateralization was best predicted by a linear, logarithmic or categorical coding of age at seizure onset, with study included as a random effect. Due to the negative skew in the residuals of these models we performed an exponential transformation of the LI values to reduce the skew. All data visualization used untransformed LI values. For the logarithmic predictor model, we added a constant of one to the age at seizure onset and then performed a logarithmic transformation. For the categorical model, we coded age at seizure onset as 'early' (< 6 years) versus 'late' (≥ 6 years), given that 6 years of age has been suggested as a cut-off, after which language networks become more specialized and plasticity declines (Berl, Mayo, et al., 2014; Olulade et al., 2020; Saltzman-Benaiah et al., 2003). We compared the Akaike information criterion (AICs) and Bayes Factor (BF) of the three model and a baseline model with random effects only and ran chi-square tests, to choose the model with best fit. These analyses allowed us to more directly compare linear and sensitive period models of plasticity. We reran these analyses in an adult sample with an age at fMRI scan of 18 years and above, as children may still be undergoing developmental changes in their language lateralization. These results are reported in the Supplementary Material.

In addition, we reran these analyses in a sample with age at precipitating injury reported. Given, that the majority of the spread of age at precipitating injuries were before age 6 years (83 %), we limited this those with precipitating injuries before age 6 years. Consequently, we examined linear and logarithmic models but not a categorical one.

2.8. Quality of reporting

The quality of reporting for each study was assessed using a modified version of the 'Patients' section of the Evidence-Based Neuropsychology checklist (Hrabok et al., 2013) which can be found in Table 4. Studies were assessed based on four criteria which determined whether studies reported sufficient information on demographic and epilepsy-associated variables as well as inclusion/exclusion criteria and patient selection. Studies were given a 'yes' for each criterion if they reported the relevant information for each participant, 'partial' if they reported this information on a group-level only, or 'no' if they failed to report this information.

3. Results

3.1. Sample characteristics

The total sample included a similar number of adults (55 %) and children. Many language tasks were used, but the largest proportion of individuals had laterality indices reported for fluency tasks (including phonemic and semantic fluency, and verb generation; 54 %), auditory description tasks (17 %), semantic decision tasks (10 %) listening tasks (7 %) or a conjunction of multiple tasks (6 %), with all other tasks being used in less than 5 % of the sample each. Most individuals had a laterality index calculated in a frontal ROI (66 %), compared to temporal (2 %), frontotemporal (27 %) or whole brain ROI (5 %).

3.2. Primary meta-analysis on total sample

There was a correlation between an earlier age at seizure onset and greater atypical language lateralization across the total sample (r = 0.1, p = .005, k = 58, n = 1240). The between-study variance was estimated at tau^2= 0.0026 (95 % CI: 0–0.0596) with an I^2 value of 8.1 % (95 % CI: 0–33.7 %) and a non-significant Q statistic (Q=62.03, p = .302), indicating low heterogeneity in the sample. Influence analysis indicated that effect size was not substantially influenced by individual studies with pooled effect sizes ranging from 0.08 to 0.11, all of which indicated a significant effect. Egger's regression test for funnel plot asymmetry was non-significant (p = .109) indicating a lack of evidence of publication bias (see the contour-enhanced funnel plot in Supplementary Fig. 1). After the removal of three identified outliers (left hemisphere samples: Appel et al., 2012; Norrelgen et al., 2015; right hemisphere samples: Cano-Lopez et al., 2018), the correlation remained (r = 0.12, p < .001, k = 55, n = 1199).

3.3. Subgroup analysis 1: Left versus right hemisphere epilepsy

There was a correlation between earlier age at seizure onset and greater atypical language lateralization in the left (r = 0.1, p = .015, k = 37, n = 919) but not right hemisphere groups (r = 0.07, p = .319, k = 21, n = 321). There was no difference in the correlation between groups (Q=0.20, p = .656). The pooled effect size and correlation coefficients of the individual samples for the left and right hemisphere groups can be seen in Fig. 2. After the removal of the previously identified outliers, the correlation was significant in both the left (r = 0.12, p < .001, k = 35, n = 887) and right hemisphere groups (r = 0.12, p = .014, k = 20, n = 312) and there remained no difference in the correlation between groups (Q=0.00, p = 1).

3.4. Subgroup analysis 2: left frontal versus temporal epilepsy

There was no significant correlation between age at onset and language lateralization in the left frontal group (r = 0.12, p = .235, k = 6, n = 82) or left temporal epilepsy groups (r = 0.09, p = .123, k = 32, n = 535), and there was no significant difference between the two groups (Q=0.05, p = .820). After the removal of two outliers (temporal samples: Appel et al., 2012; GOSH), the results remained consistent (temporal: r = 0.09, p = .073, k = 30, n = 447; Q=0.09, p = .766).

