The Impact of Early Onset Seizures and Adverse Experiences on Child Development and Mental Health

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Table Of Contents

List of Tables

Chapter 1: Systematic Review

Chapter 2b: Major Research Project Secondary Analysis Paper

List of Figures

Chapter 1: Systematic Review

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Foreword

Unfortunately, the original study could not proceed as planned due to difficulties recruiting participants and carrying out data collection in the context of the COVID-19 pandemic and related disruptions to service provision.

Firstly, it was not possible to access a control group in order to address the research question. The control group would have included healthy, typically developing children from mainstream schools across Glasgow and Edinburgh. However, due to social distancing restrictions and limited resources available to staff at this time, schools were not in a position to advertise the study or grant the team permission to attend schools for the purpose of this research study.

Secondly, it was anticipated that there would be significant challenges associated with recruiting children and young people to the clinical group. This was in part due to the recognition that clinical staff were working in the context of increased demands and limited resource. It was also acknowledged that families were experiencing ongoing disruption to their daily lives and may have had limited availability to facilitate taking part in research in the context of working from home or while contending with other issues relating to COVID-19. Due to restrictions and attempts to limit exposure to COVID-19, the alternative plan had been to carry out data collection online rather than in a hospital setting. However, this plan was also considered suboptimal; given children and young people missed a significant period of school due to the pandemic, it was agreed that it would not be in their best interests to miss more school hours for the purpose of this research project.

The decision was taken to abandon the original study as planned, with the goal for it to be progressed at a later date. Professor Liam Dorris had access to an existing dataset involving other children and young people within a neurology setting. The study used similar methods of analysis involving neurodevelopmental testing, with a view to increasing our understanding of child development in the context of neurological conditions and adverse experiences. Due to time constraints, given this data was available and suitable for analysis, it was decided that this study would be an appropriate replacement to satisfy the requirements for a DClinPsy.

Chapter 1

Mental Health Outcomes in Children and Young People following The Great Recession: A Systematic Review

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Abstract

Background: We examined the evidence on mental health outcomes for children and young people who experienced the Great Recession of 2008. The aim was to understand the potential COVID-19 pandemic related economic impacts on the mental health of children and young people. Lessons from the Great Recession could be applied to inform future practice, policy and research regarding children and young people's mental health following the pandemic.

Method: A systematic search of PsycINFO, Medline, CINAHL and Embase retrieved 1,391 papers for review.

Results: Following application of eligibility criteria, 13 articles met inclusion. These studies used cross sectional and cohort designs, and utilised formal psychological measures or retrospective hospital data to assess the mental health of children and young people during the period of the Great Recession. There is limited evidence that the mental health of young people is negatively affected during periods of economic instability among those who are socioeconomically disadvantaged. A negative mental health impact was not observed across all studies for children and young people.

Conclusions: The mental health of children and young people may be impacted as a result of an economic recession, as demonstrated during the Great Recession of 2008. These effects are not equally distributed amongst the general population and specific risk indicators include low parental educational attainment, parental and youth unemployment. These risk factors may affect young people differently according to age.

Implications for researchers, policy makers and clinical services in the context of the economic recession resulting from the COVID-19 pandemic are discussed.

Keywords: Economic Recession, Children, Adolescents, Mental Health

1. Introduction

In March 2020, the World Health Organisation (WHO) announced the presence of a global pandemic known as Coronavirus Disease 2019 (COVID-19; WHO, 2020). As of May 2021, there have been over 160 million confirmed cases and over 3 million deaths worldwide (WHO, 2021). In an attempt to contain the outbreak, countries responded by enforcing various levels of social distancing measures, disseminating public health information at speed and increasing the capacity of health services to provide care to those affected. In doing so, governments were faced with challenges to providing essential health services, maintaining economic stability, and protecting the physical and mental health of the population.

Studies are emerging rapidly in an attempt to share knowledge and increase understanding of the virus and the potential long-term impacts on global health and economies. This includes the increasing recognition of the mental health impact of the pandemic (Vindegaard & Benros, 2020; Xiong et al., 2020), with some vulnerable groups at increased risk, such as children and young people (Loades et al., 2020; Ma et al., 2021). In a review examining the mental health research priorities during the COVID-19 pandemic, Holmes et al. (2020) highlight that policy makers are tasked with responding to the psychological burden associated with both the effects of the virus itself and its containment measures (e.g. psychological distress resulting from hospitalisation, bereavement, long periods of isolation), and also due to the impact on the economy and resulting financial strain felt at an individual level. Holmes et al. (2020) suggest that understanding and mitigating the mental health consequences for vulnerable groups should be a research priority during this pandemic. In the UK, epidemiological studies of children and young people reported an increasing number of mental health difficulties before the pandemic; including social isolation and low education attainment (Sellers et

al., 2019). Studies have also reported on increasing rates of self-harm (Morgan et al., 2017) and suicide among young people (Rodway et al., 2020). Mental health problems are not evenly distributed across the population; it is well established that those who are socioeconomically disadvantaged are more likely to experience physical and mental health related difficulties (Reiss, 2013), including those who are experiencing or at risk of poverty.

The full economic impact of COVID-19 remains to be seen. Reports from the Scottish Government in June 2020 indicated that 175,000 children and young people in Scotland were receiving free school meals, an increase of 30%, due to the financial strain on families since the beginning of the coronavirus pandemic (Scottish Government, 2020). Other reports suggest that the gross national product in the UK declined by 9.1% in 2020, driven by significantly weaker growth from services. This decline is more than twice the next largest fall of 4% in 2009, during the Great Recession in 2008 (Office for National Statistics, 2021).

The Organisation for Economic Co-operation and Development (OECD) is comprised of 38 countries, representing approximately 80% of world trade and investment (OECD, 2021). It is understood that many of these countries experienced economic consequences of the Great Recession (Keeley & Love, 2010). This global economic crisis had a significant and long-lasting impact on European labour markets (European Central Bank, 2014). Existing evidence suggests that an economic recession negatively impacts mental health outcomes through high unemployment rates, a decline in living conditions, and high levels of social exclusion, particularly in groups who were already at risk (Frasquilho et al., 2015). In their review of the evidence, Hiilamo et al. (2020) found that while the Great Recession had a negative effect on children's mental health, this effect was not fully explained by parents' exposure to the recession.

Similarly, Katikireddi et al. (2012) reported that deteriorations in mental health on a population level cannot be fully explained by differences in unemployment levels. A Finnish study suggested that financial strain can lead to mental health difficulties in children through changes in family relationships and parenting quality (Solantaus et al., 2004). Evidence suggests that a strong risk factor for child and adolescent mental health difficulties is having a parent who experiences depression (Thapar et al., 2012), and it is well evidenced that an economic recession is associated with negative mental health outcomes in adults (Haw et al., 2015). Chang et al. (2013) examined the impact of the 2008 global economic crisis on suicide trends across 54 countries, and found that for European men, increases in suicide rates were highest in those aged between 15 and 24 years old. Barr et al. (2012) reported a significant increase in suicide rates in England between 2008 and 2010 and found that areas with an increase in unemployment was associated with increased suicides rates, particularly among men. However, Pfoertner et al. (2014) carried out a cross-national study of adolescents and concluded that in contrast to the existing literature, psychological difficulties in this group were related to poor job prospects for their own employment, rather than due to associations with existing adult unemployment rates and changes in the economy.

These findings highlight that the mechanisms by which economic recessions impact on children and young people's mental health are multifactorial and may reflect different age-specific risks. For example, adolescents may experience difficulties relating to reduced employment opportunities and general uncertainty about the future (Hiilamo et al., 2020; Rathmann et al., 2016), while in young children, challenges may relate to negative changes in parental mental health (Layte & McCrory, 2018).

We conducted a systematic review of the literature synthesising the evidence for mental health outcomes in children and young people following the Great Recession.

Due to the unprecedented nature of the COVID-19 pandemic, the ongoing economic effects and the lack of empirical data available thus far, our objective was to use the data that emerged from the 2008 Great Recession, another financial crisis that was experienced on a global level, to inform our understanding of the impact of the current financial crisis caused by COVID-19. The ultimate goal is to apply these learning points in order to develop policies and interventions to mitigate this relationship and reduce the psychological burden on children and young people.

The primary aim of this review was to investigate the prevalence of negative mental health outcomes in young people following the Great Recession of 2007/2008.

2. Methods

The systematic review protocol was developed in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA; Page et al., 2021) and was registered in advance with the International Prospective Register of Systematic Reviews (PROSPERO) on 17th September 2020 (registration number CRD42020199254).

Information sources

Studies published between the years 2008 and 2020 were sought from MEDLINE (Ovid; 1946 – present), Embase (Ovid; 1947 – present), PsycINFO (EBSCO; 1806 – present) and CINAHL (EBSCO; 1981 – present) electronic databases. The Cochrane Library was also examined. Other methods used included reference checking and hand searching of relevant journals and studies.

Search

The search strategy focussed broadly on three topic areas: 1) mental health, 2) children and young people, and 3) the Great Recession and economic crisis. Index and exploded terms were explored where relevant (see appendix 1.3., p.105 for full search strategies across included databases).

Eligibility criteria

This review included studies from peer reviewed journal articles published in English. It specifically focused on papers examining the mental health outcomes in children and young people following the global economic recession or "Great Recession" of 2007/2008. The comparator was mental health outcomes in the period before or after the Great Recession (i.e. before 2007). The study population was limited to individuals aged between 5 and 24 years old, living in a country which experienced the Great Recession. Full inclusion and exclusion criteria are presented in table 1.1.

Table 1.1.

Full Inclusion and Exclusion Criteria

Characteristic	Included	Excluded
Population	Studies involving the general population of young people aged between 5 and 24 years old in OECD* countries which experienced the Great Recession of 2008.	Studies focusing on countries which did not experience the global economic recession. Studies examining an adult population (or majority adult, i.e. 16+ years).
Exposure	Being a young person living in a middle-high income country that experienced the Great Recession of 2008.	Studies reporting on mental health outcomes in children and young people not including the period of the Great Recession (2008 onwards).

		Studies which use economic measures as predictor variables.
Comparator	Mental health outcomes in young people reported in the years before or after the Great Recession (i.e. before 2007 or after 2009).	Studies which report on data from another period of recession or global event (such as trauma relating to a natural disaster).
Outcomes	Mental health difficulties described by prevalence rates of common externalising and internalising mental health disorders (e.g. behavioural difficulties, mood disorders, school based problems, suicide rates, other psychological disorders) or scores on formal, standardised measures of psychological distress (e.g. behavioural difficulties, anxiety or depression symptoms, or overall psychological wellbeing).	Studies which do not examine mental health as an outcome variable.
Study design	Observational cohort or cross-sectional studies	Systematic reviews lntervention studies such as Randomised Controlled Trials Review articles or commentaries Chapters from books

*OECD: Organisation for Economic Co-operation and Development

Study selection

The first step of study selection involved two phases of screening studies meeting the inclusion criteria; firstly by examining titles and abstracts, followed by full text review. During both the first and second phase, two reviewers independently assessed all papers for inclusion, based on title and abstracts initially and subsequently on full text. In cases of disagreement at both stages, an opinion was sought from a third supervising author in order to reach a resolution. At all points, resolution of disagreements was achieved by making reference to the review protocol and inclusion criteria to ensure consistency across decision making processes. Decisions were recorded using Rayyan QCRI software (Ouzzani et al., 2016).

Risk of bias in individual studies

Study quality was assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (appendix 1.2, p.104; National Heart, Lung and Blood Institute, 2021). This tool assesses internal validity in areas of subject selection, assessment (including outcome measures and blinding), confounders and allows for an overall assessment of study quality categorised as “good”, “fair” or “poor”. Studies meeting criteria were included in the final review, taking note of their overall quality rating. Two reviewers were involved in assessing the quality of the relevant papers, and any disagreements were resolved by a third supervisory author.

Data extraction

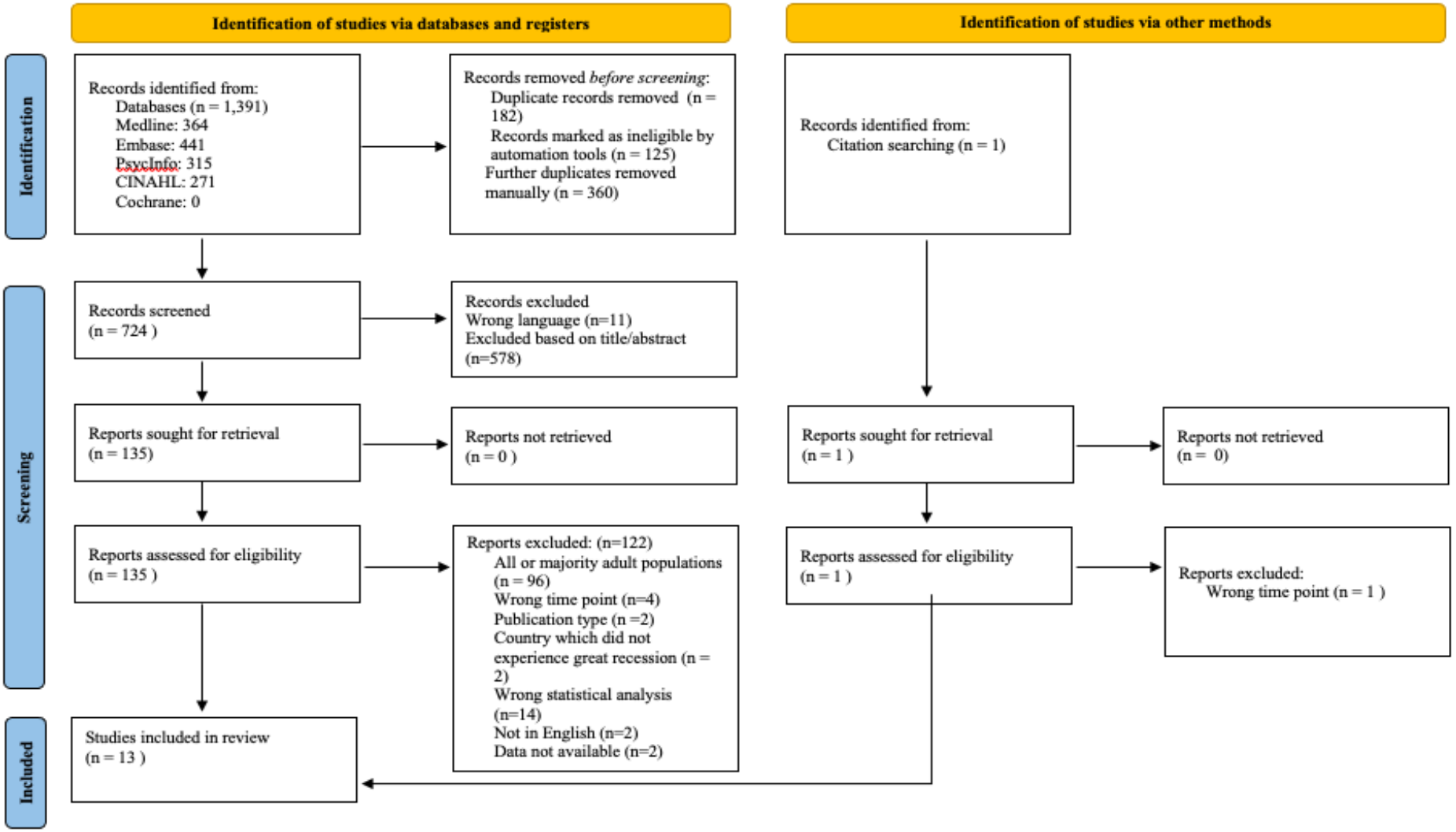
Data were extracted on study design, methodology, study population characteristics, recorded measures of mental health outcomes, and overall study findings. The information was extracted using a bespoke extraction template created for the purpose of this study (see table 1.3), which was subsequently checked by a second reviewer.

Synthesis of results

Due to the significant variability in methods used in these studies and insufficient comparable data to support quantitative synthesis/meta-analysis, data relating to mental health outcomes from relevant studies were summarised in narrative form.

Figure 1.

PRISMA Flowchart (Page et al., 2021)



3. Results

Description of the articles

The article selection process is outlined in the PRISMA flowchart (figure 1). The initial database search yielded 1,391 papers, in addition to one paper identified from the literature. Once duplicates were removed, 724 papers remained. After title and abstract screening, 135 studies underwent full text review. 122 studies were excluded, as detailed in figure 1. The characteristics of 13 included studies are detailed in table 1.3. Of the 13 included studies, 8 were cross-sectional studies, 3 used population-based cohort designs, 1 analysed data retrospectively using hospital records, and 1 used an interrupted time series analysis. The age of participants ranged from 5 – 24 years old. One study also included adults aged 24+ years (Medel-Herrero & Gomez-Beneyto, 2019). The decision to include this paper was made on the basis that a large proportion of the sample included children and adolescents within the proposed age range. Another study also included adult participants but reported specific data from young people aged 15-19 years old (Strukcinskiene et al., 2011).

There was significant heterogeneity in the methodologies of included studies. Many used formal, standardised psychological assessment tools (Aguilar-Palacio et al., 2015; Cui & Zack, 2013; Johnson et al., 2017; Motti-Stefanidi & Asendorpf, 2017; Rajmil et al., 2013; Siomos et al., 2014; Torikka et al., 2014; Torikka et al., 2017), the majority of which were based on self-report, but some included parent/teacher reports (Motti-Stefanidi & Asendorpf, 2017; Rajmil et al., 2013). Other studies used hospital admission rates (Medel-Herrero & Gomez-Beneyto, 2019; Rhodes et al., 2014), or suicide incidence rates in the population (Kõlves & De Leo, 2014; Kõlves & De Leo, 2016; Strukcinskiene et al., 2011).

Table 1.2.

*Quality Ratings of Included Studies**

	Item													
Author (year)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Aguilar-Palacio et al., 2015	Yes	Yes	CD	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes
Cui and Zack, 2013	Yes	Yes	NR	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes
Johnson et al., 2017	Yes	Yes	Yes	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes
Kõlves and De Leo, 2014	Yes	Yes	Yes	No	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	No
Kõlves and De Leo, 2016	Yes	Yes	Yes	No	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	No
Medel-Herrero and Gomez Beneyto, 2019	Yes	Yes	Yes	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	No
Motti-Stefanidi and Asendorpf, 2017	Yes	Yes	NR	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes
Rajmil et al., 2013	Yes	Yes	Yes	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes
Rhodes et al., 2014	Yes	Yes	Yes	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes
Siomos et al., 2014	Yes	Yes	NR	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes
Strukcinskiene et al., 2011	Yes	Yes	Yes	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	No
Torikka et al., 2014	Yes	Yes	NR	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes
Torikka et. al., 2017	Yes	Yes	NR	Yes	No	No	Yes	N/A	Yes	N/A	Yes	No	N/A	Yes

CD= Cannot Determine, NR= Not Recorded, N/A= Not Applicable
*Based on quality assessment tool (see appendix 1.2., p.104).

Quality ratings are provided in tables 1.2 and 1.3.

Mental Health Outcomes

All included studies used a measure of mental health as the main outcome variable. Based on these studies, the evidence for negative mental health outcomes in children and young people during the period of the Great Recession was variable (see table 1.3).

Five studies demonstrated poorer mental health outcomes in young people exposed to the Great Recession. In their study examining trends in health-related quality of life across the years 2000-2010, Cui and Zack (2013) found that adolescents from low-middle income families experienced worse outcomes than those from high income families. They conclude that the observed declines in health-related quality of life are consistent with recession effects, suggesting poorer mental health during the years of the Great Recession, but only for those who were socioeconomically disadvantaged. Medel-Herrero and Gomez-Beneyto (2019) found that psychiatric hospitalisations among young people significantly increased in 2008 for individuals experiencing difficulties with alcohol/drug related disorders, depression, disturbance of conduct and emotions, and 'neurotic' and personality disorders. They found admission rates continued to increase in the months after the onset of the recession for individuals presenting to hospital with acute reactions to stress and functional psychosis, among other diagnoses, which they understood to be related to the impact of the economic recession. Rhodes et al. (2014) reported that rates of young people presenting to the Emergency Department with suicide related behaviour decreased over time up until 2006/2007, but began to increase again in 2008. In addition, the proportion of girls who had a repeat presentation to the Emergency Department for suicide related behaviour increased from 2006 to 2010/2011 by 10%. Torikka et al. (2014) reported that in Finnish girls, the rate of depression was slightly

higher in the year 2008/2009 compared to 2000/2001, but this effect was not observed in boys. When considering the entire study period, the prevalence of depression peaked among girls in 2010/2011, and among boys in 2008/2009. In a later study, Torikka et al. (2017) found an increase in depression levels for boys and girls in 2008/2009 compared to 2002/2003, but a decrease in the frequency of 'drunkenness' for both. However, contrary to the decreasing trends in the full sample, frequent drinking did not decrease among the more socioeconomically deprived group, but actually increased over the study time period, particularly among those who scored high on a measure of depression.

