Global Summit

Autism & Epilepsy

A collaborative workshop to act as a catalyst for further research into autism and epilepsy to enable autistic people to live longer, happier, healthier lives.

AUTISTICA

Building brighter futures through autism research

Contents

Why research autism and epilepsy?

At Autistica, our vision is a world where all autistic people live a long, happy, healthy life. We aim to achieve this by delivering world-class autism research.

Between 10% and 40% of autistic people also have epilepsy and this rate increases steadily with age – in contrast to a one per cent prevalence rate in the general population.[1]

Our 2016 report **Personal Tragedies, Public Crisis** highlighted the appalling rates of early death in autistic people relative to the general population, with epilepsy being a leading cause of death.[2] The combination of disabilities significantly impacts on quality of life as well as physical and mental health, but remains under-researched.

It is more urgent than ever that we invest now to understand the interaction between autism and epilepsy and improve outcomes for people with both conditions.

At Autistica we have committed to addressing the global need for increased and improved research into autism and epilepsy to tackle the unacceptable disparity in autistic life expectancy. Research could help us to

understand the underlying mechanisms, risk factors, environmental triggers and developmental trajectory of the co-occurring disorders and how to better detect and treat seizures.

We hosted a two-day Global Summit including world-leading researchers, autistic adults, relatives and professionals to develop world-class research ideas to investigate the co-occurrence of autism and epilepsy.

[1] Tuchman, R., & Rapin, I. (2002). Epilepsy in autism. The Lancet Neurology, 1(6), 352-358.

[2] Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bölte, S. (2016). Premature mortality in autism spectrum disorder. The British Journal of Psychiatry, 208(3), 232-238.

