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ORIGINAL ARTICLE

Early development and epilepsy in tuberous sclerosis complex: A prospective longitudinal study

Natasha Lindsay[1] | **Abigail Runicles**[1] | **Mark H. Johnson**[2,3] | **Emily J. H. Jones**[3] | **Patrick F. Bolton**[4] | **Tony Charman**[1] | **Charlotte Tye**[1]

[1]Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[2]Department of Psychology, University of Cambridge, Cambridge, UK

[3]Centre for Brain & Cognitive Development, Birkbeck, University of London, London, UK

[4]Department of Child & Adolescent Psychiatry, MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

Correspondence
Natasha Lindsay, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, Henry Wellcome Building, London, SE5 8AB, UK.
Email: natasha.lindsay@kcl.ac.uk

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Abstract

Aim: To characterize early changes in developmental ability, language, and adaptive behaviour in infants diagnosed with tuberous sclerosis complex (TSC), and determine whether clinical features of epilepsy influence this pathway.

Method: Prospective, longitudinal data were collected within the Early Development in Tuberous Sclerosis (EDiTS) Study to track development of infants with TSC ($n = 32$) and typically developing infants ($n = 33$) between 3 and 24 months of age. Questionnaire and observational measures were used at up to seven timepoints to assess infants' adaptive behaviour, developmental ability, language, and epilepsy.

Results: A significant group by age interaction effect showed that infants with TSC had lower adaptive functioning at 18 to 24 months old (intercept = 88.12, slope estimate = −0.82, $p < 0.001$) and lower developmental ability scores from 10 months old (intercept = 83.33, slope estimate = −1.44, $p < 0.001$) compared to typically developing infants. Early epilepsy severity was a significant predictor of these emerging developmental ($R^2 = 0.35$, $p = 0.004$, 95% confidence interval [CI] −0.08 to −0.01) and adaptive behaviour delays ($R^2 = 0.34$, $p = 0.004$, 95% CI −0.05 to −0.01]). Lower vocabulary production (intercept = −1.25, slope = −0.12, $p < 0.001$) and comprehension scores (intercept = 2.39, slope estimate = −0.05, $p < 0.001$) in infants with TSC at 24 months old were not associated with epilepsy severity.

Interpretation: Divergence of developmental ability and adaptive functioning skills occur in infants with TSC from 10 and 18 months, respectively. Associations between early epilepsy severity and impaired development supports the importance of early intervention to reduce seizure severity.

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder caused by a mutation in the *TSC1* or *TSC2* gene.[1] Overactivation of the mammalian target of rapamycin complex 1 results in irregular cellular growth and proliferation, causing benign tumours (hamartomas) in multiple organs. Diagnosis of TSC occurs increasingly prenatally and is associated with a highly variable phenotypic expression.[2] The term 'TSC-associated neuropsychiatric disorders' describes the range of cognitive, behavioural, psychiatric, and psychosocial manifestations in TSC, affecting up to 90% of individuals with the condition.[3] The neurological impact of TSC is also significant. Epilepsy is estimated to occur in 60% to 90% of individuals with TSC and is highly heterogenous.[4] Infantile spasms and focal seizures are among the most common seizure presentations in early childhood,[5] and are clinically important because of the comorbidity associated with the disorder, as well as its potential to predict lower developmental outcome.[6]

Abbreviations: ABC, adaptive behaviour composite; ELC, early learning composite; M-CDI, MacArthur–Bates Communicative Development Inventories; MSEL, Mullen Scales of Early Learning; TSC, tuberous sclerosis complex; VABS-II, Vineland Adaptive Behavior Scales, Second Edition.

#Members of the EDiTS Study Team are listed in the Acknowledgments.

Prospective studies of TSC provide a unique opportunity to identify behavioural and developmental mechanisms that underlie such variable outcomes before their manifestation.[7] However, many studies fail to employ systematic assessments of intellectual ability and behaviour throughout early development. Hence, questions remain regarding the characterization of early development in TSC and the contributory role of epilepsy.