Other studies found variable results. In their study comparing young people assessed before and during the crisis, Motti-Stefanidi and Asendorpf (2017) reported that while young people during the crisis experienced more teacher-rated conduct problems, they did not self-report worse psychological wellbeing (as measured by self-esteem and emotional symptoms). Johnson et al. (2017) reported only slight changes observed in mean levels of self-esteem, depression, risk-taking behaviour, interpersonal aggression and property crime during the Great Recession. They concluded that trends in the above indicators of mental health in young people were relatively stable. Rajmil et al. (2013) reported that while there were no significant changes in mental health in 2010-2012 compared to 2006 overall, they observed poorer mental health in families with lower maternal education and employment status. Aguilar-Palacio et al. (2015) found no increase in psychological problems when comparing the years 2006 and 2011/2012; in fact, they found that the prevalence of psychological problems declined in young women aged 16-24 years. Similarly, Kõlves and De Leo (2016) examined suicide rates worldwide between 1990 and 2009 and found no significant increase in rates among those aged between 15 and 19 years old. Kõlves and De Leo (2014) carried out a similar study with children aged between 10 and 14 years old; their analysis also did not suggest

statistically significant difference in suicide rates across this time-period. Siomos et al. (2014) found that while there was an increase in internet addiction symptomatology between 2006 and 2011, the 2011 sample had fewer psychological complaints to report; however, when reported, these complaints were of a similar magnitude to those reported in 2006, suggesting no increase in psychopathology.

Table 1.3.

Characteristics of Included Studies

Authors and Year	Sample Characteristics	Mental Health Outcome	Study design and Statistical Methods	Main Findings	Quality Rating
Aguilar-Palacio et al., 2015	Spain; The Spanish National Health Surveys 2006 and 2011/2012 Young people aged 16-24 years old *N*=3,701	The General Health Questionnaire (>3 indicates a mental health difficulty)	Repeated cross-sectional study. Chi squares to explore differences between gender over time, logistic regression to investigate influence of employment status on health and lifestyle	GHQ >3 Odds ratios: Men: .89 (not statistically significant), 95%CI: .64 -1.23, C statistic: .504. Young Women: 0.61 (statistically significant), 95%CI: .47 -.79, C statistic: .569.	Good
Cui and Zack, 2013	The US; The 2001-2010 National Health and Nutrition Examination Survey. Children and young people aged 12-17 years old. *N*=7,087	Number of reported mentally unhealthy days during the past 30 days – a validated measure by the Centers for Disease Control and Prevention.	Repeated cross-sectional study. T-tests to detect significant differences between percentages and logistic regression to test for trends.	% reporting zero mentally unhealthy days declined significantly from 60.9% in 2005-2006 to 49.4% in 2009-2010. Significant decrease in % of zero mentally unhealthy days among adolescents from low income families (from 63% in 2003/2004, to 46% in 2009/2010). Significant increase in % reporting 14 to 30 mentally unhealthy days increased significantly among adolescents from low income families (5% in 2007-2008 to 11% in 2009-2010) and middle income families (4% in 2001/2002 to 10% in 2009/2010).	Good

Johnson et al., 2017	The US; Monitoring the Future Study. (1991 – 2014) Children and young people aged 13-16 years old *N*=245,682 – 773,862	Self-reported measures of self-esteem, depression and interpersonal aggression – measures used in other Monitoring the Future Studies.	Repeated cross-sectional study. Ordinary least squares and logistic regression models (reference category for the regression is the year 2008)	With 2008 as the reference category, no significant change in depression or self-esteem in 2005, 2006, 2007, or 2009 through to 2012. However, there was a slight increase in 2013 (OLS: -.10) and 2014 (OLS:-.17), p <.05. No significant change in levels of interpersonal aggression until they began to decrease in 2011 (OLS: -.04) , 2012 (OLS: -.08) and 2013 (OLS: -.09), in comparison to 2008 (p<.05).	Good
Kõlves and De Leo, 2014	Worldwide; WHO Mortality Database from the World Bank Data set between 1990 to 2009. Young people aged 10-14 years old. *N*= 81 countries, participant numbers not stated.	Suicide rates	Population based cohort study. Average rates for the decades 1990–1999 and 2000–2009 were calculated and t tests were used to compare across countries. Poisson regression was applied when comparing the decades, and risk ratios with 95% confidence intervals were calculated.	No significant decline in suicide rates observed in this sample. For males, 1.61 to 1.52 per 100,000 (T=0.64, df=80, p=.521) For females, 0.85 to 0.94 per 100,000 (T=-1.03, df=80, p=.309) However, some significant changes detected in particular countries.	Fair
Kõlves and De Leo, 2016	Worldwide; WHO Mortality Database from the World Bank Data set between 1990 to 2009. Young people aged 15-19 years old.	Suicide rates	Population based cohort study. T tests were carried out to compare average suicide rates for different regions. Joinpoint regression was carried out to identify the best fitting points where a statistically	No significant increase in suicide rates observed in this sample. For males, 10.30 to 9.51 per 100,000 (T=1.80, df=80, p=.076). For females, 4.39 to 4.18 per 100,000 (T=.72, df=80, p=.473).	Fair

	N= 81 countries, unsure of total number of children and young people.		significant change in trend occurred.	However, some significant changes detected in particular countries.	
Medel-Herrero and Gomez Beneyto, 2019	Spain; The National Hospital Morbidity Survey. Twelve different age ranges, including 5-34 year olds* *N*= 1,152,880	Psychiatric hospital admissions	Interrupted time series analysis to investigate the trends in psychiatric hospital admissions during the economic downturn. 69 months before and after the onset of the economic crisis (defined as April 2008).	An increase of 51.6% (95%CI% 24.2 – 85.1; *p*=.039) per month in admissions due to depression and an increase of 46.1% (95CI% 24.7 -71.2; *p*=.018) for those caused by childhood and adolescence disturbance of conduct and emotion. "Neurotic" and personality disorders increased by 26.6% (95%CI 14.2-40.3; *p*=.024) and alcohol/drug disorder increased by 26.2% (95%CI 13.6-40.3; *p*=.029) per month from the onset of the economic crisis.	Fair
Motti-Stefanidi and Asendorpf, 2017	Greece; Surveys in two classroom student cohorts Children and young people aged approximately 13 years old *N*= 2,109	Youth adaptation and wellbeing measures: school absences, school engagement, conduct, self-efficacy, emotional wellbeing outcomes included self-esteem and emotional symptoms,	Repeated cross-sectional study. Logistic regression to estimate propensity scores to account for group differences.	Standardised cohort effect (standard error): Conduct: -.505 (.143), *p*<.001 Self Efficacy: -.162 (.077), *p*<.05 Self Esteem: -.067 (.058), not significant Emotional Symptoms: -.073 (.057), not significant	Good

		assessed by the Rosenberg Self-Esteem Scale and the Strengths and Weaknesses Questionnaire.			
Rajmil et al., 2013	Catalonia; Catalan Health Survey between 2006-2010/2012. Children aged 14 years and younger *N*= 2,200 in 2006 1,967 in 2010/2012	Strengths and Difficulties Questionnaire total score	Repeated cross-sectional stud. Linear and logistic regression	Overall sample scores comparing SDQ in 2006 versus 2010-2012: *B*= 0.48 (CI95%: -0.14 – 1.1), not significant	Good
Rhodes et al., 2014	Canada; Hospital records for emergency department presentations for nonfatal suicide-related behaviour in 2002/2003 to 2010/2011. Adolescents aged 12-17 years old. *N*=15,739	Incidence and nature of suicide related behaviour presenting to the Emergency Department, classified using the ICD-10 codes.	Retrospective data analysis from hospital records. Negative binomial regression was used to test the trajectory of rates over time.	Relative risk indicated that rates were about 30% lower in time 2 (2006-2010), compared with time 1 (2002/2005); girls RR: 0.70 [95%CI: 0.65-0.77], boys RR: 0.69 [95%CI: 0.64 – 0.76]. However, when examining the yearly trend between 2006/2007 and 2010/2011, there was little change. The proportion of girls who had a repeat ED SRB increased from 2006 to 2010/2011; from 31.6% to 41.7%. The proportion of boys admitted to hospital after the index event also increased between 2005/2006 to 2010/2011 from 31.7% to 40.3%, but the 95% confidence intervals overlapped.	Good

Siomos et al., 2014	Greece; High school students survey, carried out in 2006 and 2011. Young people aged 12-18 years old *N*= 431 in 2006, 645 in 2011.	The YDQ to measure internet use and the Symptom Checklist (SCL-90) for mental health symptoms.	Repeated cross-sectional study. ANCOVA to determine effect of variables and their interaction effects on the YDQ score. Mann Whitney to examine SCL-90 scores between groups	Between 2006 and 2011, adolescents shifted to more addictive use of the internet, $\chi^2(2) = 25.114$, $p < .001$, effect size η (eta) was small = 0.153. Most indexes except for the somatisation, phobic anxiety and PSDI reported statistically significantly lower values for the 2011 sample compared with the 2006 sample.	Good
Strukcinskiene et al., 2011	Lithuania; Data obtained from the Department of Statistics for the Government of the Republic of Lithuania (Statistics Lithuania), between 1990 and 2009. Young people aged 15-19 years old. *N*= 955	Suicide rates	Population based study. The study calculated mortality rates per 100,000. Linear and quadratic regression was used to explore trends in suicide rates.	In boys, a rising trend from 1990 and decreasing trend from 2002 was observed using quadratic regression ($R^2 = .465$, $p < .05$) (linear regression: $R^2 = 0.112$, $p > .05$) No significant change was observed for girls over the study period using polynomial regression ($R^2 = .09$, $p > .05$) or linear regression ($R^2 = 0.025$, $p > .05$).	Fair

Torikka et al., 2014	Finland; The School Health Promotion Study of the National Institute for Health and Welfare is a school based survey (every second year between 2000-2010) Young people aged 14-16 years old. *N*= 618,084.	Revised Beck Depression Inventory	Repeated cross- sectional study. Logistic regression was used, time entered as an independent variable, with 2000-2001 being the reference category.	Depression reported by 4% of girls and 2.1% of boys in 2000/2001 and by 4.7% and 2.2% respectively in 2010/2011. In 2008/2009, odds ratio for boys with depression was 1.08 (CI95%: 0.99-1.18) , not statistically significant (no covariates included in this model). In the model including covariates (e.g. parent education/employment), odds ratio was 1.11 (CI95%: 1.02-1.21), statistically significant ($p<.05$). In 2008/2009, odds ratio for girls with depression, odds ratio was 1.08 (CI95%: 1.01-1.15) in model with no covariates, and 1.12 (CI95%: 1.05-1.19); both statistically significant ($p<.05$).	Good
Torikka et al., 2017	Finland; Classroom administered questionnaires from 2000/2001 to 2010/2011. Young people aged 14-16 years old. *N*= 618,084	Revised Beck Depression Inventory for depression and frequency of drunkenness as a proxy of alcohol use	Repeated cross-sectional study. Cochran–Armitage trend test was used to assess for the presence of an association between frequencies of dichotomized alcohol use, drunkenness, depression and unemployment with time from year 2000 to year 2011.	Slight increase in depression for girls (3.5% in 2002/2003 versus 4.3% in 2008/2009; $p<0.001$), but a decrease in percentage of girls who were drunk once a week or more frequently (3.1% in 2002/2003 versus 2.6% in 2008/2009; $p<0.001$) Slight increase in depression for boys (2.0% in 2002/2003 versus 2.2% in 2008/2009; $p=0.010$) and a decrease in percentage of boys who were drunk once a week or more frequently (4.8% in 2002/2003 versus 4% in 2008/2009; $p<0.001$).	Good

4. Discussion

Overall, we found limited evidence that young people's mental health was worse during the years surrounding the Great Recession (Cui & Zack, 2013; Medel-Herrero & Gomez-Beneyto, 2019; Rhodes et al., 2014; Torikka et al., 2014; Torikka et al., 2017), which is consistent with research in adult populations (Frasquilho et al., 2015). Some studies reported that child and adolescent mental health remained relatively stable during this period (Johnson et al., 2017; Motti-Stefanidi & Asendorpf, 2017).

This review found that psychological difficulties during the Great Recession were more prevalent among young people from families with less employment, lower income and less educational attainment, a further indication that health inequalities are experienced by those from lower socioeconomic backgrounds (Reiss, 2013; WHO, 2008), particularly during economic recessions (Heggebø et al., 2019). It therefore follows that the same group of young people may be more at risk of mental health difficulties following the economic crisis resulting from COVID-19, as they contend with "cumulative disadvantages" (Heggebø et al., 2019, p.636). An economic crisis is likely to affect these young people given they experience more health risks and have less resources available to support them through adversity. In addition, they may be contending with fears of unemployment and low income, worse housing conditions and uncertainty about the future (Heggebø et al., 2019). COVID-19 itself also disproportionately affects those from lower socioeconomic backgrounds (Patel et al., 2020; Williamson et al., 2020), in addition to the mental health impact of the restrictions such as a change in activities and disrupted access to health, education and support services (Vizard et al., 2020). Therefore, particular consideration should be given to the provision of mental health support to children and young people from lower socioeconomic backgrounds.

Layte and McCrory (2018) offer an explanation for the relationship between economic pressure and child psychological adjustment using the Family Stress Model, which highlights the impact of economic stress on parental mental health and how this mediates child mental health via the quality of the parent/child relationship. They highlight that social and economic policies are required to protect families from the financial consequences of a recession, in order to promote child development and wellbeing. This supports the view held by Pierce et al. (2020), who suggest a need to support parents' mental health in response to COVID-19, which may improve outcomes for children. For young children, family experience of the recession was linked to negative changes in parental mental health and child psychological adjustment, via the quality of the parent-child relationship (Layte & McCrory, 2018). For this group, it may be that parental unemployment (and less financial resource within the family) has an important role to play in influencing the child's psychological wellbeing. However, in adolescents, youth unemployment rates have been associated with psychological health complaints during the Great Recession (Rathmann et al., 2016). It has been demonstrated that frequent alcohol use also increased during the recession, particularly among groups who were socioeconomically deprived, and frequent drinking was associated with depressive symptoms (Torikka et al., 2017). Therefore, for adolescents, deteriorations in mental health may relate more to their own employment and perceived uncertainty regarding future prospects. They may also engage in risky behaviours such as alcohol use, which may perpetuate mental health difficulties, rather than factors pertaining to their individual family circumstances. As highlighted above, these factors may be more or less pertinent for young people based on socioeconomic factors. Future studies are warranted to explore age-related risk factors further.

Limitations

The majority of the studies included in this review used a cross sectional design, with measures providing a snapshot of mental health at one time; it was not possible to follow up individual participants to ascertain the natural history of these mental health effects. This method of assessment also limits our understanding of underlying causes of psychological distress. Although some studies recorded demographic and other confounding variables such as economic pressures and activities of daily living, it was not possible to understand individual risk factors contributing to mental health difficulties for children and young people at this particular time. All of these issues limit generalisability when interpreting findings. Previous studies have suggested potential reasons for a deterioration in children's psychological wellbeing during a recession, such as parental mental health (Layte & McCrory, 2018), worrying prospects about future employment (Pfoertner et al., 2014), and poverty or reduced quality of life (Cantillon et al., 2017). Qualitative studies exploring young people's attitudes during an economic recession may provide more fruitful information in this regard.

One possible explanation for the discrepancy in findings could be related to the study designs included in this review; given the objective was to examine child mental health outcomes at a population level, the decision was made not to include studies which used economic measures as the exposure to the Great Recession. Rather, the exposure employed in this review was living in a country that was exposed to the Great Recession, and as such, all studies used a time period comparison. Therefore, we may not have identified important contextual information explaining the extent of mental health difficulties, such as level of exposure to economic harm during the recession. Some of the studies included used time trend analyses of suicide rates. Although these papers provide useful information about patterns of suicide rates over time, including the period

of the Great Recession, it is difficult to isolate these data in order to understand how much of this change can be explained by exposure to the economic crisis. In their similar review of the literature, Hiilamo et al. (2020) examined various exposures to the Great Recession, including local unemployment rates, state-wide job losses and Consumer Sentiment Index (a measure of a person's confidence/uncertainty with regards to the economic state; Schneider et al., 2015). They found that the Great Recession did negatively impact on the mental health of children and young people, and that this was not fully explained by their parent's economic exposure to the recession. They also report evidence of increased drug and alcohol use, particularly among vulnerable groups. Similar to the current review, they also noted that some of their included studies (namely; those which used time comparison analysis methodology) did not identify deteriorating mental health outcomes.

The time period applied in this review included articles which assessed the mental health of children and young people during the Great Recession, which began at the end of 2007. According to a UK report, the drop in gross domestic product resulting from the financial crisis stabilised in 2009 and improved over the following 5 years (Office for National Statistics, 2018), therefore it is likely that the effects of the recession were felt beyond 2009, particularly in countries that were significantly impacted by the recession, such as Greece, Ireland and Spain, as reflected in their unemployment rates in 2013 (European Central Bank, 2014). This is also reflected in the literature, given the number of papers that emerged from these countries (e.g. Siomos et al.,2014; Layte & McCrory, 2018; Medel-Herrero & Gomez-Beneyto, 2019). Therefore, it was decided that a time limit would not be set in terms of defining the Great Recession period, but consideration would be given to this on a case-by-case basis. However, as times passes, it makes it more difficult to attribute changes observed in mental health solely to the economic

recession. In addition, given that some countries were affected more than others, it is worth considering this when interpreting the data from this review.

The quality assessment tool used to evaluate these studies, although designed for observational cohort methodologies, also had some limitations for the studies selected. Given the nature of the criteria (i.e., questions about follow up and blinding status) and the design of the studies included in this review (retrospective review of hospital records, population level surveys), there were a number of criteria that were regarded as 'not applicable' or 'cannot determine'. However, the authors of this tool acknowledged that the criteria set out would not be met by all cohort studies, such as the question relating to power and sample size (i.e. "was a sample size justification, power description, or variance and effect estimates provided?"); given a cohort study may be exploratory in nature, they may not report on power and this should not be evaluated as a "fatal flaw" of the study. However, based on the criteria that were applicable, the reviewers were able to rate the studies as "good", "fair" or "poor" (National Heart, Lung and Blood Institute, 2021).

There was significant heterogeneity within the results which indicated a narrative synthesis rather than a meta-analysis of the evidence. Although some of the studies used formal measures of mental health/emotional distress that are often used in clinical settings (e.g., ICD-10 diagnoses, hospital admissions for self-harm), other studies used less comparable measures such as "number of mentally unhealthy days in the previous 30 days" and self-reported measures of self-esteem. Moreover, some studies used self-report measures, but others used proxy-informants. Variability in outcome measures and statistical methodologies makes it more difficult to draw reliable comparisons between data from various studies.

In other economic recessions, parental education level could be considered a protective factor for children and young people, given it is stable and therefore less influenced by health-related social mobility (see Heggebø et al., 2019 for further discussion on this topic). This may also be true in the context of this particular recession, given those who had a college education were less likely to lose employment (Adams-Prassl et al., 2020). However, one of the most significant predictors of losing employment during the pandemic across Germany, the US and the UK was working in a job which meant an individual could not carry out employment tasks at home, such as those working in the accommodation and food service industry (Adams-Pressl et al., 2020). It was reported that after accounting for job characteristics, there was no longer a significant difference in job loss between workers with and without a university degree. In addition, reports suggest that those who were more at risk of losing jobs during the COVID-19 pandemic included women (Adams-Prassl et al., 2020), and it is worth considering how this may impact on child and adolescent mental health (e.g., Layte & McCrory, 2018). These findings should be considered when drawing comparisons between risk factors from the Great Recession and the financial crisis resulting from COVID-19.

Finally, as described by Hiilamo et al. (2020), there are notable differences between the worldwide government responses to mitigating the impact of the Great Recession versus the impact of the COVID-19 pandemic. For instance, they highlighted that in response to COVID-19, most countries adopted an approach which served to alleviate the impact of the economic recession (for example: the UK provided the furlough scheme and financial support for businesses, alongside offering mental health support for vulnerable groups) rather than introducing reactive, austerity measures and budget cuts (Richardson, 2010). Previous evidence from the Great Recession suggests that the response from government and social policies matters in terms of influencing

health outcomes (see Karanikolos et al., 2013 for a review). It is hoped that lessons learned from the Great Recession may help to inform our understanding of the psychological burden held by children and young people, a group which are understood to be particularly vulnerable to mental health difficulties following the COVID-19 pandemic (Newlove-Delgado et al., 2021). This has implications for policy in terms of informing the appropriate and necessary service provision. For instance, given parental distress increased during the pandemic (a trend that was also observed during the Great Recession; Layte & McCrory, 2018), Pierce et al. (2020) suggest that mental health support for parents is likely to make a difference for the mental health of children and young people. Given this review highlighted the needs for young people from lower socioeconomic backgrounds, it highlights a particular area of need and consideration.

Conclusions

We reviewed whether the Great Recession had a negative impact on the mental health of children and young people, with an aim of applying these findings to our understanding of the impact of the current economic crisis resulting from the COVID-19 pandemic. At a population level, the evidence for harm was inconclusive, with evidence for and against significant negative mental health effects attributable to the recession. However, several studies reported a negative mental health impact on children and young people, particularly those from a lower socioeconomic demographic, highlighting the health inequalities faced by those experiencing economic and social disadvantage, perpetuated in times of an economic recession. There is some evidence to suggest that there may be age-specific risk factors for mental health difficulties in this context. These findings have implications for social, health and education policies. These should be adapted to meet the needs of vulnerable families to promote wellbeing in the context of COVID-19

recovery plans, taking into account the economic uncertainty and potential long-lasting effects on physical and mental health.

Conflicts of Interest

The author has declared that they have no competing or potential conflicts of interest.