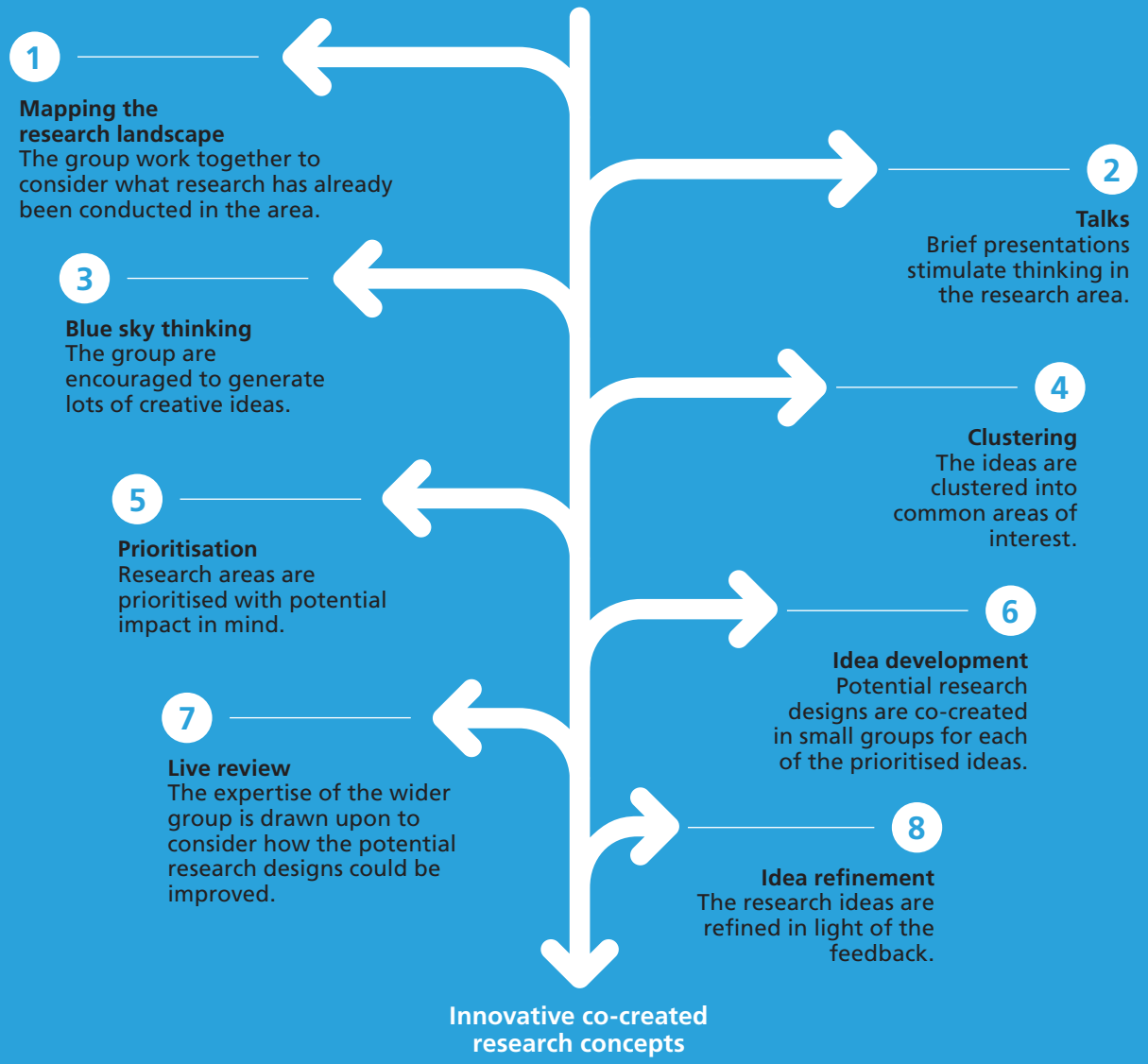
How a collaborative workshop is run

Three core values underpin everything Autistica does. Our community is involved at all levels, we are confident in our vision and the ability to change lives through autism research and we collaborate with others. Collaborative workshops are centred on these three values.

The workshops enable autistic people and families to collaborate with multi-disciplinary researchers across institutions and with professionals to co-create prospective research designs to accelerate previously under-investigated research areas. By bringing the leading experts together, including experts by experience, the research area can move forward in an innovative and efficient way.

Collaborative workshop agendas place a strong focus on establishing future research possibilities through group discussion. Workshops are independently facilitated to ensure that everyone in attendance has an equal voice in the process.

The Process

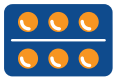


Research ideas that came out of the workshop

Research themes generated at the workshop

1
Distribution and determinants of autism and co-occurring epilepsy

2
Understanding epilepsy onset in autism



3
Medication and onset of epilepsy

4
Epilepsy medication side effects

5
Autism characteristics versus epilepsy seizures

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Stress/anxiety

7
Sleep

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Genetics – which genes?

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Genetics – understanding seizures

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Risk factors for premature death

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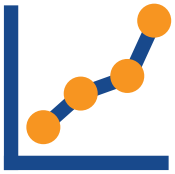
Premature death education

1 Distribution and determinants of autism and co-occurring epilepsy



What is the prevalence and incidence of epilepsy in autism / autism in epilepsy and what is the relationship to: age, gender, intellectual ability, familial risk, type of epilepsy, medication, and secular changes?

How?

Initial thoughts on the research design

- Form an international expert group to conduct a scoping review of academic literature and identify relevant international datasets.
- Perform a meta-analysis - a statistical approach to combine the results from multiple studies in an effort to improve estimates.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people and an international multi-disciplinary research team including epidemiologists and biostatisticians.

Why?

Potential impact of the research project

- Improve understanding of the pattern of co-occurrence.
- Potentially highlight unknown risk factors and mechanisms of the co-occurrence (e.g. specific seizure types, age of onset etc.).
- Enable future research that can save care and management costs.

To consider

Important factors to consider when further refining the research design

- Definitions of autism and epilepsy and mode of ascertainment.
- Whether international differences in terminology would need to be adjusted in datasets.
- Whether datasets are derived from surveillance or survey.
- Whether other conditions could be included, such as catatonia and chronic fatigue.
- How far this study has been achieved, and whether existing work could be built upon.

2 Understanding epilepsy onset in autism

Which autistic people develop autism, when and why?

How?

