Child and Parental Outcomes Following Adverse Life Events

Ms Suzanne A. Felix (BSc, MSc)

Submitted in partial fulfilment of the requirements for the degree of

Doctorate in Clinical Psychology

Institute of Health and Wellbeing

College of Medical, Veterinary and Life Sciences

University of Glasgow

Date of submission:

July 2021

Table of Contents

List of Tables

List of Figures

Acknowledgements

I would like to express my gratitude to Professor Liam Dorris, Dr Claire Adey, and Dr Emanuela Molinari for their support and expertise throughout this project. I would also like to thank the teams at RHSC Edinburgh and RHC Glasgow for their enthusiasm and support and Dr Cullen, Dr Fish, and Dr Young for their invaluable advice.

I cannot write my acknowledgements without mentioning the final integral part of the research team. I want to give a massive thank you to Ms (soon to be Dr) Lauren Delahunty for her patience and teamwork over the last three years.

Sanne: thank you for being an invaluable support and just all-round great human. Stephanie: *jeweetzelluf matje.* Pernille: thank you for showing me what true female friendship is. Danielle: get ready for your support to be returned ten-fold! Iain: thank you for knowing when I needed a laugh. Fiona: here's to new adventures, we've got this! Laura: your voice notes trained my working memory and got me through this. My extensive Scottish family: thank you for always looking out for me, it means the world.

Last but certainly not least, I need to thank my family and especially my Mum for their unwavering belief in me. Although we have been apart for more than I would have ever wanted during these last two years, you have been there for me throughout and I love and miss you all an impossible amount.

"Gaat het niet rechtsom, dan gaan we maar linksom, of rechtdoor, of dwars erdoorheen."

A lesson in flexibility and perseverance by Marjolein Felix (a.k.a. mama).

Foreword

In March 2020, COVID19 turned our lives around. It was only a matter of time before it would impact on my cohort's Major Research Projects (MRPs). In a bid to show flexibility to the ever-changing reality, I changed my Systematic Review topic from 'Executive Functioning in childhood ALL survivors' to 'Child Maltreatment during the Great Recession' to make the review more relevant.

With regards to my MRP, we initially adapted the proposal to go ahead as planned within the parameters of local COVID19 restrictions. We for example planned to change our data collection to remote neuropsychological assessments and had started to make adjustments to our ethics proposal as appropriate. However, with time the COVID19 restrictions tightened, and it became apparent that even this adjusted proposal would not be feasible in the current climate.

It was therefore decided that my original project (social cognition in childhood leukaemia survivors) would be discarded in favour of a data analysis project (parental stress in infants with early-onset seizures) in line with the University of Glasgow's DClinPsy thesis contingency plans. The extended proposal in Chapter 2 is the original research proposal submitted to the University of Glasgow and does not include the subsequent Covid19-related changes we considered. Furthermore, the below thesis does not have a clear connection between the Systematic Review and the Major Research Project(s). However, all parts of this thesis are relevant to paediatric psychology and health and I hope that they can all inform future research in the area.

Chapter 1: Systematic Review

Child Maltreatment During The Great Recession: A Systematic Review

Prepared in accordance with the author requirements for:

Child Abuse and Neglect (details in Appendix I)

Abstract

Introduction

It has been established that economic hardship can influence parental adjustment and coping as well as child wellbeing. We review evidence for a relationship between exposure to the Great Recession (2007-2009) and increases in the incidence of reported child maltreatment. We aimed to develop insights from this earlier economic crisis that may be instructive in recovery planning from the Covid-19 global pandemic, which has caused a significant global economic crisis.

Methods

A literature search was conducted using the MEDLINE, EMBASE, PsychINFO, and Web of Science Core Collection databases. Keyword and MeSH searches were completed to identify relevant articles. Inclusion criteria and risk of bias were assessed by two blinded reviewers.

Result

From 607 reports screened for eligibility, 11 papers were included in the final qualitative synthesis and quality assessment. We found limited evidence that young people faced an increased risk of maltreatment between 2007 and 2009, especially when compared to maltreatment rates before 2007. However, although the reviewed papers were of acceptable quality, generalisability was constrained due to heterogeneity in methods and outcome measures between reviewed articles.

Conclusion

Despite the currently limited evidence that child maltreatment increases during periods of deep economic recession, it is important that societies act to protect the welfare of children and young people during these challenging periods.

Protocol can be found here:

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=193636.

Key words

The Great Recession, economic recession, child maltreatment, child abuse, child neglect

Introduction

Rationale

In January 2021, the BBC reported that suspected child maltreatment rates had increased by 30% since the Covid-19 restrictions had been put in place (BBC News, 2021). Covid-19, officially known as acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused physical, emotional, and practical challenges for families across the globe. Apart from the health and psychological demands put on families during this pandemic, further challenges regarding financial instability have been raised.

To protect the health and healthcare resources of the population, governments have put strict restrictions on movement and trade throughout the pandemic. Since March 2020, the United Kingdom (UK) have introduced restrictions which caused the UK economy to move into a recession. The HM Treasury defines a recession in the United Kingdom as "two or more consecutive quarters (a period of three months) of contraction in national GDP" (HM Treasury, 2010).

Unfortunately, economic recessions have been associated with an increase in mental health difficulties such as depression, suicidal ideation, and substance misuse (Frasquilho et al., 2015; Hiilamo et al., 2021). In addition, there is evidence to suggest that the pressures of parenting during an economic recession increases the risk of child maltreatment (Rajmil et al., 2014) and low family income and/or low socioeconomic status (SES) have also consistently been associated with increases in child abuse and neglect (Coulton et al., 2018; Slack et al., 2011).

Lawson and colleagues (2020) have furthermore reported that parental job loss during the Covid-19 pandemic significantly increased the risk of maltreatment. This finding, coupled with the fact that national quarantine is known to increase emotional distress in adults (Brooks et al., 2020), highlights the need for timely intervention to protect young people at risk of abuse and neglect.

Objectives

Large parts of the world economy were affected by The Great Recession (TGR) from December 2007 to June 2009. Although the impact of the current economic recession is complicated by the contiguity with a global health crisis, outcome data in relation to child maltreatment during TGR could provide useful for Covid-19 recovery planning and longer-term policy-making with regards to child wellbeing.

Research question

We aimed to assess whether rates in child maltreatment increased during The Great Recession (2007-2009) when compared to child maltreatment rates before and after this period.

Methods

Protocol and registration

To structure this systematic review, the PRISMA 2020 checklist was used (Page et al., 2021). This systematic review and its protocol are furthermore registered on the PROSPERO prospective register of systematic reviews (found here:

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=193636).

Inclusion criteria

Cohort studies that focused on the incidence of child (aged 0-18) maltreatment during The Great Recession (2007-2009) were included. The comparison criterion was considered to have been met if the study compared incidence data reported during TGR to data reported before and/or after this period. In order to allow for a clear comparison, studies were only included if at least part of their design included a direct comparison between the different time points (e.g. Poisson or Logistic Regression). Although incidence rates reported after 2009 will likely include a cohort that have also been exposed to The Great Recession, it was felt this would still be a useful comparison as it could potentially highlight long-term effects. Studies were only included if they had been published in a peer-reviewed journal in English. Systematic reviews and grey literature were excluded.

Study selection

A literature search was conducted using the MEDLINE (OVID; 1946-present), EMBASE (OVID; 1947-present), PsychINFO (EBSCOhost; 1806-present), and Web of Science Core Collection (1900-present) databases. Keyword and MeSH searches were completed to identify papers that mentioned “economics” (or equivalent), "economic recession" (or equivalent) and “child maltreatment” (or equivalent). Key journals (*Child Abuse and Neglect*, *Academic Pediatrics*, and *Pediatrics*) were also hand-searched for relevant papers. The searches were completed on 23rd September 2020 and full search terms can be found in Appendix II.

Two researchers (SF and LDe) applied the eligibility criteria to select studies for inclusion. The researchers were blinded to each other's decisions and disagreements were resolved by a research supervisor (LDo or CA). Rayyan QCRI (Ouzzani et al., 2016) was used to record decisions. Titles and abstracts of papers were screened for eligibility and if found potentially eligible, the full manuscripts were assessed. All papers found eligible during the manuscript stage were included in the final review.

Data extraction

Bibliographic information, primary outcome measure, sample characteristics (sample size and relevant demographic characteristics), primary statistical analyses, primary outcome, other relevant findings, and quality ratings were recorded on a Microsoft Excel spreadsheet. No further data was obtained from authors and data was narratively

synthesised. The main outcome measures were (relative) risk ratios as well as differences in means.

Quality assessment

The National Heart Lung and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohorts and Cross-Sectional Studies (NHLBI, n.d.) was used to assess the internal validity of the papers included in this systematic review. The full checklist can be found in Appendix III. It also allows for an overall assessment of the study; namely 'Good', 'Fair', or 'Poor'. Studies of all quality ratings were included in the final review.

Two researchers (SF and LDe) completed this quality assessment, and they were blinded to each other's ratings. Any disagreements between reviewers were resolved through discussion between SF, LDe and a research supervisor (LDo or CA).

Results

Study selection results

As illustrated in Figure 1.1, 607 individual papers were identified through the systematic and hand searches. During the screening stage, 568 records were removed for a variety of reasons such as: published before 2007; grey literature; systematic review; or clearly not relevant to the current topic. At this stage, five rater disagreements were resolved by a research supervisor. Thirty-nine manuscripts were then screened for eligibility. Reasons for exclusion at this stage were: exposure to The Great Recession unclear (N =

12); inappropriate statistical analysis in relation to the current research question (N = 10); no data collected during TGR (N = 4); and inappropriate outcome measures in relation to the current research question (N = 2). Two papers were included as they contained relevant results despite not specifically focusing on the impact of TGR (Emrick et al., 2019; Zins et al., 2019). No further disagreements between researchers were identified at this stage. Eleven peer-reviewed journal articles were then included in the quality assessment and the qualitative synthesis. All included studies concerned child maltreatment rates in the United States of America (USA).

Risk of bias

All 11 included papers were rated using the NHLBI checklist described, and full results can be found in Table 1.1. Two disagreements were resolved through discussion with the research supervisors.

All papers were judged to be of acceptable (i.e. 'fair' or 'good') quality (see Table 1.2), with some risk of bias noted in relation to potential confounders in three papers (Emrick et al., 2019; Leventhal & Gaither, 2012; Shanahan et al., 2013). In addition, none of the studies provided a sample size justification, but this is not uncommon for retrospective and exploratory studies. In the guidance for using the NHLBI checklist is it noted that this should not be considered a "fatal flaw" in terms of quality assessment.