References

Adams-Prassl, A., Boneva, T., Golin, M., & Rauh, C. (2020). Inequality in the impact of the coronavirus shock: Evidence from real time surveys. *Journal of Public Economics, 189,* 104245. https://doi.org/10.1016/j.jpubeco.2020.104245

Aguilar-Palacio, I., Carrera-Lasfuentes, P., & Rabanaque, M. J. (2015). Youth unemployment and economic recession in Spain: influence on health and lifestyles in young people (16- 24 years old). *International Journal of Public Health*, *60*(4), 427-435. https://doi.org/10.1007/s00038-015-0668-9

Barr, B., Taylor-Robinson, D., Scott-Samuel, A., McKee, M., & Stuckler, D. (2012). Suicides associated with the 2008-10 economic recession in England: time trend analysis. *BMJ, 345*, e5142. https://doi.org/10.1136/bmj.e5142

Cantillon et al., 2017. *Children of austerity: Impact of the great recession on child poverty in rich countries.* UNICEF, Oxford University Press. https://www.unicef-irc.org/publications/pdf/Children_of_austerity.pdf.

Chang, S. S., Stuckler, D., Yip, P., & Gunnell, D. (2013). Impact of 2008 global economic crisis on suicide: time trend study in 54 countries. *BMJ*, *347*, f5239. https://doi.org/10.1136/bmj.f5239

Cui, W., & Zack, M.M (2013). Trends in Health-Related Quality of Life Among Adolescents in the United States, 2001-2010. *Preventing Chronic Disease, 10,* 120334. https://doi.org/10.5888/pcd10.120334

European Central Bank (2014). *The impact of the economic crisis on euro area labour markets.* https://www.ecb.europa.eu/pub/pdf/other/art1_mb201410_pp49-68.en.pdf.

Frasquilho, D., Matos, M. G., Salonna, F., Guerreiro, D., Storti, C. C., Gaspar, T., & Caldas- de-Almeida, J. M. (2015). Mental health outcomes in times of economic recession: a systematic literature review. *BMC Public Health*, *16*(1), 115. https://doi.org/10.1186/s12889-016-2720-y

Haw, C., Hawton, K., Gunnell, D., & Platt, S. (2015). Economic recession and suicidal behaviour: Possible mechanisms and ameliorating factors. *International Journal of Social Psychiatry*, *61*(1), 73-81. https://doi.org/10.1177/0020764014536545

Heggebø, K., Tøge, A. G., Dahl, E., & Berg, J. E. (2019). Socioeconomic inequalities in health during the great recession: a scoping review of the research literature. *Scandinavian Journal of Public Health*, *47*(6), 635-654. https://doi.org/10.1177/1403494818801637

Hiilamo, A., Hiilamo, H., Ristikari, T., & Virtanen, P. (2020). Impact of the Great Recession on mental health, substance abuse and violence in families with children: a systematic review of the evidence. *Children and Youth Services Review*, 105772. https://doi.org/10.1016/j.childyouth.2020.105772

Holmes, E. A., O'Connor, R. C., Perry, V. H., Tracey, I., Wessely, S., Arseneault, L., ... & Ford, T. (2020). Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *The Lancet Psychiatry*, *7* (6),547-560. https://doi.org/10.1016/S2215-0366(20)30168-1

Johnson, M. K., Staff, J., Patrick, M. E., & Schulenberg, J. E. (2017). Adolescent adaptation before, during and in the aftermath of the Great Recession in the USA. *International Journal of Psychology*, *52*(1), 9-18. https://doi.org/10.1002/ijop.12389

Karanikolos, M., Mladovsky, P., Cylus, J., Thomson, S., Basu, S., Stuckler, D., Mackenbach, J.P., & McKee, M. (2013). Financial crisis, austerity, and health in Europe. *The Lancet*, *381*(9874), 1323-1331. https://doi.org/10.1016/S0140-6736(13)60102-6

Katikireddi, S. V., Niedzwiedz, C. L., & Popham, F. (2012). Trends in population mental health before and after the 2008 recession: a repeat cross-sectional analysis of the 1991–2010 Health Surveys of England. *BMJ Open*, *2*(5), e001790. https://doi.org/10.1136/bmjopen-2012-001790

Keely, B., & Love, P. (2010). *From Crisis To Recovery*. OECD. https://www.oecd.org/insights/46156144.pdf

Kõlves, K., & De Leo, D. (2014). Suicide rates in children aged 10–14 years worldwide: changes in the past two decades. *The British Journal of Psychiatry*, *205*(4), 283-285. https://doi:10.1192/bjp.bp.114.144402

Kõlves, K., & De Leo, D. (2016). Adolescent suicide rates between 1990 and 2009: Analysis of age group 15–19 years worldwide. *Journal of Adolescent Health*, *58*(1), 69-77. https://doi.org/10.1016/j.jadohealth.2015.09.014

Layte, R., & McCrory, C. (2018). Fiscal crises and personal troubles: the great recession in Ireland and family processes. *Social Psychiatry and Psychiatric Epidemiology*, *53*(9), 987-1001. https://doi.org/10.1007/s00127-018-1551-9

Loades, M. E., Chatburn, E., Higson-Sweeney, N., Reynolds, S., Shafran, R., Brigden, A., Linney, C., McManus, M. N., Borwick, C., & Crawley, E. (2020). Rapid systematic review: the impact of social isolation and loneliness on the mental health of children and adolescents in the context of COVID-19. *Journal of the American Academy of Child & Adolescent Psychiatry*, 59 (11), 1218-1239. https://doi.org/10.1016/j.jaac.2020.05.009

Ma, Z., Idris, S., Zhang, Y., Zewen, L., Wali, A., Ji, Y., Pan, Q., & Baloch, Z. (2021). The impact of COVID-19 pandemic outbreak on education and mental health of Chinese children aged 7–15 years: an online survey. *BMC Pediatrics, 21*(1), 1-8. https://doi.org/10.1186/s12887-021-02550-1

Medel-Herrero, A., & Gomez-Beneyto, M. (2019). The impact of the 2008 economic crisis on the increasing number of young psychiatric inpatients. *Revista de Psiquiatría y Salud Mental (English Edition), 12*(1), 28-36. https://doi.org/10.1016/j.rpsm.2017.10.002

Morgan, C., Webb, R. T., Carr, M. J., Kontopantelis, E., Green, J., Chew-Graham, C. A., Kapur, N., & Ashcroft, D. M. (2017). Incidence, clinical management, and mortality risk following self harm among children and adolescents: Cohort study in primary care. *BMJ, 359*, j4351-j4351.https://doi.org/10.1136/bmj.j4351

Motti-Stefanidi, F., & Asendorpf, J. B. (2017). Adaptation during a great economic recession: A cohort study of Greek and immigrant youth. *Child Development*, *88*(4), 1139-1155. https://doi.org/10.1111/cdev.12878

National Heart, Lung and Blood Institute (2021). *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.* https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Newlove-Delgado, T., McManus, S., Sadler, K., Thandi, S., Vizard, T., Cartwright, C., & Ford, T (2021). Child mental health in England before and during the COVID-19 lockdown. *The Lancet Psychiatry, 8*(5), 353-354. https://doi.org/10.1016/S2215-0366(20)30570-8

Office for National Statistics (2018). *The 2008 recession 10 years on.* https://www.ons.gov.uk/economy/grossdomesticproductgdp/articles/the2008reces

sion10yearson/2018-04-30#:~:text=This%20is%20what%20a%20recession,smaller%20for%20five%20successive%20quarters

Office for National Statistics (2021). *Coronavirus and the impact on output in the UK economy: December 2020.* https://www.ons.gov.uk/economy/grossdomesticproductgdp/articles/coronavirusandtheimpactonoutputintheukeconomy/december2020#:~:text=6.-,The%20UK%20economy%20during%20the%20coronavirus%20(COVID%2D19)%20pandemic,declined%20by%209.9%25%20in%202020.&text=The%20fall%20in%202020%20was,from%20services%20(Figure%2014).

Organisation of Economic Co-operation and Development (2021). *Where: Global Reach.* https://www.oecd.org/about/members-and-partners/

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1), 1-10. https://doi.org/10.1186/s13643-016-0384-4

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Patel, A. P., Paranjpe, M. D., Kathiresan, N. P., Rivas, M. A., & Khera, A. V. (2020). Race, socioeconomic deprivation, and hospitalization for COVID-19 in English participants of a national biobank. *International Journal for Equity in Health*, *19*(1), 1-4. https://doi.org/10.1186/s12939-020-01227-y

Pierce, M., Hope, H., Ford, T., Hatch, S., Hotopf, M., John, A., Kontopantelis, E., Webb, R., Wessely, S., McManus, S., & Abel, K. M. (2020). Mental health before and during the COVID-19 pandemic: A longitudinal probability sample survey of the

UK population. *The Lancet. Psychiatry*, *7*(10), 883-892. https://doi.org/10.1016/S2215-0366(20)30308-4

Pfoertner, T., Rathmann, K., Elgar, F. J., de Looze, M., Hofmann, F., Ottova-Jordan, V., Ravens-Sieberer, U., Bosakova, L., Currie, C., & Richter, M. (2014)Adolescents' psychological health complaints and the economic recession in late 2007: a multilevel study in 31 countries. *The European Journal of Public Health*, *24*(6), 961-967. https://doi.org/10.1093/eurpub/cku056

Rajmil, L., Medina-Bustos, A., de Sanmamed, M. J. F., & Mompart-Penina, A. (2013). Impact of the economic crisis on children's health in Catalonia: a before–after approach. *BMJ Open*, *3*(8), e003286. https://doi.org/10.1136/bmjopen-2013-003286

Rathmann, K., Pförtner, T. K., Hurrelmann, K., Osorio, A. M., Bosakova, L., Elgar, F. J., & Richter, M. (2016). The great recession, youth unemployment and inequalities in psychological health complaints in adolescents: a multilevel study in 31 countries. *International Journal of Public Health*, *61*(7), 809-819. https://doi.org/10.1007/s00038-016-0866-0

Reiss, F. (2013). Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. *Social Science & Medicine*, *90*, 24-31. https://doi.org/10.1016/j.socscimed.2013.04.026

Rhodes, A. E., Bethell, J., Carlisle, C., Rosychuk, R. J., Lu, H., & Newton, A. (2014). Time trends in suicide-related behaviours in girls and boys. *The Canadian Journal of Psychiatry*, *59*(3), 152-159. https://doi.org/10.1177/070674371405900307

Richardson, D. (2010). Child and family policies in a time of economic crisis. *Children & Society*, *24*(6), 495-508. https://doi.org/10.1111/j.1099-0860.2010.00334.x

Rodway, C., Tham, S. G., Ibrahim, S., Turnbull, P., Kapur, N., & Appleby, L. (2020). Children and young people who die by suicide: childhood-related antecedents, gender differences and service contact. *BJPsych Open*, *6*(3), E49. https://doi:10.1192/bjo.2020.33

Schneider, W., Waldfogel, J., & Brooks-Gunn, J. (2015). The great recession and behavior problems in 9-year old children. *Developmental psychology*, *51*(11), 1615-1629. https://doi.org/10.1037/dev0000038

Scottish Government (2020). *Free School Meals Extended*. https://www.gov.scot/news/free-school-meals-extended/

Sellers, R., Warne, N., Pickles, A., Maughan, B., Thapar, A., & Collishaw, S. (2019). Cross-cohort change in adolescent outcomes for children with mental health problems. *Journal of Child Psychology and Psychiatry*, *60*(7), 813-821. https://doi.org/10.1111/jcpp.13029

Siomos, K., Floros, G., Makris, E., Christou, G., & Hadjulis, M. (2014). Internet addiction and psychopathology in a community before and during an economic crisis. *Epidemiology and Psychiatric Sciences*, *23*(3), 301-310. https://doi.org/10.1017/S2045796013000437

Solantaus, T., Leinonen, J., & Punamäki, R. L. (2004). Children's mental health in times of economic recession: replication and extension of the family economic stress model in Finland. *Developmental Psychology*, *40*(3), 412- 429. https://doi.org/10.1037/0012-1649.40.3.412

Strukcinskiene, B., Andersson, R., & Janson, S. (2011). Suicide mortality trends in young people aged 15 to 19 years in Lithuania. *Acta Paediatrica*, *100*(11), 1476-1480. https://doi.org/10.1111/j.1651-2227.2011.02347.x

Thapar, A., Collishaw, S., Pine, D. S., & Thapar, A. K. (2012). Depression in adolescence. *The Lancet*, *379*(9820), 1056-1067. https://doi.org/10.1016/S0140-6736(11)60871-4

Torikka, A., Kaltiala-Heino, R., Rimpelä, A., Marttunen, M., Luukkaala, T., & Rimpelä, M. (2014). Self-reported depression is increasing among socio-economically disadvantaged adolescents–repeated cross-sectional surveys from Finland from 2000 to 2011. *BMC Public Health*, *14*(1), 1-10. https://doi.org/10.1186/1471-2458-14-408

Torikka, A., Kaltiala-Heino, R., Luukkaala, T., & Rimpelä, A. (2017). Trends in alcohol use among adolescents from 2000 to 2011: the role of socioeconomic status and depression. *Alcohol and Alcoholism*, *52*(1), 95-103. https://doi.org/10.1093/alcalc/agw048

Vindegaard, N., & Benros, M. E. (2020). COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. *Brain, Behavior, and Immunity*, *89*, 531-542. https://doi.org/10.1016/j.bbi.2020.05.048

Vizard, T., Sadler, K., Ford, T., Newlove-Delgado, T., McManus, S., Marcheselli, F., Davis, J., Williams, T., Leach, C., Mandalia, D., & Cartwright, C. (2020). *Mental Health of Children and Young People in England, 2020, Wave 1 follow-up to the 2017 survey*. https://files.digital.nhs.uk/CB/C41981/mhcyp_2020_rep.pdf.

Williamson, E. J., Walker, A. J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C. E., ... & Goldacre, B. (2020). Factors associated with COVID-19-related death using OpenSAFELY. *Nature*, *584*(7821), 430-436. https://doi.org/10.1038/s41586-020-2521-4

World Health Organisation (2008). *Closing the Gap in a Generation. Health Equity through Action on the Social Determinants of Health. Geneva:* WHO, 2008. http://whqlibdoc.who.int/publications/2008/9789241563703_eng.pdf

World Health Organisation (2020). *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020.* https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

World Health Organisation (2021). *WHO Coronavirus (COVID-19) Dashboard.* https://covid19.who.int.

Xiong, J., Lipsitz, O., Nasri, F., Lui, L. M., Gill, H., Phan, L., ... & McIntyre, R. S. (2020). Impact of COVID-19 pandemic on mental health in the general population: A systematic review. *Journal of Affective Disorders, 277* (2020), 55-64. https://doi.org/10.1016/j.jad.2020.08.001

Chapter 2

A) Major Research Project: Extended Proposal

Social Cognition in Childhood Cancer Survivors with Posterior Fossa Tumours

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Abstract

Background

Paediatric brain tumour survivors are at high-risk of experiencing neuropsychological 'late effects' as a result of the tumour and its treatment, which may impact on psychological wellbeing, educational attainment and quality of life. Emerging evidence suggests that young people who received treatment for a tumour in the posterior fossa area at risk of experiencing deficits in social cognition, with associated negative psychosocial outcomes.

Aims

This study aims to examine whether children and young people with posterior fossa tumours experience deficits in cognitive empathy compared to healthy age matched controls.

Methods

This study will use a case control design. Participants will be assessed using direct and proxy measures of cognitive empathy: The Reading the Mind in the Eyes Test (RMET), the "Faux Pas" test (FPT) and the Empathy Systemizing Quotient (ESQ). Cognitive ability and processing speed will be assessed with standardised tests.

Participants

Participants for the clinical group will be children and young people aged between 6 and 18 years old, recruited from oncology/neurology clinics in tertiary paediatric centres in Glasgow and Edinburgh. They will be at least one year post treatment for a posterior fossa tumour. Participants for the control group will be healthy, typically

developing children and young people between 6 and 18 years old from schools in Glasgow and Edinburgh.

Applications

Results from this study could inform long-term follow up care for paediatric brain tumour survivors and highlight potential areas for intervention in order to improve psychological wellbeing and overall quality of life.

1. Introduction

Tumours of the brain and central nervous system are the most common solid tumours in children (Gatta et al., 2009), with over 400 new childhood brain and CNS tumour diagnoses made each year in the UK (Cancer Research UK, 2019). There has been increasing concern regarding neuropsychological 'late effects' of both the disease and treatment, which are deficits that can emerge in the years following treatment and require ongoing monitoring. Factors predicting late effects include tumour variables (e.g. location and size), treatment variables (e.g. type of treatment, complications arising from treatment) and individual patient characteristics, such as age, premorbid ability and time since diagnosis (Stavinoha et al., 2018).

Childhood cancer survivors are at risk of experiencing neurocognitive deficits (De Ruiter et al., 2013), showing poor outcomes across a wide range of cognitive functions, including IQ, attention, memory and executive functions (Castellino et al., 2014). Studies have shown that rates of neurocognitive deficits can reach up to 100% in children treated for a brain tumour (Duffner, 2010; Palmer et al., 2013). Previous longitudinal studies focussing on cognitive functions showed that the pattern of cognitive decline changes depending on the age at diagnosis and treatment (Palmer et al, 2003), suggesting that for children of pre-school age, the decline starts immediately post treatment; for others, it may present many years later. The developing brain is more susceptible to damage induced by radiation, causing younger children to have more pronounced cognitive difficulties (Carrol et al., 2013; Gheysen et al, 2018). This, coupled with the gap produced by the difficulties in learning and acquiring new information (Palmer et al., 2001), puts younger children at risk of worse cognitive outcomes.

It has also been reported that paediatric brain tumour survivors are at increased risk of poor social functioning (Bonner et al., 2008), although this area of late effects is

less well understood. Studies have indicated that childhood brain tumour survivors experience lower peer-acceptance, increased isolation (Vannatta et al., 1998), and demonstrate poorer social awareness (Emond et al., 2016). In addition to late effects caused by the tumour and/or its treatment, this patient group are likely to experience missed opportunities for social engagement in formative years; they will require time away from peers in order to receive medical treatment and allow for time to recover (Brinkman et al., 2012), thereby preventing them from spending time among peers to develop these skills.

Yeates et al. (2007) proposed a model of social competence by which we can understand social outcomes in children and young people affected by brain disorder. They suggest social competence is made up of social adjustment, social interactions, and social information processing. The model indicates that factors related directly to the neurological insult and other independent factors (both risk and protective factors) can influence social competence and the relationship between these components (see Yeates et al., 2007 for review). By applying this model, Hocking et al. (2015) carried out a review on social competence in paediatric brain tumour survivors and reported that neurocognitive deficits may act as a mediator of poor social outcomes. They suggest that although the occurrence of neurocognitive late effects is well recognised, less is known about how these impact on functioning in other areas. For example, they suggest that in social situations, those who take longer to process information and respond may be more likely to experience negative social interactions and decreased peer acceptance. There appears to be limited empirical evidence for deficits in social competence, as many studies use parent, peer or teacher measures, and this has been identified as a limitation to conducting research in this area (Hocking et al., 2015; Willard et al., 2017).

There is emerging evidence that children with tumours in the posterior fossa area of the brain (part of the intracranial cavity that contains the brain stem and the cerebellum, e.g., medulloblastomas or ependymomas) are at an increased risk of experiencing negative psychological and social outcomes. Riva and Giorgi (2000) reported Autism Spectrum Disorder - like behaviours in children who had undergone cerebellar tumour resection, such as a decreased tolerance being around others and a tendency to avoid physical and eye contact. Additionally, survivors of a childhood brain tumour are at increased risk of psychological difficulties such as depression (Zyrianova et al., 2016) and poor quality of life (Bell et al., 2018). The capacity to understand another individual's mental state and the ability to understand empathy has often been associated with the cerebellum via imaging studies (see O'Halloran et al., 2012 for review). It is now recognised that the cerebellum is not only responsible for motor control but is critically involved in a wide range of neuropsychological functions (Schmahmann, 2004), including the regulation of cognitive affective processes (Schmahmann, 2004; Zyrianova et al., 2016). Thus, we raise questions about the role of the cerebellum in cognitive empathy; and specifically, how empathy may be implicated in children and young people with tumours in the posterior fossa area of the brain.

Understanding the mechanisms underlying deficits in cognitive empathy may help to identify targets for intervention in this group, in order to help them achieve social integration, thereby reducing their risk of developing ongoing psychological difficulties and improving overall quality of life.

Aims

This study aims to determine whether cognitive empathy is impacted in children recovering from tumours in the posterior fossa area of the brain, compared to healthy typically developing age-matched peers.

Hypotheses

The primary hypothesis is that children and young people recovering from brain tumours in the posterior fossa will score lower on measures of cognitive empathy, compared to typically developing peers. The secondary and exploratory hypothesis is that younger age and greater time since diagnosis will predict poorer scores of cognitive empathy in this population.

2. Plan of Investigation

2.1. Participants

Participants will be children and young people aged 6 to 18 years old, who have had treatment for a tumour in the posterior fossa and with a minimum post-treatment period of one year. The research team have identified a clinical cohort in Scotland of approximately 55 patients who will be contacted and invited to take part. A control group of approximately 40 – 50 healthy children and young people matched for age, sex and socioeconomic status will be recruited from schools across Glasgow and Edinburgh.

2.2.Inclusion and Exclusion Criteria

Inclusion Criteria: The study will include children and young people who have a diagnosis of a posterior fossa tumour. Participants will have received treatment in the form of surgery, chemotherapy, radiotherapy, or a combination of the above. They will

be at least one-year post-treatment and will not be receiving active therapy for their brain tumour. We will include children and young people with fluent command of the English language, as the measures used in the study have UK normative data for this population.

