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BRIEF COMMUNICATION

Epilepsy severity mediates association between mutation type and ADHD symptoms in tuberous sclerosis complex

Charlotte Tye[1] | **Fiona S. McEwen**[1] | **Holan Liang**[1] | **Emma Woodhouse**[1] | **Lisa Underwood**[1] | **Elizabeth Shephard**[1] | **Edward D. Barker**[2] | **Fintan Sheerin**[3] | **Nicholas Higgins**[4] | **Juul Steenbruggen**[1] | **Tuberous Sclerosis 2000 Study Group** | **Patrick F. Bolton**[1]

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

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

[3]Department of Neuroradiology, Oxford University Hospital NHS Foundation Trust, Oxford, UK

[4]Department of Radiology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK

Correspondence
Charlotte Tye, Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK.
Email: charlotte.tye@kcl.ac.uk

Present address
Fiona S. McEwen, Department of Biological and Experimental Psychology, School of Biological and Behavioural Sciences, Queen Mary University of London, London, UK; Holan Liang, Great Ormond Street Hospital NHS Trust, London, UK; Emma Woodhouse, Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; Emma Woodhouse, Compass Psychology Services, Bromley, UK; Lisa Underwood, Department of Population Health, University of Auckland, Auckland, New Zealand; Elizabeth Shephard, Department of Psychiatry, University of São Paulo, São Paulo, Brazil; and Patrick F. Bolton, Social, Genetic & Developmental Psychiatry Centre, Institute of

Abstract

The association between attention-deficit/hyperactivity disorder (ADHD) and tuberous sclerosis complex (TSC) is widely reported, with support for the role of epilepsy, yet the mechanisms underlying the association across development are unclear. The Tuberous Sclerosis 2000 Study is a prospective longitudinal study of TSC. In Phase 1 of the study, baseline measures of epilepsy, cortical tuber load, and mutation were obtained with 125 children ages 0–16 years. In Phase 2, at an average of 8 years later, ADHD symptoms were measured for 81 of the participants. Structural equation modeling revealed an indirect pathway from genetic mutation, to cortical tuber load, to epileptic spasm severity in infancy, to ADHD symptoms in middle childhood and adolescence, in addition to a pathway linking current seizure severity to ADHD symptoms. Findings were retained when intelligence quotient (IQ) was entered as a correlated factor. The findings support a cascading developmental pathway to ADHD symptoms mediated by early-onset and severe epilepsy in the first 2 years of life. This warrants detailed investigation of seizure characteristics and cognitive and behavioral sequelae associated with ADHD from early in life, to further the understanding of the association between ADHD and early-onset epilepsy across syndromic and non-syndromic populations.

KEYWORDS

ADHD, epilepsy, longitudinal, tuberous sclerosis complex

Psychiatry, Psychology & Neuroscience, King's College London, London, UK

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1 | INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic condition caused by mutations in the *TSC1* and *TSC2* genes, which lead to marked upregulation of the mammalian target of rapamycin (mTOR) pathway and consequently the development of hamartomatous lesions.[1] Cortical tubers and subependymal nodules are associated with a high prevalence of epilepsy in TSC, which occurs in up to 90% of individuals and often begins in the first year of life.[2] In addition to the physical manifestations, individuals with TSC may also experience an array of intellectual, neurodevelopmental, behavioral, psychiatric, and psychosocial difficulties, recently termed TSC-associated neuropsychiatric disorders (TAND[3]). Diagnosis and symptoms of attention deficit hyperactivity disorder (ADHD) are prevalent in TSC, with wide-ranging estimates of prevalence from 20% to 60%.[4,5] Individuals with TSC and ADHD diagnosis or symptoms are more likely to have a low intelligence quotient (IQ) and/or diagnosis of intellectual disability (ID), and co-occurring diagnoses, including autism and mood or anxiety disorders.[5]