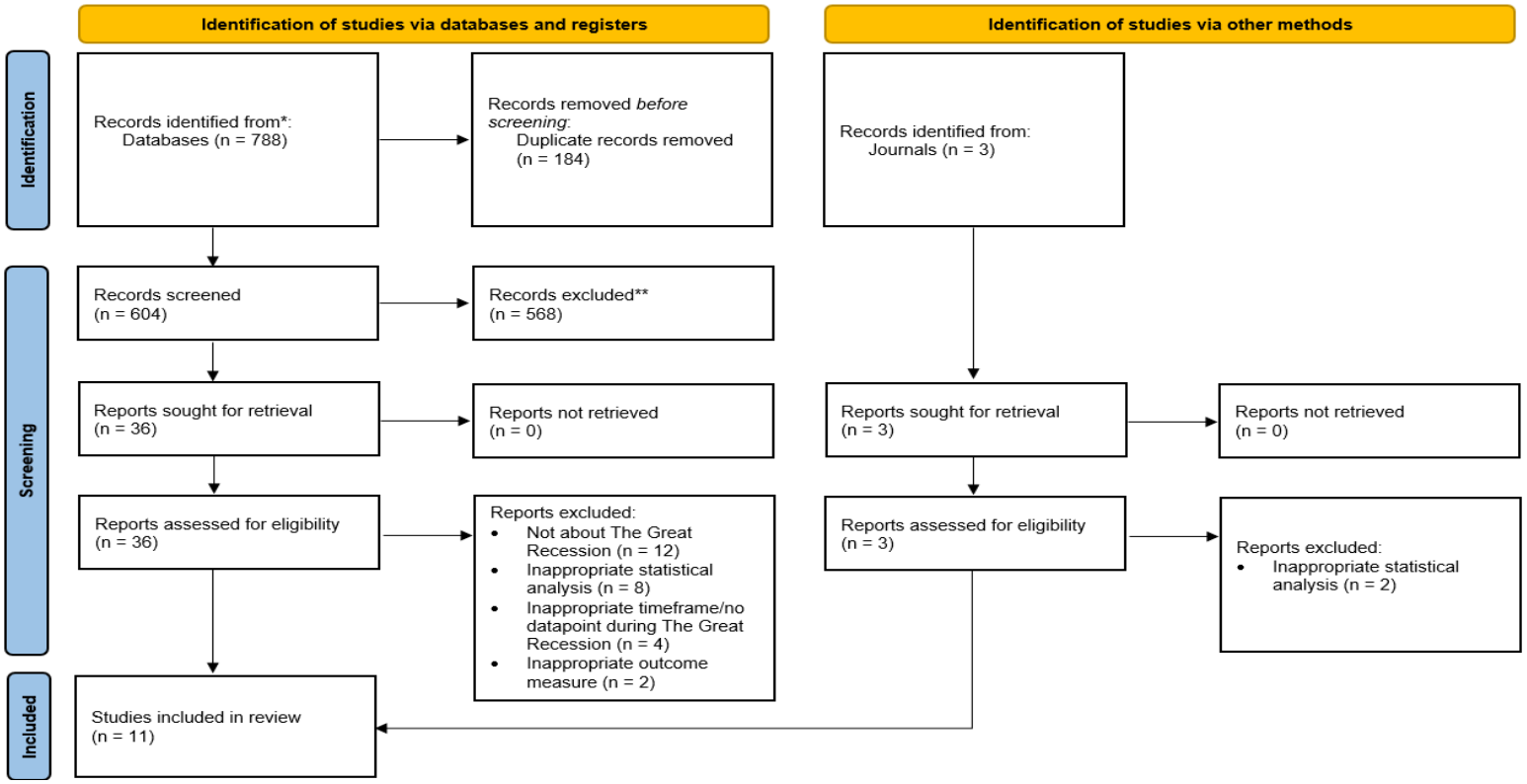


Figure 1. 1: PRISMA Flow Diagram taken and edited from Page et al. (2021)

The NHLBI checklist also has several items in relation to the measurement, rather than the impact, of the exposure. For the purpose of this systematic review, 'exposure' was inferred from the timepoint(s) included in the papers. As such, an argument could be made that there was a measurement bias in all reviewed studies due to exposure not being clearly assessed. Similarly, raters were not blinded to exposure status in most studies.

The current reviewers however felt this would not significantly detract from the study quality as it would be unlikely that any USA study population assessed during TGR time-period would not have been exposed to the recession. Furthermore, all studies included large samples so any individual differences in terms of impact of exposure were unlikely to have had a large influence on reported trends due to deviations to the group mean.

Table 1. 1: Ratings of internal validity according to the NHLBI checklist (NHLBI, n. d.) of review articles

	Criteria													
Authors (year)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Berger et al. (2011)	Yes	Yes	NA	Yes	No	NA	Yes	NA	Yes	NA	Yes	No	NA	Yes
Emrick et al. (2019)	Yes	Yes	NA	Yes	No	NA	No	NA	Yes	NA	Yes	No	NA	No
Finkelhor et al. (2014)	Yes	Yes	NR	Yes	No	NA	Yes	NA	Yes	NA	Yes	NR	NA	Yes
Frioux et al. (2014)	Yes	Yes	NA	Yes	No	NA	Yes	NA	Yes	NA	Yes	No	NA	Yes
Huang et al. (2011)	Yes	Yes	NA	Yes	No	NA	Yes	NA	Yes	NA	Yes	No	NA	Yes
Leventhal & Gaither (2012)	Yes	Yes	NA	Yes	No	NA	Yes	NA	Yes	NA	Yes	No	NA	No
Millet et al. (2011)	Yes	Yes	NA	Yes	No	NA	No	NA	Yes	NA	Yes	No	NA	Yes
Shanahan et al. (2013)	Yes	Yes	NA	Yes	No	NA	Yes	NA	Yes	NA	Yes	No	NA	No
Wood et al. (2012)	Yes	Yes	NA	Yes	No	NA	Yes	NA	Yes	NA	Yes	No	NA	Yes
Wood et al. (2016)	Yes	Yes	NA	Yes	No	NA	Yes	NA	Yes	NA	Yes	No	NA	Yes

NB. NA = Not Applicable; NR = Not Reported

Child Protection Services Reports

Two studies, (Frioux et al., 2014; Millett et al., 2011) operationalised child maltreatment rates as the number of reports made by the Child Protection Services (CPS). Whilst there was an overall decline in maltreatment reports in children aged 0-18 years, evidence was mixed.

Millet et al. (2011) investigated aggregated rates of CPS reports at state level during (2007- 2009) and immediately after TGR (2009 - 2010), reporting mixed results (see Table 1.2). They found that some states showed an increase in CPS reports, whereas in

others this had decreased or stayed the same. They did not differentiate between investigated and substantiated reports. They also analysed whether unemployment rate, food stamp usage, and labour force participation explained changes in maltreatment rates while controlling for time. This association was only found for California; unemployment rate was positively associated with maltreatment incidence, whereas the other two indicators showed a negative association. They also noted that for North Carolina (b^2 = -0.001, $p < .001$), Missouri (b^2 = 0.001, $p < .05$), and Wisconsin (b^2 = 0.001, $p < .05$) there were significant quadratic as well as linear relationships between exposure and outcome. In North Carolina maltreatment rates peaked between 2007 and 2010, whereas they appeared to decline before increasing in Missouri and Wisconsin.

Frioux and colleagues (2014) considered both investigated and substantiated CPS reports of child maltreatment in Pennsylvania between 1990 and 2010. They found that investigated, but not substantiated, reports of maltreatment showed a declining trend until 2000 across all counties of Pennsylvania. The rates then increased again until they peaked at 9.2 investigations per 1000 children in 2008. Substantiated reports declined over the whole 21-year period (see Table 1.2). In relation to macroeconomic indicators, they reported that county-level increases in unemployment and foreclosure rates resulted in increases in both investigated and substantiated CPS reports, even when controlling for time trend. They also investigated lagged effects, but only the foreclose rate of the previous year was associated with current CPS reports. In fact, this lagged effect of home foreclosures was associated with the biggest changes in both investigated and substantiated reports.

Table 1. 2: Data extraction table of review articles, including an overall quality rating.

Authors (year)*	**Primary outcome measure**	**Sample characteristics**	**Statistical analysis**	**Primary/Relevant outcome**	**Relevant other findings**	**Quality Rating**
Berger et al. (2011)	Aggregated unequivocal county-level AHT rates per 100,000 between January 2004 and June 2009 for children <5 years.	422 children with AHT < 5 years (range: 0-58 months; *M* = 8.9 months).	Poisson Regression, with unemployment rate as a covariate.	Significant overall increase of AHT during recession. Rates increased from 8.9 (95% CI:7.8–10.0) pre-recession to 14.7 (95% CI: 12.5–16.9) during the recession (IRR = 1.65 95% CI: 1.60-1.69, $p < .001$).	Unemployment increased from prerecession to recession period but was not associated with AHT rates either current or lagged.	Good
Emrick et al. (2019)	Incidence per 100,000 of AHT between 2000 and 2010 as recorded by paediatric care centres using relevant ICD-9 codes.	120 children with AHT < 24 months old (*M* = 6.25 months).	Student's *t*-test was used for continuous variables, and either Chi-square or Fischer's exact was used for categorical variables.	Incidence average rates increased from 14.5 (95% CI: 10.3-18.7) in 2000-2005 to 30.3 (95% CI: 16.3-44.2) in 2006-2010 ($p < .05$).	When only including infants < 12 months incidence rates increased from 24.0 (95% CI: 15.7-32.4) to 51.8 (95% CI: 32.4-71.2) ($p < .01$)	Fair
Finkelhor et al. (2014)	Juvenile Victimisation Questionnaire (self-report) completed over the telephone in 2003, 2008, and 2011.	10183 (parent/carer of) young people aged 2 – 17 years.	Logistic Regression on pooled data with demographic variables as control variables.	The overall rate of child maltreatment declined by 26% (OR: -2.3, $p < .01$) from 2003 to 2011 (not 2008-2011). This decline was significant only for emotional abuse (OR: -2.3, $p < .01$).	Larger declines in maltreatment were found in families from lower SES backgrounds ($p < .01$).	Fair
Frioux et al. (2014)	Aggregated investigated reports and substantiated cases of child maltreatment per 1,000 children between 1990 and 2010 per county of Pennsylvania.	500,896 reports investigated by CPS (annual mean: 23,876) of children < 18 years.	Fixed-effect Poison Regression and Spearman's Rho for secondary analyses.	Unadjusted *rate of investigations* showed a quadratic trend ($p < .001$). Decreasing from 8.7 in 1990 to 7.8 in 2000 and rising to a peak 9.2 in 2008. *Substantiated reports* only declined each year ($p < .001$). From 2.8 in 1990 to 1.3 in 2010.	Significant associations ($p < .05$) between current unemployment and investigated (+1.99%) and substantiated rates (+2.42%) of abuse. Similar pattern found for current home foreclosures: +3.94% and +4.49% respectively. Lagged foreclosure was +6.34% and +7.30% respectively.	Good
Huang et al. (2011)	Mean monthly incidence of children on the PTR with NAHT between December 2001 and June 2010.	639 children (aged 0-24 months) on PTR, 93 of which had NAHT.	Mann Whitney U-tests and Chi-Square/Fisher exact test as appropriate.	Mean monthly incidence rates increased form 0.7 pre-recession (2001-2007) to 1.4 during/post-recession (2007-2010) ($p = .01$).	Accidental Head Trauma was observed to decrease. Increase in NAHT observed before rise in unemployment.	Good