Exclusion Criteria: Children and young people with prior neurodevelopmental disorder will not be included in this study. Individuals with significant cognitive, physical or mental health impairment that would impact on their ability to engage in the cognitive assessment process will not be included in the study. This may include children and young people with a significant learning disability.

2.3.Recruitment Procedures

Participants for the clinical group will be recruited from long-term follow up oncology/neurology clinics in tertiary paediatric centres in Glasgow and Edinburgh. Due to the COVID-19 pandemic, routine out-patient appointments are being offered by telephone or by the video-conferencing technology Attend Anywhere. Participants will be informed about the study over the phone by a member of the clinical team, and if interested in taking part, the clinician will make a record of this in their case notes. A member of the research team will then make contact with the child's parent/carer, or with the young person themselves where appropriate, in order to send them an information pack about the study. Participants will be invited to take part in the research study during school hours. Written consent to take part in the study will be sought from the child or young person above the age of 12 years and written assent and their parent consent for those under the age of 12 years.

For the control group, permission will be sought from local education departments in Glasgow and Edinburgh to recruit participants and carry out assessments in schools. A brief information sheet about the study will be distributed to young people and their carers via an email from school. Families will be invited to read this information, and if interested in taking part, to reply to the email in order to register interest. The research team will then make telephone contact in order to send an information pack with consent forms to the family to recruit to the study, as per the procedure for the clinical group.

2.4.Measures

Demographic and Clinical Information

Demographic information such as age, sex, and socioeconomic status as measured by the Scottish Index for Multiple Deprivation (SIMD; Scottish Government, 2020) will be collected for all participants. For those in the clinical group, medical notes will be examined by a member of the research team for diagnostic and treatment information, including age of symptom onset, type and location of tumour, treatment received, complications arising from surgery and subsequent treatment received.

General Intellectual Functioning

This will be measured using the Weschler Abbreviated Scale of Intelligence – 2nd edition (WASI-II; Weschler, 2014).

Cognitive Empathy

This study will use the "Reading the Mind in the Eyes" test (RMET; Baron-Cohen et al., 2001) as a primary measure. The "Faux Pas" test (FPT; Baron-Cohen et al., 1999) will also be administered as a verbal assessment of cognitive empathy. The RMET child

version (28 items) will be administered to young people aged 6-12 years old. The RMET adult version (36 items) will be shortened to match the child version and will be administered to young people aged 12 and over. The completion time for these tests is around 20 minutes and scores will be adjusted for guessing. For the FPT, there is a child (6-12 years old) and adult version (13+ years) which will be administered as appropriate.

Parents will complete the "Empathy Systemizing Quotient" (Auyeung et al., 2012) questionnaire about their child as a proxy measure of cognitive empathy. The child (6-11 years), adolescent (12-15 years) and adult version (16+ years) will be completed as appropriate.

Processing speed

Participants will complete symbol search from the Weschler Intelligence Scale for Children – 5th Edition (WISC-V; Weschler, 2011). They will also complete the finger tapping test (Shirani et al., 2017), which has been regarded as a sensitive measure of cognitive-motor speed in those with a neurological condition (Shirani et al., 2017) and cerebellar injury (Harrington et al., 2004).

Social Interactions during COVID-19

The COVID-19 global pandemic and the resulting social distancing measures employed by the government may have an impact on psychosocial function. In order to assess the duration of severe social restrictions, and also to make a preliminary assessment of how participants maintained social contacts (for example, through the use of social media and contact with siblings) we have developed a short questionnaire. This may allow us to identify participants who were not able to use social media effectively and look for

correlations with cognitive empathy test data. The impact on the development of social cognition in children and young people who have not been attending school and have been isolated from family and friends is unknown, and children with significant cognitive disorder may be less able to use social media as effectively as peers. The researchers will therefore make a preliminary assessment of the child's social interactions between the period of data collection and March 2020 (see appendix 2.2, p.129).

2.5. Design

This study uses a case-control design. Participants will be invited to complete the assessment with a member of the research team at their school. This should take approximately 90 minutes. Participants and/or their carers will be invited to complete a questionnaire online; a link for these will be sent to participants via email.

2.6. Data Analysis

In order to answer the primary research question, a dependent samples t-test will be used to examine whether young people with posterior fossa tumours differ on a measure of cognitive empathy (RMET), when compared with typically developing peers. In order to examine the secondary question, correlational tests will be used to investigate the relationship between age at diagnosis and measures of cognitive empathy.

2.7. Justification of sample size

A power calculation is difficult to provide due to the paucity of research examining theory of mind in a paediatric neuro-oncology population. Therefore, estimates are informed by previous studies using similar methods in paediatric and adult brain injury populations. A study by Snodgrass and Knott (2006) demonstrated a large effect size

using the Reading the Mind in the Eyes test (d=1.45) in a group of children with moderate to severe traumatic brain injury, when compared against healthy age matched controls. Extrapolating information from the adult literature, studies by Henry et al. (2006) and Geraci et al. (2010) found medium and large effect sizes (d=.66 and 1.21, respectively) on the same measure in adults with traumatic brain injury. Given some children in this population are likely to have a moderate to severe brain injury resulting from extensive cancer treatment (chemotherapy, radiotherapy and surgery), deficits in theory of mind are expected based on the overall impact of treatment on their neurocognitive functioning. Therefore, using a conservative effect size of .80 and power level of .80 (p<.05, one-tailed), this study will require a minimum sample size of 21 participants in the clinical group to draw informative conclusions, and therefore we will aim to recruit between 20 and 25 children and young people.

2.8. Settings and Equipment

Cognitive assessments will be borrowed from the university department and local services. Proxy measures used in this study are freely available online. The assessment will take place at the participant's school.

3. Health and Safety Issues

3.1. Researcher safety issues

The researcher will notify another member of the research team when they are meeting with participants. Data collection will take place during school hours.

3.2. Participant safety issues

If, during the process of data collection, a member of the research team has concerns about the safety of the child or young person, they will inform the young person's parent/guardian. The researcher is also aware of child protection issues and will discuss appropriate governance and statutory responsibilities with the chief investigator as required.

4. Ethical Issues

The research team will seek ethical approval from NHS ethics through the Integrated Research Application System (IRAS). The researchers aim to recruit from two health boards (NHS Greater Glasgow and Clyde and NHS Lothian), therefore will require a letter of approval to access patients in NHS Lothian. The research team will apply to local councils and education departments to recruit participants for the control group, to seek permission to disseminate information about study to families via school communication methods (e.g., email), and to carry out the assessments at school.

The research team have engaged with SCOTCRN and Young Person Group to develop age-appropriate patient information sheets, to ensure patient involvement in the design thereby increasing its accessibility to young people and their families. Information sheets and consent forms will be developed for young people of all ages, so that either consent or assent can be sought from all participants.

All data gathered from this study will be stored safely and securely on NHS password protected servers.

The cognitive assessments will be reviewed by a Consultant Neuropsychologist. If the research team identify significant cognitive impairments that warrant further investigation, the family will be informed and offered advice or signposting to relevant services, where appropriate.

5. Financial Issues

It is anticipated that this study will require the allocated £200 from the University of Glasgow, in order to fund the stationary required to gain consent from families to be contacted by the research team and also to collect data from the control group.

6. Timetable

A final proposal will be submitted in April 2020. Once reviewed and finalised by the University, the study will be submitted for ethical approval. Due to issues relating to the COVID-19 global pandemic, the proposed timeline is tentative. It is hoped that ethical approval will be granted by September 2020 and data collection can begin. This will take place until approximately April 2021. Data analysis will then take place and a report will be written up for submission in July 2021.

7. Practical Applications

Results from this study could inform the long-term care for children and young people recovering from posterior fossa tumours, with a view to improving their psychosocial outcomes and reducing their risk of psychological difficulties later in life. It may highlight potential avenues for intervention from a neuropsychological point of view, and also identify areas where young people may benefit from the support of their families,

with an ultimate goal to increase social integration and improve quality of life for young people who have experienced disruption to their neurodevelopmental trajectory.

8. Brief critical appraisal of proposed method

Neuropsychological late effects are an area of increasing concern for the paediatric brain tumour population. There is emerging evidence that this group are at risk of cognitive deficits, including impairments in the area of social competence and cognitive empathy. These deficits may impact on friendships, education and overall psychological wellbeing, rendering this population vulnerable to mental health difficulties and suboptimal quality of life. This study would attempt to examine the nature and extent of cognitive empathy deficits in this group, compared to typically developing age-matched peers, with an aim to highlight the need to monitor these deficits in order to ensure early intervention for young people and their families. However, this study has some methodological and statistical limitations.

Due to time constraints and related participant recruitment issues, the projected sample size for this study, while powered sufficiently to answer the specific questions highlighted above, would be limited. Given the low incidence rates of paediatric brain tumours (Cancer Research UK, 2019), it is likely to be a research area which contends with small sample sizes. In this study, this issue would be further compounded given that children with an identified learning disability (possibly acquired via the tumour and it's treatment) would not meet inclusion criteria. Owing to the small sample size, the study would not be sufficiently powered to statistically examine the impact of some of the mediating factors discussed in the introduction section, such as location and size of tumour, in addition to treatment variables and individual patient characteristics (Stavinoha et al., 2018).

Secondly, there are some disadvantages to using the chosen measures of cognitive empathy, effecting the interpretation of results. Currently, there are no appropriate norms available for the RMET and FPT with which to compare, though studies have used the RMET and FPT to compare individuals on the Autism Spectrum with neurotypical controls (Baron-Cohen et al., 1999; 2001). Although results from this study may have demonstrated a statistically significant difference between the two groups, it would be difficult to ascribe clinical significance in the absence of an appropriate reference group. However, a recent study (Dorris et al., in press) used a shortened version of the RMET with a representation of young people from the general population. In order to remedy against the lack of normative data available for the RMET, this study had planned to use a similarly shortened version of the measure so that this reference group could be used as an appropriate comparator.

Another consideration is the potential recruitment bias to the control group. For instance, it may be that families are interested in taking part in order to access an assessment of the young person's learning or socioemotional needs, particularly if the family are having difficulties having their child's learning needs identified through education or clinical services (e.g., McKenzie et al., 2019; Voigt, 2016). In this way, it may be that the control group is overrepresented by young people for whom there are concerns regarding their social cognition or wider learning needs.

Finally, although this is beyond the scope of this study, some evidence suggests that when identifying emotions from facial expressions, individuals with insult to the cerebellum (i.e. the area of the brain affected by posterior fossa tumours) have difficulty deciphering emotion from the eyes. It is thought that they preferentially attend to the lips as a compensatory mechanism (Hoche, 2016). This is an important methodological factor to consider in this study, given that the primary measure of cognitive empathy relies on

reading emotion from the eyes. Although there are a limited number of alternative validated measures of cognitive empathy available, it is important to consider whether the RMET is an appropriate measure for use with a population of young people who may have cerebellar damage and difficulties reading emotion from the eyes.

Notwithstanding the above limitations, it is hoped that this study would contribute to the evidence suggesting that children and young people recovering from brain tumour treatment require additional monitoring and support from a neuropsychological perspective, with a particular focus on social cognition, in order to ensure interventions are in place from the earliest stage. These interventions should be set up to recognise difficulties in cognitive empathy, scaffold the young person's understanding of social situations, and facilitate inclusion via reintegration into school life following a period of illness, missed opportunity and possible resulting disability.

References

Auyeung, B., Allison, C., Wheelwright, S., & Baron-Cohen, S. (2012). Brief report: development of the adolescent empathy and systemizing quotients. *Journal of Autism and Developmental Disorders, 42*(10), 2225-2235. https://doi.org/10.1007/s10803-012-1454-7

Baron-Cohen, S., O'Riordan, M., Stone, V., Jones, R., & Plaisted, K. (1999). Recognition of faux pas by normally developing children and children with asperger syndrome or high-functioning autism. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1023/A:1023035012436

Baron-Cohen, S., Wheelwright, S., Spong, A., Scahill, V., & Lawson, J. (2001). Are intuitive physics and intuitive psychology independent? A test with children with Asperger Syndrome. *Journal of Developmental and Learning Disorders, 5(*1), 47-78.

Bell, H., Ownsworth, T., Lloyd, O., Sheeran, N., & Chambers, S. (2018). A systematic review of factors related to children's quality of life and mental health after brain tumor. *Psycho-oncology*, *27*(10), 2317-2326. https://doi.org/10.1002/pon.4850

Bonner, M. J., Hardy, K. K., Willard, V. W., Anthony, K. K., Hood, M., & Gururangan, S. (2008). Social functioning and facial expression recognition in survivors of pediatric brain tumors. *Journal of Pediatric Psychology*, *33*(10), 1142-1152. https://doi.org/10.1093/jpepsy/jsn035

Brinkman, T. M., Palmer, S. L., Chen, S., Zhang, H., Evankovich, K., Swain, M. A., Bonner, M.J.,Janzen, L., Knight, S., Armstrong, C.L., Boyle, R., & Gajjar, A. (2012). Parent-reported social outcomes after treatment for pediatric embryonal tumors: a prospective longitudinal study. *Journal of Clinical Oncology*, *30*(33), 4134. https://doi.org/10.1200/JCO.2011.40.6702

Cancer Research UK (2019). *Children's Cancer Statistics.* https://www.cancerresearchuk.org/sites/default/files/cstream-node/child_inc_iccc_groups_0.pdf.

Carroll, C., Clare, I., Watson, P., Hawkins, M. M., Spoudeas, H., Walker, D., Holland, A., & Ring, H. A. (2013). Effects of early childhood posterior fossa tumours on IQ. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(9), e1. https://doi.org/10.1136/jnnp-2013-306103.8

Castellino, S. M., Ullrich, N. J., Whelen, M. J., & Lange, B. J. (2014). Developing interventions for cancer-related cognitive dysfunction in childhood cancer survivors. *Journal of the National Cancer Institute*, *106*(8), dju186. https://doi.org/10.1093/jnci/dju186

De Ruiter, M. A., Van Mourik, R., Schouten-Van Meetren, A. Y., Grootenhuis, M. A., & Oosterlaan, J. (2013). Neurocognitive consequences of a paediatric brain tumour and its treatment: A meta-analysis. *Developmental Medicine & Child Neurology*, *55*(5), 408-417. https://doi.org/10.1111/dmcn.12020

Dorris, L., Young, D., Barlow, J., Byrne, K., & Hoyle, R. *Human Cognitive Empathy across the Lifespan.* (in-preparation)

Duffner, P. K. (2010). Risk factors for cognitive decline in children treated for brain tumors. *European Journal of Paediatric Neurology*, *14*(2), 106-115. https://doi.org/10.1016/j.ejpn.2009.10.005

Emond, A., Edwards, L., Peacock, S., Norman, C., & Evangeli, M. (2016). Social competence in children and young people treated for a brain tumour. *Supportive Care in Cancer*, *24*(11), 4587-4595. https://doi.org/10.1007/s00520-016-3301-4

Gatta, G., Zigon, G., Capocaccia, R., Coebergh, J. W., Desandes, E., Kaatsch, P., Pastore, G., Peris-Bonet, R., Stiller, C. A., & the EUROCARE Working Group. (2009). Survival of European children and young adults with cancer diagnosed 1995–2002. *European Journal of Cancer*, *45*(6), 992-1005. https://doi.org/10.1016/j.ejca.2008.11.042

Geraci, A., Surian, L., Ferraro, M., & Cantagallo, A. (2010). Theory of Mind in patients with ventromedial or dorsolateral prefrontal lesions following traumatic brain injury. *Brain Injury*, *24*(7-8), 978-987. https://doi.org/10.3109/02699052.2010.487477

Gheysen, M., Sleurs, C., Jacobs, S., Lemiere, J., & Uyttebroeck, A. (2018). Therapy-related long-term effects in childhood posterior fossa tumors. *Journal of Neurology and Neuroscience, 9(2),* 252. https://doi.org/10.21767/2171-6625.1000252

Harrington, D. L., Lee, R. R., Boyd, L. A., Rapcsak, S. Z., & Knight, R. T. (2004). Does the representation of time depend on the cerebellum? Effect of cerebellar stroke. *Brain*, *127*(3), 561-574. https://doi.org/10.1093/brain/awh065

Henry, J. D., Phillips, L. H., Crawford, J. R., Ietswaart, M., & Summers, F. (2006). Theory of mind following traumatic brain injury: The role of emotion recognition and executive dysfunction. *Neuropsychologia*, *44*(10), 1623-1628. https://doi.org/10.1016/j.neuropsychologia.2006.03.020

Hoche, F., Guell, X., Sherman, J. C., Vangel, M. G., & Schmahmann, J. D. (2016). Cerebellar contribution to social cognition. *The Cerebellum*, 15(6), 732-743. https://doi.org/10.1007/s12311-015-0746-9

Hocking, M. C., McCurdy, M., Turner, E., Kazak, A. E., Noll, R. B., Phillips, P., & Barakat, L. P. (2015). Social competence in pediatric brain tumor survivors: Application of a model from social neuroscience and developmental psychology. *Pediatric Blood & Cancer*, *62*(3), 375-384. https://doi.org/10.1002/pbc.25300

McKenzie, K., Murray, G., Murray, A., Delahunty, L., Hutton, L., Murray, K., & O'hare, A. (2019). Child and Adolescent Intellectual Disability Screening Questionnaire to identify children with intellectual disability. *Developmental Medicine & Child Neurology*, 61(4), 444-450. https://doi.org/10.1111/dmcn.13998

O'Halloran, C. J., Kinsella, G. J., & Storey, E. (2012). The cerebellum and neuropsychological functioning: a critical review. *Journal of Clinical and Experimental Neuropsychology*, *34*(1), 35-56. https://doi.org/10.1080/13803395.2011.614599

Palmer, S. L., Goloubeva, O., Reddick, W. E., Glass, J. O., Gajjar, A., Kun, L., Merchant, T.E., & Mulhern, R. K. (2001). Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. *Journal of Clinical Oncology*, *19*(8), 2302-2308. https://doi.org/10.1200/JCO.2001.19.8.2302

Palmer, S. L., Gajjar, A., Reddick, W. E., Glass, J. O., Kun, L. E., Wu, S., Xiong, X., & Mulhern, R. K. (2003). Predicting intellectual outcome among children treated with 35-40 Gy craniospinal irradiation for medulloblastoma. *Neuropsychology*, *17*(4), 548. https://doi.org/10.1037/0894-4105.17.4.548

Palmer, S. L., Armstrong, C., Onar-Thomas, A., Wu, S., Wallace, D., Bonner, M. J., Schreiber, J., Swain, M., Chapieski, L., Mabbott, D., Knight, S., Boyle, R., & Gajjar, A. (2013). Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. *Journal of Clinical Oncology*, *31*(28), 3494. https://doi.org/10.1200/JCO.2012.47.4775

Riva, D., & Giorgi, C. (2000). The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain*, *123*(5), 1051-1061. https://doi.org/10.1093/brain/123.5.1051

Schmahmann, J. D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *16*(3), 367-378. https://doi.org/10.1176/jnp.16.3.367

Scottish Government (2020). *Introducing The Scottish Index of Multiple Deprivation 2020.* https://www.gov.scot/collections/scottish-index-of-multiple-deprivation-2020/

Shirani, A., Newton, B. D., & Okuda, D. T. (2017). Finger tapping impairments are highly sensitive for evaluating upper motor neuron lesions. *BMC Neurology*, *17*(1), 55. https://doi.org/10.1186/s12883-017-0829-y

Snodgrass, C., & Knott, F. (2006). Theory of mind in children with traumatic brain injury. *Brain Injury*, *20*(8), 825-833. https://doi.org/10.1080/02699050600832585

Stavinoha, P. L., Askins, M. A., Powell, S. K., Pillay Smiley, N., & Robert, R. S. (2018). Neurocognitive and psychosocial outcomes in pediatric brain tumor survivors. *Bioengineering*, *5*(3), 73. https://doi.org/10.3390/bioengineering5030073

Vannatta, K., Gartstein, M. A., Short, A., & Noll, R. B. (1998). A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self-ratings. *Journal of Pediatric Psychology*, *23*(5), 279-287. https://doi.org/10.1093/jpepsy/23.5.279

Voigt, R. G., & Accardo, P. J. (2016). Mission impossible? Blaming primary care providers for not identifying the unidentifiable. *Pediatrics*, *138*(2). https://doi.org/10.1542/peds.2016-0432

Wechsler, D. (2011). *Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II)*. San Antonio, TX: NCS Pearson.

Wechsler, D. (2014). *Wechsler intelligence scale for children-fifth edition. Bloomington,* MN: Pearson.

Willard, V. W., Allen, T. M., Hardy, K. K., & Bonner, M. J. (2017). Social functioning in survivors of pediatric brain tumors: Contribution of neurocognitive and social-cognitive skills. *Children's Health Care*, *46*(2), 181-195. https://doi.org/10.1080/02739615.2015.1124769

Yeates, K. O., Bigler, E. D., Dennis, M., Gerhardt, C. A., Rubin, K. H., Stancin, T., Taylor, H.G., & Vannatta, K. (2007). Social outcomes in childhood brain disorder: a heuristic integration of social neuroscience and developmental psychology. *Psychological Bulletin*, *133*(3), 535-556. https://doi.org/10.1037/0033-2909.133.3.535

Zyrianova, Y., Alexander, L., & Faruqui, R. (2016). Neuropsychiatric presentations and outcomes in children and adolescents with primary brain tumours: Systematic review. *Brain Injury*, *30*(1), 1-9. https://doi.org/10.3109/02699052.2015.1075590

Chapter 2

B) Major Research Project: Secondary Analysis Paper

Adaptive Functioning in Children with Early Onset Seizures

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Plain Language Summary

Title: Adaptive Functioning in Children with Early Onset Seizures

Background: Repeated seizures in infancy can lead to negative impacts on adaptive functioning (Reilly et al., 2019), our ability to carry out tasks of everyday living. Studies demonstrate that experiencing seizures early in life can affect the brain during an important time of child development, later impacting on their education, psychological functioning and overall quality of life (Reilly et al., 2015). If problems with adaptive functioning are identified early, support can be offered to parents/carers to help them understand these difficulties, during a time when they may be experiencing increased stress (Bakula et al., 2021). This understanding can also help to support the child's learning so that they can achieve the best quality of life.