3.5. Multivariate meta-analysis: comparison of frontal and temporal ROIs for LI calculation

The multivariate meta-analysis revealed no significant moderating effect of the ROI chosen for LI calculation (frontal vs temporal) on the correlation between age at onset and LI (QM=0.63, p = .730). There was no significant correlation between age at onset and LI when using a frontal (r = 0.07, p = .478, k = 15, n = 491) or temporal ROI (r = 0.05, p = .482, k = 15, n = 491).

Table 4
Quality of reporting criteria (adapted from Hrabok et al., 2013).

Criteria
1. Were patients described demographically (i.e., age & sex)?
2. Were the patients described clinically? (i.e., age at seizure onset, epilepsy pathology and location)
3. Were the inclusion/exclusion criteria specified?
4. Was patient selection specified (e.g., consecutive patients included)?

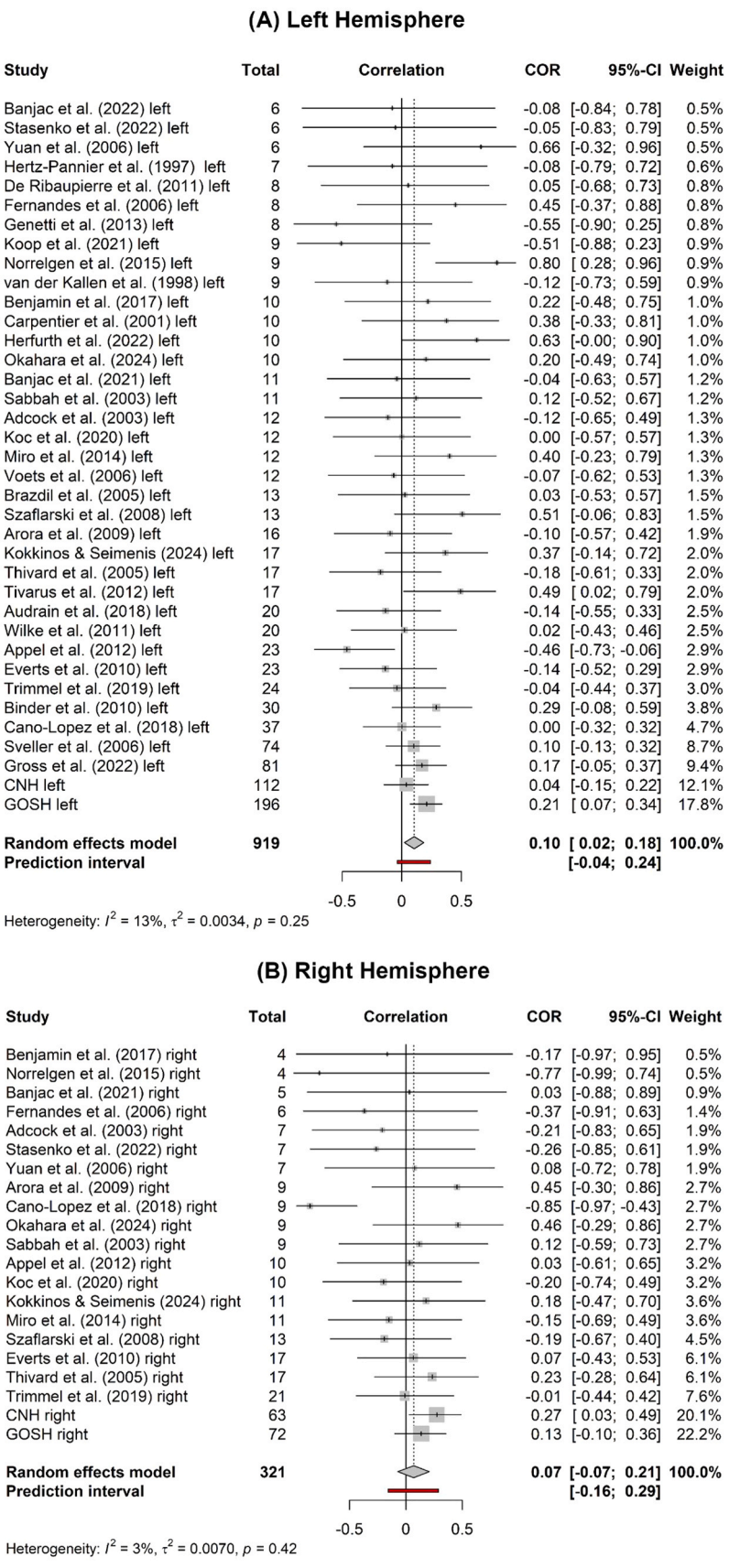

Fig. 2. Forest plots showing the individual effect sizes for each study and pooled effect size (dashed line) of the correlation between age at seizure onset and LI in the left (A) and right hemisphere (B) epilepsy groups.