Initial thoughts on the research design

- Conduct a prospective study following multiple cohorts for five years across the age range 0-25 years to understand more about the onset and course of epilepsy in autism.
- Potential risk and protective factors (e.g. family history, prenatal and perinatal environment, and hormones) would be measured by repeated questionnaires and genetic samples. The use of wearable sensors and/or brain activity measures i.e. electroencephalogram (EEG) could also be explored.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, third sector organisations, and a multi-disciplinary research team including epidemiologists, biostatisticians, geneticists and endocrinologists.
- The project could be multi-site, capitalising on existing cohorts.
- Participants would have an established childhood diagnosis of autism. Both genders would be well represented and people with learning disability would be included.

Why?

Potential impact of the research project

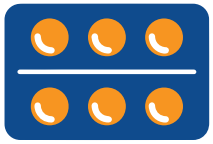
- Determine who is at risk to enable early prevention measures and/or treatment.
- Identify the frequency, duration, severity, type and treatment response of seizures to inform treatment plans.

To consider

Important factors to consider when further refining the research design

- Recruitment strategy, including consideration of late autism diagnoses.
- Retention strategies and a protocol for participant drop-outs, considering how this will affect the age distribution of the study.
- Whether data / genetic samples could be collected from parents and/or siblings.
- Whether the age range could be extended beyond 25 years.

3 Medication and onset of epilepsy



Does medication, including anti-psychotic medication, prescribed at critical developmental stages lead to onset of epilepsy?

How?

Initial thoughts on the research design

- Utilise NHS datasets to look at prescribing patterns and epileptogenesis in autistic people with late-onset epilepsy and compare with a control group of autistic people without epilepsy.
- Establish associations between medications and onset of epilepsy.
- Consider the dose and duration of medication use and time lag to symptom onset.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, relatives, Department of Health, NHS England and the devolved nations, NHS Digital, Public Health England and researchers.
- Participants would be autistic people whose epilepsy began between 12 and 30 years of age.

Why?

Potential impact of the research project

- Build knowledge of associations between medication usage and epilepsy onset in autism to inform safe medication practices.

To consider

Important factors to consider when further refining the research design

- How to determine whether an association is meaningful.

4 Epilepsy medication side effects

Which side effects are more or less common / problematic in autistic people with epilepsy?

How?

Initial thoughts on the research design

- Telephone or virtual interviews to establish a detailed understanding of medication history, adherence, and side effect profiles.
- Compare to pharmaceutical companies' published side effect lists.
- Participants would be recruited via existing cohorts (ideally with contemporaneous clinical data). There would be an initial focus on people in the typical IQ range, with people with learning disability included at a later stage.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, relatives, third sector organisations, and researchers.
- Participants would be 100-300 autistic people, families and carers.

Why?

Potential impact of the research project

- Build knowledge of epilepsy medication side effect profiles.
- Inform treatment plan amendments to improve quality of life and life expectancy.

To consider

Important factors to consider when further refining the research design

- How to account for recall bias when retrospectively discussing side effects.
- How to distinguish between medication side effects and autism characteristics.
- The effect of medication adherence on side effect profiles.
- Gender differences in side effect profiles.
- Age range of the sample - parents could be asked about side effects for young children.
- Whether reviewing medical records and prescription forms might be beneficial to the study design.

5 Autism characteristics versus epilepsy seizures

Can wearable technology be used to help distinguish between seizures and other behaviours?

How?

Initial thoughts on the research design

- Conduct a scoping review of the application of wearable technology to detect seizure in epilepsy and engage research groups to add an autism comparison group to ongoing epilepsy studies.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, companies specialising in wearable technology and a multi-disciplinary research team including experts in epilepsy, signal detection and behaviour observation.

Why?

Potential impact of the research project

- Optimise treatment (e.g. withdrawal of anti-epileptic drugs).
- Improve participant identification for research studies.

To consider

Important factors to consider when further refining the research design

- Definitions of seizures and 'other behaviours'.
- Stratification of the sample (e.g. by age and autism characteristics severity).
- Whether 'other behaviours' could be related to later onset of seizures.
- Whether certain behavioural profiles are associated with different seizure treatments.