Leventhal and Gaither (2012)	Incidence per 100,000 of children discharged following physical abuse injury according to KIDs codes between 1997 and 2009.	Sample size per year (aged <18) years): 1997 = 4237, 2000 = 4305, 2003 = 4409, 2006 = 4473, 2009 = 4782	Chi-squared test for linear trends.	Significant increase over time (p <.01) from 6.1 in 1997 to 6.4 in 2009. Further analysis showed increase in infants <12 months (56.2 to 62.3, p < .05), but a slight decrease in older children (3.3 to 3.0, p < .05).	Incidence of other injuries significantly decreased (p < .05). Length of stay following abuse remained unchanged (p > .05). Mortality following physical abuse increased (0.25 to 0.36, p < .01).	Fair
Millet et al. (2011)	State-level child maltreatment rate per 1,000 using publicly available datasets. Timeframes differed between states, but they included a pre-, during, and post-recession datapoint for each state.	Data of maltreatment rates for children <18 years provided for the states Arizona, California, Massachusetts, Missouri, North Carolina (NC), Oregon, and Wisconsin.	Ordinary Least Squares Regression. Pearson's bivariate correlations for secondary analyses.	Neglect, but not sexual or physical abuse, decreased in Arizona (b = -0.02, p < .05), whereas neglect (b = 0.03, p < .05) and sexual abuse (b = 0.0003, p < .05) increased in Oregon. In California neglect (b = 0.03, p < .05) increased, whereas physical (b = -0.01, p < .05) and sexual abuse (b = -0.01, p < .05) increased. Missouri overall maltreatment rates increased (p < 0.05), whereas NC and Wisconsin rates decreased (p < .05).	Unemployment rate (b = 8.71, p = <.05), food stamp usage (b = -1.49, p < .05), and labour force participation (b = -1.17, p <.05) were only significant predictors of maltreatment, while controlling for time, for the California analyses.	Fair
Shanahan et al. (2013)	National, Regional, and State incidences of child maltreatment per 100,000 of broad and narrow AHT in 2000, 2003, 2006, 2009 using KID data.	Narrowly defined AHT: N = 5437, aged <1 years Annual average incidence: 33.4 Broadly defined AHT: N = 6317, aged <1 years Annual average incidence: 38.8	Poisson Regression to determine change of time. CHI-squared goodness of fit analysis was implemented,	No overall national trend of change for either broad (b = 1.00, SE = 0.010, p = .72) or the narrow definitions (b = 1.00, SE = 0.009, p = .80) of child maltreatment.	Boys appeared more at risk on both broad (x^2 = 37.20, p < .001) and narrow definitions (x^2 = 31.09, p <.001)	Fair

Wood et al. (2012)	Rate of monthly admissions per 1,000 for physical abuse and high-risk TBI according to the relevant ICD-9 codes on the PHIS between 2000 and 2009.	11822 admissions for young people presenting with ICD-9 physical abuse (ages <6 years) or high-risk TBI (aged < 12 months) codes.	Poisson regression to analyse the time trends (time unit = 1 month), initially only with time then MEIs included in subsequent models.	Physical abuse in <6s: Overall rise, with a peak in 2008 (+0.79% per year, 95% CI: 0.13-1.44, p = .020). TBI in <12 months: Similar pattern (+3.1% per year, 95% CI: 2.36-3.87, p <.001). All-cause injuries decreased (0.80% per year, p < .001).	Increase in 90-day mortgage delinquency (+1.38%), foreclosure rate (+2.55%), but not unemployment was associated with an increase in admission rates for physical abuse. Increase in all MEIs were significantly associated with high-risk TBI (+1.83%, +4.10%, and +1.23% respectively). Increase in MEIs significantly associated with decrease in all-cause injuries.	Good
Wood et al. (2016)	Aggregated unequivocal county-level AHT rates per 100,000 between January 2004 and December 2012.	712 children with AHT < 5 years (range: 0.7-59.8 months; median = 4.9 months).	Zero-inflated Poisson Regression with time and then with MEIs while accounting for time.	The overall AHT rate (adjusted for region) increased from Q1 (2004-2007) at 9.8 to 15.6 at Q2 (2007-2009) and then decreased again to 12.8. in Q3 (2009-2012). Q2 vs Q1 IRR: 1.68 (95% CI 1.41-2.00), p < .001 Q3 vs Q1 IRR: 1.31 (95% CI 1.09-1.56), p = .004 Q3 vs Q2 IRR: 0.78 (95% CI 0.65-0.92), p = .005	No significant association between any of the MEIs and AHT after accounting temporal trend and region.	Good
Zins et al. (2019)	Incidence of definite and probable physical maltreatment in children per 100,000 on the NIS and NEDS using relevant ICD-9 codes between 2006 and 2014.	Full sample size not provided, but some data available in supplementary documents. All young people included were < 10 years of age.	Linear Regression Models with year as independent variable. Logistic Regression for secondary analyses.	Rates (definite or probable) of maltreatment were unchanged (ED visit p = .460, inpatient stays p = .270). AHTs presenting to ED declined (p = .020)	Males, infants <1 year, and children >6 years more likely to receive a definite maltreatment diagnosis. Low household income, public insurance/self-pay, busy EDs, and white race also increased these odds.	Fair

AHT = Abusive Head Trauma, PTR = Pediatric Trauma Registry, NAHT = Non-Accidental Head Trauma, TBI = Traumatic Brain Injury, CI = Confidence Interval, IRR = Incidence Rate Ratio, OR = Odds Ratio, SES = socioeconomic status, CPS = Child Protective Services, KIDS = Kids' Inpatient Database, ICD = International Classification of Diseases, MEIs = Macroeconomic Indicators, PHIS = Pediatric Health Information System, NIS = National Inpatient Sample, NEDS = Nationwide Emergency Department Sample, ED = Emergency Department

*All studies completed in the United States of America

Medical Records

The majority of the articles reviewed in this paper analysed medical records and in particular focused on Abusive Head Trauma (AHT). Several authors found that physical abuse operationalised in this way increased over time and a peak was noted during the recession period in four studies (Berger et al., 2011; Emrick et al., 2019; Leventhal & Gaither, 2012; Wood et al., 2012), whereas the trend appeared to plateau or reverse after the recession (Wood et al., 2016; Zins et al., 2019). In contrast, Shanahan et al (2013) did not find any change in the period before and during TGR.

Wood et al. (2012) analysed discharge data from the Pediatric Health Information System (PHIS) to find relevant records of young people admitted to 43 hospitals in the USA. Using relevant ICD-9-CM (World Health Organisation (WHO), 1996) codes they aimed to identify children under the age of six, admitted for physical abuse. Between 2000 and 2009, they found that physical abuse admissions increased and peaked at the start of 2008. Interestingly, 'all-cause' injury admissions declined during their study period, with current, but not lagged, 90-day mortgage delinquency and foreclosure rates positively associated with an increase in physical child abuse, but negatively associated with all-cause injuries. Unemployment rate was not significantly associated with physical abuse but was negatively associated with all-cause injuries. Finally, they reported that the change in 90-day mortgage delinquency and foreclosure rates between 2008 and 2009 was associated with a significant increase in physical abuse.

Leventhal and Gaither (2012) instead looked at the Kids' Inpatient Databases (KIDs) between 1997 and 2009 and they included all young people with relevant ICD-9-CM (WHO, 1996) codes under the age of 18. Overall, they found that physical abuse significantly increased between 1997 (6.1/100,000) and 2009 (6.4/100,000), although this appeared to be mainly due to an increase in serious abusive injuries in children younger than 12 months. The incidence in this group increased from 56.2 in 1997 to 62.3 in 2009. Some fluctuations during this 12-year period were noted, for example overall physical abuse rates in 2000 decreased slightly when compared to 1997. They also reported that the proportion of abused children on Medicaid (a state-funded health insurance programme) increased significantly from 59% in 1997 to 74% in 2009. Similar to Wood et al (2012), this study found that incidence of non-abusive injuries decreased during this time.

In a more recent paper, Zins and colleagues (2019) included both physical abuse and neglect injuries in their analyses of maltreatment during and after TGR. They identified children under the age of 10 with the relevant ICD-9-CM (WHO, 1996) codes from the National Inpatient Sample (NIS) and the Nationwide Emergency Department Sample (NEDS). They did not find any significant change in either admission or ER presentations with physical maltreatment between 2006 and 2014. Incidentally, this was the only paper that included neglect as well as physical abuse in their outcome measures.

Abusive Head Trauma

Wood et al. (2012) and Zins et al. (2019) also looked at AHT specifically and reported that probable AHT had increased between 2000 and 2009 and decreased between 2006 and 2014 respectively. Of note, Zins and colleagues (2019) did not find any significant change over time for diagnoses of definite AHT.

Berger and colleagues (2011) looked exclusively at AHT and reviewed medical records in 74 counties of the USA. They found that unequivocal AHT diagnosis in children under the age of 5 significantly increased from 2004 to 2009 (see Table 1.2). They did not find an association between current or lagged county-level unemployment and AHT rates. A continuation to this study was then published in 2016 and these authors (Wood et al., 2016) revealed that the initial increase during the recession period was followed by a decline in AHT rates post-recession. However, AHT rates in the period after recession remained higher than they had been before the recession (IRR: 1.31, p = .004). Wood and colleagues looked at the Gini coefficient, a measure of income equality, to assess the impact of macroeconomic indicators. As in the Berger (2011) study, no association between the macroeconomic indicator and AHT rate was found.

Huang et al. (2011) commented that AHT rates appeared to increase following the start of TGR before unemployment increased, although they did not provide statistical support for this claim. They investigated how many infants (aged 0-2) were admitted for AHT according to the Pediatric Trauma Registry (PTR) between 2001 and 2010. They found

that the average monthly rate of AHT increased significantly from 0.7 prior to TGR (2001-2007) to 1.4 during TGR (2007-2010).

Similarly, Emrick and colleagues (2019) compared rates of AHT before (2000-2005) and during (2006-2010) TGR in West Virginia, although they did not explicitly aim to assess the impact of a recession. They initially used ICD-9 (WHO, 1979) codes to identify any infant less than 24 months old that presented with potential AHT. They then reviewed the identified case notes and included infants whose presentation was consistent with a more sensitive definition of AHT (Parks et al., 2012). They reported that the incidence of AHT increased significantly over time (see Table 1.2), though they observed that this increase appeared to pre-date TGR. They noted a peak in 2007, followed by decline until 2009, after which another peak was observed in 2010. However, they did not assess the significance of this trend.

Finally, Shanahan et al. (2013) also used the KIDs to analyse the national AHT rates between 2000 and 2009 in infants younger than 12 months. They noted some regional variation in AHT incidences, but no significant change in AHT rates was found on either national, regional, or state level. A more broad definition of AHT, as opposed to the more traditional narrow definition described in Emrick et al. (2019), also did not result in a significant trend over time.

Exposure to violence

The final study included in this review examined childhood exposure to violence by analysing data from three national telephone surveys in 2003, 2008, and 2011. Using nationwide sampling in the USA, Finkelhor and colleagues (2014) interviewed either a primary adult caregiver if the child was younger than 10 years or the young person themselves if they were between 10 and 17 years of age. Due to the nature of their chosen instrument (the Juvenile Victimization Questionnaire), children younger than 2 years were not included. This self-report study found amongst other things that young people's exposure to emotional abuse, but not other types of maltreatment, declined significantly from 2003 to 2011 (OR: -2.3, $p < .01$). Interestingly, this decline appeared to level off over time with no further decline found between 2008 and 2011 (i.e. after the recession; OR: -0.2, $p > .05$). Furthermore, they reported that this decline between 2003 and 2011 was stronger for families from a low SES background when compared families from medium ($p = .010$) and high ($p = .001$) SES backgrounds. No such significant difference in trajectory was observed between the medium and high SES young people ($p > .05$).