Previously reported associations between atypical neurological features and development in TSC suggest shared mechanisms underlying epilepsy, cognitive ability, and behaviour. Reduced adaptive functioning in infant and child TSC cohorts[8,9] has previously been linked to poorer long-term outcomes.[10] A prospective longitudinal study of TSC also found that spasm severity in the first and second year of life was associated with reduced adaptive behaviour, highlighting the association between specific clinical features of epilepsy and behaviour.[11] Unlike this study, many others are limited by retrospective, inaccurate parent recall, and incompleteness of the data collected. Hence, gaps remain in our understanding of behavioural changes during infant years and the role of epilepsy in its presentation.

Cognitive impairment is estimated to affect up to 70% of individuals living with TSC, and has been linked to mutation type *TSC2*, infantile spasms, and earlier age at seizure onset.[12] Significant language and nonverbal cognitive delays have previously been identified in infants with TSC at 12 months old, and associated with an increased likelihood of receiving an autism diagnosis at 36 months.[13,14] Despite this, few studies have assessed language development prospectively in infants with TSC. A high number of seizures close to initial epilepsy diagnosis and uncontrolled seizures at follow-up are also potential indicators of cognitive impairment.[15] Early detection of epileptiform discharges have been associated with worse developmental outcome at 24 months old, including delayed cognitive skills.[16] This highlights the need to better understand the relationship between epilepsy and development in infants with TSC.

The present study aims to build upon existing knowledge of neurodevelopmental profiles in TSC, by (1) examining changes in adaptive behaviour, language, and development in the first 2 years of life to identify a diverging pathway between TSC and typically developing infants, and (2) assessing whether these differences are associated with clinical features of epilepsy.

What this paper adds

- Slower acquisition of developmental skills presents from 10 to 24 months in infants with tuberous sclerosis complex (TSC).
- Lower adaptive functioning is evident in infants with TSC from 18 to 24 months.
- Parent-reported vocabulary production and comprehension skills are impaired at 24 months.
- Broader observed developmental and language skills are affected within the first year in infants with TSC.
- Early increased seizure severity is associated with delayed adaptive functioning and developmental ability across the first 2 years of life.

METHOD

Design

Data were collected via the Early Development in Tuberous Sclerosis (EDiTS) Study which longitudinally tracked behavioural and neurocognitive development of infants and preschool children diagnosed with TSC. Families were enrolled to take part in a minimum of three consecutive assessments at ages 3, 5, 8, 10, 14, 18, and 24 months (referred to as 'age timepoints'). Entry into the study was possible from birth up to 14 months of age. The EDiTS Study protocol received approval from a medical ethics committee (London Camden and King's Cross NHS REC ref: 15/LO/1949). Written informed consent was obtained from parents/caregivers before assessments took place.

Protocol

Infants' development was assessed by completing a battery of neurocognitive and behavioural assessments in families' homes. A series of standardized online or paper parent-report questionnaires, interviews, and child observational measures of developmental ability, behaviour, language, and epilepsy were completed at various timepoints. All assessments were home-based, but infants with TSC were invited to the Centre for Brain and Cognitive Development Research Centre at 10 months and 14 months of age for additional optional assessments.

Participants

A total of 32 infants with TSC and 33 typically developing infants were recruited. All infants with TSC were screened for a definite or possible TSC diagnosis, or presenting with cortical tubers or cardiac rhabdomyoma at routine scans at the point of study entry. Criteria for TSC study participation included a confirmed diagnosis from the lead clinician, and in utero or aged between birth and 14 months old. Criteria for typically developing infants to take part included no first-degree relatives diagnosed with epilepsy, autism, and/or attention-deficit/hyperactivity disorder, and in utero or aged between birth and 14 months old. It was also a requirement that all infants hear English from at least one parent to ensure standardized measures were not invalidated.