Aims and Questions: This study aimed to examine adaptive functioning skills in infants who experienced early onset seizures.

Methods: This study included children and families who took part in a larger project called the 'GACE' study, which explored genetic and autoimmune causes of epilepsy. This study included 301 young children who had a diagnosis of epilepsy or experienced repeated seizures in the first 3 years of life. Parents/carers completed questionnaires at two time-points: 1) at registration with the study and 2) 1-2 years later. The questionnaires measured adaptive functioning and level of parental stress.

Ethical Issues: Ethical approval for this study was obtained by the National Health Service Integrated Research Application System and from the local authorities within which the study took place. All information is stored safely in accordance with GDPR

(2018) and local NHS policy. Results from this study were anonymised and therefore individual results are not identifiable.

Main Findings and Conclusions: This study found that over 40% of children with early onset seizures experienced difficulties in adaptive functioning at preschool age. Regular monitoring of development and support for parents/carers is needed at an early stage.

Practical applications and dissemination: These results inform our understanding of how seizures in the early years can impact on child development. The findings highlight the importance of monitoring adaptive functioning skills from an early age. This study will be published in a scientific journal, presented at relevant conferences and will also be shared with clinicians from local NHS services.

References

Bakula, D. M., Wetter, S. E., Peugh, J. L., & Modi, A. C. (2021). A Longitudinal Assessment of Parenting Stress in Parents of Children with New-Onset Epilepsy. *Journal of Pediatric Psychology*, *46*(1), 91-99. https://doi.org/10.1093/jpepsy/jsaa091

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F., Aylett, S. E., Burch, V., Gilberg, C., Scott, R.C., & Neville, B. G. (2015). Factors associated with quality of life in active childhood epilepsy: a population-based study. *European Journal of Paediatric Neurology*, *19*(3), 308-313. https://doi.org/10.1016/j.ejpn.2014.12.022

Reilly, C., Atkinson, P., Memon, A., Jones, C., Dabydeen, L., Das, K. B., Gilberg, C., Neville, B.G.R., Mahoney, J.M., & Scott, R. C. (2019). Global development and adaptive behaviour in children with early-onset epilepsy: a population-based case–control study. *Developmental Medicine & Child Neurology*, *61*(2), 145-151. https://doi.org/10.1111/dmcn.13926

Abstract

Background

We describe the adaptive functioning of infants with newly diagnosed seizures and explore the relationship with clinical and demographic factors in identifying those at increased risk of developmental issues.

Materials and Methods

Participants included 120/301 parent/carers of children who were part of a larger study of genetic aetiologies (GACE study). Index children were aged <3 years and presented with: 1) a new diagnosis of epilepsy, 2) >2 seizures that occurred within a 24 hour period, or 3) recurrent seizures that lasted longer than 10 minutes. Parents completed two measures at baseline and follow up: Adaptive Behaviour Assessment Scale-2 (ABAS-2) and the Parenting Stress Index-Short Form (PSI-SF). Relevant clinical and demographic information was collated from a proforma used at clinic and a parent/carer questionnaire.

Results

Findings suggest that over 22% of participants had significant impairment in adaptive functioning at baseline (mean age 21 months) and over 41% of those who completed data at follow up experienced difficulties in adaptive functioning at preschool age (mean age 41 months). At the time of registration with the study, 31% of children had global developmental delay and 21% had drug resistant seizures. Over 50% of participants resided in areas of relative socioeconomic deprivation. Clinician rated global developmental delay and parental stress were found to predict adaptive functioning at baseline and follow up.

Conclusions

Many infants with early onset seizures present with developmental vulnerabilities which are identifiable from a young age. Regular monitoring is indicated to support those at increased risk of poorer cognitive development.

Key words: Epilepsy, Infants, Adaptive Functioning, Parental Stress.

1. Introduction

Children diagnosed with epilepsy in the early years are at increased risk of impairments in cognitive and adaptive functioning (Berg, 2011; Reilly et al., 2019), particularly those diagnosed before the age of 3 years (Berg et al., 2004). It is estimated that the prevalence of epilepsy in children under 2 years old is 70/100,000 (Eltze et al., 2013) and it has been suggested that seizures presenting before the age of 24 months independently contribute to lower quality of life (Reilly et al., 2015).

There is increasing recognition that although neurodevelopmental impairments can be attributed to underlying causes of epilepsy (for example, due to a structural lesion), they can also be a consequence of the seizure activity itself, particularly in the context of the developing brain (Scheffer et al., 2017). Reilly et al. (2019) reported in their sample of children with early onset epilepsy, 71% had delayed global development and 56% had significant deficits in adaptive behaviour, which refers to the skills required to complete tasks of everyday living, highlighting that these children were at increased risk of intellectual disability. Early adaptive behaviour predicts later school achievement in children with epilepsy, even after considering factors such as IQ and parental education (Berg et al., 2013). Given the associated neurodevelopmental difficulties, these findings suggest that young children experiencing seizures should be monitored and supported in order to meet their ongoing needs during a critical period of brain development (Berg et al., 2014).

A population-based study of newly diagnosed epilepsy in infants under 24 months demonstrated that an aetiology could not be identified in 49% of the cohort, an important finding given that 67% of the infants in their study presented with poor seizure control and developmental impairment (Eltze et al., 2013). Symonds et al. (2019) reported that seizure presentations before the age of 6 months were more likely to yield a genetic

diagnosis, highlighting the need for routine genetic testing in this population. They argued this would facilitate targeted treatment of underlying disease mechanisms and minimising the impact of seizures on the developing brain. This is important given that young age at onset of seizures has been identified as a risk factor for lower scores in adaptive functioning (Kerne & Chapieski, 2015).

Parents of children with epilepsy are at increased risk of experiencing stress and anxiety (Carson & Chapieski, 2016, Kerne & Chapieski, 2015), which may be influenced by concerns regarding their child's condition, monitoring the child's safety in the context of ongoing seizures and managing treatment plans, or perceptions of stigma towards their child's epilepsy, particularly in the first year following diagnosis (Wu et al., 2014). Although parents are likely to experience elevated parental stress at the time of diagnosis, this stress does not necessarily decrease over time (Bakula et al., 2021). Increased parental anxiety has been associated with problematic social behaviour (Carson & Chapieski, 2016) and lower scores on measures of adaptive functioning and quality of life (Jones & Reilly, 2016) in children with epilepsy.

There is evidence for an association between lower socioeconomic status and epilepsy in adults (Heaney, 2002; Hesdorferr et al., 2005), but the evidence for this relationship appears less conclusive in children, as demonstrated by another Scottish population-based study in children with early onset seizures (Hunter et al., 2020). Socioeconomic status may render families more vulnerable to both physical and mental health difficulties which may affect parental coping, due to the health inequalities experienced by those living with socioeconomic disadvantage (Reiss, 2013). Given the evidence that parental stress plays a role in child mental health (Hattangadi et al., 2020), it is crucial that attempts are made to recognise when families need support in order to promote healthy child development, particularly in the early years.

This study examined the relationship between early onset seizures and adaptive functioning to inform our understanding of the factors which influence child development in young children with epilepsy. The study was conducted in parallel with another study examining the role of parental stress within the same cohort.

Objectives

This study was interested in the following questions:

1. What is the prevalence of adaptive behaviour issues in infants with newly diagnosed seizures?
2. What is the relationship between clinical and demographic features and adaptive functioning in infants with newly diagnosed seizures?

2. Methods and Materials

This study used developmental data from the Genetic and Autoimmune Childhood Epilepsy (GACE) study, a large population level study examining the clinical features of genetic and autoimmune childhood epilepsy (Symonds et al., 2019), carried out over a three-year period in regional paediatric clinics and children's hospitals across Scotland. For full GACE protocol see Symonds et al. (2019).

2.1 Participants

Participants were children under 3 years of age at the time of recruitment. Children were invited to participate if they presented with: 1) a new diagnosis of epilepsy; 2) recurrent prolonged (>10 minutes) febrile seizures; 3) clusters of two or more febrile or afebrile seizures within a 24 hour period, or 4) febrile or afebrile status epilepticus (>30 minutes).

These inclusion criteria are based on the International League Against Epilepsy definition of epilepsy (Fisher et al., 2014).

2.2 Procedure

Parents/carers were asked to complete a range of postal questionnaires at two time points: 1) within two months of registration with the study and 2) at follow up one-year following baseline measures.

2.3 Measures

Genetic Testing

In the larger GACE study, participants underwent genetic testing to identify whether there was an underlying genetic aetiology for their seizures.

Adaptive Functioning

Parents completed the Adaptive Behaviour Assessment System, 2nd Edition (ABAS-2; Oakland & Harrison, 2008). This has been normed and validated for children aged 0 to 5 years old. It measures the child's adaptive functioning across three domains: conceptual, social and practical skills of everyday living, which are then combined to provide the General Adaptive Composite (GAC). This is an overall measure of adaptive functioning, which can be understood by comparing this to other children of a similar age. The ABAS-2 has demonstrated good psychometric properties in a US population (Oakland & Algna, 2011).

Parenting Stress

Parents completed the Parenting Stress Index- Short Form, 4th edition (PSI-SF-4; Abidin, 2012) as a measure of stress in the parent-child system. It operationalises parental stress across three domains: parental distress (PD), parent-child dysfunctional interaction (P-CDI) and difficult child (DC). These scores are then combined to provide a total stress score. The PSI-SF-4 has been validated and demonstrated acceptable psychometric properties (Holly et al., 2019).

Clinical and Demographic Information

Clinical data was extracted from the larger GACE study (appendix 2.4, p.136) . For the purpose of this study, a sub-selection of demographic and clinical variables was included in the analysis. This includes age at first seizure, presence of an identified aetiology of seizures (genetic or other), whether the seizures were drug resistant, whether the child had clinician rated global developmental delay, and if they had a diagnosis of epilepsy. Demographic information collected included age at baseline and follow up, sex, and socioeconomic status. Socioeconomic status was measured using the Scottish Index of Multiple Deprivation (SIMD), which is ascertained from an individual's postcode and ranks areas from most deprived to least deprived quintile (1 to 5). It takes into account relative disadvantage based on factors such as income, crime, health and housing (Scottish Government, 2020a).

2.4 Data Analysis

Descriptive statistics and incidence data were reported to examine developmental risk in this population. Correlational, one way analysis of variance and non-parametric equivalent tests were used to investigate the relationship between clinical features of early

onset seizures, parental stress and adaptive functioning. T-tests were carried out to investigate whether there was a difference in adaptive functioning scores at baseline and follow up. Hierarchical linear regressions were used to examine the predictors of adaptive functioning.

2.5 Ethics

Ethical approval for this study was obtained by the National Health Service Integrated Research Application System and from the local authorities within which the study took place; REC Reference 13/WS/0299; R&D Reference GN12KH569 (appendix 2.5, p.139).

3. Results

Descriptive statistics are displayed in table 2.1. 121/301 participants (39.9%; 54% male) completed a measure of adaptive functioning at baseline, of which 52 (43.3%) were lost to follow up. Almost 53% of our sample were children living in SIMD quintiles 1 and 2, the most deprived areas in Scotland. Those from higher SIMD quintiles (i.e. the least deprived areas) were more likely to complete this part of the study x^2 (4, N=289) = 10.092, p=.039, phi =.192) and more likely to take part at both baseline and follow up x^2 (4, N=289) = 15.517, p=.004, phi= .232). The average time between completing questionnaires at time 1 (baseline) and time 2 (follow-up) was 21 months (SD = 9.49). 98% of participants underwent testing to identify an underlying aetiology, of which 27% had a confirmed genetic aetiology. The types of first seizures experienced by children included febrile, tonic clonic, focal, absences and status epilepticus.

Table 2.1.

Descriptive Statistics of Clinical Features

		N	Missing (%)	Mean (median)	Min	Max	*SD*	% in 'Extremely Low' range***
Age (months)								
	Baseline	132	169 (56.15)	22.13 (21)	1	57	11.65	
	Follow up	75	226 (75.08)	41.05 (40)	13	71	14.86	
Global Adaptive Composite (GAC)								
	Baseline	120	181 (60.13)	85.18 (86.50)	42	144	19.10	22.5
	Follow up	68	233 (77.41)	81.37 (84.50)	40	133	27.01	41.2
Parenting Stress Index (PSI)								
	Baseline	125	176 (58.47)	68.58	36	135	23.85	
	Follow up	74	227 (75.42)	70.55	37	124	23.51	
Age at first seizure (months)		300	1	12.95 (11)	0	36	9.14	
		N	**%**					
Scottish Index of Multiple Deprivation (SIMD*)								
Quintile	1	94	31.2					
	2	65	21.6					
	3	54	17.9					
	4	38	12.6					
	5	38	12.6					
	Total	289	96					
	Missing/unknown	12	4					
Sex								

Male	162	53.8
Female	139	46.2
Aetiology		
Genetic	82	27.21
Infectious	1	.3
Metabolic	1	.3
Structural	10	3.3
Unknown	201	66.8
Missing (not tested)	6	2
Global Developmental Delay**		
Yes	92	30.6
No	209	69.4
Drug Resistant Seizures		
Yes	66	21.9
No	235	78.1
Diagnosis of Epilepsy		
Yes	202	67.1
No	99	32.9

Total N=301

*SIMD: Scottish Index of Multiple Deprivation

**Global Developmental Delay as rated by clinician, defined by significant delay in two or more domains

***'Extremely Low' range on the ABAS-2 (>2 standard deviations below the mean; GAC score ≤70, <2nd percentile)

22.5% of participants scored within the “extremely low” range on the ABAS-2 at baseline (>2 standard deviations below the mean; GAC score ≤70, <2nd percentile), and 41.2% at follow up, highlighting a high prevalence of “extremely low” adaptive functioning scores over time. When considering only the participants who completed data at both baseline and follow up (N=49), the prevalence rates of “extremely low” scores on the ABAS-2 were 18.4% and 28.6%, respectively. There was a wide range in adaptive functioning scores, highlighting the variability in this sample. 30.6% of children were rated by their clinician as having global developmental delay, 21.9% had drug resistant seizures and 67.1% received a diagnosis of epilepsy, indicating that this group of children are at risk of developmental vulnerabilities. The average age of children taking part in the study was 22 months at baseline and 41 months at follow up (median ages were 21 and 40 months, respectively). The average age at first seizure was 13 months (median 11 months).

With regards to levels of parental stress, 6.4% of parents at baseline and 5.4% at follow up reported levels within the clinically significant range (scores greater than 110, >85th percentile in the normative sample; Abidin, 2012).

Pearson’s correlation, chi squared and analysis of variance tests were carried out, where assumptions were met, to explore the relationship between clinical features and adaptive functioning at baseline (see appendix 2.7, p.140).

Table 2.2.

Significant Associations with Adaptive Functioning at Baseline

	GAC at Baseline		
	Pearson's R	*N*	*p*
Parental Stress at baseline	-.558	114	<.001
Parental Stress at follow up	-.458	54	.001
Global Developmental Delay	-.361	120	<.001
Male	-.256	120	.005
Age at baseline	-.242	120	.008
Epilepsy Diagnosis	-.222	120	.015
Drug resistant seizures	-.191	120	.037

GAC= Global Adaptive Composite Score

Results suggest that parents of children with lower adaptive functioning had higher parental stress at baseline and follow up. Lower adaptive functioning at baseline was associated with having global developmental delay, a diagnosis of epilepsy, drug resistant seizures, with older age of child and male sex of the child. There was a strong correlation between adaptive functioning at baseline and follow up (see table 2.3). Spearman's Rho tests were carried out to investigate the relationship with clinical variables at follow up.

Table 2.3.

Significant Associations with Adaptive Functioning at Follow Up

	GAC at Follow Up		
	Spearman's Rho	*N*	*p*
Global Developmental Delay	-.607	68	<.001
GAC at baseline	.580	49	<.001
Parental Stress at follow up	-.494	67	<.001
Drug Resistant Seizures	-.491	68	<.001
Parental Stress at Baseline	-.324	52	.019

GAC=Global Adaptive Composite Score

Lower adaptive functioning scores at follow up were associated with clinician rated global developmental delay, having drug resistant seizures, and parental stress at baseline and follow up (table 2.3).

There was no statistically significant difference in adaptive functioning at baseline (M= 87.04, SD= 16.44) and follow up (M= 87.20, SD= 25.17), T (48) = -.058 , p=.954), and no statistically significant difference in adaptive functioning between those who had an identified aetiology and those who did not at baseline (F (2, 117) = 1.341 , p= .266) or follow up (x^2 (2, N= 68) = 3.494 , p= .174).

There was a significant relationship between having an identified aetiology and drug resistant seizures, x^2 (2, N= 295) = 47.641, p =<.001, phi = .402, and a diagnosis of global developmental delay, x^2(2, N=295) = 40.837, p<.001, phi = .372, indicating that children who had seizures with a genetic cause were more likely to have treatment resistant seizures and global developmental impairments.

A statistically significant difference was identified in adaptive functioning scores at follow up according to SIMD quintile, x^2 (4, N=64) = 18.991, p=.001, but not at baseline, (F (4, 108) = .371, p= .829). There was also a significant association between completing follow up questionnaires and the index child both having a diagnosis of epilepsy x^2(1, N= 301) = 4.13, phi=.13, p=<.05, and an identified aetiology x^2(2, N=295) = 7.13, p=.05, phi=.16, highlighting that those clinical factors can influence the retention of participants across time.

Relationship between clinical features and adaptive functioning at baseline

A hierarchical multiple regression was carried out to assess the predictors of adaptive functioning measures at baseline and assumptions were met. Parental stress and global developmental delay were entered at Step 1, explaining 37.4% of the variance in adaptive functioning. After entry of sex, age and epilepsy were entered at step 2, the

total variance explained by the model as a whole was 41.4%, $F(5,108) = 15.284$, $p < .001$. The other variables explained an additional 4% of the variance in adaptive functioning, but this was not statistically significant, R squared change = .040, F change (3,108) = .2.470, p=.066. In the second model, three clinical features were statistically significant; with parental stress being the strongest predictor, followed by global developmental delay and sex (being male; appendix 2.7, p.143).

Relationship between clinical features and adaptive functioning at follow up

A hierarchical multiple linear regression was then carried out to assess the predictors of adaptive functioning measures at follow up, as described above. Parental stress and global developmental delay were entered at Step 1, explaining 49.1% of the variance in adaptive functioning at follow up. After entry of SIMD at step 2, the total variance explained by the model as a whole was 60%, $F(3, 60) = 29.994$, $p<.001$. These variables explained an additional 11% of the variance in adaptive functioning, R squared change = .109, F change (1,60) = 16.398, $p<.001$. In the final model, all features were statistically significant, with global developmental delay being the strongest predictor, followed by SIMD and then parental stress (appendix 2.7, p.143).

4. Discussion

We found high rates of deficits in adaptive functioning observable during the first three years of life, highlighting that these children experienced significant difficulties in everyday living skills, compared to age matched peers. The prevalence of adaptive functioning impairments appeared to be higher in this sample at follow up, however, the analysis suggests there was no statistically significant difference across the two time points. This may be explained by the high attrition rate in those who completed data at

only one time point (i.e. at baseline or follow up only) and reduced statistical power to detect change. Difficulties in adaptive functioning may become more apparent over time as a child develops; for instance, due to changes in parental expectations as the child gets older, or due to resulting deficits in adaptive functioning among those with difficult to treat seizures or complex clinical presentations.

Although developmental vulnerabilities are observable to the clinical care team at a very early stage, a formal measure of adaptive functioning, such as the ABAS, acts as a screening tool to highlight those in need of support and offers useful information in terms of how these developmental vulnerabilities manifest through everyday living skills. Having a genetic aetiology was associated with global developmental delay and seizures resistant to treatment. Perhaps the underlying genetic mechanisms responsible for difficult to treat seizures render the developing brain vulnerable to repeated neurological insult over time, leading to reduced adaptive functioning (Papazoglou et al., 2010; Scheffer et al., 2017) that becomes more apparent over time.

Age at first seizure was not significantly associated with adaptive functioning, which was surprising given previous research emphasising the negative impact of seizures on the developing brain (Scheffer et al., 2017). This may be partly related to parent expectations based on developmental stage and the relatively young age of the index children. Furthermore, developmental questionnaires have only a moderate correlation with later IQ tests (Alexander & Reynolds, 2020). However, as predicted, parental stress was associated with adaptive functioning at baseline and follow up, suggesting that parents who report higher levels of stress perceive their children to be functioning at a level lower than their peers. Parental stress did not change over time, which is in line with previous research (Bakula et al., 2021). Boys were more likely to score lower on adaptive functioning, which is in keeping with previous studies suggesting

they may be more at risk of developmental vulnerabilities (Woolfenden et al., 2014), although further research on sex differences is required (Oakland & Algina, 2011).