Although the association between TSC and ADHD is widely reported, little is known about the possible neurobiological mechanisms underlying it.[6] *TSC1*/*TSC2* mutations appear to have a similar frequency in individuals with an ADHD diagnosis[3]; however, downstream effects of the mutation on neural development may be implicated. Cortical tubers are likely to impact brain development, for example, frontal systems involved in regulatory activities associated with ADHD, which have been associated with cognitive ability in TSC.[7] There is substantial support for the role of epilepsy in ADHD, regardless of cause,[8] and a history of seizures, intractable epilepsy, and epileptic spasms has been associated with ADHD symptoms in TSC.[4,9] Although the limited research to date suggests that the association between TSC and ADHD is likely to be multifactorial in nature, the majority of studies have relied on retrospective report and chart review. In a well-characterized prospective longitudinal cohort study, we aimed to chart multifactorial longitudinal pathways to individual differences in ADHD symptoms using structural equation modeling, with a focus on the role of epilepsy.

2 | METHODS

(See also Section 1 in Appendix S1.)

2.1 | Participants

The Tuberous Sclerosis 2000 Study is a population-based, prospective longitudinal study of the natural history of TSC.[10] In Phase 1 of the study (2001–2005), 125 participants met diagnostic criteria for TSC and completed study assessments ($n = 62$ male; median age = 39 months, range = 4–254). At the initial assessment, a full medical history was obtained and a physical examination carried out using a standardized protocol. Full details of the study assessment protocol have been reported elsewhere.[10] During Phase 2 of the study (2012–2015), clinical researchers gathered information on behavior and development, including ADHD symptoms with 74 of the participants (male $n = 33$; median age = 147 months, range = 93–323) and intellectual abilities with 88 of the participants (male $n = 39$; median age = 148 months, range = 93–323), at an average of 8.3 years (range 5.5–10.8) after Phase 1. A medical ethics committee approved the study protocol (Research Ethics Committee ref: 00/7/061). Written informed consent was obtained prior to assessment.

2.2 | Measures

2.2.1 | Clinical features of TSC

A causal *TSC* mutation was determined for 96 children (*TSC1* $n = 19$; *TSC2* $n = 77$). Copies of clinical brain scans were obtained from the hospitals where imaging had been conducted during Phases 1 and 2 ($n = 109$) and coded for

number and location of cortical tubers and subependymal nodules. A tuber total latent factor score was calculated for each participant using confirmatory factor analysis.[7] Seizure severity scores were generated using the E-Chess.[11] A factor score was calculated for each participant for the first and second years of life ($n = 120$) and the 3-month period leading up to the Phase 2 assessment (current seizure severity; $n = 94$), comprising number of seizure types, time period over which seizures occur, seizure frequency at most severe, number of antiepileptic drugs used, and response to treatment. To disentangle the effect of epileptic spasms from other seizure types (including generalized and focal seizures) on ADHD symptoms, spasm severity was separately coded from "non-spasm seizure severity" for the first and second years of life, when spasms tend to occur.

2.2.2 | ADHD symptoms

A primary caregiver completed the Strengths and Difficulties Questionnaire (SDQ; $n = 74$) and the Development and Wellbeing Assessment (DAWBA; $n = 54$). The "hyperactivity" subscale of the SDQ was used to characterize ADHD symptoms, and diagnostic symptom counts were calculated based on parent ratings of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) ADHD criteria on the DAWBA, separately for inattention and hyperactivity/impulsivity (maximum 9 each) symptoms. These measures were used in combination with diagnostic interviews, the Schedule for Affective Disorders and Schizophrenia for School-Age Children, or Diagnostic Interview for ADHD in Adults, to define a multi-informant best-estimate clinical diagnosis ($n = 81$; authors PB, HL).

2.2.3 | Intellectual ability

Estimated IQ was available for 88 participants, combining scores on the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-2; $n = 57$), British Picture Vocabulary Scale (BPVS; $n = 1$), and the Vineland Adaptive Behavior Scales, Second Edition (VABS-II; $n = 81$). The adaptive behavior composite from the VABS-II was used to estimate IQ when the participant was not able to complete the WASI-2 or BPVS, either due to level of functioning ($n = 24$) or when administration of the WASI-2 was not possible ($n = 2^7$).