3.6. Unplanned exploratory subgroup analysis: active versus passive baseline conditions

We excluded one study from this analysis which used a conjunction of language tasks with a mix of active and passive baseline conditions (Koop et al., 2021). There was a significant correlation between younger age at seizure onset and rightward LI in both studies using active ($r = 0.11$, $p = .028$, $k = 20$, $n = 619$) and passive baselines ($r = 0.13$, $p < .001$, $k = 17$, $n = 625$), and there was no significant difference between the two groups ($Q=0.07$, $p = .793$).

3.7. Comparison of linear, logarithmic and categorical models

Individual participant data were available for 1157 participants. Separate multilevel models were used to compare a linear, logarithmic and categorical coding of age at seizure onset in predicting language lateralization. Given that in our primary analyses, there was no differences in the correlation between age at seizure onset and language lateralization in left and right epilepsy groups, we included left and right hemisphere groups together in this analysis. All three models were significantly better at predicting language lateralization than a model containing only the random effects (AIC: 2306; all $p < .01$). The individual estimates for the onset predictors in each model can be seen in Table 5. The logarithmic model had the lowest AIC (2287), followed by the categorical (2294) and linear models (2299). There was strong evidence that the logarithmic model was a better fit than the linear model ($BF=350$) and categorical model ($BF=36$) and weak evidence that the categorical model was a better fit than the linear model ($BF=10$). The different models overlayed on the raw data can be seen in Fig. 3. We reran these analyses using an adult only sample and identified consistent results. These are presented in full in the Supplementary Material.

In addition, we also reran these analyses in a sample with an age at precipitating injury before the age of 6 years reported. Only a logarithmic model performed significantly better than a model containing only the random effects (AIC: 209 versus 211; all $p = .045$). The full results are presented in the Supplementary Material.

3.8. Quality of reporting

Each published study was assessed on four criteria adapted from the patient section of the Evidence-Based Neuropsychology checklist. The proportion of studies reporting relevant information for each criterion is demonstrated in Fig. 4.

4. Discussion

In our meta-analyses we demonstrated a small but significant correlation between an earlier age at seizure onset and greater atypical language lateralization. There was no difference in the correlation between left and right hemisphere epilepsy groups. This result was unexpected in the right hemisphere epilepsy group, given that the reorganization of language functions to the right hemisphere has often been associated with the presence of structural lesions or seizures in the left hemisphere only (Adcock et al., 2003; Berl et al., 2005; Carpentier et al., 2001; Liégeois et al., 2004). It is possible that an early onset of epilepsy in the left or right hemisphere may similarly disrupt typical trajectories of language lateralization, leading to atypical representation regardless of the side of epilepsy. This appears consistent with the contribution of the right hemisphere in early language development which has been demonstrated to decline over childhood, while left hemisphere involvement remains consistent (Olulade et al., 2020). Although early right hemisphere injury has been shown to cause delays in language development (Thal et al., 1991; Trauner et al., 2013), it is still unclear what effect, if any, such an injury has on the development of lateralized language networks.

Table 5
Individual coefficients for the fixed effects of each multilevel model.

Model	Variable	Estimate	t	p value
Linear				
	ASO	0.01	2.99	.003 * *
Logarithmic				
	Log(ASO)	0.11	4.57	< .001 * **
Categorical				
	Early ASO (< 6 years)	−0.15	−3.66	< .001 * **

ASO = age at seizure onset; *p < 0.05, * *p < .01, * **p < .001

4.1. Evidence for a nonlinear relationship

We found strong evidence that a logarithmic model fitted the data better than a linear model, indicating that there may be a greater likelihood of reorganisation at an earlier age, which rapidly reduces over early childhood before stabilizing. Presumable this would reflect an exponential decline in plasticity over the first several years of life, compared to a more gradual linear decline in later childhood. This provides some support for the sensitive period hypothesis. There still appears to be an effect of age at seizure onset on language lateralization after six years of age, although less strong that in early childhood. This suggests that there is not a definitive cut-off point for language reorganization, and that after six years of age there may still be a subtle influence of epileptic pathology/activity on language lateralization.