6 Stress / anxiety

What are the factors leading to build-up of anxiety in autistic people with epilepsy and how can these inform management?

How?

Initial thoughts on the research design

- Use a mixed method approach, including focus groups and objective measures (e.g. wearable devices; galvanic skin conductance), to explore the factors leading to anxiety in autistic people with epilepsy and develop a severity scale.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people with epilepsy and lived experience of stress and/or anxiety and a multi-disciplinary research team including sociologists, psychologists, and clinicians with experience of autism and epilepsy.
- The sample would be stratified by age, gender, ability level – and later by seizure type and stress / anxiety level. Medication use would also be taken into consideration.

Why?

Potential impact of the research project

- Inform the design of stress / anxiety management tools, which can be tested for efficacy of stress / anxiety and seizure reduction.
- Improved quality and duration of life.

To consider

Important factors to consider when further refining the research design

- Definitions of stress / anxiety and epilepsy.
- How far existing stress / anxiety scales apply to autistic people with epilepsy.
- Whether measures of depression can be integrated.
- Impact of participant lifestyle (e.g. exercise).

7 Sleep

Does sleep in autism differ in those with and without co-morbid epilepsy?

How?

Initial thoughts on the research design

- Utilise wearable technology to investigate group differences in a) behavioural impact of sleep (e.g. anxiety) and b) physiological impact of sleep (e.g. drug absorption).

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people and relatives, companies specialising in wearable technology, pharmacists, and a multi-disciplinary research team including experts in sleep.

Why?

Potential impact of the research project

- Better understanding of how sleep can be managed for autistic people with and without epilepsy, improving daily living for them and their families.
- Inform understanding of how sleep could relate to seizure onset.

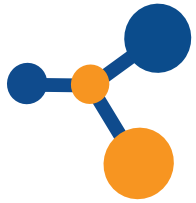
To consider

Important factors to consider when further refining the research design

- How sleep quality will be defined and measured, taking into account that 'sleep' may not be characterised in the same way as in the general population.
- Whether sleep quality measured during the study represents general sleep quality.
- The expense of using wearable technology.
- Whether a measure of brain activity i.e. electroencephalogram (EEG) can be integrated.
- Whether pharmacogenomics - the study of how genes affect a person's response to drugs – can be integrated.
- Whether an epilepsy only comparison group might be beneficial to the study design.

8 Biomarkers

Are there biomarkers that will predict the development of epilepsy in autism and do they correlate with autism characteristics, severity, and/or co-occurring conditions?



How?

Initial thoughts on the research design

- Longitudinal study with multimodal data collection, including classic brain activity measures i.e. electroencephalogram (EEG), neuroimaging, blood-based biomarkers, wearable devices / activity trackers, and medication use. High density EEG data collection and investigation of participants' microbiome would also be considered.
- Machine learning / big data analysis approaches (e.g. connectivity, cluster, features selection and dimensionality reduction) would be used to investigate potential biomarkers.
- A qualitative study (e.g. focus groups or interviews) evaluating the experiences of autistic people and families.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people and relatives, companies specialising in wearable technology, and a multi-disciplinary research team including experts in electrophysiology, neuroimaging, metabolomics and machine learning data analysis.
- Cohorts with high risk of autism and epilepsy (e.g. genetic disorder groups) may be included to enhance the sample.

Why?

Potential impact of the research project

- Improved knowledge of risk of developing epilepsy in autism.
- Potential to inform prevention strategies.
- Potential to inform treatment options.

To consider

Important factors to consider when further refining the research design

- Incentive strategy to prevent participants from dropping out.
- How to avoid the research procedures, which some people may find intrusive, preventing people from taking part or inducing anxiety and potentially triggering seizures.
- How co-occurring conditions might affect biomarker correlations.
- How medication may affect data.
- Whether the inclusion of a control group, such as people with epilepsy without autism or autistic people without epilepsy, might be beneficial to the study design.

9 Genetics – which genes?

What, if any, are the genes that drive autism, epilepsy and the co-occurrence of both?

How?