Infants who met any of the following criteria based on parent-report interviews at screening were excluded: (1) significant uncorrected visual or hearing problems; (2) other

serious medical or developmental conditions (e.g. cerebral palsy); and (3) other genetic conditions, such as Down syndrome or Fragile X syndrome.

Measures

Demographic characteristics

Demographics data were collected via a bespoke parent-report questionnaire at study entry. The questionnaire included the Index of Multiple Deprivation[17] which measured relative poverty level based on families' postcodes. Decile 1 represents the 10% most deprived areas and decile 10 represents the 10% least deprived areas.

Adaptive behaviour assessment

The parent-report Vineland Adaptive Behavior Scale, Second Edition (VABS-II)[18] is a standardized caregiver interview administered by researchers during home visits at each timepoint. The scores generate an adaptive behaviour composite (ABC) score based on communication, daily living, and socialization skills.

Developmental ability assessment

The Mullen Scales of Early Learning (MSEL)[19] is a standardized observational measure of child development including language, motor, and visual reception skills. Raw scores were converted to early learning composite (ELC) scores and verbal/nonverbal developmental quotients. This measure was administered by assessors at each timepoint. The verbal developmental quotients include visual reception and fine motor subscales, and verbal developmental quotients include expressive and receptive language subscales, calculated as an average of the age equivalent, divided by chronological age multiplied by 100.

Language assessment

The MacArthur–Bates Communicative Development Inventories (M-CDI) Words and Gestures version[20] is a standardized parent-report tool used to assess infants' language production, comprehension, and gesture use at 10, 14, and 24 months of age. Language production and comprehension scores were collected as part of a vocabulary checklist, which generated a raw score of the number of words infants can say and understand.

Epilepsy assessment

Detailed information on seizure history and status was collected for infants with TSC at each timepoint, through administration of parent-report questionnaires, including the Early Childhood Epilepsy Severity Scale (E-Chess)[21] and a bespoke medical history questionnaire. The E-Chess is used to quantify the severity of epilepsy by collecting information on frequency of seizures, number of seizure types, antiseizure medication used, and treatment response. Medical records for each infant were divided into 1-year time periods (i.e. 0–12 months, 12–24 months). Information derived from parent-report interviews, seizure diary, and medical records were combined by an assessor (AR) to generate a global seizure severity score during the first year of life, using the E-Chess.

Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics (version 28; IBM Corp., Armonk, NY, USA) and RStatistics and RStudio (4.2.3; R Foundation for Statistical Computing, Vienna, Austria). Various data points were missing, because of either the inability to schedule a home visit with the family or a lack of questionnaire/interview completion by parents.

Changes in developmental ability and adaptive behaviour

A linear and a generalized mixed model were used to investigate whether (1) changes in adaptive behaviour, developmental level, and language vocabulary production/comprehension varies between 3 and 24 months old in infants with TSC ($n = 32$) compared to typically developing infants ($n = 33$), and (2) the age at which this divergence may present. A linear model was fit for adaptive behaviour level and developmental ability, and a generalized linear model (specifying a Poisson distribution used for count data) was fit for language production/comprehension scores due to non-normally distributed data. The dependent variables were MSEL ELC scores measuring developmental ability, VABS-II ABC scores summarizing adaptive functioning level, and M-CDI number of words 'said' and 'understood'. Infants with a minimum of two assessment timepoints completed were included in these analyses to ensure data reflected changes in development over time (two typically developing infants and one infant with TSC were removed on this basis). Because of the age-standardized scoring systems of MSEL and VABS-II, typically developing population-based cohorts' scores would be expected to remain relatively constant over time. However, because of sampling differences, some variation in typically developing infants' scores over time was anticipated. The fixed effects added to the model were 'group' (i.e., infants diagnosed with TSC compared to typically developing infants), age at assessment (in months), and their interaction. Participant was included as a random effect. Post hoc tests (Tukey adjusted) were run to compare group differences between each age timepoint. A mixed effects model is a flexible method of analysis for longitudinal

data which allows for comparison of group means across highly correlated timepoints, whilst accounting for missing datapoints and skewed outcome variables.