2.3 | Statistical analysis

Structural equation modeling was conducted in MPlus (version 7.31) to test indirect pathways from genetic mutation to ADHD symptoms measured by the SDQ and DAWBA symptom counts for inattention and hyperactivity/impulsivity (see Figures 1 and 2). To account for missing values, full information maximum likelihood estimation was used. A bootstrap model (1000 resamples) was used to estimate the standard errors of parameter estimates and the bias-corrected confidence intervals of the indirect effects.

3 | RESULTS

3.1 | Prevalence of ADHD symptoms in TSC

A significant proportion of participants demonstrated elevated ADHD symptoms on the SDQ (17.5% [$n = 13$] borderline ADHD symptoms; 36.5% [$n = 27$] high ADHD symptoms) and DAWBA (37% [$n = 20$] met DSM-5 criteria for inattention, 11% [$n = 6$] for hyperactive/impulsive symptoms, and 9% [$n = 5$] for combined symptoms of ADHD). There were significant associations with estimated IQ (SDQ rho = −0.44, $p < .001$; inattention rho = −0.45, $p = .001$; hyperactive/impulsive rho = −0.33, $p = .02$). Clinician-rated best-estimate diagnosis indicated that 15% of participants ($n = 12$) met criteria for definite ADHD and a further 26% ($n = 21$) met criteria for possible ADHD. There was a statistically significant group difference in IQ ($F_{(2, 75)} = 4.86$, $p = .01$); participants not meeting clinical ADHD criteria had higher IQ (76.68) compared to definite cases (57.25, $p = .03$).

3.2 | Longitudinal pathways to ADHD symptoms in TSC

Bivariate correlations between variables and ADHD symptoms and further information on epilepsy characteristics are provided in the Section 2 in Appendix S1. There were no significant indirect pathways to DAWBA-rated hyperactive/impulsive symptoms; findings are not reported. All significant path coefficients are shown in Figures 1 for SDQ-rated ADHD symptoms and Figure 2 for DAWBA-rated inattention symptoms.

Two indirect paths were significant for SDQ-rated ADHD symptoms (Figure 1), through: (1) mutation type (TSC2 vs TSC1), to increased tuber load, to increased spasm severity to increased ADHD symptoms (β = 0.28; 95% confidence interval [CI] 0.03, 0.72); and (2) mutation type, to tuber load, to increased nonspasm seizure severity, to increased current seizure severity to ADHD symptoms (β = 0.20; 95% CI 0.06, 0.50).