Initial thoughts on the research design

- The project would focus on assembling a large cohort of autistic people, people with epilepsy and people with both disorders with existing genetic data to enable the investigation of the genes that drive the conditions.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, relatives, Health Maintenance Organizations (e.g. Kaiser Permanente and Geisinger), an outreach team and a multidisciplinary research team including geneticists, biologists, psychiatrists and neurologists.
- Data could be collated from existing cohorts in the US and UK and mined for relevant data (e.g. brain activity measures i.e. electroencephalogram (EEG), epileptiforms in autism cohorts and neuropsychology measures in epilepsy cohorts).

Why?

Potential impact of the research project

- Inform screening and early diagnosis.
- Enable genetic counselling - the process by which people or relatives at risk of an inherited disorder are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, and the options open to them in management and family planning.
- Inform the development of prevention and treatment options.

To consider

Important factors to consider when further refining the research design

- The types and quality of genetic data available.
- How autism and epilepsy are defined with regard to inclusion and exclusion criteria.
- Whether other common co-occurring conditions should be included.
- Timeframe to establish cohort, gain access to data and investigate data.
- Social consequences of identifying genetic drivers e.g. stigma.

10 Genetics – the biological consequences

What are the biological consequences of the genetic changes that drive autism, epilepsy and the co-occurrence of both?

How?

Initial thoughts on the research design

- Regular (less than one per year) pathway analyses of genes would be conducted.
- Causative genetic changes would be modelled through a) animal models of single gene changes and b) induced pluripotent stem cells of copy number variants and complex genetics.
- Biological consequences in the models would be examined and interrogated through a) synapses b) neuronal morphology c) neuronal differentiation d) neuronal activity e) behaviour f) identified biomarker (see project 8).

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, relatives, an outreach team and a multidisciplinary research team including geneticists, biologists and experts in electrophysiology and bioinformatics.

Why?

Potential impact of the research project

- To reveal potential drug targets.
- Develop potential therapies based on biological mechanisms.

To consider

Important factors to consider when further refining the research design

- How to account for social and environmental factors.
- How this project could link to establishing an autism and epilepsy genetics cohort (project 9).

11 Genetics – understanding seizures

Are there genetic components to
i) age of onset
ii) type/frequency of seizures
iii) treatment resistance of epilepsy in autism?

How?

Initial thoughts on the research design

- Population study of autism and seizures.
- Exclusion criteria of a) prematurity, b) evidence of prenatal or perinatal injury, c) single gene disorder or cortical malfunctions with no variation in phenotype outcome (e.g. treatment resistance).
- Genotyping and epigenetics may be done on existing ASD and epilepsy cohorts.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, relatives and a multidisciplinary research team including geneticists and experts in bioinformatics.

Why?

Potential impact of the research project

- Greater understanding of seizure characteristics.
- Better preparation for seizure onset.
- Improved and targeted seizure management.

To consider

Important factors to consider when further refining the research design

- Specificity and justification of exclusion criteria.
- How to acquire treatment histories for participants.
- Whether 'treatment resistance' includes surgery and/or brain stimulation as well as medication.
- How this project could link to establishing an autism and epilepsy genetics cohort (project 9).

12 Risk factors for premature death

What are the key risk factors for premature death (including SUDEP) in autism and epilepsy?

How?

Initial thoughts on the research design

- Literature review for causes (and age) of death among people with autism and epilepsy.
- Interrogate death records for cause of death utilising post-mortem reports and health records.
- Look for cognitive ability and health conditions (e.g. cardiac, respiratory, mental health).
- Use statistical analyses to consider group differences across cohorts of autism / epilepsy / autism and epilepsy participants.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, families, caregivers and researchers, including epidemiologists.

Why?

Potential impact of the research project

- Generate accurate information on the risk of premature death in autism and epilepsy.
- Enable premature death prevention strategies to be identified.

To consider

Important factors to consider when further refining the research design

- Whether family interviews will be required to establish diagnoses and cause of death due to poor quality of death records.
- Influence of other co-occurring conditions on premature death.
- Comparison to premature death in intellectual disability.