Group differences of MSEL, verbal/nonverbal developmental quotients, M-CDI words understood and said scores, and VABS-II domain standard scores were also examined. Reported *p*-values used 2-tailed tests of significance ($p < 0.01$).

Associations between epilepsy, adaptive functioning, and developmental ability

Individual intercept and slope estimates were extracted from the generalized and linear mixed models for MSEL ELC, VABS-II ABC, and M-CDI scores to quantify the initial level and rate of change in development, adaptive behaviour, and language between 3 and 24 months old. A linear regression was used to determine whether epilepsy severity and type in the first year of life was associated with these changes across the first 2 years, and at outcome (24 months old). Assumptions for linear regression analysis were met.

A multiple linear regression was used to examine the effect of seizure severity in the first year, age at seizure onset (a continuous variable calculated using infants' age in days), history of infantile spasms, and focal seizures (predictors) on developmental ability at 24 months old.

A priori and post hoc sample size calculations for all analyses are described in Appendix S1.

RESULTS

Assessment and sample clinical/genetic characteristics

Table 1 and Table S1 show the sample demographic and assessment information and Table 2 shows the genetic and clinical characteristics of the infants with TSC.

TABLE 1 Sample demographic and assessment information.

	Tuberous sclerosis complex ($n = 32$)	Typically developing ($n = 33$)
Infant male:female	14:18	17:16
Assessment timepoints completed, *n* (%)		
3 months	12 (38)	16 (48)
5 months	19 (59)	22 (66)
8 months	20 (62)	21 (63)
10 months	27 (84)	27 (81)
14 months	29 (91)	27 (81)
18 months	25 (78)	24 (73)
24 months	29 (91)	27 (82)
Number of visits completed, *n* (%)		
1 visit	0	2 (6)
2 visits	0	1 (3)
3 visits	6 (18)	0
4 visits	7 (22)	9 (27)
5 visits	3 (9)	8 (24)
6 visits	8 (25)	7 (21)
7 visits	8 (25)	6 (18)
Mean age of infant entry to study in months (SD)	7.5 (4.3)	5.8 (3.09)
Age range of infants' first home visit (months)	2–15	3–16
Mean number of assessment timepoints completed (SD)	5 (1.56)	5 (1.57)

Developmental and adaptive functioning level changes over time

A linear mixed model revealed that there was a significant main effect of age (slope estimate = 0.93, $p < 0.001$) and interaction group by age effect (slope estimate = −1.44, $p < 0.001$) on MSEL ELC scores (intercept = 83.33, $p < 0.001$). There was no independent group effect ($p = 0.29$). Post hoc comparisons of each age timepoint showed that infants with TSC demonstrated significantly lower MSEL ELC scores at 10, 14, 18, and 24 months old compared to typically developing infants (Figure 1 and Table S2). Group comparisons of MSEL ELC scores (Table 3) show an increasing group divergence between 10 and 24 months old. No significant differences were observed at 3, 5, and 8 months old. Lower MSEL ELC scores at 24 months old in infants with TSC were also not associated with genetic mutation type (*TSC1* vs *TSC2*) ($p = 0.67$), presence of subependymal nodules ($p = 0.61$), or presence of cortical tubers ($p = 0.21$) (Appendix S2).

Verbal developmental quotients scores (Appendix S3) were significantly lower in infants with TSC compared to typically developing infants from 10 months up to 24 months old ($p < 0.001$). Nonverbal developmental quotients scores were also significantly delayed in infants with TSC compared to typically developing infants from 8 months up to 24 months old ($p < 0.001$) (Table S3).

There was a significant effect of age (slope = 0.61, $p < 0.001$) and group by age (slope estimate = −0.82, $p < 0.001$) on VABS-II ABC scores (intercept = 88.12, $p < 0.001$). There was no independent group effect ($p = 0.74$). A post hoc comparison of each age timepoint confirmed that at 18 and 24 months old, infants with TSC presented with significantly lower scores of adaptive functioning compared to typically developing infants. No significant differences were observed between 3 and 14 months old (Figure 2).