Discussion

We found some evidence that young people appeared to be at increased risk of maltreatment between 2007 and 2009, particularly when compared to maltreatment rates before 2007. This appeared to be true for reports to child protective services and physical abuse as indicated by medical records.

However, although the reviewed papers were of acceptable quality, the findings were mixed which limits generalisability. For example, Leventhal and Gaither (2012) and Shanahan et al. (2013) investigated the same database over a similar time period, but reported conflicting findings. This could indicate that physical abuse more generally accounts for the increase in maltreatment rates, rather than AHT per se, as Leventhal and Gaither (2012) included a range of maltreatment injuries in their analyses. On the other hand, five of the seven studies investigating AHT rates reported significant increases during the recession period. The discrepancy between Leventhal and Gaither (2012) and Shanahan et al. (2013) might also partly be explained by the fact that the former included young people aged 0-18, whereas the latter only included infants up to 12 months of age. This wide heterogeneity of study population and outcome measures across all reviewed articles is another reason why an interpretation of this systematic review should be made with caution.

Some authors identified a peak in child maltreatment rates during TGR (Berger et al., 2011; Huang et al., 2011; Wood et al., 2012, 2016), whereas others did not note any change (Millett et al., 2011; Shanahan et al., 2013; Zins et al., 2019). Interestingly, Finkelhor and colleagues (2014) found that self-reported child maltreatment rates had been steadily declining until the recession, but that this decline halted during and after TGR. It is possible that this stagnated decline in maltreatment rates following TGR could explain some of the non-significant findings. However, Emrick et al. (2019) and Huang et al. (2011) described a peak in maltreatment rates that appeared to pre-date TGR in the

USA, and Frioux et al. (2014) reported a steady increase in maltreatment rates from 2000 onwards.

Although not the aim of this review, many of the included studies also investigated macroeconomic indicators (e.g. unemployment, foreclosure rates) as potential predictors of child maltreatment during a recession, again with significant heterogeneity in methods and results. Further research to elucidate the association between these factors and child maltreatment is needed, with a particular focus on lagged effects as these long-term outcomes might be of particular interest to policy makers. Some authors also reported specific risk factors for abuse during TGR such as being an infant, having a low household income, and not having private health insurance (Zins et al., 2019). Although type of health insurance is considered an imperfect proxy for SES in the USA (Casey et al., 2018), this finding is in line with studies conducted in other countries such as Spain (Gracia et al., 2017), Taiwan (Hsin et al., 2018), and Croatia (Ajduković et al., 2018) and should be taken into account when identifying at-risk families.

Similarly, Lawson and colleagues (2020) reported that the association between parental job loss during the Covid-19 pandemic and child maltreatment was moderated by the extent to which parents implemented 'cognitive reframing'. They assessed whether parents used this protective coping strategy, whereby stressors are reframed to make them appear more manageable, using the Family Crisis Oriented Personal Evaluation Scale (McCubbin, Olsen & Larsen, 1981). They found that parents who reported using more positive reframing were less likely to have a history of psychological or physical

maltreatment towards their children (Lawson et al., 2020). This is an important finding as it could inform preventative strategies aimed at parents and carers. The Scottish Government (2020) has, for instance, recently published a transition and recovery plan to support the population's mental health after Covid-19. Within that plan specific mention is given to early intervention, relationship trauma, family distress, and poverty. The findings from the current review, coupled with studies such as those by Lawson et al. (2020), could support governments to identify and support young people at risk of maltreatment.

Limitations

A key limitation in any retrospective child maltreatment study is that fact that child maltreatment rates are potentially under-reported (Eads, 2013). Studies examining self-reported incidence, such as those used in Finkelhor et al. (2014), are especially sensitive to this bias. However, as the main aim of this review was to identify trends in reported child maltreatment rates, rather than absolute rates, it is likely that sample sizes of all the reviewed papers were large enough to identify trends. In addition, a study completed in The Netherlands reported that unemployment rates between 1994 and 2008 predicted increases in attempted calls to the national child helpline ('De Kindertelefoon'), including calls about violence, with a peak in calls noted in the second half of 2008 (van Dolen et al., 2013). This trend appears to be consistent with at least three of the reviewed papers (Frioux et al., 2014; Wood et al., 2012, 2016) and uniquely provides anonymised self-report data from young people themselves. On the other hand, the decision to exclude

studies that did not assess maltreatment rates during TGR might have led to the exclusion of papers that allowed us to identify if and when maltreatment rates returned to pre-recession rates.

Another limitation that should be discussed here is the fact that only studies researching maltreatment rates in the USA were included in this review. Questions then should be raised about the generalisability of these papers, especially considering that there seemed to be differences at state level (Millett et al., 2011). It is also important to note here that different countries will have different thresholds for child maltreatment, and cultural and political differences should therefore be carefully considered before generalising these findings. In addition, the USA experienced two other recessions in 1990 and 2001, whereas the United Kingdom for example did not experience the 2001 recession. This might then have also confounded the findings and could explain some of the mixed results due to the variety of timeframes included in the reviewed articles. This also relates to the potential bias discussed earlier regarding exposure status not being measured as it was a global event rather than a specific circumstance, which in turn limits our ability to assign causality to TGR and its impact on maltreatment.

Finally, child maltreatment was operationalised in three different ways in this review and each operationalisation had its own limitations. For example, CPS reports are subject to limited resources and changing thresholds for what is considered maltreatment, whereas analysis of diagnostic codes is sensitive to over-inclusion as it does not account for individual young people who might be re-admitted several times during the study period.

We included a range of outcome measures as this allowed us to increase the scope of maltreatment rates, but this may have made comparisons more complex as it increased the heterogeneity of results.

Conclusion

Despite these limitations, we have found some evidence of an increased risk of child maltreatment during a recession and this has implications for early intervention and preventative measures as well as further research. Considering that many countries around the world will have to live through a recession and its consequences for some time to come, it is key that at-risk young people are identified at the earliest opportunity. There is potential for early identification, but further research is required. If these findings can be elucidated, then services can perhaps offer tailored support to prevent adverse child outcomes in future.

References

Ajduković, M., Rajter, M., & Rezo, I. (2018). Individual and contextual factors for the child abuse potential of Croatian mothers: The role of social support in times of economic hardship. *Child Abuse & Neglect*, *78*, 60–70. https://doi.org/10.1016/j.chiabu.2018.01.008

BBC News. (2021). *Covid-19: Rise in suspected child abuse cases after lockdown.* BBC News. https://www.bbc.co.uk/news/uk-55682745

Berger, R. P., Fromkin, J. B., Stutz, H., Makoroff, K., Scribano, P. V, Feldman, K., Tu, L. C., & Fabio, A. (2011). Abusive Head Trauma During a Time of Increased Unemployment: A Multicenter Analysis. *Pediatrics*, *128*(4), 637–643. https://doi.org/10.1542/peds.2010-2185

Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: rapid review of the evidence. In *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30460-8

Casey, J. A., Pollak, J., Glymour, M. M., Mayeda, E. R., Hirsch, A. G., & Schwartz, B. S. (2018). Measures of SES for Electronic Health Record-based Research. *American Journal of Preventive Medicine*, *54*(3). https://doi.org/10.1016/j.amepre.2017.10.004

Coulton, C. J., Richter, F. G. C., Korbin, J., Crampton, D., & Spilsbury, J. C. (2018). Understanding trends in neighborhood child maltreatment rates: A three-wave panel study 1990-2010. *Child Abuse & Neglect*, *84*, 170–181. https://doi.org/10.1016/j.chiabu.2018.07.025

Emrick, B. B., Smith, E., Thompson, L., Mullett, C., Pino, E., Snyder, K., Kroll, M.-A., Ayoubi, S., Phillips, J., Istfan, S., Welch, C. A., & McJunkin, J. E. (2019). Epidemiology of abusive head trauma in West Virginia children <24 months: 2000-2010. *Child Abuse & Neglect*, *93*, 215–221. https://doi.org/https://dx.doi.org/10.1016/j.chiabu.2019.05.011

Finkelhor, D., Shattuck, A., Turner, H. A., & Hamby, S. L. (2014). Trends in children's exposure to violence, 2003 to 2011. *JAMA Pediatrics*, *168*(6), 540–546. https://doi.org/http://dx.doi.org/10.1001/jamapediatrics.2013.5296

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*. https://doi.org/10.1186/s12889-016-2720-y

Frioux, S., Wood, J. N., Fakeye, O., Luan, X. Q., Localio, R., & Rubin, D. M. (2014). Longitudinal Association of County-Level Economic Indicators and Child Maltreatment Incidents. *Maternal and Child Health Journal*, *18*(9), 2202–2208. https://doi.org/10.1007/s10995-014-1469-0

Gracia, E., Lopez-Quilez, A., Marco, M., & Lila, M. (2017). Mapping child maltreatment risk: a 12-year spatio-temporal analysis of neighborhood influences. *International Journal of Health Geographics*, *16*(1), 38. https://doi.org/http://dx.doi.org/10.1186/s12942-017-0111-y

Hiilamo, A., Hiilamo, H., Ristikari, T., & Virtanen, P. (2021). Impact of the Great Recession on

mental health, substance use and violence in families with children: A systematic review of the evidence. *Children and Youth Services Review, 121*. https://doi.org/10.1016/j.childyouth.2020.105772

HM Treasury (2010). *Glossary of Treasury terms.* HM Treasury. https://web.archive.org/web/20121102095705/http://www.hm-treasury.gov.uk/junebudget_glossary.htm

Hsin, Y. C., Chang, Y. C., Lee, E. P., Chiu, C. H., Chou, I. J., Hsia, S. H., Lin, K. L., Lee, J., Huang, J. L., Wang, C. J., Wu, H. P., & Prevention Protection, A. (2018). Risk factors for child maltreatment by the utilization of medical service and socioeconomic environment in Taiwan. *Medicine*, *97*(52). https://doi.org/10.1097/md.0000000000013728

Huang, M. I., O'Riordan, M. A., Fitzenrider, E., McDavid, L., Cohen, A. R., & Robinson, S. (2011). Increased incidence of nonaccidental head trauma in infants associated with the economic recession. *Journal of Neurosurgery. Pediatrics*, *8*(2), 171–176. https://doi.org/https://dx.doi.org/10.3171/2011.5.PEDS1139

Lawson, M., Piel, M. H., & Simon, M. (2020). Child Maltreatment during the COVID-19 Pandemic: Consequences of Parental Job Loss on Psychological and Physical Abuse Towards Children. *Child Abuse and Neglect*. https://doi.org/10.1016/j.chiabu.2020.104709

Leventhal, J. M., & Gaither, J. R. (2012). Incidence of serious injuries due to physical abuse in the United States: 1997 to 2009. *Pediatrics*, *130*(5), e847-52. https://doi.org/https://dx.doi.org/10.1542/peds.2012-0922

McCubbin, H. I., Thompson, A. I., McCubbin, M. A. (Eds.). (1981). *Family assessment: Resiliency, coping and adaptation-inventories for research and practice.* University of Wisconsin System, 455-507.

Millett, L., Lanier, P., & Drake, B. (2011). Are economic trends associated with child maltreatment? Preliminary results from the recent recession using state level data. *Children and Youth Services Review*, *33*(7), 1280–1287. https://doi.org/10.1016/j.childyouth.2011.03.001

Moher D, Liberati A, Tetzlaff J, A. D. (2009). PRISMA 2009 Flow Diagram. In *The PRISMA statement*.