13 Premature death education

How can we better educate autistic people, families and caregivers about the risks of premature death, including Sudden Unexpected Death in Epilepsy (SUDEP), and risk factors?

How?

Initial thoughts on the research design

- Qualitative study interviewing autistic people, families and caregivers to understand existing knowledge of premature death (including SUDEP), preferred method of information dissemination (e.g. face-to-face, media, written), attitudes towards medication adherence, and knowledge of brain donation possibilities.

Who?

Likely partnerships and research population

- Partnerships would be formed with autistic people, families, caregivers, third sector organisations such as SUDEP Action and qualitative researchers.

Why?

Potential impact of the research project

- Provision of accurate information on the risk of premature death in autism and epilepsy to enable stakeholders to make informed decisions.
- Enable premature death prevention strategies to be identified.

To consider

Important factors to consider when further refining the research design

- If it is possible to build predictors of SUDEP and sensitively communicate these to autistic people (in an autism-friendly way) and families.

What's next and how you can get involved

What's next?

These collaborative workshops are only the beginning of the process. Autistica is committed to taking the research concepts forward and evolving them into fundable research proposals that will lead to longer, happier and healthier lives for autistic people.

Autistica will work with partner organisations and funders over the coming months to get the remaining questions addressed.

How can you get involved?

Join us on the journey

We'd love to work with you and keep in touch with you.

- Share your experiences of the issues discussed in this report.
- Put us in touch with anyone you think might be interested in supporting our work.
- Follow us on social media for the latest research news and developments on this project.
- Join our Discover network for updates.

Who attended the workshop?

Organisers

Dr Georgina Warner – Autistica

Dr James Cusack – Autistica

Dr Abigail Thompson – Autistica

Jon Spiers – Autistica

Funders

Fraser Hardie

The Waterloo Foundation

Wellcome Trust

Autism Science Foundation

Roche

Attendees

Gill Ackers – Parent and Autistica Trustee

Sir Christopher Ball – Vice-President of Autistica

Dr Tom Berney – Newcastle University

Professor Patrick Bolton – Kings College London

Dr Susan Daniels – Office of Autism Research Coordination & National Institute of Mental Health

Christopher Eaton – Cardiff University

Renato Fantoni – Parent

David Gill – NHS England

Jane Green – Autistic advocate and parent

Fraser Hardie – Parent

Dr Kelly Hubble – Waterloo Foundation

Sarah Jackson – NHS England

Jane Kachika – NHS England

Jen Leavesley – Autistic advocate and parent

Dr Georgina MacKenzie – Wellcome Trust

Professor Benjamin Neale – Harvard Medical School

Professor Charles Newton – University of Oxford

Dr Jonathan O'Muircheartaigh – King's College London

Dr Susy Ridout – Autistic advocate, mentor and researcher

Dr Howard Ring – University of Cambridge

Dr Ian Roberts – Healx

Joseph Scanlon – Autistic advocate

Jayne Scanlon – Parent

Dr Stephanie Schorge – University College London

Professor Elliott Sherr – University of California, San Francisco

Alison Singer – Autism Science Foundation

Professor Sarah Spence – Harvard Medical School

David Thorpe – The Autism Academy UK

Rosie Tozer – Parent and Disability Researcher

Dr Charlotte Tye – King's College London

Dr Yujiang Wang – Newcastle University

What did people think of the workshop?

> ‘It was one of the most welcoming and inclusive experiences I have had the pleasure of taking part in.’
>
> **Jen Leavesley,**
> Autistic advocate and parent

> ‘It was inspiring. We got to interact directly with families and individuals who deal with this every day – you get to think about the issues from a different perspective and you learn from hearing what they have to say.’
>
> **Elliott Sherr,** US Professor

> ‘The workshop was truly collaborative – the way it was set up for everyone to work together was just remarkable.’
>
> **Sarah Spence,** US Professor

> ‘In terms of breadth and speed, it was one of the most intense brainstorming sessions I’ve ever had.’
>
> **Stephanie Schorge,** UK Researcher

Help us fund the research

Support our groundbreaking research into mental and physical health, language and communication and epilepsy.

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