The VABS-II communication subdomain scores were significantly lower in infants with TSC from 10 months up to 24 months old, whereas daily living and socialization skills were significantly lower in TSC from 14 months and 18 months old respectively (Table S4 and Figure S1, S2, and S3).

TABLE 2 Genetic and clinical characteristics of tuberous sclerosis complex sample.

	n (%)
Genetic information	
Mutation	
TSC1	8 (25)
TSC2	19 (59)
Unknown/no mutation identified	5 (16)
MRI/CT scan[a]	
Cortical tubers	14 (44)
Subependymal nodule	14 (44)
SEGA	2 (6)
Results unknown	9 (28)
Ultrasonography[a]	
Cardiac rhabdomyoma	12 (38)
Cardiac harmartoma	9 (28)
Ultrasonography results unknown	8 (25)
Skin lesions[a]	
Hypopigmented macules	12 (38)
Shagreen patch	2 (6)
Skin lesion history unknown	6 (19)
Seizure information	
Received an epilepsy diagnosis	24 (75)
History of infantile spasms	11 (46)
Epilepsy onset in 1st year	20 (83)
>1 seizure type in 1st year	6 (25)
Received treatment	23 (96)
Mean age of seizure onset in months (SD)	6 (6.5)
Seizure type[a]	
Infantile spasms	11 (46)
Tonic clonic	3 (13)
Absence	3 (13)
Focal +/− awareness	13 (54)
Febrile convulsions	4 (17)
Atonic	1 (4)
Myoclonic jerks	1 (4)
Multiple seizure types	13 (54)

[a]Not mutually exclusive.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SEGA, subependymal giant cell astrocytoma.

Language profile

There was a significant group by age interaction effect on the number of words infants produced (intercept = −1.25, slope = −0.12, $p < 0.001$) and understood (intercept = 2.39, slope estimate = −0.05, $p < 0.001$). The TSC group demonstrated a significantly lower number of words said and understood at 24 months old compared to typically developing infants. No significant differences were observed at 10 and 14 months old (Table S5 and Table S6).

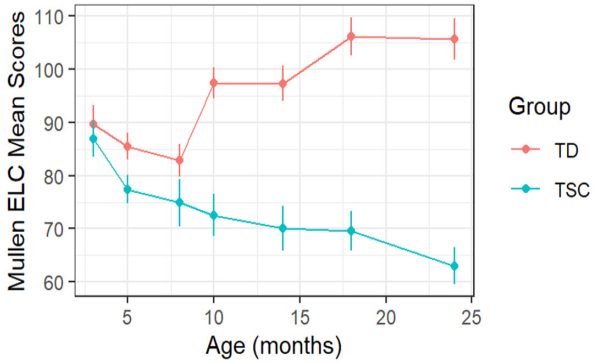

FIGURE 1 Longitudinal changes in developmental ability level scores (± standard error) between 3 and 24 months in infants with TSC and typically developing (TD) infants.

Associations with epilepsy

Out of the infants with TSC enrolled, 24 infants received a diagnosis of epilepsy. Eleven had a history of infantile spasms, 13 had focal seizures, and seven had both. Twenty infants experienced seizures in their first year of life. Severity scores were higher in infants with focal seizures (mean = 8.76, SD = 4.53) compared to infantile spasms (mean = 7.2, SD = 4.98). Two infants were removed from the analyses as global epilepsy severity scores were not available.