4.2. Subtle effect as opposed to robust clinical indicator

Regardless of how it was characterized, the relationship between age at seizure onset and language lateralization was subtle and diminished in sub-analyses with smaller sample sizes. This indicates that an earlier age at seizure onset, as a single predictor, may not be a good clinical marker of language lateralization at the individual patient level. There may be other factors which have a greater or combined influence on reorganization, such as the presence of early acquired injuries (Duchowny et al., 1996; Gaillard et al., 2007; Rathore et al., 2009). In patients where the onset of habitual seizures is preceded by an earlier developmental event such as an acquired brain injury, the age at habitual seizure onset may not accurately reflect the point of initial reorganization of language functions. Consequently, there could be a stronger relationship between language lateralization and the age at precipitating event or first seizure.

We aimed to address this by rerunning our analyses in a smaller sample of 105 individuals with a reported age at precipitating injury. A logarithmic transformation of age at precipitating injury was a significant predictor of language lateralization, as with age at seizure onset. However, there was only weak evidence that this model was better than the non-significant linear model. The association of language lateralization with age at precipitating injury may not have been as strong as that with age at seizure onset, due to the much smaller sample size and limited spread of age at precipitating injury (83 % under 6 years of age; 57 % under 2 years of age.) This is consistent with previous research suggests that both age at habitual seizures and precipitating events are associated with language lateralization (Rathore et al., 2009; Woermann et al., 2003), and in fact the former association may be stronger (Springer et al., 1999).

4.3. Limitations

Studies included in this meta-analysis used different language tasks and ROIs for the calculation of language lateralization, and this may explain some of the heterogeneity in effect sizes between studies. Where possible, we extracted LI for frontal ROI, however, a third of the sample included LIs from temporal, fronto-temporal, or whole brain ROI. Our multivariate meta-analysis indicated that ROI choice did not have a significant moderating effect on the correlation between age at seizure

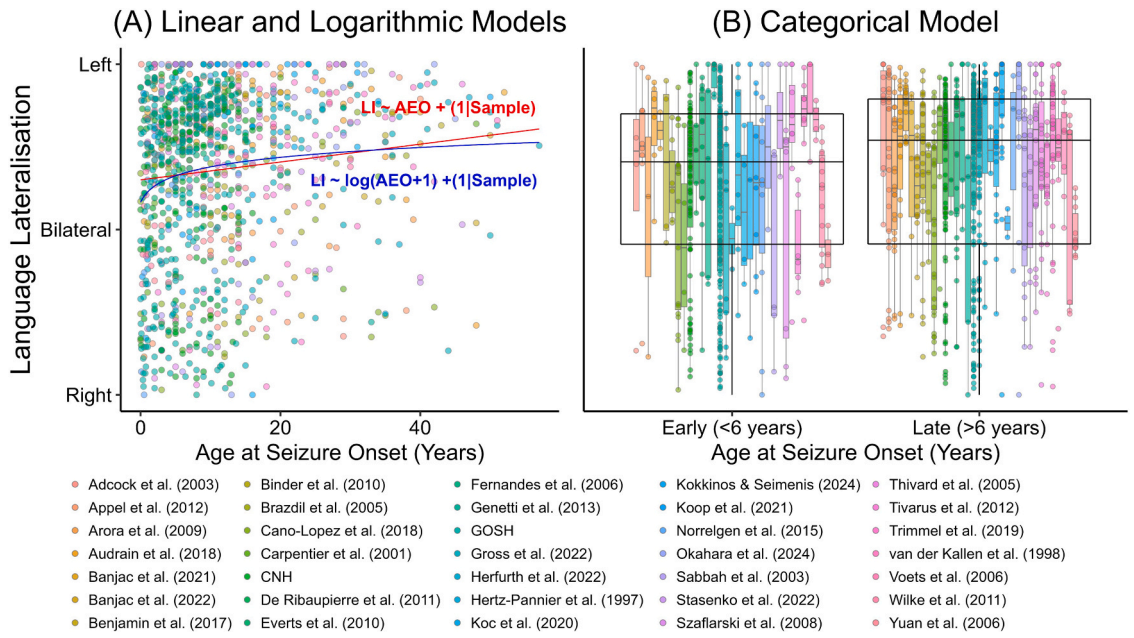

Fig. 3. Relationship between age at seizure onset and language lateralization as characterized by linear (red), logarithmic (blue) and categorical multilevel models.