National Health Lung and Blood Institute (NHLBI). (2018). *Study quality assessment tools*. NHLBI. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed 25th November 2020.

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1). 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., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline

for reporting systematic reviews. In *The BMJ* (Vol. 372). https://doi.org/10.1136/bmj.n71

Parks, S. E., Annest, J. L., Hill, H. A., & Karch, D. L. (2012). *Pediatric abusive head trauma: Recommended definitions for public health surveillance and research.* Atlanta, GA: Centers for Disease Control and Prevention, 5–16.

Rajmil, L., de Sanmamed, M. J. F., Choonara, I., Faresjo, T., Hjern, A., Kozyrskyj, A. L., Lucas, P. J., Raat, H., Seguin, L., Spencer, N., Taylor-Robinson, D., & Inrich. (2014). Impact of the 2008 Economic and Financial Crisis on Child Health: A Systematic Review. *International Journal of Environmental Research and Public Health*, *11*(6), 6528–6546. https://doi.org/10.3390/ijerph110606528

Shanahan, M. E., Zolotor, A. J., Parrish, J. W., Barr, R. G., & Runyan, D. K. (2013). National, regional, and state abusive head trauma: application of the CDC algorithm. *Pediatrics*, *132*(6), e1546-53. https://doi.org/https://dx.doi.org/10.1542/peds.2013-2049

Slack, K. S., Berger, L. M., DuMont, K., Yang, M. Y., Kim, B., Ehrhard-Dietzel, S., & Holl, J. L. (2011). Risk and protective factors for child neglect during early childhood: A cross-study comparison. *Children and Youth Services Review*. https://doi.org/10.1016/j.childyouth.2011.04.024

The Scottish Government. (2020). *Coronavirus (COVID-19): mental health - transition and recovery plan.* The Scottish Government. https://www.gov.scot/publications/mental-health-scotlands-transition-recovery/

Eads, K. (2013). Breaking Silence: Underreported Child Abuse in the Healthcare Setting. *Online Journal of Health Ethics*, *9*(1).

van Dolen, W. M., Weinberg, C. B., & Ma, L. (2013). The influence of unemployment and divorce rate on child help-seeking behavior about violence, relationships, and other issues. *Child Abuse and Neglect*. https://doi.org/10.1016/j.chiabu.2012.09.014

Wood, J. N., French, B., Fromkin, J., Fakeye, O., Scribano, P. V, Letson, M. M., Makoroff, K. L., Feldman, K. W., Fabio, A., & Berger, R. (2016). Association of Pediatric Abusive Head Trauma Rates With Macroeconomic Indicators. *Academic Pediatrics*, *16*(3), 224–232. https://doi.org/10.1016/j.acap.2015.05.008

Wood, J. N., Medina, S. P., Feudtner, C., Luan, X. Q., Localio, R., Fieldston, E. S., & Rubin, D. M. (2012). Local Macroeconomic Trends and Hospital Admissions for Child Abuse, 2000-2009. *Pediatrics*, *130*(2), E358–E364. https://doi.org/10.1542/peds.2011-3755

World Health Organisation (WHO). (1979). *ICD-9: International Classification of Diseases, Ninth Revision.*. Salt Lake City, Utah: Medicode.

World Health Organisation (WHO). (1996). *ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification.* Salt Lake City, Utah: Medicode.

Zins, Z. P., Wheeler, K. K., Brink, F., Armstrong, M., Shi, J., Groner, J. I., & Xiang, H. (2019). Trends in US physician diagnosis of child physical abuse and neglect injuries, 2006-2014. *Child Abuse & Neglect*, *98*, 104179. https://doi.org/https://dx.doi.org/10.1016/j.chiabu.2019.104179

Chapter 2: Major Research Project

(extended discarded proposal)

Social Cognition in Childhood Leukaemia Survivors

Extended Research Proposal

Abstract

Background

'Late effects' of childhood cancer might arise due to changes in the brain as a result of the illness itself and/or because of the areas impacted by the treatment. Childhood Acute Lymphoblastic Leukaemia (ALL) is one of the more common childhood cancers and research shows that ALL treated with chemotherapy significantly impacts long-term neurocognitive functioning. There is some evidence that childhood ALL survivors present deficits in social adjustment.

Aims

This study aims to identify whether young people at least one-year post-treatment show impaired cognitive empathy when compared to healthy age-matched controls.

Methods

Participants will be recruited from tertiary oncology centres and schools in Edinburgh and Glasgow. Demographic (and clinical if applicable) information will be collected and they will be assessed with three cognitive empathy tests; the Reading The Eyes in The Mind Test, The Faux Pas Test, and ESQ questionnaire. The WASI-II and Symbol Search subtest from the WISC-V; and the Finger Tapping test will be completed to assess cognitive and psychomotor abilities. Assessments will be completed at the young people's school or at the paediatric psychology outpatient clinic.

Application

Results from this study could inform long-term care for ALL survivors, thereby improving their psychosocial adjustment and ultimately their quality of life.

Introduction

Between 2007 and 2016, 1275 children under the age of 14 years were diagnosed with cancer in Scotland and leukaemia accounted for 31% of these diagnoses (ISD Scotland, 2019). Fortunately, medical advancement has allowed for the full recovery of over 80% of young people diagnosed with cancer (Stewart & Wild, 2014), and researchers are continuing to develop our understanding of childhood cancers. As such, some of the research perspective has shifted to instead focus on so-called 'late effects' of oncological diseases and their treatments.

Children who survived a childhood cancer have been found to be at a significantly increased risk of later cognitive, behavioural, and emotional difficulties and these difficulties have been coined late effects. These secondary difficulties might arise due to organic or functional changes in the brain as a result of the illness itself (i.e. when the central nervous system (CNS) or brain is involved in the disease) and/or because of the areas impacted by the treatment. Furthermore, the psychological impact of being diagnosed with and treated for a life-threatening illness is far reaching. For example, inpatient stays as well as poor health can limit the young person's social and educational opportunities, which can have long-term consequences for the re-integration with their peer group and their general social and cognitive development. It has also been reported that patients and their families experience high levels of stress throughout the disease process (Myers et al., 2014). This is particularly problematic when considering that high levels of stress are associated with several mental health difficulties (McLaughlin, 2016). As more young people are surviving cancer, acknowledging and potentially preventing

these numerous late effects is becoming more important. Although late effects are associated with all childhood cancers, only those relevant to childhood Acute Lymphoblastic Leukaemia (ALL) will now be discussed briefly due to the aim of this project.

ALL is a haematological cancer, which has chemotherapy as its first-line treatment (Cheung & Krull, 2015). Several chemotherapy agents are administered concurrently during the initial as well as the maintenance phase of the treatment and a range of these agents (e.g. methotrexate, cytarabine) have been associated with late neurocognitive effects. Damage to cortical white matter as a result of CNS exposure to chemotherapy could provide an explanation for the cognitive impairments in some young people as white matter is particularly vulnerable to toxicity in the developing brain (De Luca, 2015). In addition, executive functioning (e.g. planning, behavioural inhibition, and emotional regulation) deficits are relatively common in childhood ALL survivors, which is potentially related to structural and functional changes to the fronto-parietal attentional network (Cheung & Krull, 2015). The impact on frontal systems is particularly relevant in childhood cancers, as it is known that the frontal neurodevelopment occurs in a non-linear fashion, with peaks in development/synaptic pruning occurring during late childhood and again during post-adolescence (Blakemore & Choudhury, 2006). It is known that cranial and total body radiation can lead to cognitive decline above and beyond the effects of chemotherapy (Cheung & Krull, 2015; Willard et al., 2014) and for this reason, radiation therapy is no longer the first-line treatment for leukaemia. However, this treatment is still implemented following relapse and this project will therefore only

consider young people who have been treated with chemotherapy only (i.e. have not relapsed).

A full review of neurocognitive late effects of ALL is outside the scope of this proposal, but some researchers have reported that ALL in childhood is associated with poorer social competence including maintaining peer relationships (Stam, Grootenhuis, & Last, 2001). Adolphs (2001) argues that our complex social world requires us to develop social cognition and he defines this as "the ability to construct representations of the relations between oneself and others, and to use those representations flexibly to guide social behaviour" (Adolphs, 2001, p. 231). Unfortunately, literature around social adjustment in childhood ALL survivors is inconsistent and social cognition has never been directly assessed in this population. In line with a treatment related social-cognitive deficit hypothesis, however, it can be argued the negative impact of chemotherapy on the frontal lobes and its associated networks also explains potential poorer social functioning as the frontal areas have consistently been shown to play a role in social cognition and emotional regulation (Blakemore & Choudhury, 2006). Similarly, Yeates and colleagues (2007) suggest that social competence is comprised of social information processing (cognitive-executive functions, social-affective functions, and social problem-solving), social interaction (affiliative, aggressive, and withdrawn), and social adjustment (self-perceptions and perceptions of others). They argue that a brain insult, particularly in the frontotemporal and limbic regions, can therefore influence social competence as well as the relationships between the different components of their model. Finally, the relatively long treatment protocol associated with ALL potentially further endangers social

development due to prolonged time away from healthy peers. The impact of ALL on social cognition should thus be studied further because humans are inherently social creatures and their quality of life is strongly connected with their ability to thrive in a social environment.

The aim of this project is therefore to investigate the effects of leukaemia treatment on social cognition in childhood leukaemia survivors. In order to operationalise social cognition for this study, it was decided to explore cognitive empathy initially. Cognitive empathy is the ability understand one's own and others' emotional states using contextual appraisals (De Waal, 2008) and as such a key part of social cognition. This can be differentiated from the affective aspect of empathy, which involves an emotional response to the mental states of others and as such is less straightforward to assess. As this is a relatively small-scale study, it was also decided to only include ALL survivors as they constitute the largest proportion of childhood leukaemia.

Research questions

Primary research question

Do survivors of ALL show decreased cognitive empathy when compared to healthy age-matched controls?

Secondary research questions

1. Does cognitive empathy ability correlate with general intellectual ability and processing speed, and is the strength of association different for survivors of ALL?
2. Does age at diagnosis and/or time since treatment predict the impact of ALL on cognitive empathy?

Hypotheses

It is expected that childhood ALL survivors will show decreased cognitive empathy when compared to healthy age-matched controls. The secondary research questions will be of an exploratory nature and as such no hypotheses are made.

Plan of investigation

Participants

To perform a power analysis using G*Power 3.1, an effect size of $d = 0.8$ on the primary measure Reading The Mind in the Eyes Test (RMET) (Baron-Cohen et al., 2001) was used. This was based on similar research by Henry et al. (2006) (Cohen's $d = 0.66$) and by Geraci *e*t al. (2010)(Cohen's $d = 1.21$). Although these studies examine cognitive empathy in an adult population and their participants had traumatic brain injuries not related to ALL, the brain damage described in these papers is likely to be similar to brain damage following paediatric ALL as described above (Cheung & Krull, 2015).

Therefore, for a power level of .80 ($p < .05$, one-tailed) a minimum of 21 young people (aged 6-18) at least 1 year post-treatment and 21 age-matched healthy young people from Glasgow and Edinburgh schools will be recruited.

Following discussions with clinical teams in Edinburgh and Glasgow, it was estimated that each team will see around 30 young people a month for ALL follow-up (excluding those <1 year post-treatment). As such, recruiting 21 young people with a history of paediatric ALL seems very feasible. Please note that in order to age-match we will need to recruit more young people for the control group (estimated: 60), however we aim to assess several young people per school class to allow this and this would therefore also seem feasible.