Over 50% of participants from this sample resided in areas of relative socioeconomic deprivation, reflected by representation from SIMD quintiles 1 and 2, the most deprived areas in Scotland. This is consistent with other studies demonstrating a high representation of individuals from lower socioeconomic backgrounds in early onset seizures (Hunter et al., 2020), which is important to consider given the variety of health inequalities already experienced by these families (Reiss, 2013) that may impact on parental stress in the context of children with developmental vulnerabilities. Those living with less socioeconomic disadvantage were more likely to take part in this study and scored higher on measures of adaptive functioning at follow up, which should be taken into account when interpreting these findings. Further studies are warranted to explore the relationship between environmental and epilepsy risk factors on child development.

Limitations

Given infants often experience seizures that are not epileptic in nature (Patel et al., 2015; Verity & Goulding, 1991), seizures likely resolved for many children in this study, for whom we would not expect to see the same impairments in adaptive functioning. However, 67% of participants received a diagnosis of epilepsy during the study period. Given the specific inclusion criteria used in this study, it was agreed that this sample was reasonably representative of early onset epilepsy and could provide useful information to add to the evidence base for this patient group.

Analyses on the overall sample highlighted that a number of families from lower socioeconomic areas did not complete any questionnaire data, and as such, our findings may not capture information from those who experience socioeconomic disadvantage.

Conclusion

Clinicians should carefully review child development and involve multi-disciplinary colleagues to address developmental difficulties and psychosocial risks, given the risks of poor educational attainment and cognitive disorders amongst children with epilepsy. These results highlight that developmental difficulties are prevalent and observable to families and clinicians from an early age and impact on their ability to carry out everyday activities. Support for parents is indicated for those caring for a child with developmental needs in order to scaffold the family system to promote adaptive functioning and quality of life. This is particularly important for "hard to reach" populations, such as those living with socioeconomic disadvantage. These families may be more vulnerable to health inequalities impacting on their ability to manage a chid with additional needs and access appropriate care. These findings have implications for service providers particularly in the context of promoting infant mental health and early interventions for better long-term outcomes, which is reflected in Scottish government policy and political drivers (Scottish Government, 2020b).

Conflicts of Interest

The author has declared that they have no competing or potential conflicts of interest.

References

Abidin, R. R. (2012). *Parenting Stress Index-Short Form, Fourth Edition (PSI-4).* Lutz, FL: Psychological Assessment Resources.

Alexander, R. M., & Reynolds, M. R. (2020). Intelligence and adaptive behavior: a meta-analysis. *School Psychology Review*, *49*(2), 85-110. https://doi.org/10.1080/2372966X.2020.1717374

Bakula, D. M., Wetter, S. E., Peugh, J. L., & Modi, A. C. (2021). A Longitudinal Assessment of Parenting Stress in Parents of Children with New-Onset Epilepsy. *Journal of Pediatric Psychology*, *46*(1), 91-99. https://doi.org/10.1093/jpepsy/jsaa091

Berg, A. T., Smith, S. N., Frobish, D., Beckerman, B., Levy, S. R., Testa, F. M., & Shinnar, S. (2004). Longitudinal assessment of adaptive behavior in infants and young children with newly diagnosed epilepsy: influences of etiology, syndrome, and seizure control. *Pediatrics*, *114*(3), 645-650. https://doi.org/10.1542/peds.2003-1151-L

Berg, A. T. (2011). Epilepsy, cognition, and behavior: the clinical picture. *Epilepsia*, *52*, 7-12. https://doi.org/10.1111/j.1528-1167.2010.02905.x

Berg, A. T., Caplan, R., Baca, C. B., & Vickrey, B. G. (2013). Adaptive behavior and later school achievement in children with early-onset epilepsy. *Developmental Medicine & Child Neurology*, *55*(7), 661-667. https://doi.org/10.1111/dmcn.12143

Berg, A. T., Loddenkemper, T., & Baca, C. B. (2014). Diagnostic delays in children with early onset epilepsy: impact, reasons, and opportunities to improve care. *Epilepsia*, *55*(1), 123-132. https://doi.org/10.1111/epi.12479

Carson, A. M., & Chapieski, L. (2016). Social functioning in pediatric epilepsy reported by parents and teachers: Contributions of medically related variables, verbal skills,

and parental anxiety. *Epilepsy & Behavior*, *62*, 57-61. https://doi.org/10.1016/j.yebeh.2016.06.021

Eltze, C. M., Chong, W. K., Cox, T., Whitney, A., Cortina-Borja, M., Chin, R. F., Scott, R.C., & Cross, J. H. (2013). A population-based study of newly diagnosed epilepsy in infants. *Epilepsia*, *54*(3), 437-445. https://doi.org/10.1111/epi.12046

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475-482. https://doi.org/10.1111/epi.12550

Hattangadi, N., Cost, K. T., Birken, C. S., Borkhoff, C. M., Maguire, J. L., Szatmari, P., & Charach, A. (2020). Parenting stress during infancy is a risk factor for mental health problems in 3-year-old children. *BMC Public Health*, *20*(1), 1-7. https://doi.org/10.1186/s12889-020-09861-5

Heaney, D. C., MacDonald, B. K., Everitt, A., Stevenson, S., Leonardi, G. S., Wilkinson, P., & Sander, J. W. (2002). Socioeconomic variation in incidence of epilepsy: prospective community based study in south east England. *BMJ*, *325*(7371), 1013-1016. https://doi.org/ 10.1136/bmj.325.7371.1013

Hesdorffer, D. C., Tian, H., Anand, K., Hauser, W. A., Ludvigsson, P., Olafsson, E., & Kjartansson, O. (2005). Socioeconomic status is a risk factor for epilepsy in Icelandic adults but not in children. *Epilepsia*, *46*(8), 1297-1303. https://doi.org/10.1111/j.1528-1167.2005.10705.x

Holly, L. E., Fenley, A. R., Kritikos, T. K., Merson, R. A., Abidin, R. R., & Langer, D. A. (2019). Evidence-base update for parenting stress measures in clinical

samples. *Journal of Clinical Child & Adolescent Psychology*, *48*(5), 685-705. https://doi.org/10.1080/15374416.2019.1639515

Hunter, M. B., Yoong, M., Sumpter, R. E., Verity, K., Shetty, J., McLellan, A., & Chin, R. F. (2020). Incidence of early-onset epilepsy: A prospective population-based study. *Seizure*, *75*, 49-54. https://doi.org/10.1016/j.seizure.2019.12.020

Jones, C., & Reilly, C. (2016). Parental anxiety in childhood epilepsy: a systematic review. *Epilepsia*, *57*(4), 529-537. https://doi.org/ 10.1111/epi.13326

Kerne, V., & Chapieski, L. (2015). Adaptive functioning in pediatric epilepsy: contributions of seizure-related variables and parental anxiety. *Epilepsy & Behavior*, *43*, 48-52. https://doi.org/ 10.1016/j.yebeh.2014.11.030

Oakland, T., & Algina, J. (2011). Adaptive behavior assessment system-II parent/primary caregiver form: Ages 0–5: Its factor structure and other implications for practice. *Journal of Applied School Psychology*, *27*(2), 103-117. https://doi.org/10.1080/15377903.2011.565267

Oakland, T., & Harrison, P. L. (Eds.). (2011). *Adaptive behavior assessment system-II: Clinical use and interpretation*. Academic Press.

Papazoglou, A., King, T. Z., & Burns, T. G. (2010). Active seizures are associated with reduced adaptive functioning in children with epilepsy. *Seizure*, *19*(7), 409-413. https://doi.org/10.1016/j.seizure.2010.06.007

Patel, N., Ram, D., Swiderska, N., Mewasingh, L. D., Newton, R. W., & Offringa, M. (2015). Febrile seizures. *BMJ*, *351*, 1-7. https://doi.org/10.1136/bmj.h4240

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F., Aylett, S. E., Burch, V., ... & Neville, B. G. (2015). Factors associated with quality of life in active childhood epilepsy: a population-based study. *European Journal of Paediatric Neurology*, *19*(3), 308-313. https://doi.org/10.1016/j.ejpn.2014.12.022

Reilly, C., Atkinson, P., Memon, A., Jones, C., Dabydeen, L., Das, K. B., ... & Scott, R. C. (2019). Global development and adaptive behaviour in children with early-onset epilepsy: a population-based case–control study. *Developmental Medicine & Child Neurology*, *61*(2), 145-151. https://doi.org/10.1111/dmcn.13926

Reiss, F. (2013). Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. *Social Science & Medicine*, *90*, 24-31. https://doi.org/ 10.1016/j.socscimed.2013.04.026

Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., ... & Zuberi, S. M. (2017). ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*, *58*(4), 512-521. https://doi.org/ 10.1111/epi.13709

Scottish Government (2020a). *Introducing The Scottish Index of Multiple Deprivation 2020.* https://www.gov.scot/publications/scottish-index-multiple-deprivation-2020/.

Scottish Government (2020b). *Perinatal and Infant Mental Health: Equality Impact Assessment Record.* https://www.gov.scot/publications/perinatal-infant-mental-health-eqia/pages/2/.

Symonds, J. D., Zuberi, S. M., Stewart, K., McLellan, A., O 'Regan, M., MacLeod, S., ... & Wilson, M. (2019). Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. *Brain*, *142*(8), 2303-2318. https://doi.org/10.1093/brain/awz195

Verity, C. M., & Golding, J. (1991). Risk of epilepsy after febrile convulsions: a national cohort study. *BMJ*, *303*(6814), 1373-1376. https://doi.org/ 10.1136/bmj.303.6814.1373

Woolfenden, S., Eapen, V., Williams, K., Hayen, A., Spencer, N., & Kemp, L. (2014). A systematic review of the prevalence of parental concerns measured by the Parents' Evaluation of Developmental Status (PEDS) indicating developmental risk. *BMC Pediatrics*, *14*(1), 1-13. https://doi.org/ 10.1186/1471-2431-14-231

Wu, Y. P., Follansbee-Junger, K., Rausch, J., & Modi, A. (2014). Parent and family stress factors predict health-related quality in pediatric patients with new-onset epilepsy. *Epilepsia*, *55*(6), 866-877. https://doi.org/ 10.1111/epi.12586

Appendices

Appendix 1.1: Author Guidelines for Child and Adolescent Mental Health

For full guidance, see:

https://acamh.onlinelibrary.wiley.com/hub/journal/14753588/forauthors.html

Contributions from any discipline that further clinical knowledge of the mental life and behaviour of children are welcomed. Papers need to clearly draw out the clinical implications for mental health practitioners. Papers are published in English. As an international journal, submissions are welcomed from any country. Contributions should be of a standard that merits presentation before an international readership. Papers may assume any of the following forms: Original Articles; Review Articles; Innovations in Practice; Narrative Matters; Debate Articles. CAMH considers the fact that services are looking at treating young adults up until the age of 25, with the evidence that brains continue to develop until the age of 25, as well as the fact that a lot of issues that affect young adults and students are also relevant and topical to older adolescents. CAMH offers a discretionary approach and will take into consideration papers that extend into young adulthood, if they are pertinent developmentally to the younger population and contribute further to a developmental perspective across adolescence and early adult years.

Research Articles offer our readers a critical perspective on a key body of current research relevant to child and adolescent mental health and maintain high standards of scientific practice by conforming to systematic guidelines as set out in the PRISMA statement. These articles should aim to inform readers of any important or controversial

issues/findings, as well as the relevant conceptual and theoretical models, and provide them with sufficient information to evaluate the principal arguments involved. All review articles should also make clear the relevancy of the research covered, and any findings, for clinical practice. We ask authors to include within their review article a flow diagram that illustrates the selection and elimination process for the articles included in their review or meta-analysis, as well as a completed PRISMA Checklist. The journal requires the pre-registration of review protocols on any publicly accessible platform (e.g. The International Prospective Register of Systematic Reviews, or PROSPERO).

The journal requires the pre-registration of review protocols on any publicly accessible platform (e.g. The International Prospective Register of Systematic Reviews, or PROSPERO). Your Review Article should be no more than 8,000 words excluding tables, figures and references and no more than 10,000 including tables, figures and references.

The Equator Network is recommended as a resource on the above and other reporting guidelines for which the editors will expect studies of all methodologies to follow.

The title page of the manuscript should include the title, name(s) and address(es) of author(s), an abbreviated title (running head) of up to 80 characters, a correspondence address for the paper, and any ethical information relevant to the study (name of the authority, data and reference number for approval) or a statement explaining why their study did not require ethical approval.

Summary: Authors should include a structured Abstract not exceeding 250 words under the sub-headings: Background; Method; Results; Conclusions.

Key Practitioner Message: Below the Abstract, please provide 1-2 bullet points answering each of the following questions:

- **What is known?** - What is the relevant background knowledge base to your study? This may also include areas of uncertainty or ignorance.
- **What is new?** - What does your study tell us that we didn't already know or is novel regarding its design?
- **What is significant for clinical practice?** - Based on your findings, what should practitioners do differently or, if your study is of a preliminary nature, why should more research be devoted to this particular study.

Keywords: Please provide 4-6 keywords use MESH browser for suggestions

Headings: Original articles should be set out in the conventional format: Methods, Results, Discussion and Conclusion. Descriptions of techniques and methods should only be given in detail when they are unfamiliar. There should be no more than three (clearly marked) levels of subheadings used in the text.

All manuscripts should have an Acknowledgement section at the end of the main text, before the References. This should include statements on the following:

Study funding: Please provide information on any external or grant funding of the work

(or for any of the authors); where there is no external funding, please state this explicitly.

Conflicts of interest: Please disclose any conflicts of interest of potential relevance to the work reported for each of the authors. If no conflicts of interest exist, please include an explicit declaration of the form: "The author(s) have declared that they have no competing or potential conflicts of interest".

Appendix 1.2: Quality Assessment Tool from the National Heart, Lung and Blood Institute

Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Appendix 1.3: Systematic Review Search Strategies

Table 1

EBSCO CINAHL Search Strategy (completed 17/07/20).

S21	S9 AND S14 AND S20
S20	S15 OR S16 OR S17 OR S18 OR S19
S19	TI (("2007" or “2008” or “2009”) N5 (economic crash or cris*) OR AB (("2007" OR “2008” or “2009”) N5 (economic crash or cris*))
S18	TI (("2007" or “2008” or “2009”) N5 (financial crash or cris*) OR AB (("2007" OR “2008” or “2009”) N5 (financial crash or cris*))
S17	TI ((econom* N5 (recession* or depress*))) OR AB ((econom* N5 (recession* or depress*)))
S16	TI ("great recession") OR AB ("great recession")
S15	(MH "Economic Recession")
S14	S10 OR S11 OR S12 OR S13
S13	TI (("adolescent*" or "teenage*" or "young person*")) OR AB (("adolescent*" or "teenage*" or "young person*"))
S12	TI (child*) OR AB (child*)
S11	(MH "Adolescence+")
S10	(MH "Child+")
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S8	TI (suicide) OR AB (suicide)
S7	TI ((depression or anxiety)) OR AB ((depression or anxiety))
S6	TI (("mental health" or "mental* disorder*")) OR AB (("mental health" or "mental* disorder*"))
S5	(MH "Suicide+")
S4	(MH "Anxiety+")
S3	(MH "Depression+")
S2	(MH "Mental Disorders+")
S1	(MH "Mental Health")

Table 2

EBSCO PsycINFO Search Strategy (completed 17/07/20).

S24	S10 AND S17 AND S23
S23	S18 OR S19 OR S20 OR S21 OR S22
S22	TI (("2007" or “2008” or “2009”) N5 (economic crash or cris*) OR AB (("2007" OR “2008” or “2009”) N5 (economic crash or cris*))
S21	TI (("2007" or “2008” or “2009”) N5 (financial crash or cris*) OR AB (("2007" OR “2008” or “2009”) N5 (financial crash or cris*))
S20	TI ((econom* N5 (recession* or depress*))) OR AB ((econom* N5 (recession* or depress*)))
S19	TI ("great recession") OR AB ("great recession")
S18	TI ("economic recession") OR AB ("economic recession")
S17	S11 OR S12 OR S13 OR S14 OR S15 OR S16
S16	TI (("adolescent*" or "teenage*" or "young person*")) OR AB (("adolescent*" or "teenage*" or "young person*"))
S15	TI ("child*") OR AB ("child*")
S14	DE "Adolescent Psychology"
S13	DE "Child Psychology"
S12	DE "Adolescent Psychopathology"
S11	DE "Child Psychopathology"
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S9	TI ("suicid*") OR AB ("suicid*")
S8	TI ((depression or anxiety)) OR AB ((depression or anxiety))
S7	TI (("mental health" or "mental* disorder*")) OR AB (("mental health" or "mental* disorder*"))
S6	DE "Suicide" OR DE "Attempted Suicide" OR DE "Suicidality"
S5	DE "Anxiety" OR DE "Anxiety Sensitivity" OR DE "Computer Anxiety" OR DE "Health Anxiety" OR DE "Mathematics Anxiety" OR DE "Performance Anxiety" OR DE "Social Anxiety" OR DE "Speech Anxiety" OR DE "Test Anxiety"
S4	DE "Depression (Emotion)"
S3	DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive

	Depression" OR DE "Recurrent Depression" OR DE "Treatment Resistant Depression"
S2	DE "Mental Disorders" OR DE "Borderline States" OR DE "Thought Disturbances" OR DE "Affective Disorders" OR DE "Anxiety Disorders" OR DE "Autism Spectrum Disorders" OR DE "Bipolar Disorder" OR DE "Chronic Mental Illness" OR DE "Dissociative Disorders" OR DE "Eating Disorders" OR DE "Gender Dysphoria" OR DE "Mental Disorders due to General Medical Conditions" OR DE "Neurocognitive Disorders" OR DE "Neurodevelopmental Disorders" OR DE "Neurosis" OR DE "Paraphilias" OR DE "Personality Disorders" OR ...
S1	DE "Mental Health" OR DE "Mental Status"

Table 3

OVID Medline Search Strategy (completed 17/07/20).

1. exp Mental Health/
2. exp Mental Disorders/
3. exp Depression/
4. exp Anxiety/
5. exp Suicide/
6. (mental health or mental* disorder*).ti,ab.
7. psychological disorder*.ti,ab.
8. (depression or anxiety).ti,ab.
9. suicid*.ti,ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 8 or 9
11. exp Child/
12. exp Adolescent/
13. child*.ti,ab.
14. (adolescent* or teenager* or young person*).ti,ab.
15. 11 or 12 or 13 or 14
16. exp Economic Recession/
17. great recession.ti,ab.
18. (econom* adj5 (recession* or depress* or cris* or crash*)).ti,ab.
19. (("2007" or "2008" or "2009") adj5 (financial crash or cris*)).ti,ab.
20. (("2007" or "2008" or "2009") adj5 (economic crash or cris*)).ti,ab.
21. 16 or 17 or 18 or 19 or 20
22. 10 and 15 and 21
23. limit 22 to yr=”2008-Current”

Table 4

OVID Embase Search Strategy (completed 17/07/20).

1. exp mental health/
2. exp mental disease/
3. exp depression/
4. exp anxiety/
5. exp adolescent depression/
6. exp suicide/
7. (mental health or mental* disorder*).ti,ab.
8. psychological disorder*.ti,ab.
9. (depression or anxiety).ti,ab.
10. suicid*.ti,ab.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp child/
13. exp adolescent/
14. child*.ti,ab.
15. (adolescent* or teenage* or young person*).ti,ab.
16. 12 or 13 or 14 or 15
17. exp economic recession/
18. great recession.ti,ab.
19. (econom* adj5 (recession* or depress* or crash or cris*)).ti,ab.
20. (("2007" or "2008" or "2009") adj5 (financial crash or cris*)).ti,ab.
21. (("2007" or "2008" or "2009") adj5 (economic crash or cris*)).ti,ab.
22. 17 or 18 or 19 or 20 or 21
23. 11 and 16 and 22
24. limit 23 to yr="2008-Current"

Appendix 2.1: Original MRP Proposal

Cover Page

Title: Social Cognition in Childhood Cancer Survivors with Posterior Fossa Tumours

Student ID:

University Supervisor: Prof Liam Dorris

Field Supervisors: Dr Emanuela Molinari and Dr Claire Adey

Date of submission: 16th April 2020

Version number: 4

Abstract

Background

Paediatric brain tumour survivors are at high-risk of experiencing neuropsychological 'late effects' as a result of the tumour and its treatment, which may impact on psychological wellbeing, educational attainment and quality of life. Emerging evidence suggests that those who have tumours in the posterior fossa area of the brain are more likely to experience deficits in social cognition with associated negative social outcomes.

Aims

This study aims to examine whether children and young people with posterior fossa tumours experience deficits in cognitive empathy compared to healthy age matched controls.

Methods

This study will use a case control design. Participants will be assessed using direct and proxy measures of cognitive empathy: The Reading Eyes in the Mind Test (RMET), the "Faux Pas" test and the Empathy Systemizing Quotient. Cognitive ability and processing speed will also be assessed with standardised tests.

Participants

Participants for the clinical group will be children and young people aged between 6 and 18 years old, recruited from oncology/neurology clinics in tertiary paediatric centres in Edinburgh and Glasgow.

Applications

Results from this study could inform long-term follow up care for paediatric brain tumour survivors and highlight potential areas for intervention in order to improve psychological wellbeing and overall quality of life.