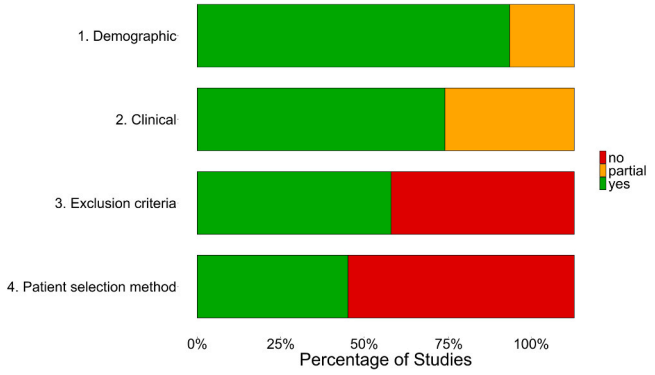

Fig. 4. Proportion of included studies reporting relevant patient and study characteristics.

onset and LI. This is perhaps unsurprising, given that most of the temporal LIs were calculated for the same tasks as frontal LIs were calculated for. It may be that temporal LIs calculated for different, and more traditionally receptive, tasks would differ from frontal LIs calculated using expressive tasks.

Given the many different language tasks included which all tap different combinations of language-specific and domain-general processes, it was difficult to systematically analyze whether the different correlation coefficients between studies. There were no clear systematic differences between studies which found a strong negative correlation and those with a positive correlation. Studies findings a negative correlation varied in task (e.g., verb comprehension, semantic decision, story comprehension) and ROI (frontal, frontotemporal). All used an active baseline condition, but the type of active baseline task itself also varied (reverse speech, word repetition, presentation of alphabet-like stimuli). We did examine the effect of using an active versus passive baseline condition. The correlation between age at seizure onset and language lateralization was similar in both groups, and both were significant. This was unexpected given that active and passive baseline have been shown to produce systematically differently lateralizing LIs (Binder et al., 2008). This may be due to the fact that within the two baseline groups there were many different combinations of language and baseline task used.

Our findings may have limited generalizability to other epilepsy samples. Studies included in our meta-analysis may be biased in their epilepsy sample, as many patients will have language fMRI as part of a presurgical evaluation for resective or disconnective surgery. It is likely that this surgical cohort would vary compared to a non-surgical focal epilepsy cohort, most obviously in terms of seizure burden, as these patients tend to have medication-resistant seizures. It is therefore possible that these findings do not generalize to samples with focal epilepsy which is well controlled by medication. As can be seen in Fig. 4, more than half of the included studies failed to report their exclusion criteria or patient selection procedures, which makes it difficult to determine what other biases might be present in these groups.

4.4. Future directions

A question remains as to whether the association between earlier age at seizure onset and atypical language lateralisation really reflects reorganization of language functions after an initial period of left language lateralisation or atypical development of language lateralization in the first instance. This speaks to the debate on whether left language lateralization is predetermined from birth. Lashley (1929), and later Lenneberg (1967), proposed that the two hemisphere are initially equipotential for language functions. Over childhood, language functions become progressively specialized to the left hemisphere as a consequence of language learning. Consequently, we might expect that an early seizure onset would result in atypical development, as opposed to reorganization. Proponents of the opposing early hemispheric specialization model argue that the left hemisphere is necessary and sufficient for the development of language functions from birth (Woods and Carey, 1979; Woods and Teuber, 1978; also referred to as 'irreversible determinism', Bates et al., 1999). If this is the case, atypical lateralisation is likely to reflect reorganization of functions regardless of the age at seizure onset.

To further examine this question, serial fMRI scans of children soon after seizure onset, and later follow-up, would be needed. This should involve not just comparison of LIs, but also of activation in both hemispheres, which has already been shown to elucidate trajectories of language development not apparent when using LIs only (Olulade et al., 2020). In addition, to examine this question across a wider

developmental sample will require the use of functional language mapping techniques more suitable for younger children, such as Optically Pumped Magnetometers – Magnetoencephalography (OPM-MEG).

4.5. Conclusions

In our meta-analysis we identified a small but significant correlation between age at seizure onset and language lateralization in a large focal epilepsy sample of 1254 individuals, regardless of the side of epilepsy pathology. This relationship was best characterized with a logarithmic curve, likely reflecting an exponential decline in plasticity over early childhood, but with no clear definitive cut-off for reorganization. Given that the effect of age at seizure onset on language lateralization was subtle and only present in large samples, an early age at seizure onset would not serve as a good indicator of atypical language lateralization on the individual patient level.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2025.106110.

Data availability

The summary statistics and meta-analyses script can be found on the Open Science Framework. Data sharing requests should be directed to the corresponding author of the original article.

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