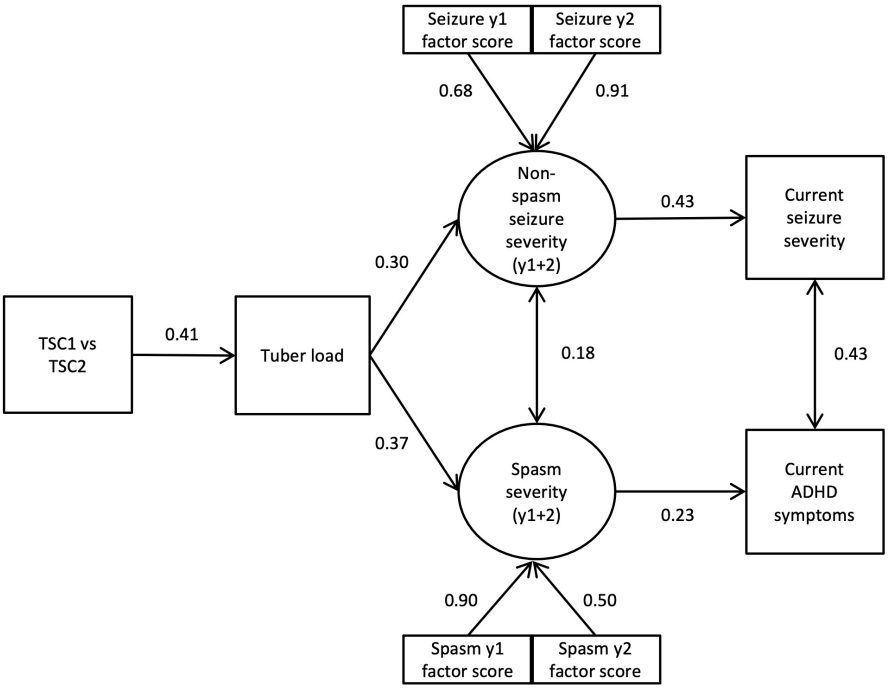

FIGURE 1 Full mediation model for Strengths and Difficulties Questionnaire (SDQ) hyperactivity scale: Paths linking genotype and SDQ hyperactivity scores through tuber load and epilepsy severity. Ovals represent latent variables and rectangles represent observed variables. Only significant paths are shown; absence of a line connecting variables implies no direct effect (path was not significant). Standardized betas for each path are shown; all paths shown are significant at $p < .05$. Model fit: RMSEA = 0.07 (90% CI = 0.01–0.11); standardized RMR = 0.06, CFI = 0.95.

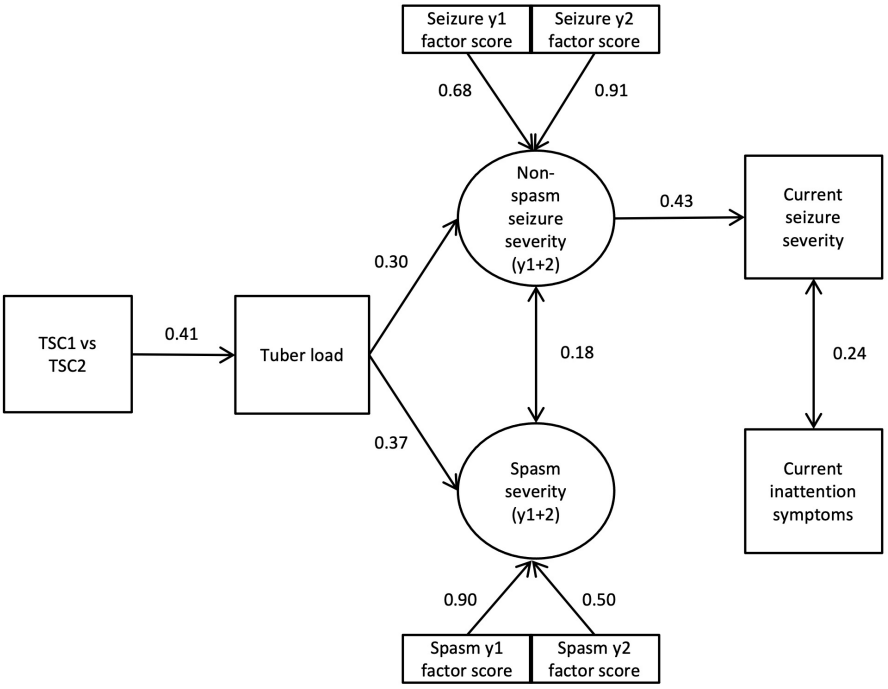

FIGURE 2 Full mediation model for Development and Wellbeing Assessment (DAWBA) Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) inattention symptom count: Paths linking genotype and inattention symptoms through tuber load and epilepsy severity. Ovals represent latent variables and rectangles represent observed variables. Only significant paths are shown; absence of a line connecting variables implies no direct effect (path was not significant). Standardized betas for each path are shown; all paths shown are significant at $p < .05$. Model fit: RMSEA = 0.05 (90% CI = 0.01–0.10); standardized RMR = 0.07, CFI = 0.97.

One significant indirect path was indicated between mutation and DAWBA-rated inattention symptoms (Figure 2), observed through: mutation type, to tuber load, to increased nonspasm seizure severity, to increased current seizure severity, to ADHD symptoms (β = 0.14; 95% CI 0.03, 0.44).

To control for intellectual ability, current estimated IQ was added into the models as a correlated factor. The significant pathways to ADHD were retained, whereas pathways to IQ replicated our previous findings (Figures S1 and S2).