Epilepsy and developmental ability

There was a significant association between increased epilepsy severity in the first year of life and declining developmental ability slope estimates between 3 and 24 months old in infants with TSC and a history of seizures ($R^2 = 0.35$, $F(1, 20) = 10.84$, $\beta = -0.05$, $p = 0.004$, 95% confidence interval [CI] −0.08 to −0.01) (Table S7). In the infantile spasms subgroup, the association was weaker but showed a trend toward significance ($R^2 = 0.32$, $F(1, 8) = 3.81$, $\beta = -0.04$, $p = 0.087$, 95% CI −0.10 to 0.008). Increased seizure severity in the first year of life predicted lower developmental ability scores at 24 months old in infants with TSC and a history of seizures ($R^2 = 0.30$, $F(1, 18) = 7.78$, $\beta = -1.81$, $p = 0.012$, 95% CI −3.18 to −0.440) (Figure S4).

Epilepsy severity in the first year of life, age at seizure onset, history of infantile spasms, and focal seizures were entered together as predictors of developmental ability at 24 months old. The model was statistically significant ($R^2 = 0.42$, $F(4, 16) = 2.94$, $p = 0.05$). Increased epilepsy severity in the first year was associated with lower developmental ability at 24 months old (95% CI −4.44 to −0.74, $p = 0.007$); however, age at seizure onset ($p = 0.09$), history of infantile spasms ($p = 0.15$), and history of focal seizures ($p = 0.33$) were not.

Epilepsy severity and adaptive behaviour

Increased epilepsy severity in the first year of life was associated with declining VABS-II ABC slope estimates between

TABLE 3 Mean (SD) developmental, behavioural, and language scores of infants with TSC and typically developing infants between 3 and 24 months old.

	TSC				Typically developing			
Timepoint	**MSEL**	**VABS-II**	**M-CDI words said**	**M-CDI words understood**	**MSEL**	**VABS-II**	**M-CDI words said**	**M-CDI words understood**
3 months	86.90 (10.11)	88.92 (12.79)	-	-	89.73 (13.16)	89.06 (8.97)	-	-
n	10	12			14	15		
5 months	77.42 (10.80)	94.11 (11.30)	-	-	85.47 (10.11)	91.95 (11.84)	-	-
n	18	19			22	19		
8 months	74.87 (17.25)	90.30 (14.28)	-	-	82.84 (12.98)	91.75 (14.48)	-	-
n	16	20			19	19		
10 months	72.54[a] (19.29)	81.68[a] (16.02)	6.25 (13.91)	57.92 (87.06)	97.37[a] (14.37)	92.00[a] (6.46)	<1 (1.59)	23.55 (22.82)
n	27	25	16	12	26	25	21	20
14 months	70.04[a] (20.78)	89.96[a] (12.71)	27.41 (56.60)	72.91 (87.85)	97.32[a] (15.54)	99.44[a] (11.03)	20.88 (21.98)	103.63 (68)
n	26	23	24	22	25	27	22	24
18 months	69.65[a] (17.10)	80.08[a] (13.94)	-	-	106.17[a] (16.60)	105.71[a] (11.55)	-	-
n	23	24			23	24		
24 months	63.00[a] (16.40)	83.57[a] (14.75)	73.29[a] (122.55)	160.00[a] (128.64)	105.73[a] (19.03)	101.26[a] (13.01)	268.78[a] (146.56)	323.24[a] (88.69)
n	26	23	16	16	26	27	18	17

Abbreviations: M-CDI, MacArthur–Bates Communicative Development Inventories (words said/understood raw scores); MSEL, Mullen Scales of Early Learning composite scores; TSC, tuberous sclerosis complex; VABS-II, Vineland Adaptive Behavior Scales, Second Edition adaptive composite scores.

[a]Significance at $p < 0.01$.