1. Introduction

Tumours of the brain and central nervous system are the most common solid tumours in children (Gatta et al., 2009). There are over 400 new childhood brain and CNS tumour diagnoses made each year in the UK (Cancer Research UK, 2019). Research suggests that up to 75% of children diagnosed with a brain tumour will now survive at least 5 years post diagnosis (Ostrom et al., 2015; Siegel et al., 2015), which reflects the significant advances in detection and intervention.

As a result of improving survival rates, there has been an increasing concern regarding neuropsychological late effects of both the disease and treatment, which are deficits that can emerge in the years following treatment and require ongoing monitoring. Factors predicting late effects include tumour variables (e.g. location and size), treatment variables (e.g. type of treatment, complications arising from treatment) and individual patient characteristics, such as age, premorbid ability and time since diagnosis (Stavinoha et al., 2018). It is well reported that childhood cancer survivors are at risk of experiencing neurocognitive deficits (De Ruiter et al., 2013; Robinson et al., 2010), showing poor outcomes across a wide range of cognitive functions, including IQ, attention, memory and executive functions (Castellino et al., 2014). Studies have shown that rates of neurocognitive deficits can reach up to 100% in children treated for a brain tumour (Duffner, 2010; Palmer et al., 2013). Previous longitudinal studies focussing on cognitive functions showed that the pattern of cognitive decline changes depending on the age at diagnosis and treatment (Palmer et al., 2003), suggesting that for children of pre-school age, the decline starts immediately post treatment. This, coupled with difficulties learning and acquiring new information (Palmer et al., 2001), puts younger children at risk of poor cognitive outcomes. In addition, the developing brain is more susceptible to damage

induced by radiation, which can further contribute to cognitive difficulties in younger children (Gheysen et al., 2018; Carrol et al., 2013).

It has also been reported that paediatric brain tumour survivors are at increased risk of poor social functioning (Bonner et al., 2008), although this area of late effects is less well understood. Studies have indicated that childhood brain tumour survivors experience lower peer-acceptance, increased isolation (Vannatta et al.,1998), and demonstrate poorer social awareness (Emond et al., 2016). In addition to late effects caused by the tumour and/or its treatment, this patient group are likely to experience missed opportunities for social engagement in formative years; they will require time away from peers in order to receive medical treatment and allow for time to recover (Brinkman et al., 2012), thereby preventing them from spending time among peers to develop these skills.

Yeates et al. (2007) proposed a model of social competence by which we can understand social outcomes in children and young people affected by brain disorder. They suggest social competence is made up of social adjustment, social interactions, and social information processing. The model indicates that factors related directly to the neurological insult and other independent factors (both risk and protective factors) can influence social competence and the relationship between these components (see Yeates et al., 2007 for review). By applying this model, Hocking et al. (2015) carried out a review on social competence in paediatric brain tumour survivors and reported that neurocognitive deficits may act as a mediator of poor social outcomes. They suggest that although the occurrence of neurocognitive late effects is well recognised, less is known about how these impact on functioning in other areas. For example, they suggest that in

social situations, those who take longer to process information and respond may be more likely to experience negative social interactions and decreased peer acceptance. There appears to be limited empirical evidence for deficits in social competence, as many studies use parent, peer or teacher measures, and this has been identified as a barrier to conducting research in this area (Hocking et al., 2015; Willard et al., 2017).

There is emerging evidence that children with tumours in the posterior fossa area of the brain (part of the intracranial cavity that contains the brain stem and the cerebellum, e.g. medulloblastomas or ependymomas) are at an increased risk of experiencing negative psychological and social outcomes, possibly due to the role of the cerebellum in regulating cognitive affective processes (Schmahmann, 2004; Zyrianova et al., 2016). The capacity to understand another individual's mental state and the ability to understand empathy has often been associated with the cerebellum via imaging studies (see O'Halloran et al., 2012 for review). Riva and Giorgi (2000) reported Autism Spectrum Disorder - like behaviours in children who had undergone cerebellar tumour resection, such as a decreased tolerance being around others and a tendency to avoid physical and eye contact. It is now recognised that the cerebellum is not only responsible for motor control but is critically involved in a wide range of neuropsychological functions (Schmahmann, 2004). This raises questions about the role of the cerebellum in cognitive empathy; and specifically, how empathy may be implicated in children and young people with tumours in the posterior fossa area of the brain.

Childhood brain tumour survivors are at increased risk of psychological difficulties such as depression (Zyrianova et al., 2016) and poor quality of life (Bell et al., 2018). Understanding the mechanisms underlying deficits in cognitive empathy may help to identify targets for intervention for this group, in order to help them achieve social

integration, thereby reducing their risk of developing ongoing psychological difficulties and improving overall quality of life.

Therefore, this study aims to examine whether cognitive empathy is impacted in children and young people recovering from posterior fossa tumours.

Aims & Hypotheses

This study aims to determine whether cognitive empathy is impacted in children recovering from tumours in the posterior fossa area of the brain.

The primary hypothesis is that children and young people recovering from brain tumours in the posterior fossa will score lower on measures of cognitive empathy, compared to typically developing peers. The secondary and exploratory hypothesis is that younger age and greater time since diagnosis will predict poorer scores of cognitive empathy.

2. Plan of Investigation

2.1. Participants

Participants will be children and young people aged 6 to 18 years old, with a diagnosis of a tumour in the posterior fossa and with a minimum post-treatment period of 1 year. The research team have identified a clinical cohort in Scotland of around 55 patients who will be contacted. A control group of approximately 40 – 50 healthy children and young people matched for age, sex and socioeconomic status will be recruited from schools across Glasgow and Edinburgh.

2.9.Inclusion and Exclusion Criteria

Inclusion Criteria: The study will include children and young people who have had a diagnosis of a posterior fossa tumour. These children will have received treatment in the form of surgery, chemotherapy, radiotherapy, or a combination of the above. They will be at least one year post-treatment and will not be receiving active therapy. We will include children and young people with English as a first language, as the measures used in the study have UK normative data for this population.

Exclusion Criteria: Children and young people with prior neurodevelopmental disorder will not be included in this study. Individuals with significant cognitive, physical or mental health impairment that would impact on their ability to engage in the cognitive assessment process will not be included in the study. This may include children and young people with a significant learning disability.

2.10. Recruitment Procedures

Participants will be recruited from long-term follow up clinics with a Consultant Neurologist or Oncologist at RHSC Edinburgh and RHC Glasgow. Due to the COVID-19 pandemic, routine out-patient appointments are being offered by telephone or by the video-conferencing technology Attend Anywhere. Participants will be informed about the study over the phone by a member of the clinical team, and if interested in taking part, the clinician will make a note of this in their case notes. A member of the research team will then make contact with the child's parent/carer, or with the young person themselves where appropriate, in order to send them an information pack about the study. Participants will be invited to take part in the research study at their school during normal hours. Written consent to take part in the study will be sought from the child or young

person above the age of 12 years and written assent and their parent consent for those under the age of 12 years.

For the control group, this information pack will be distributed to children and young people via their school teacher. Children and young people will be invited to take the information pack home for review by their parents/guardian (if applicable) and if interested in taking part, they will be asked to return a signed consent form to a member of the research team who will then make contact and recruit to the study as per the procedure for the clinical group.

2.11. Measures

Demographic and Clinical Information:

Demographic information such as age, sex, and socioeconomic status (as measured by the Scottish Index for Multiple Deprivation (SIMD), an index based on postcode) will be collected for all participants. For those in the clinical group, medical notes will be examined by a member of the clinical team for diagnostic and treatment information, including age of symptom onset, type and location of tumour, treatment received, complications arising from surgery and subsequent treatment received.

Social Interactions during Covid-19

The Covid-19 global pandemic and the resulting social distancing measures employed by the government may have an impact on psychosocial function. In order to assess the duration of severe social restrictions, and also to make a preliminary assessment of how participants maintained social contacts e.g. through use of social media and contact with siblings, we have developed a short questionnaire. This may allow us to identify participants who were not able to use social media effectively and look for correlations

with ToM test data. The impact on the development of social cognition in children and young people who have not been attending school and have been isolated from family and friends is unknown, and children with significant cognitive disorder may be less able to use social media as effectively as peers. The researchers will therefore make a preliminary assessment of the child's social interactions between the period of data collection and March 2020 (see appendix I).

General Intellectual Functioning

This will be measured using the WASI-II (Weschler, 2014).

Cognitive Empathy

This study will use the "Reading the Mind in the Eyes" test (RMET; Baron-Cohen et al., 2001) as a primary measure. The "Faux Pas" test (FPT; Baron-Cohen et al., 1999) will also be administered. For both of these measures, there is a child (6-12 years old) and adult version (13+ years) which will be administered as appropriate.

Parents will complete the "Empathy Systemizing Quotient" (Auyeung et al., 2012) questionnaire about their child as a proxy measure of cognitive empathy. The child (6-11 years), adolescent (12-15 years) and adult version (16+ years) will be completed as appropriate.

Processing speed

Participants will complete symbol search from the WISC-IV (Weschler, 2011). They will also complete the finger tapping test (Shirani et al., 2017), which has been regarded as a

sensitive measure of cognitive-motor speed in those with a neurological condition (Shirani et al., 2017) and cerebellar injury (Harrington et al., 2004).

2.12. Design

This study uses a case-control design.

2.13. Research Procedures

Participants from the clinical and control group will be invited to complete the cognitive assessment at their school during school hours. Parents/guardians will be sent the parent questionnaire by post and asked to complete and return to the research team using a stamped addressed envelope provided.

2.14. Data Analysis

In order to answer the primary research question, an independent samples t-test will be used to examine whether young people with posterior fossa tumours differ on a measure of cognitive empathy (RMET), when compared with typically developing peers. In order to examine the secondary question, correlational tests will be used to investigate the relationship between age at diagnosis and cognitive empathy.

2.15. Justification of sample size

A power calculation is difficult to provide due to the paucity of research examining theory of mind in a paediatric neuro-oncology population. Therefore, estimates are informed by previous studies using similar methods in paediatric and adult brain injury populations. A study by Snodgrass and Knott (2006) demonstrated a large effect size using the Reading the Mind in the Eyes test (d=1.45) in a group of children with moderate

to severe traumatic brain injury, when compared against healthy age matched controls. Borrowing from the adult literature, studies by Henry et al. (2006) and Geraci et al. (2010) found medium and large effect sizes (d=.66 and 1.21, respectively) on the same measure in adults with traumatic brain injury. Given some children in this population are likely to have a moderate to severe brain injury resulting from extensive cancer treatment (chemotherapy, radiotherapy and surgery), deficits in theory of mind are expected based on the overall impact of treatment on their neurocognitive functioning. Therefore, using a conservative effect size of .80 and power level of .80 (<.05, one-tailed), this study will require a minimum sample size of 21 participants in the clinical group to draw informative conclusions, and therefore we will aim to recruit between 20 and 25 children and young people.

2.16. Settings and Equipment

Cognitive assessments will be borrowed from the university department and local services. Proxy measures used in this study are freely available online. Permission will be sought from local education departments in Glasgow and Edinburgh to carry out data collection in schools.

3. Health and Safety Issues

4.1 Researcher safety issues

Data collection will take place at school for the clinical and control group. The researcher will notify another member of the research team when they are meeting with participants. Data collection will take place during school hours; therefore, the researcher will have access to a member of school staff at all times.

4.2 Participant safety issues

The researcher will ask in advance of the appointment if they should be aware of any medical conditions that may compromise the child or young person's safety during data collection. If, during the process of data collection, a member of the research team has concerns about the safety of the child or young person, they will inform the young person's parent/guardian. The researcher is also aware of child protection issues and will discuss appropriate governance and statutory responsibilities with the chief investigator as required.

3. Ethical Issues

The research team will seek ethical approval from NHS ethics through the Integrated Research Application System (IRAS). The researchers aim to recruit from two health boards (NHS Greater Glasgow and Clyde, and NHS Lothian), therefore will require a letter of approval to access patients in NHS Lothian. The research team will apply to local councils and education departments to recruit participants and carry out data collection in school.

We will engage with SCOTCRN and Young Person Group to develop age appropriate patient information sheets, to ensure patient involvement in the design thereby increasing its accessibility to young people and their families.

All data gathered from the cognitive assessments will be reviewed by a Consultant Neuropsychologist. If the research team identify any significant cognitive impairments that warrant further investigation, the family will be informed and offered advice or follow up from services where appropriate.

Information sheets and consent forms will be developed for young people of all ages, so that either consent or assent can be sought from all participants.

4. Financial Issues

It is anticipated that this study will require the allocated £200 from the University of Glasgow, in order to fund the stationary required to gain consent from families to be contacted by the research team and also to collect data from the control group.

5. Timetable

A final proposal will be submitted in April 2020. Once blind reviewed and finalised by the University, the study will be submitted for ethical approval. Due to issues relating to the COVID-19 global pandemic, the proposed timeline is tentative. It is hoped that ethical approval will be granted by September 2020 and data collection can begin. This will take place until approximately April 2021. In the months following, it is hoped that data analysis will take place and a report will be written up for submission in July 2021.

6. Practical Applications

Results from this study could inform the long-term care for children and young people recovering from posterior fossa tumours, with a view to improving their psychosocial outcome and reducing their risk of psychological difficulties later in life. It may highlight potential avenues for intervention from a neuropsychological point of view, and also identify areas where young people may benefit from the support of their families, with an ultimate goal to increase social integration and improve quality of life for young people who have experienced disruption to their neurodevelopmental trajectory.

References

Auyeung, B., Allison, C., Wheelwright, S., & Baron-Cohen, S. (2012). Brief report: development of the adolescent empathy and systemizing quotients. *Journal of Autism and Developmental Disorders, 42*(10), 2225-2235.

Baron-Cohen, S., Wheelwright, S., Spong, A., Scahill, V., & Lawson, J. (2001). Are intuitive physics and intuitive psychology independent? A test with children with Asperger Syndrome. *Journal of Developmental and Learning Disorders, 5(*1), 47-78.

Baron-Cohen, S., O'Riordan, M., Jones, R., Stone, V.E. & Plaisted, K. (1999). A new test of social sensitivity: Detection of faux pas in normal children and children with Asperger syndrome. *Journal of Autism and Developmental Disorders, 29*, 407-418.

Bell, H., Ownsworth, T., Lloyd, O., Sheeran, N., & Chambers, S. (2018). A systematic review of factors related to children's quality of life and mental health after brain tumor. *Psycho-oncology*, *27*(10), 2317-2326.

Bonner, M. J., Hardy, K. K., Willard, V. W., Anthony, K. K., Hood, M., & Gururangan, S. (2008). Social functioning and facial expression recognition in survivors of pediatric brain tumors. *Journal of Pediatric Psychology*, *33*(10), 1142-1152.

Brinkman, T. M., Palmer, S. L., Chen, S., Zhang, H., Evankovich, K., Swain, M. A., ... & Boyle, R. (2012). Parent-reported social outcomes after treatment for pediatric embryonal tumors: a prospective longitudinal study. *Journal of Clinical Oncology*, *30*(33), 4134.

Cancer Research UK (2019). Children's Cancer Statistics. https://www.cancerresearchuk.org/sites/default/files/cstream-node/child_inc_iccc_groups_0.pdf. Accessed 9th December 2019.

Carroll, C., Clare, I., Watson, P., Hawkins, M. M., Spoudeas, H., Walker, D., ... & Ring, H. A. (2013). Effects of early childhood posterior fossa tumours on IQ. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(9), e1.

Castellino, S. M., Ullrich, N. J., Whelen, M. J., & Lange, B. J. (2014). Developing interventions for cancer-related cognitive dysfunction in childhood cancer survivors. *Journal of the National Cancer Institute*, *106*(8), dju186.

De Ruiter, M. A., Van Mourik, R., Schouten-Van Meetren, A. Y., Grootenhuis, M. A., & Oosterlaan, J. (2013). Neurocognitive consequences of a paediatric brain tumour and its treatment: A meta-analysis. *Developmental Medicine & Child Neurology*, *55*(5), 408-417.

Duffner, P. K. (2010). Risk factors for cognitive decline in children treated for brain tumors. *European Journal of Paediatric Neurology*, *14*(2), 106-115.

Emond, A., Edwards, L., Peacock, S., Norman, C., & Evangeli, M. (2016). Social competence in children and young people treated for a brain tumour. *Supportive Care in Cancer*, *24*(11), 4587-4595.

Gatta, G., Zigon, G., Capocaccia, R., Coebergh, J. W., Desandes, E., Kaatsch, P., ... & EUROCARE Working Group. (2009). Survival of European children and young adults with cancer diagnosed 1995–2002. *European Journal of Cancer*, *45*(6), 992-1005.

Geraci, A., Surian, L., Ferraro, M., & Cantagallo, A. (2010). Theory of Mind in patients with ventromedial or dorsolateral prefrontal lesions following traumatic brain injury. *Brain Injury*, *24*(7-8), 978-987.

Gheysen, M., Sleurs, C., Jacobs, S., Lemiere, J., & Uyttebroeck, A. (2018). Therapy-related long-term effects in childhood posterior fossa tumors. *Journal of Neurology and Neuroscience, 9(2),* 252.

Harrington, D. L., Lee, R. R., Boyd, L. A., Rapcsak, S. Z., & Knight, R. T. (2004). Does the representation of time depend on the cerebellum? Effect of cerebellar stroke. *Brain*, *127*(3), 561-574.

Henry, J. D., Phillips, L. H., Crawford, J. R., Ietswaart, M., & Summers, F. (2006). Theory of mind following traumatic brain injury: The role of emotion recognition and executive dysfunction. *Neuropsychologia, 44*(10), 1623-1628.

Hocking, M. C., McCurdy, M., Turner, E., Kazak, A. E., Noll, R. B., Phillips, P., & Barakat, L. P. (2015). Social competence in pediatric brain tumor survivors: Application of a model from social neuroscience and developmental psychology. *Pediatric Blood & Cancer*, *62*(3), 375-384.

O'Halloran, C. J., Kinsella, G. J., & Storey, E. (2012). The cerebellum and neuropsychological functioning: a critical review. *Journal of Clinical and Experimental Neuropsychology*, *34*(1), 35-56.

Ostrom, Q. T., Gittleman, H., Fulop, J., Liu, M., Blanda, R., Kromer, C., ... & Barnholtz-Sloan, J. S. (2015). CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. *Neuro-oncology*, *17*(suppl_4), iv1-iv62.

Palmer, S. L., Goloubeva, O., Reddick, W. E., Glass, J. O., Gajjar, A., Kun, L., ... & Mulhern, R. K. (2001). Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. *Journal of Clinical Oncology*, *19*(8), 2302-2308.

Palmer, S. L., Gajjar, A., Reddick, W. E., Glass, J. O., Kun, L. E., Wu, S., ... & Mulhern, R. K. (2003). Predicting intellectual outcome among children treated with 35-40 Gy craniospinal irradiation for medulloblastoma. *Neuropsychology*, *17*(4), 548.

Palmer, S. L., Armstrong, C., Onar-Thomas, A., Wu, S., Wallace, D., Bonner, M. J., ... & Knight, S. (2013). Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. *Journal of Clinical Oncology*, *31*(28), 3494.

Riva, D., & Giorgi, C. (2000). The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain*, *123*(5), 1051-1061.

Robinson, K. E., Futtesch, J. F., Champion, J. E., Andreotti, C. F., Hipp, D. W., Bettis, A., & Compas, B. E. (2010). A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatric Blood & Cancer, 55*(3), 525–531.

Schmahmann, J. D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *16*(3), 367-378.

Siegel, R. L., Miller, K. D., & Jemal, A. (2015). Cancer statistics, 2015. *CA: A Cancer Journal for Clinicians*, *65*(1), 5-29.

Shirani, A., Newton, B. D., & Okuda, D. T. (2017). Finger tapping impairments are highly sensitive for evaluating upper motor neuron lesions. *BMC Neurology, 17*(1), 55.

Siegel, R. L., Miller, K. D., & Jemal, A. (2015). Cancer statistics, 2015. *CA: A Cancer Journal for Clinicians*, *65*(1), 5-29.

Snodgrass, C., & Knott, F. (2006). Theory of mind in children with traumatic brain injury. *Brain Injury*, *20*(8), 825-833.

Stavinoha, P. L., Askins, M. A., Powell, S. K., Pillay Smiley, N., & Robert, R. S. (2018). Neurocognitive and psychosocial outcomes in pediatric brain tumor survivors. *Bioengineering*, *5*(3), 73.

Vannatta, K., Gartstein, M. A., Short, A., & Noll, R. B. (1998). A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self-ratings. *Journal of Pediatric Psychology*, *23*(5), 279-287.

Wechsler, D. (2011). *Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II)*. San Antonio, TX: NCS Pearson.

Wechsler, D. (2014). *Wechsler intelligence scale for children-fifth edition. Bloomington*, MN: Pearson.

Willard, V. W., Allen, T. M., Hardy, K. K., & Bonner, M. J. (2017). Social functioning in survivors of pediatric brain tumors: Contribution of neurocognitive and social-cognitive skills. *Children's Health Care*, *46*(2), 181-195.

Yeates, K. O., Bigler, E. D., Dennis, M., Gerhardt, C. A., Rubin, K. H., Stancin, T., ... & Vannatta, K. (2007). Social outcomes in childhood brain disorder: a heuristic integration of social neuroscience and developmental psychology. *Psychological Bulletin*, *133*(3), 535.

Zyrianova, Y., Alexander, L., & Faruqui, R. (2016). Neuropsychiatric presentations and outcomes in children and adolescents with primary brain tumours: Systematic review. *Brain Injury*, *30*(1), 1-9.