Inclusion/exclusion criteria

Young people aged between 6 and 17 years who are at least 1 year post ALL treatment will be included in this study. The young people will be in or will have completed mainstream education. Young people with neurodevelopmental disorders and those in specialist education will be excluded. For the control group, healthy young people in mainstream education will be included; those with a previous life-threatening condition will be excluded from this group.

Recruitment procedures

Young people attending the leukaemia out-patient clinic will be invited to participate in the study by their clinician. Age appropriate information leaflets will be distributed, and informed consent and assent will be collected from young people and/or their parents where appropriate. For the control group, schools will be approached, and information and consent forms sent out to interested families. Data will be collected, ethics permitting, between September 2020 and April 2021.

Measures

Demographics and treatment history

Participant characteristics such as age, gender, and level of deprivation will be collected for all participants. For those in the post-treatment ALL group, clinical information will also be collected through clinical case note review by a clinician within the hospital oncology team.

Cognitive empathy

The RMET (Baron-Cohen et al., 2001) and the Faux Pas Test (FPT) (Baron-Cohen et al., 1999; Gregory et al., 2002) will be administered. The RMET will allow us to assess cognitive empathy visually, whereas the FPT is a verbal assessment. The RMET child version (28 items) will be administered to young people between 6 and 11 years. The

adult version 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.

Parents will also be requested to complete the Empathy Systemizing Quotient questionnaire (ESQ) (Auyeung et al., 2012) to rate their child's empathy. This measure will serve as a proxy of cognitive empathy. The child (6 – 11), adolescent (12 – 15), and adult (16+) versions will be completed as appropriate. The completion time for this measure is around 10 minutes.

General intellectual ability

The Wechsler Abbreviated Scale of Intelligence, second edition, (WASI-II; Wechsler, 2011) will be used to estimate current general intellectual ability. The completion time for these tests is around 30 minutes.

Processing speed

The Symbol Search from the Wechsler Intelligence Scale for Children, fifth edition, (WISC-5; Wechsler, 2014) and the Finger Tapping Test will be used to measure processing speed. The completion time for this measure is around 10 minutes.

Impact of Covid-19 pandemic

The Covid-19 pandemic and measures imposed to halt the spread of the disease could have impacted on psychological functioning and well-being. Although a full assessment of this is beyond the scope of the current study, we wanted to consider the way the young people in this study managed the social distancing measures in an exploratory way.

To assess the impact of prolonged social distancing/isolation measures, all parents/participants will be asked to answer a short questionnaire in relation to the young person's social functioning during this period (e.g. the use of video conferencing to meet with friends) (see Appendix V).

Design

Young people in the ALL group and their parent(s) will be invited to attend an outpatient appointment at the Royal Hospital for Children in Glasgow to complete neuropsychological assessment. This assessment will last approximately one hour and 10 minutes. Parents will be asked to complete the ESQ during this time. Control participants will be assessed in their school. Questionnaires for the parents in this group will be send to their home with a pre-stamped envelope.

Research procedures

Collected data will be stored on secure NHS computers or in locked cabinets at the Royal Hospital for Children for a period of ten years. Data will be anonymised for analyses and dissemination. The lead investigator (Prof Liam Dorris) will be responsible for destroying the collected data securely.

Data analysis

Primary analysis

To answer the primary question whether ALL survivors differ on a measure of social cognition when compared to a matched healthy control group, a t-test for independent samples with the score on the RMET as the dependent variable and group as the independent variable will be used. The RMET was chosen as the primary measure as this task has been widely used by researchers assessing social cognition (e.g. Dorris et al, in prep; Geraci et al., 2010). Confidence intervals, group means, standard deviations, and Cohen's *d* will also be reported. If assumptions for the t-test cannot be met, a Mann Whitney U test will be done instead.

Secondary analyses

As this study will not be adequately powered for below analyses, these will be of an exploratory nature.

A MANCOVA with group as independent variable, direct cognitive empathy measures (i.e. scores on the RMET and FPT) as dependent variables and general intellectual ability (WASI-II FSIQ-4 score) and processing speed (WISC-V processing speed index score and Finger Tapping Test score) as covariates is proposed to examine whether ALL impacts cognitive empathy. An ANCOVA with above independent variable and covariates, but with ESQ rating as dependent variable is also suggested. Confidence intervals, group means, standard deviations, and partial η^2 will also be reported.

To examine whether age at diagnosis predicts the impact of ALL on cognitive empathy, age will be divided in three brackets ([6-9], [10-12], [13-17]) in accordance with literature around the development of social cognition (Blakemore & Choudhury, 2006; Dorris et al, in prep). A MANCOVA with age range as independent variable, and direct cognitive empathy measures as dependent variables, and with the same covariates as above would be conducted. Confidence intervals, group means, standard deviations, and partial η^2 will also be reported.

Settings and equipment

Young people will attend an approximately one-hour session to complete the described tests at either their school or at the paediatric psychology out-patient units in Edinburgh or Glasgow. A NHS encrypted laptop will be acquired for data collection.

Health and safety issues

No health and safety concerns are raised at this time for either the researcher or the participants. Local Covid-19 guidelines will be adhered to.

Ethical considerations

Ethical approval for this project will be sought from the Ethics Committee, the Caldicott Guardian, and the Scottish government for the inclusion of healthy school pupils. We will request sponsorship from NHS R&D. We will liaise with SCOTCRN and Young Patient Group Advisory to maximise the benefit/value of this study and to ensure our information and consent forms are appropriate. We will provide a brief report of neuropsychology findings to patients and to those in the control group where we identified significant difficulties. Young people in the control group will receive a summary of the study's findings due to practical constraints otherwise.

Informed consent will be sought from young people over the age of 12 and from the parents of younger children. From these younger children, assent will be sought to ensure that the young persons' wishes are respected. Consent/assent will be sought through teachers and oncologists as appropriate.

Finance and Indemnity

It is anticipated that these studies will require the allocated £200 from the University of Glasgow, in order to fund the stationary and postage costs that will be needed to provide information sheets and reports to participants and also for the families to return completed consent forms. The NHS Indemnity Scheme and the University of Glasgow clinical trials insurance will apply.

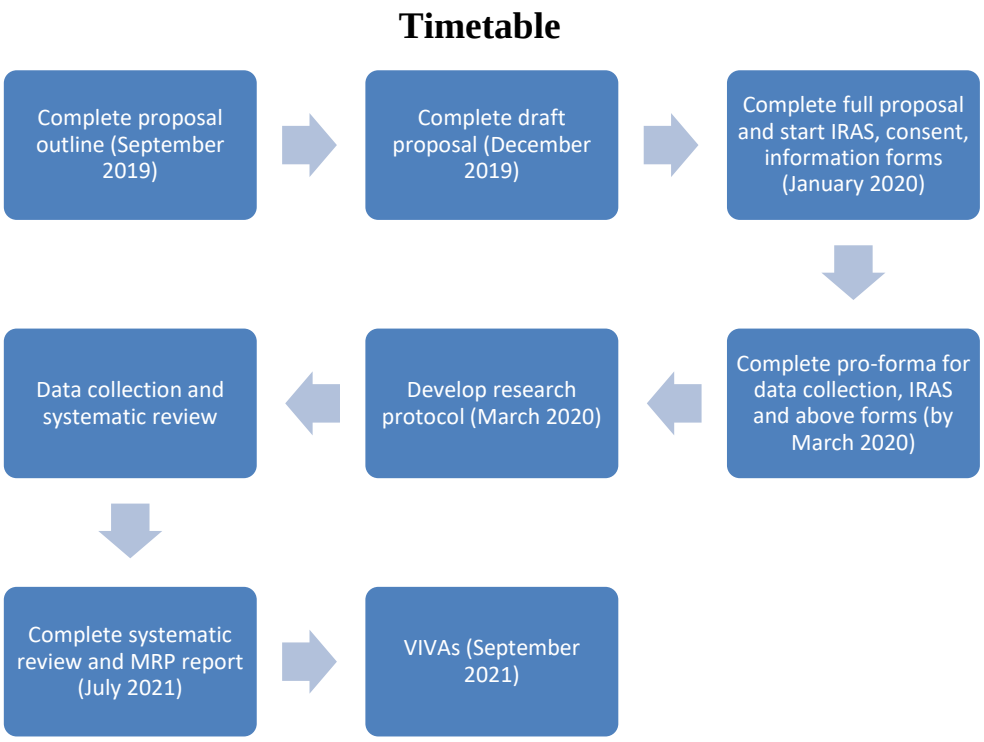


Figure 2. 1: Illustration of proposed research timeline

Practical applications

Results from this study could inform long-term care for ALL survivors, thereby improving their psychosocial adjustment and ultimately their quality of life. This study might, for example, feed into the standard follow-up care of paediatric ALL survivors by assessing for social deficits post-treatment and offering early intervention where appropriate, which in turn might improve some of these deficits before they impact significantly on the young person's social functioning. Other research has suggested, for instance, that interventions aimed at increasing parental nurturance can improve social outcomes in children with traumatic brain injuries (Deighton et al., 2019).

Brief critical appraisal of proposed method

Cognitive empathy in the paediatric cancer population has not previously been researched, although there is some evidence available that suggests poorer social functioning in this population (Stam et al., 2011). The results of this study could have informed further much-needed research in this area as well as inform clinical practice to improve care for these young people. Overall, this study has the potential to be a robust research project, although some limitations will be discussed below.

With regards to the primary research question, a concern around the interpretation of the statistical analyses could be raised. It is possible that we could have found a statistically significant difference between the groups, but due to the lack of a 'normal range' it would have potentially been difficult to assign clinical significance to this. Although we planned

to compare the ALL group with a matched healthy control group, neither the RMET nor the FPT have normative samples available. Some work has been done to compare people on the Autistic Spectrum with neurotypical controls (Baron-Cohen et al., 1999, 2001), but no straightforward interpretation of test scores would be possible other than the group comparison within our present study. To address this limitation, we could have used Ferguson's suggestions (2009) to interpret Cohen's *d* in a clinically useful way.

In addition, in line with previous research (Gunther Moor et al., 2012), we decided to shorten the adult version of the RMET so all participants in our study would have to make the same number of decisions on this task. It is possible, however, that this could have reduced the validity of any interpretation regarding the participants' cognitive empathy. On the other hand, Dorris et al. (in prep) have used this shortened version of the RMET with a very large cohort of the general population and we could have used this study group as a reference for our smaller population.

With regard to the data analysis plan, the suggested independent samples t-test to address the primary research question would not account for confounding variables. This is partly addressed by the suggested MANCOVA, but due to limited timeframe associated with a DClinPsy project this study would have been unlikely to be powered enough to find any significant results using this more complex analysis. This proposal also offers a range of other exploratory analyses, but no correction for multiple testing is suggested. Although it is acknowledged that the study would likely be underpowered to explore these questions fully, some considerations around this could have been made.

Finally, although ALL is a common form of childhood leukaemia in the United Kingdom (ISD Scotland, 2019), the treatment group chosen for this study is quite specific and it is possible that the findings in this study would not be widely generalisable. Similarly, this study aimed to exclude young people whose ALL had relapsed as these young people will have likely received full body radiation and stem-cell transplant. As discussed, this treatment has a significantly bigger impact on neurodevelopment and adaptive functioning than chemotherapy alone (Cheung & Krull, 2015; Willard et al., 2014). On the other hand, this exclusion criterion was discussed with the Paediatric Oncologists and they felt this was an appropriate decision in the context of this project.

