Comments and Queries by the audiences on 6th Mar 2024

1. In your research regarding pathways to neurodevelopmental outcomes in TSC (slides 10, 11), how did you conclude that the first two years of life are critical developmental and behavioural outcomes in TSC? A detail explanation on that is much appreciated, thank you.

Our previous research on the longitudinal prospective Tuberous Sclerosis 2000 (TS 2000) Study indicated that seizure severity in the first two years of life predicted later elevated autism and ADHD traits, and lower cognitive ability, while controlling for current seizure severity. There appeared to be a cascading developmental pathway from type of genetic TSC mutation, through increased number of cortical tubers, through seizure severity in the first two years of life, through to behavioural and developmental outcomes in later childhood and adolescence. We concluded from our work, and others' work showing similar findings, that the infant years are particularly key for understanding later outcomes in TSC (Tye et al. 2020, 2023).

2. In the same research (slide 11), what was the predictability power of ASD/ADHD symptoms at 7-16 years? What are the protective factors against the risk if it is not very high? (Do you have any data on this point? What are the predictions for this point in the future, if any?)

There is support for the interplay of genetic mutation (e.g. a TSC1 mutation is associated with a less severe phenotype), cortical tuber load and location, and epilepsy severity, in predicting outcomes in TSC. In our TS 2000 Study, approximately 40% met diagnostic criteria for ADHD with similar rates for autism spectrum disorder. Our findings suggest that, in particular, the severity of infantile spasms (a particularly severe form of early-onset epilepsy) predict elevated ADHD and autism traits. In line with this, other groups have started to investigate the effect of early seizure management on behaviour (e.g. Moavero et al. 2020), as well as mTOR inhibitor treatment (e.g. Mizuguchi et al., 2019), and new behavioural interventions (McDonald et al., 2020). Our current and future work following the infants enrolled in the Early Development in Tuberous Sclerosis (EDiTS) Study cohort will enable systematic assessment of early-life predictors of later outcomes, spanning medical, environmental, and family factors, to shed light on factors linked with positive outcomes and improved quality of life. I would be pleased to share findings with the JSDP as they emerge.

3. Regarding the developmental pathways to neurodevelopmental outcomes in TSC, how should your findings be received in education and childcare settings? A

re there any points for teachers, therapists or other practitioners to cons ider?

Our research ultimately aims to provide evidence-based resources to educational an d health professionals. We are currently planning the primary school follow-up of the EDiTS Study cohort, in which we will be working closely with teachers to bette r understand the challenges and opportunities faces in educational settings when s upporting children with TSC and other rare genetic conditions. More generally, our emerging findings (and others) support the management of seizures early in life (L indsay et al., 2024), and an emphasis on tracking development and behaviour more s ystematically in these populations (Lindsay et al., 2024 in press). See also my re sponse to question 2 for other ongoing early intervention work.

4. Recently, the fetal period has been getting much attention for early develo pment. Your research seems to focus on postnatal periods, but how do you pl ace the period theoretically or predictively?

We know that the genetic mutation occurring in TSC (for example) at conception wil l have cascading effects of brain development both pre- and post-natally. An incre asing proportion of cases of TSC are diagnosed prenatally, through routine ultraso und scans and/or genetic testing in familial cases, which provides an opportunity to study changes in-utero using new advanced imaging techniques. Our research prov ides a first step to understanding development from the first few months of life, but a future critical step is to examine changes before a baby is born, for exampl e in brain structure and function, and link this with early development and behavi our.

5. I had the impression that “two-year-olds” were more emphasized in your pr esentation, is there any specific reason why two-year-olds were targeted?

Children aged between 2 and 2.5 years of age are starting to show important change s in temperament, social communication, executive function, sleep, and so on, and more standardised measures of these domains are available. This timepoint therefor e provides with a critical window into development and behaviour in these under-st udied populations. Our first ‘outcome’ period in the EDiTS Study was around two years old to capture behaviour in emerging toddlerhood, and we have since seen the se children again in their ‘preschool’ years (3-5 years old). It will be importa nt to continue following these cohorts to track both stable and fluctuating change s over development, and the factors that predict different trajectories.

6. May I ask why “sensory processing disorder” and “auditory processing dis order” were presented separately on slide 3 in your presentation?

Thank you for pointing this out! This is not a specific distinction, and rather sensory processing would also cover auditory processing and other modalities.

7. You mentioned that EEG measurements were taken in the participants' homes. What type of EEG equipment did you use? How did you use the tool to conduct research at home, e.g., noise reduction, arrangement of settings, and so on?

For the EDiTS Study cohort, we collected EEG with a limited number of infants at the Birkbeck Babylab in London. It was not easy for families to visit us in London, due to the practicalities of travelling across the UK alongside multiple medical appointments, work and childcare responsibilities. To tackle this, in our new study of early-onset epilepsy (the Brain development in Early Epilepsy, or BEE Study, which I introduced towards the end of my talk), we have been using a portable and wireless system developed by Enobio, with 20 channels. It has been used in our collaborators' work in the UK and globally, and has shown good quality in non-lab settings. In our home-based work, we try to limit noise by setting up the equipment in a quiet room with no other electrical equipment, and we use a screen to minimise distraction. It is not perfect (!), but our quality control statistics indicate we are obtaining adequate data to examine brain responses to stimuli in children with epilepsy as young as 10 months old. Watch this space!

Study websites (family-facing):

www.beestudy.co.uk
www.edits-study.org
www.ts2000study.co.uk

References

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