Appendix 2.2: Assessment of Young Person's Social Interactions during COVID-19

Pandemic Social Contact Questionnaire

(Parent rated version for CYP aged 5-12 years)

As health researchers, we are very aware of the impact the COVID-19 pandemic might have had on children and families. With this in mind, we would like to get a sense of your child's social interactions during periods of social restriction and isolation.

Gathering this data on lots of young people could be important in understanding what might help children to cope with situations like this in the future.

We have assumed that most children will have had internet access through this pandemic, however if this was not the case for your family please ignore Questions 3 – 7.

Please tick the box that best describes the situation for your child. If unsure of the answer, please make your best guess.

1. How long would you estimate that your child faced severe social restrictions i.e. the period of being unable to leave the house other than for essential reasons-

☐ *Less than 3 months* ☐ *3 months* ☐ *3-5 months* ☐ *6 months* ☐ *more than 6 months*

2. Was your child in a 'very high risk' vulnerable group and advised to use 'Shielding' during the pandemic?

☐ *Yes* ☐ *No*

3. Did your child access school lessons/materials through the internet, and for <u>how many hours per week?</u>

☐ No hours ☐ 1-3 hours ☐ 4-6 hours ☐ 7-9 hours ☐ 10+

4. Did your child have social contact with *other family* (not in their home) through social media where they could <u>see</u> the other person(s) (e.g. Facebook, WhatsApp, Skype, Snapchat)?

☐ ☐ ☐ ☐ ☐

No Once per month Once per week 2-3 times per week 4+ times per week

5. Did your child have social contact with *friends* through social media where they could <u>see</u> the other person(s) (e.g. Facebook, WhatsApp, Skype, Snapchat) and for <u>how many hours per week?</u>

☐ ☐ ☐ ☐ ☐

No 1-3 hours 4-6 hours 7-9 hours 10+ hours

6. Did your child engage in activities/clubs through social media (e.g. using Youtube for exercise or weekly video-classes of clubs they attend)?

☐ ☐ ☐ ☐ ☐

No Once per month Once per week 2-3 times per week 4+ times per week

7. Did your child play online video games where they could speak/chat with their friends?

☐ ☐ ☐ ☐ ☐

No Once per month Once per week 2-4 times per week 5+ times per week

8. If Yes to Q.7, <u>how many hours per day</u> did your child spend using online gaming?

☐ ☐ ☐ ☐ ☐

0.5 hour 1 hours 2 hours 3-4 hours 5+ hours

9. Did your child have non-visual contact with *other family* e.g. by phone call?

☐ ☐ ☐ ☐ ☐

No Once per month Once per week 2-3 times per week 4+ times per week

10. Did the young person have non-visual contact with *peers* (e.g. phone call)

☐ ☐ ☐ ☐ ☐

No Once per month Once per week 2-3 times per week 4+ times per week

11. Does your child have any brothers or sisters at home?

☐ ☐ ☐ ☐ ☐

No 1 2 3 4+

Please return this form to the researcher who asked you to complete it.

Many thanks for your time ☺

Pandemic Social Contact Questionnaire

(self-rated version for young people aged 13-18 years)

As health researchers, we are very aware of the impact the COVID-19 pandemic might have had on children and families. With this in mind, we would like to get a sense of your social interactions during periods of social restriction and isolation.

Gathering this data on lots of young people could be important in understanding what might help young people to cope with situations like this in the future.

We have assumed that most people will have had internet access through this pandemic, however if this was not the case for your family please ignore Questions 3 – 7.

Please tick the box that best describes your situation. If unsure of the answer, please make your best guess.

1. How long would you estimate that you faced severe social restrictions i.e. the period of being unable to leave the house other than for essential reasons-

☐ *Less than 3 months*

☐ *3 months*

☐ *3-5 months*

☐ *6 months*

☐ *more than 6 months*

2. Were you in a 'very high risk' vulnerable group and advised to use 'Shielding' during the pandemic?

☐ *Yes*

☐ *No*

3. Did you access school lessons/materials through the internet, and for <u>how many hours per week?</u>

☐ No hours

☐ 1-3 hours

☐ 4-6 hours

☐ 7-9 hours

☐ 10+

4. Did you have social contact with *other family* (not in your home) through social media where you could see the other person(s) (e.g. Facebook, WhatsApp, Skype, Snapchat)?

☐ No ☐ Once per month ☐ Once per week ☐ 2-3 times per week ☐ 4+ times per week

5. Did you have social contact with *friends* through social media where you could see the other person(s) (e.g. Facebook, WhatsApp, Skype, Snapchat), and for how many hours per week?

☐ No ☐ 1-3 hours ☐ 4-6 hours ☐ 7-9 hours ☐ 10+ hours

6. Did you engage in activities/clubs through social media (e.g. using Youtube for exercise or weekly video-classes of clubs you attend)?

☐ No ☐ Once per month ☐ Once per week ☐ 2-3 times per week ☐ 4+ times per week

7. Did you play online video games where you could speak to friends?

☐ No ☐ Once per month ☐ Once per week ☐ 2-4 times per week ☐ 5+ times per week

8. If Yes to Q.7, how many hours per day did you spend using online gaming (please be honest ☺) ?

☐ 0.5 hour ☐ 1 hours ☐ 2 hours ☐ 3-4 hours ☐ 5+ hours

9. Did you have non-visual contact with *other family* e.g. by phone call?

☐ No ☐ Once per month ☐ Once per week ☐ 2-3 times per week ☐ 4+ times per week

10. Did you have non-visual contact with *friends* (e.g. phone call)?

☐ ☐ ☐ ☐ ☐

No Once per month Once per week 2-3 times per week 4+ times per week

11. Do you have any brothers or sisters at home?

☐ ☐ ☐ ☐ ☐

No 1 2 3 4+

Please return this form to the researcher who asked you to complete it.

Many thanks for your time ☺

Appendix 2.3: Author Guidelines for European Journal of Paediatric Neurology

For full guidance, see:

https://www.elsevier.com/wps/find/journaldescription.cws_home/623032?generatepdf=true

Scope: This multi-disciplinary journal publishes exciting clinical and experimental research in this rapidly expanding field. High quality papers written by leading experts encompass all the major diseases including epilepsy, movement disorders, neuromuscular disorders, neurodegenerative disorders and intellectual disability.

The European Journal of Paediatric Neurology is the official journal of the European Paediatric Neurology Society. It aims at rapid publication of high quality, original, clinical and experimental work in and relating to all aspects of paediatric neurology and paediatric neurosciences, including molecular and genetic research, and studies of animal models of relevance to human disease.

Original Articles: The main text of original articles should generally be in the format of: Abstract, Keywords, Introduction, Materials and Methods, Results and Discussion.

The abstract should not exceed 250 words.

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of').

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details: • E-mail address
• Full postal address

All necessary files have been uploaded:
Manuscript:
• Include keywords
• All figures (include relevant captions)
• All tables (including titles, description, footnotes)
• Ensure all figure and table citations in the text match the files provided

Appendix 2.4: Clinical Proforma Used for GACE Study

West of Scotland Genetic Services
Level 2B, Laboratory Medicine
Southern General Hospital
Govan Road
Glasgow
G51 4TF
tel: +44 (141) 354 9330

CPA
Accredited Medical Laboratory
Lab No: 0658

NHS
Greater Glasgow and Clyde

Referral Form for Diagnostic and Advisory Service for Genetic Epilepsy

A completed version of this form should accompany the blood/ DNA specimen. Please send 5ml EDTA blood (1ml for neonates) or DNA specimens (2-6ug depending on analysis required) to the above address.

The results and advice we are able to give you are dependent on a combined clinical epileptology and molecular genetic approach, incorporating information in the referral form, clinical correspondence (when available) and analysis of a DNA sample. This information is required to offer an informed opinion because of the complex phenotypes and heterogeneity within the genetic epilepsies. We cannot process samples unless this form is completed.

Please note: Outside of the Scottish NHS there is a charge for diagnostic testing. Tests with UKGTN approval are indicated below. See our website www.nhsggc.org.uk/content/default.asp?page=home_medicalgenetics for our user manual. Advice on laboratory and clinical aspects of epilepsy genetic testing are available at the number above or by contacting: **Clinical Genetic Scientist –Eleanor Reavey** (eleanor.reavey@ggc.scot.nhs.uk), **Consultant Paediatric Neurologist – Dr Sameer Zuberi** (sameer.zuberi@nhs.net)

Patient details		**Referrer details**
Forename:	Surname:	Name:
Date of birth:	Gender:	Speciality:
NHS/ CHI number:		Address for report:
Address and postcode:		Address for invoice:

Clinical diagnosis at referral – circle more than one as required	
Dravet syndrome / severe myoclonic epilepsy in infancy: Definite Suspected	SCN1A related childhood onset epilepsy
Neonatal onset epileptic encephalopathy / Ohtahara syndrome	Infantile / childhood onset epileptic encephalopathy
Adult onset genetic epilepsy	Glucose transporter 1 deficiency syndrome: Definite Suspected
Early onset childhood absences	Unclassified epilepsy
Specific epilepsy syndrome	Details :

Epileptic seizures			
Age / date of first epileptic seizure		Details	
Neonatal onset epilepsy	Y / N	Day of life & gestation	
Any factors precipitating seizure?	Y / N	Details	
Seizure within 48h of immunisation?	Y / N	Age at onset	Details of immunisation

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Prolonged (>10 minutes) febrile convulsions	Y / N	Age at onset:	Duration (minutes)		
Status epilepticus	Y / N	Age at onset:	Recurrent Y / N		
Non-convulsive status	Y / N	Age at onset:	Recurrent Y / N		
Clusters of seizures	Y / N	Age at onset:	Febrile Y / N	Number in a cluster	Duration (days)
Hemi-clonic focal seizures	Y / N	Age at onset:	Neonatal Y / N	Febrile Y / N	
Generalised clonic / tonic-clonic seizures	Y / N	Age at onset:			
Myoclonic seizures	Y / N	Age at onset:	Neonatal Y / N		
Focal seizures with impairment of awareness	Y / N	Age at onset:			
Drop attacks	Y / N	Age at onset:	Type : tonic / atonic / myoclonic / myoclonic-astatic		
Infantile spasms/epileptic spasms	Y / N	Age at onset:			
Tonic seizures	Y / N	Age at onset:	Neonatal Y / N		
Atypical absences	Y / N	Age at onset:			
Response to specific medication / therapy	Y / N	Details:			
Any medications increase seizures?	Y / N	Details:			
Seizures / movement disorder better after eating?	Y / N	Details:			
Prolonged seizure free period?	Y / N	Details:			
Current seizure frequency	Details:				
Current medications	Details :				

Cognitive Development

Normal Y / N Specific learning difficulties Y / N Global learning disability Y / N Severity of GLD: Mild / Moderate/ Severe / Profound

Details:

Normal development prior to epilepsy onset	Y /N	Epileptic encephalopathy / cognitive decline or stagnation	Y / N
Behaviour problems	Y / N	Details:	
Autistic features	Y / N	Progressive intellectual and neurological deterioration	Y / N Uncertain

Movement disorder

None Hypotonia Ataxia Spasticity Chorea Dystonia (please circle)

Paroxysmal movement disorder	Y / N	Exercise induced	Y / N	Details:
Kinesigenic (induced by starting to move)	Y / N	Details		

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EEG features			
Normal interictal EEG (at any age)	Y / N Date:	Generalised spike & wave	Y / N Age:
Photosensitivity	Y / N Age:	Focal EEG abnormalities – where?	Y / N Age:
Slowing	Y / N Age:	Multifocal EEG abnormalities	Y / N Age
Neonatal burst suppression pattern	Y / N	Hypsarrhythmia / modified hypsarhythmia	Y / N Age:
Did EEG change over time?	Y / N	Details	

MRI brain				
Not done	Normal	Abnormal	Date performed:	Details if abnormal:

Other investigations			
CSF/ plasma glucose ratio	CSF glucose	CSF lactate	Not done
Other relevant investigations.			

Family history – please provide details (draw pedigree), use an extra sheet if required	**Syndromic features**– please provide details, use an extra sheet if required
	Dysmorphisms: Growth Abnormalities: Malformations: Head circumference (cm): Any other information:

Required genetic analysis – **please tick the gene/s you would like to have analysed.** Note for price information please contact the laboratory on 0141 354 9330

SCN1A MLPA & Sequence		***MECP2*** MLPA & Sequence		****KCNQ2*** MLPA & Sequence		***POLG*** Sequence	
****PCDH19*** MLPA & Sequence		****STXBP1*** Sequence		****GABRG2*** MLPA & Sequence			
****SLC2A1*** MLPA & Sequence		****ARX*** MLPA & Sequence		***CACNA1A*** MLPA & Sequence			
****CDKL5*** MLPA & Sequence		***PRRT2*** Sequence		***SLC25A22*** Sequence			

I would like to be contacted for research purposes if further genes become available Y / N
Shaded genes are under development. Delayed reporting times expected.

*UKGTN approved test. UKGTN approval for all other genes is being sought.
We adhere to the department of health guidelines for reporting times. All full screens are completed within 40 working days from the date that a specimen and completed referral form are received.

Is this patient part of the GACE study (please tick if yes) ☐

Appendix 2.5: Evidence of Ethical Approval for Researchers to Access and Use Data for GACE study

GACE Study

From: Isla Birnie [mailto:Isla.Birnie@glasgow.ac.uk]
Sent: 21 May 2021 09:22
To: Dorris, Liam
Cc: Lauren Delahunty (PGR); Felix, Suzanne; Zuberi, Sameer
Subject: [ExternalToGGC]GACE Study

Dear *****,

RE: Genetic and Autoimmune Childhood Epilepsy Study
REC Reference 13/WS/0299
R&D Reference GN12KH569

I can confirm that the GACE study mentioned above has full ethical approval.
Suzanne Felix and Lauren Delahunty were added to the delegation log and had access to the database for this study.

Best wishes,
Isla

Isla Birnie
Research Administrator
Paediatric Neurosciences Research Group
Institute of Health and Wellbeing
Tel: 0141 451 5879

Mon-Fri 09:00-17:00

Appendix 2.6: Correlations between Continuous and Binary Categorical Variables (Pearson's Correlation for General Adaptive Composite, Conceptual, Social and Practical Domains at Baseline; Spearman's Rho at Follow Up)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
2	.607**																
3	.008	-.007															
4	-.174*	-.017	.031														
5	-.253*	-.149	.052	.762**													
6	-.251**	-.157**	.025	.728**	.745**												
7	-.191*	-.361**	-.256**	-.242**	-.214	-.152											
8	*-.491***	*-.607***	*-.186*	*-.053*	*.000*	*.078*	*.580***										
9	-.213*	-.373**	-.255**	-.202*	-.213	-.132	.937**	*.540***									
10	*-.491***	*-.603***	*-.223*	*-.099*	*-.005*	*.034*	*.597***	*.962***	*.613***								
11	-.228*	-.353**	-.209*	-.282**	-.167	-.160	.922**	*.622***	.828**	*.598***							
12	*-.522***	*-.598***	*-.222*	*.040*	*.086*	*.173*	*.466***	*.963***	*.432***	*.899***	*.553***						
13	-.067	-.305**	-.240**	-.370**	-.270*	-.239**	.912**	*.477***	.782**	*.492***	.788**	*.370***					
14	-.473**	-.596**	-.182	.007	-.006	.079	.610**	*.981***	.600**	*.907***	.600**	*.944***	.444**				

	1	**2**	**3**	**4**	**5**	**6**	**7**	***8***	**9**	***10***	**11**	***12***	**13**	**14**	**15**	**16**	**17**
15	.322**	.207*	.206*	.288**	.333*	.264**	-.558**	-.*324**	-.519**	-.*358**	-.601**	-.*300**	-.447**	-.293*			
16	.246*	.245*	.281*	.085	.134	.165	-.458**	-.*494**	-.422**	-.*495**	-.435**	-.*515**	-.303*	-.457**	.768**		
17	-.211	-.089	.047	-.111	.560**	.188	.029	*.124*	.044	*.162*	-.004	*.136*	.104	.080	.155	.159	
18	.337**	-.372**	-.024	-.023	-.115	-.135*	-.222*	-.*231*	-.276**	-.*217*	.-.189*	-.*212*	-.093	-.246*	.175	.014	-.186

* $p < .05$, two-tailed *N* Ranged from 49- 301

** $p < .01$, two-tailed *Italicised* font refers to Spearman's rho, non-italicised refers to Pearson's Correlation

Legend

1. Drug-resistant seizures (0 = no, 1 = yes)
2. Global development delay, rated by clinician (0 = no, 1 = yes)
3. Sex (0 = female, male = 1)
4. Age at baseline
5. Age at follow-up
6. Age at first seizure
7. General Adaptive Composite at baseline
8. General Adaptive Composite at follow-up
9. Conceptual domain at baseline
10. Conceptual domain at follow up
11. Social domain at baseline
12. Social domain at follow up
13. Practical domain at baseline
14. Practical domain at follow up
15. Total parental stress at baseline
16. Total parental stress at follow up
17. Time between baseline and follow-up
18. Epilepsy diagnosis (0 = no, 1= yes)

Appendix 2.7: Supplementary Material from GACE Study

Table 1

Differences between responders and non-responders to questionnaire data (categorical variables)

	X^2 (df)	***N***	***p***	***Phi***
Scottish Index of Multiple Deprivation	10.092 (4)	289	.039	.187
Global Developmental Delay*	.004 (1)	301	.947	.011
Drug Resistant Seizures*	.296 (1)	301	.587	-.039
Sex*	1.256 (1)	301	.262	.071
Identified Aetiology	4.205 (2)	295	.122	.119
Epilepsy Diagnosis*	1.051 (1)	301	.305	.066

*Continuity Correction as 2x2 variables

Table 2

Differences between responders and non-responders to questionnaire data (continuous variable)

	Responders	**Non Responders**	***T***	***df***	***p***
	M (SD)	***M (SD)***			
Age at first seizure	13.48 (8.990)	12.43 (9.249)	-.922	298	.322

Table 3

Differences between those who completed follow up and those who did not (categorical variable)

	X^2 (df)	***N***	***p***	***Phi***
Scottish Index of Multiple Deprivation	7.634 (4)	289	.106	.163
Global Developmental Delay*	.000 (1)	301	1.000	.001
Drug Resistant Seizures*	.438(1)	301	.508	.047
Sex*	.092 (1)	301	.762	.025
Identified Aetiology	7.134 (2)	295	.028	.156
Epilepsy Diagnosis*	4.133 (1)	301	.042	.125

*Continuity Correction as 2x2 variables

Table 4

Differences between those who completed follow up and those who did not (continuous variable)

	Completed Follow up	**Did not Complete follow up**	***T***	***df***	***p***
	M (SD)	***M (SD)***			
Age at first seizure	12.52 (9.084)	13.09 (9.150)	.471	298	.638

Table 5

Examining the relationship between Adaptive Functioning and other clinical features

	GAC at Baseline			**GAC at follow up**			
	Analysis of Variance			**Kruskal Wallis**			
	F	*df*	*p*	*Chi-sq*	*df*	*N*	*p*
Scottish Index of Multiple Deprivation	.371	4, 108	.829	18.991	4	64	.001
Identified Aetiology	1.341	2, 117	.266	3.494	2	68	.174

Table 6

Hierarchical Regression for Adaptive Functioning at Baseline (Models)

Model		*df*	*F*	*p*	R^2
1	Regression	2	33.187	<.001	.374
	Residual	111			
	Total	113			
2	Regression	5	15.284	<.001	.414
	Residual	108			
	Total	113			

Table 7

Hierarchical Regression for Adaptive Functioning at Baseline (Coefficients)

Model		Unstandardized Coefficients				95% CI for B	
		B	*SE*	*T*	*p*	Lower	Upper
1	(Constant)						
	Parenting Stress at Baseline	-.404	.061	-6.575	<.001	-.526	-.282
	Global Developmental Delay	-10.625	3.176	-3.345	.001	-16.919	-4.331
2	(Constant)						
	Parenting Stress at baseline	-.341	.065	-5.230	<.001	-.470	-.212
	Global Developmental Delay	-10.510	3.332	-3.155	.002	-17.114	-3.906
	Age at baseline	-.196	.127	-1.548	.124	-.447	.055
	Male	-6.418	-.168	-2.223	.028	-12.141	-.695
	Diagnosis of Epilepsy	-2.446	-.060	-.753	.453	-8.882	3.991

SE = Standard Error

Table 8

Hierarchical Regression for Adaptive Functioning at Follow-Up (Models)

Model		***df***	***F***	***p***	R^2
1	Regression	2	29.376	<.001	.491
	Residual	61			
	Total	63			
2	Regression	3	29.994	<.001	.600
	Residual	60			
	Total	63			

Table 9

Hierarchical Regression for Adaptive Functioning at Follow-Up (Coefficients)

Model		Unstandardized Coefficients				95% CI for B	
		B	*SE*	*T*	*p*	Lower	Upper
1	(Constant)						
	Parenting Stress at Follow-Up	-.420	.108	-3.882	<.001	-.637	-.204
	Global Developmental Delay	-30.095	5.517	-5.455	<.001	-41.127	-19.062
2	(Constant)						
	Parenting Stress at Follow-Up	-.290	.102	-2.848	.006	-.494	-.086
	Global Developmental Delay	-30.098	4.930	-6.105	<.001	-39.960	-20.237
	Scottish Index of Multiple Deprivation	6.744	1.665	4.049	<.001	3.413	10.076

SE = Standard Error