References

Adolphs, R. (2001). The neurobiology of social cognition. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/S0959-4388(00)00202-6

American Childhood Cancer Organisation. (September, 2017). Drugs: Chemotherapy Drugs and Other Pharmaceuticals. Retrieved from: http://www.acco.org/drugs-chemotherapy-drugs-and-other-pharmaceuticals/

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*. 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. *Learning*.

Blakemore, S. J., & Choudhury, S. (2006). Development of the adolescent brain: Implications for executive function and social cognition. In *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/j.1469-7610.2006.01611.x

British Psychological Society (2020). https://www.bps.org.uk/sites/www.bps.org.uk/files/Member%20Networks/Divisions/DoN/DON%20guidelines%20on%20the%20use%20of%20tele-neuropsychology%20%28April%202020%29.pdf

Cheung, Y. T., & Krull, K. R. (2015). Neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia treated on contemporary treatment protocols: A systematic review. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2015.03.016

De Luca, C. (2015). *A compendium of evidence and framework for neuropsychological services in paediatric cancer*. Retrieved from: https://pics.org.au/health-professionals/useful-resources-and-links/

De Waal, F. B. M. (2008). Putting the altruism back into altruism: The evolution of empathy. *Annual Review of Psychology*. https://doi.org/10.1146/annurev.psych.59.103006.093625

Deighton, S., Durish, C. L., Taylor, H. G., Rubin, K., Dennis, M., Bigler, E. D., Vannatta, K., Gerhardt, C. A., Stancin, T., & Yeates, K. O. (2019). Theory of Mind and Parental Nurturance as Predictors of Peer Relationships After Childhood Traumatic Brain Injury: A Test of Moderated Mediation. *Journal of the International Neuropsychological Society*. https://doi.org/10.1017/S135561771900064X

Dorris L, Young D, Barlow J, Byrne K & Hoyle R. *Human Cognitive Empathy across the*

Lifespan. (in-preparation)

Ferguson, C. J. (2009). An Effect Size Primer: A Guide for Clinicians and Researchers. *Professional Psychology: Research and Practice*. https://doi.org/10.1037/a0015808

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*. https://doi.org/10.3109/02699052.2010.487477

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., & Hodges, J. R. (2002). Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: Theoretical and practical implications. *Brain*. https://doi.org/10.1093/brain/awf079

Gunther Moor, B., Op de macks, Z. A., Güroğlu, B., Rombouts, S. A. R. B., Van der molen, M. W., & Crone, E. A. (2012). Neurodevelopmental changes of reading the mind in the eyes. *Social Cognitive and Affective Neuroscience*, *7*(1). https://doi.org/10.1093/scan/nsr020

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*. https://doi.org/10.1016/j.neuropsychologia.2006.03.020

Information Services Division (ISD) Scotland (2019). *Children and Young People with Cancer in Scotland: 2007-2016.* Retrieved from: https://www.isdscotland.org/Health-Topics/Cancer/Publications/

McLaughlin, K. A. (2016). Future Directions in Childhood Adversity and Youth Psychopathology. *Journal of Clinical Child and Adolescent Psychology*. https://doi.org/10.1080/15374416.2015.1110823

Myers, R. M., Balsamo, L., Lu, X., Devidas, M., Hunger, S. P., Carroll, W. L., Winick, N. J., Maloney, K. W., & Kadan-Lottick, N. S. (2014). A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: A report from the Children's Oncology Group. *Cancer*. https://doi.org/10.1002/cncr.28578

Stam, H., Grootenhuis, M., & Last, B. (2001). Social and emotional adjustment in young survivors of childhood cancer. In *Supportive Care in Cancer*. https://doi.org/10.1007/s005200100271

Stewart, B. and Wild, C.P. (eds.), International Agency for Research on Cancer, WHO. (2014) World Cancer Report 2014 [Online]. Available from: http://www.thehealthwell.info/node/725845 [Accessed: 23rd February 2017].

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., Leung, W., Huang, Q., Zhang, H., & Phipps, S. (2014). Cognitive outcome after pediatric stem-cell transplantation: Impact of age and total-body irradiation. *Journal of Clinical Oncology*. https://doi.org/10.1200/JCO.2014.56.2223

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*. https://doi.org/10.1037/0033-2909.133.3.535

Chapter 3: Major Research Project

Parental stress in infants with early-onset seizures: Insights from a population level study exploring genetic aetiologies.

Prepared in accordance with the author requirements for:

Developmental Medicine and Child Neurology (details in Appendix VI)

Plain Language Summary

Epilepsy is a neurological condition characterised by repeated seizures. Previous research has shown that parents of children with epilepsy tend to have higher levels of parenting stress and higher levels of parental stress are associated with negative outcomes such as poorer mental health and child maltreatment. In this study we looked at parenting stress in parents of infants with seizures.

Children who had a seizure before their third birthday were included, but they were excluded if a clear cause for the seizures was known, such as a stroke. Their parents were asked to undergo genetic testing and to complete two questionnaires. The ABAS-2 measures adaptive functioning and gives an overall score that reflects how well the child copes with day-to-day age-appropriate activities. The PSI-4-SF measures parental stress.

We found that parents in this study had low levels of parenting stress overall. However, poorly controlled seizures, older age of the child, and lower adaptive functioning were related to an increase in parental stress. We also found that parents of older girls whose epilepsy was well-managed and who scored higher on adaptive functioning, were more likely to under-report their concerns.

Limitations of the study have to be considered before drawing conclusions, but overall we recommend that our findings are taken into account when supporting families with a child who presents with seizures before the age of three. We should ensure that families receive appropriate guidance and support as early as possible to avoid the negative consequences of parental stress.

Abstract

Aim

Identify whether parents of children with early-onset seizures are at risk of increased parenting stress (PS) and consider the role of genetic diagnosis.

Methods

301 families whose child presented with a seizure without clear aetiology before age three were included. Parents completed the PSI-4-SF and/or ABAS-2 at diagnosis and 1-year follow-up. Regression analyses examined predictors of PS and 'defensive reporting' (DR) at baseline (N = 125) and follow-up (N = 74).

Results

Overall, 55% lived in the most deprived areas, but response rate was higher for families living in affluent areas. Low levels of PS were found at baseline and follow-up. Significant PS was lower in our sample compared to the normative cohort (5% vs 10%). Over 30% of parents showed DR, indicating under-reporting of concerns. DR was more likely when the child was female, younger, had well-controlled seizures, and higher adaptive behaviour. Drug-resistant seizures, older age, and lower levels of adaptive functioning predicted increased PS. Aetiology of seizures did not predict PS, but a mediation model is proposed.

Interpretation

Low PS was found amongst parents of infants with early-onset seizures. The high levels of DR need to be considered further, but adjustment in parents of children with seizures should be assessed.

Rationale

Prevalence of epilepsy in children under the age of five is estimated around 60/100,000 (Hauser et al., 1993) and diagnosis before the age of three is usually associated with cognitive and behavioural concerns (Berg et al., 2012). In a recent prospective cohort study, it was also estimated that the incidence of a single-gene aetiology in those under three years was 47.2/100,000 live births. Moreover, 95% of those with an identified single-gene cause received an epilepsy diagnosis at the end of the three-year study period (Symonds et al., 2019). Some single-gene epilepsies such Dravet's Syndrome (typically associated with an SCN1A mutation) tend to cause drug-resistant seizures and developmental delay in infancy, with the subsequent cognitive and behavioural comorbidities considered to be both a consequence of the ongoing epileptic activity and the wider neurodevelopmental vulnerability (Noebels, 2015; Symonds & McTague, 2020).

Parents of children with neurodevelopmental (Pastor-Cerezuela et al., 2016) and chronic health conditions (Cousino & Hazen, 2013) have shown higher levels of parental stress when compared to parents of typically developing children. Parents of children with epilepsy specifically also report more stress than parents of children with other chronic paediatric conditions such asthma or diabetes (Chiou & Hsieh, 2008; Cousino & Hazen, 2013). Less is known about the parenting impact of early-onset seizures and the importance of the identification of a single-gene aetiology. Increased levels of parental stress have been associated with adverse child outcomes such as internalising problems and child maltreatment (Crum & Moreland, 2017; Jones et al., 2021).

We therefore aimed to investigate whether identified clinical and demographic risk factors, including the addition of a genetic diagnosis, impacts on parental stress in this population. Based on existing literature (e.g. Chiou & Hsieh, 2008; Cousino & Hazen, 2013), we expected that parental stress levels would be elevated in this cohort. We also expected that more complex epilepsy and poorer adaptive functioning would increase stress. No a-priori hypotheses with regards to changes in parental stress over time were made.

Research questions

1. What is the prevalence and natural history of parenting stress amongst parents of infants with seizures?
2. What are the clinical and demographic risk factors associated with parenting stress amongst parents of infants with seizures?
3. Does parental stress change over time and what is the role of seizure aetiology?

Method

Recruitment and procedure

The data analysed in this article were collected as part of the Genetic & Autoimmune Childhood Epilepsy (GACE) study between May 2014 and May 2017. Children who presented with a first seizure before their third birthday were asked to participate in this study if they had: (a) received a new diagnosis of epilepsy (for criteria see ILAE, n.d.); (b) presented with febrile or afebrile status epilepticus (a seizure lasting >30 minutes); (c) presented with two or more febrile or afebrile epileptic seizures within a 24-hour period; and/or (d) presented with a second prolonged (>10 minutes) febrile seizure within any time period. Children whose seizures could be fully explained by an existing aetiology (e.g. perinatal stroke) were excluded.

Following study consent, DNA was extracted from whole blood samples from the recruited children and their biological parents. The DNA was tested on either a custom-designed 104-genes epilepsy panel or on an accelerated single-gene test if indicated. Demographic and clinical information was collected (see Appendix VIII) and deprivation level was calculated using the Scottish Index of Multiple Deprivation (SIMD; Scottish Government, 2020).

Parents were asked to complete a range of questionnaires within two months of registration with the study (baseline) and again one year after diagnostic outcome (follow-up). For a more detailed description of the recruitment, procedures and protocol see Symonds et al. (2019).

Questionnaires

Multiple questionnaires were used during the GACE study, however only the Parenting Stress Index, fourth edition, short form (Abidin, 2012) and Adaptive Behavior Assessment System, second edition (Oakland & Harrison, 2008) were analysed for the purposes of this paper.

The Parenting Stress Index – fourth edition, short form (PSI-4-SF)

The PSI short form, Fourth Edition (PSI-4-SF) (Abidin, 2012) is a self-report questionnaire that is commonly used to assess stress in the parent-child system for children up to 12 years. It assesses parental stress in three domains: Parental Distress; Parent-Child Dysfunctional Interaction; and Difficult Child. These scores are then combined to calculate a Total Stress score. A higher score on these scales suggests higher levels of stress and percentiles are provided through comparison with English norms of 800 well children from paediatric settings. The PSI-4-SF also includes a Defensive Responding (DR) score, whereby a score below 10 on Parental Distress indicates defensive responding (i.e. under-reporting of stress). Abidin (2012) describes this binary (yes/no) scale as an embedded validity measure and suggests that DR could undermine the validity of an individual PSI-4-SF score. The PSI-4-SF has acceptable psychometric properties (Mert et al., 2008; Rivas et al., 2021; Whiteside-Mansell et al., 2007).