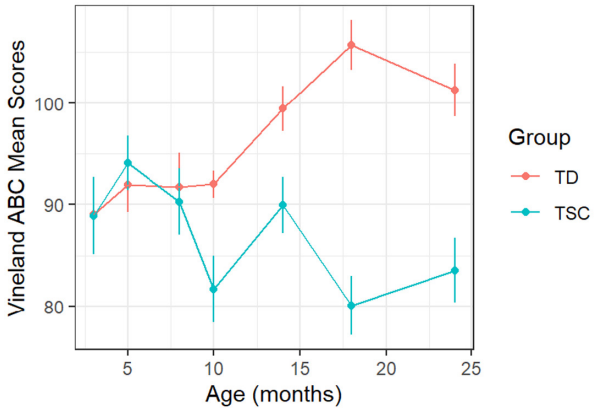

FIGURE 2 Longitudinal changes in adaptive functioning level scores (± standard error) between 3 and 24 months in infants with TSC and typically developing (TD) infants.

3 and 24 months old in infants with TSC and a history of seizures ($R^2 = 0.34$, $F(1, 20) = 10.43$, $\beta = -0.03$, $p = 0.004$, 95% CI −0.05 to −0.01) (Table S7), and in the infantile spasms subgroup ($R^2 = 0.52$, $F(1, 8) = 8.75$, $\beta = -0.03$, $p = 0.018$, 95% CI −0.05 to −0.007). At outcome, increased epilepsy severity in the first year was associated with lower VABS-II ABC scores at 24 months old in infants with TSC and a history of seizures ($R^2 = 0.48$, $F(1, 16) = 14.87$, $\beta = -2.07$, $p < 0.001$, 95% CI −3.21 to −0.93) (see Figure S5).

Epilepsy severity and language development

Epilepsy severity was associated with the number of words understood at 14 months of age ($R^2 = 0.24$, $F(1,19) = 9.96$, $\beta = -4.70$, $p = 0.008$, 95% CI −7.93 to −1.48); however there was no association between early epilepsy severity and number of words produced at 14 months and 24 months of age.

DISCUSSION

The present study tracked longitudinal changes in adaptive functioning, developmental ability, and language to identify when delays begin to emerge in TSC, and tested associations with epilepsy. When accounting for age by group interactions, developmental ability (between 10–24 months old) and adaptive functioning with specificity to socialization skills (between 18–24 months old) increased at a considerably slower rate in infants with TSC compared to typically developing infants, and relative to population-specific norms. Parent-reported vocabulary production and comprehension skills were lower in the TSC group compared to typically developing infants at 24 months old, whereas observed broader receptive and expressive development became delayed from as early as 10 months old.

In line with previous work, a slower increase in developmental ability and nonverbal skills was observed in infants with TSC from 10 and 8 months old, respectively. Existing longitudinal work has also identified early cognitive delays by 9 months old in infants with TSC, with relative specificity to nonverbal skills at age 6 months.[22] Our findings contribute to indications that nonverbal skills may be one of the first cognitive domains impacted in TSC-specific development, which could affect later social behaviours. The utility of the study measures to detect early changes in

development may be influencing the reported divergence. The MSEL has been shown to lack sensitivity to detect behavioural changes before 12 months old in infants with autism;[23] however other studies have shown its sensitivity from as young as 6 months old in TSC, and for assessing changes in developmental trajectory from 12 months old.[8] Diverging developmental ability is also likely to reflect atypical brain development and subsequent seizure emergence. The data showed that seizure severity in the first year of life was strongly associated with lower developmental ability scores over the 2-year period, and predicted lower scores at 24 months old. Recent investigations suggest a cascading risk pathway from TSC diagnosis to long-term intellectual disabilities which is mediated in part by early life seizure severity.[11]

It should be highlighted that parent-reported vocabulary production and comprehension ability in infants with TSC begins to diverge comparatively later (at 24 months) than observational measures of nonverbal and verbal developmental ability (from 8 and 10 months respectively). Previous investigations have shown infants with TSC present with lower receptive and expressive language skills from as early as 6 and 8 months old respectively.[13,24] As such, it may be less likely to be evidence of an isolated skill impacted later in infancy, and instead possibly a methodological difference that is inherent to parent report versus observational measures of developmental ability.