4 | DISCUSSION

This study aimed to characterize the interdependence of clinical features of TSC on the developmental pathway to ADHD symptoms in a prospective longitudinal cohort study. Although there was no difference in ADHD symptoms by type of TSC mutation in line with previous work,[3] sophisticated structural equation modeling indicated a significant indirect pathway linking genetic mutation (*TSC2*), to increased tuber load, to increased severity of

epileptic spasms, to increased SDQ-rated ADHD symptoms. This pathway suggests that the association between genetic mutation and ADHD symptoms in later childhood/adolescence is mediated by tuber burden and epileptic spasm severity in the early years. This is consistent with previous reports of increased ADHD in individuals with a history of spasms.[4] Given that spasms are associated with more severe and intractable epilepsy,[2] this suggests that early control of seizures is key for long-term behavioral outcomes.

An additional pathway was demonstrated, operating via tuber load, to increased severity of nonspasm seizures, to increased current seizure severity, through to increased ADHD symptoms, both SDQ-rated and DAWBA-rated inattention. There is considerable stability of seizure severity over time, and this might reflect the chronic impact of seizures over time culminating in higher ADHD symptoms. It is unknown whether characteristics of ADHD antedate onset of epilepsy or fluctuate with severity. The role of early seizure severity should, therefore, be systematically explored through repeated measurement from early in life prior to the emergence of ADHD traits.

There were moderate correlations between ADHD symptoms and estimated IQ. When entering intellectual ability as a correlated outcome the indirect pathways were retained for both SDQ-rated ADHD and DAWBA-rated inattention symptoms. In this cohort, the pathway through early life nonspasm seizure severity to cognitive ability in middle childhood and adolescence was previously implicated,[7] suggesting a potential distinction between pathways to later IQ and later ADHD in TSC. Although our findings suggest that risk pathways for ID and ADHD in TSC do not completely overlap, it is likely that reduced cognitive ability may influence symptoms of ADHD, and characteristics of ADHD may impact intellectual and adaptive skills, in a bidirectional way.[12]

There are several challenges associated with measurement of ADHD in cognitively-impaired individuals. Although the selected measures may produce high prevalence scores in this population, their validity and reliability have been demonstrated previously.[13] Still, it is unclear whether the symptoms measured represent ADHD in TSC, or difficulties associated with ID, and current antiepileptic medication and seizure severity may present as attentional difficulties. Direct comparison of ADHD in syndromic and nonsyndromic individuals is required, alongside more objective measurement of activity[14] and neurocognitive impairment associated with ADHD, which may be independent of etiological factors shared with IQ.[15] Because diagnostic overshadowing of ID may limit reports of additional behavioral challenges, it is also important to consider the role of other TAND manifestations, including autism (Section 2 in Appendix S1) and mood and anxiety disorders.[4]

In conclusion, the findings support a cascading developmental risk pathway linking the type of genetic mutation to neurological manifestations of TSC through to ADHD symptoms. Detailed investigation of seizure characteristics and cognitive and behavioral sequelae associated with ADHD in the first years of life is warranted.

AUTHOR CONTRIBUTIONS

CT designed the study; acquired, analyzed and interpreted the data; and drafted the manuscript. FSM designed the study, acquired the data, and revised the manuscript. HL, EW, LU, and ES acquired the data and revised the manuscript. EDB interpreted the data and revised the manuscript. FS, NH, and JS analyzed the data and revised the manuscript. PFB designed the study, interpreted the data, and revised the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ORCID

Charlotte Tye https://orcid.org/0000-0002-8567-9547
Fiona S. McEwen https://orcid.org/0000-0002-5562-481X
Holan Liang https://orcid.org/0000-0001-6650-9449
Emma Woodhouse https://orcid.org/0000-0003-3209-6329
Lisa Underwood https://orcid.org/0000-0001-7775-8272
Elizabeth Shephard https://orcid.org/0000-0002-5952-3565
Edward D. Barker https://orcid.org/0000-0002-9914-8958
Fintan Sheerin https://orcid.org/0000-0002-9891-7612
Patrick F. Bolton https://orcid.org/0000-0002-5270-6262

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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