Importantly, these findings confirm and extend evidence that there is a link between early epilepsy severity and considerably slowed development across the first 2 years of life. In an infant study of TSC, seizure frequency measured at 6, 12, 18, and 24 months old was negatively correlated with subsequent performance across all developmental domains from 12 months up to 24 months old.[8] Contrary to existing literature, seizure severity was the only epilepsy variable associated with a poorer developmental outcome at 24 months old. Longitudinal investigations have observed associations between earlier age at seizure onset, infantile spasms, and later impaired intellectual and adaptive functioning by 24 months old in infants with TSC.[2,8,16] These investigations have important implications for the timely use of antiseizure medication to attenuate or eliminate seizure-related risk in infants. Recent clinical trials investigating early treatment before the onset of seizures suggest this may inhibit progression of epileptogenesis and seizure onset, hence improving long term developmental outcomes.[25]

Some limitations were evident because of the study design. Smaller sample sizes, in particular at the 3-month timepoint, within the epilepsy subgroups and those diagnosed with genetic, heart, or brain abnormalities, were statistically underpowered. Subsequent analysis was treated as exploratory and may limit the conclusions that can be drawn. The present study also did not include data on autism-related traits or diagnostic outcomes and how this relates to neurodevelopment in TSC. The co-occurrence of epilepsy and autism is well established,[26] and the greatest risk factor for autism in patients with TSC is earlier age at seizure onset.[27] Given that infants with TSC who develop autism have been found to demonstrate social communication deficits by 9 months of age,[28] the first year of life may be critical for identifying neurodevelopmental markers of emerging autism. Although not within the scope of the current study, it will be important to follow the sample beyond 24 months old, to examine the evolution of early development in light of epilepsy status and continued seizure management.

Various external factors, such as frequency and duration of hospitalization, rehabilitation, and preschool attendance, may serve as protective and risk factors against slower acquisition of skills in TSC.[29] Data were not systematically collected on these factors; however, we acknowledge their potential to impact development during a period of exuberant neuroplasticity, and encourage consideration of these variables in future longitudinal studies of TSC.

The infant years are a critical period for detection of variable and significant developmental delays in TSC. The findings highlight the need for early, repeated neurodevelopmental assessments of infants before the age of 2 years to identify risk factors for the manifestation of such delays. The link between early epilepsy severity and impaired domains of development suggest that early treatment of seizures is important to improve developmental outcomes.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Natasha Lindsay https://orcid.org/0000-0003-3781-6890
Charlotte Tye https://orcid.org/0000-0002-8567-9547

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Sample size calculations

Appendix S2: Genetic/clinical manifestations in TSC and associations with developmental ability

Appendix S3: Verbal and non-verbal developmental quotients

Table S1: Sample demographics

Table S2: Post hoc pairwise comparisons at each age timepoint in infants with TSC and typically developing infants for developmental and adaptive behaviour level

Table S3: Between-group differences in nonverbal and verbal developmental quotients between 3 and 24 months old
Table S4: Between-group mean differences in VABS-II domain standard scores between 3 and 24 months old
Table S5: Post hoc pairwise comparisons at each age timepoint in infants with TSC and typically developing infants for language production and comprehension scores
Table S6: Median and interquartile range of M-CDI 'words said' and 'words understood' scores at 10, 14, and 24 months old
Table S7: Comparing mean developmental ability and adaptive functioning scores of infants with and without epilepsy between 3 and 24 months old
Figure S1: Changes in VABS-II communication subscale standard scores in infants with TSC and typically developing infants between 3 and 24 months old
Figure S2: Changes in VABS-II daily living subscale standard scores in infants with TSC and typically developing infants between 3 and 24 months old
Figure S3: Changes in VABS-II socialization subscale standard scores in infants with TSC and typically developing infants between 3 and 24 months old
Figure S4: Scatter plot with regression line presenting the relationship between E-Chess scores for the first year of life and MSEL ELC scores at 24 months old
Figure S5: Scatter plots with regression line presenting the relationship between E-Chess scores for the first year of life and VABS-II ABC scores

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