Adaptive Behavior Assessment System - second edition (ABAS-2)

The ABAS parent form for children aged 0 to 5 years, Second Edition (ABAS-2) (Oakland & Harrison, 2008) aims to assess the child's adaptive functioning on three domains: Conceptual; Social; and Practical. These scores are then combined to calculate the General Adaptive Composite (GAC), which indicates a child's overall adaptive functioning when compared to its peers. The ABAS-2 has adequate psychometric properties (Oakland & Algina, 2011) and the ABAS, currently in its third iteration, remains widely used.

Statistical analyses

Preliminary analyses were completed to ensure assumptions for the main analyses were met. Nine predictors were considered for regression analyses (see Table 3.1), but to reduce over-fitting some predictors were omitted. The decision to include a predictor into the model(s) was based on correlations between predictors and outcome variables (Table 3.1; Table A3 in Appendix IX), the research questions, and the sample sizes at baseline and follow-up.

Stepwise multiple linear regression analyses were used to investigate whether aetiology of seizures (genetic, other, or unknown); adaptive functioning (i.e. Global Adaptive Composite (GAC) score on ABAS-2); age; sex; SIMD quintile; or presence of drug-resistant seizures (DRS) predicted parental stress levels. To analyse the change in parenting stress over time, a Repeated Measures ANCOVA with total stress at baseline

and follow-up was used, with aetiology of seizures as a covariate. Finally, due to the preliminary analyses that identified an unexpectedly high level of Defensive Reporting (DR), we used a post-hoc stepwise logistic regressions to investigate whether aetiology of seizures; GAC; age; SIMD; sex; and DRS predicted DR at baseline and follow-up. Data was analysed using SPSS 27.0 (IBM Corp., 2020). Complete regression tables can be found in Appendix IX.

Table 3. 1: Associations between potential predictors and outcome measures at baseline and follow-up on the PSI-4-SF (Abidin, 2012)

	Baseline Total Stress			**Follow-up Total Stress**		
	R	*p*	*N*	*R*	*p*	*N*
SIMD quintile*	-0.16	.086	118	-0.32	.007	69
GAC	-0.43	<.001	114	-0.49	<.001	67
Aetiology of seizures*†	0.11	.216	125	0.03	.788	74
Child's sex*	0.21	.021	125	0.28	.015	74
Child's age	0.29	.001	125	0.13	.255	74
Child's age at first seizure	0.27	.003	125	0.11	.350	74
Drug-resistant seizures*	0.32	<.001	125	0.25	.035	74
Global developmental delay*	0.21	.021	125	0.25	.035	74
Diagnosis of epilepsy*	0.18	.051	125	0.01	.904	74
	Baseline Defensive Parenting*			**Follow-up Defensive Parenting***		
	R/Phi	*p*	*N*	*R/Phi*	*p*	*N*
SIMD quintile*	0.07	.961	119	0.05	.867	69
GAC	0.31	.001	115	0.29	.019	67
Aetiology of seizures*†	-0.04	.692	126	-0.04	.810	74
Child's sex*	-0.26	.004	126	-0.34	.007	74
Child's age	-0.21	.018	126	-0.14	.235	74
Child's age at first seizure	-0.16	.076	126	-0.09	.454	74
Drug-resistant seizures*	-0.22	.020	126	-0.12	.408	74
Global developmental delay*	-0.15	.132	126	-0.12	.428	74
Diagnosis of epilepsy*	-0.02	.798	126	0.01	.907	74

Pearson's *R* or *Phi* reported as appropriate.
* categorical variables
† for the purpose of correlational analyses, aetiology of seizures was divided into known and unknown
NB. SIMD = Scottish Index of Multiple Deprivation; GAC = General Adaptive Composite

Ethical considerations

Ethical permission was sought from NHS Greater Glasgow and Clyde Research and Development to allow the first author access to the data for the purpose of analyses and dissemination (see Appendix VII). The GACE study received ethical approval from The United Kingdom NHS National Research Ethics Service (see Symonds et al., 2019 for details).

Results

Population demographics

Three-hundred-and-one children were included in the GACE study and just under half of parents completed a questionnaire in full at baseline (N = 132) and at follow-up (N = 75). Only SIMD was significantly associated with questionnaire completion (Table A1 in Appendix IX). Specifically, those in the bottom two quintiles (i.e. those from more deprived areas) were less likely to engage in this part of the study, whereas those in the third, fourth, and fifth quintiles were more likely to return the questionnaires (χ^2 (4) = 10.09, p = .039, *Phi* = 0.19). Thirty-four families were excluded due to not meeting the inclusion criteria and two further families were excluded due to data input errors. The attrition rate between baseline and follow-up was 43.3% for the ABAS-2 and 40.8% for the PSI-4-SF and, on average, the follow-up questionnaires were completed 20.9 months (SD = 9.49) after the baseline questionnaires. Aetiology of seizures (χ^2 (2) = 6.11, p = .047, *Phi* = 0.15) and SIMD (χ^2 (4) = 14.17, p = .007, *Phi* = 0.23) differed significantly

between those that completed follow-up questionnaires and those who did not. SIMD followed the same pattern as at baseline, with those from more deprived areas being more likely to drop-out. Parents whose child's seizures were of an unknown aetiology were also more likely to drop out at follow-up (Tables A1-A2b in Appendix IX).

Table 3. 2: Demographic and clinical characteristics of GACE index patients (N = 301)

Sex (%)	
Male	162 (53.8%)
Female	139 (46.2%)
SIMD quintile (%)	
1st	94 (31.2%)
2nd	65 (21.6%)
3rd	54 (17.9%)
4th	38 (12.6%)
5th	38 (12.6%)
No data available	12 (4.0%)
Aetiology of seizures (%)	
Genetic	82 (27.2%)
Infectious	1 (0.3%)
Metabolic	1 (0.3%)
Structural	10 (3.3%)
No identified cause	201 (66.8%)
Not tested/missing	6 (2.0%)
Age at first seizure (in months)	
Range	0 - 36
Mean	11
Global developmental delay* (%)	
Yes	92 (30.6%)
No	209 (69.4%)
Drug-resistant epilepsy (%)	
Yes	66 (21.9%)
No	235 (78.1%)
Diagnosis of Epilepsy (%)	
Yes	202 (67.1%)
No	99 (32.9%)

*As rated by clinician, whereby "yes" signifies a delay in at least 2 domains (e.g. language and motor)

Preliminary analyses

Correlational analyses indicated strong associations between Total Stress (TS) and the three PSI-4-SF domains (Pearson's $R \geq 0.85$, $p < .01$) and TS was therefore selected as an overall outcome variable. Correlation coefficients between the outcome and the predictor variables can be found in Table 3.1 (see Table A3 in Appendix IX for full matrix).

Assumptions for parametric analyses with TS as the outcome variable were met and descriptive statistics can be found in Table 3.3. Parental stress at baseline ($t(140.59) = 1.10$, $p = .274$) and follow-up ($t(78.90) = 0.16$, $p = .872$) was not significantly different from the PSI normative sample ($M = 71.0$, $SD = 15.4$) reported by Abidin (2012).

Parenting stress at baseline

The first regression model included GAC and aetiology of seizures as predictors. This model significantly predicted 31% of the variance in TS scores at baseline ($F(2, 110) = 25.17$, $p < .001$). However, only GAC score was a significant individual predictor in this model ($b = -0.69$, $t(2) = -6.96$, $p < .001$, 95% CI: [-0.89, -0.50]).

SIMD, sex, age at questionnaire completion, and drug-resistant seizures (DRS) were added to the second model. The prediction of TS significantly improved (F_{change} (4, 106) = 5.15, $p = .001$, $R^2_{change} = 0.11$) and GAC remained a significant predictor ($b = -0.52$, $t(6) = -5.08$, $p < .001$, 95% CI: [-0.72, -0.32]). Furthermore, older age ($b = 0.49$, $t(6) = 2.99$, $p = .003$, 95% CI: [0.17, 0.82]) and the presence of drug-resistant epilepsy ($b =$

15.77, $t(6) = 3.33$, $p = .001$, 95% CI: [6.38, 25.16]) were also associated with an increase in parenting stress at baseline. Please see Appendix IX, Tables A4a,b for full details.

Table 3. 3: Age, Global Adaptive Composite score (ABAS-2; Oakland & Harrison, 2008), and Total Stress score (PSI-4-SF; Abidin, 2012) at baseline and follow-up

	N	***M***	***SD***	**Range**	**Clinically significant**
Age (in months)					
Baseline	132	22.13	11.65	1 – 57	n/a
Follow-up	75	41.05	14.86	13 – 71	n/a
Global Adaptive Composite					
Baseline	120	85.18	19.10	42 – 144	22.5%*
Follow-up	68	81.37	27.01	40 – 133	41.2%*
Total Parent Stress					
Baseline	125	68.58	23.85	36 – 135	4.6%**
Follow-up	74	70.55	23.51	37 – 124	4.1%**

	Defensive parenting indicated	
	Yes (%)	**No (%)**
Baseline	39 (31.0%)	87 (69.0%)
Follow-up	27 (36.5%)	47 (63.5%)

* Global Adaptive Composite ≤ 70 (≤ 2nd percentile in normative sample)
**Total Parent Stress ≥ 114 (≥ 90th percentile in normative sample)

Parenting stress at follow-up

The first model had GAC at follow-up as the sole predictor ($b = -0.43$, $t(1) = -4.45$, $p < .001$, 95% CI: [-0.62, -0.24]) and this model significantly explained 24% of the variance in TS at follow-up ($F(1, 62) = 19.81$, $p < .001$).

The addition of SIMD, DRS, and sex did not significantly improve the predictive ability of the model ($F_{change}(3, 59) = 1.45$, $p = .238$), although this model did significantly predict 29% of the variance in TS at follow-up ($F(4,59) = 6.15$, $p < .001$). Only GAC was a significant predictor ($b = -0.31$, $t(4) = -2.32$, $p = .024$, 95% CI: [-0.57, -0.04]). Please see Appendix IX, Tables A5a,b for full details.

Parenting stress over time

Parenting stress did not change significantly over time regardless of whether seizure aetiology was included as a covariate ($F(1,55) = 0.65$, $p = .423$) or not ($F(1,55) = 1.46$, $p = .233$).

Defensive reporting at baseline

The first model explored whether seizure aetiology or GAC predicted DR at baseline. This model was significant (χ^2 (3) = 10.87, $p = .012$, Cox & Snell $R^2 = 0.10$) and correctly predicted whether parents 'under-reported' in 72% of cases. Only GAC was a significant predictor ($b = 0.04$, $W(1) = 8.84$, $p = .003$, OR = 1.04, 95% CI OR: [1.01, 1.06]).

SIMD, age at baseline, sex, and DRS were added to the second model. This model also reached significance (χ^2 (10) = 28.17, $p = .002$, Cox & Snell $R^2 = 0.32$) and predicted correctly in 75% of cases. In this model, GAC ($b = 0.03$, $W(1) = 3.91$, $p = .048$); sex ($b = -1.31$, $W(1) = 6.55$, $p = .010$); age ($b = -0.05$, $W(1) = 3.92$, $p = .048$), and DRS ($b =$ -

2.59, $W(1) = 4.56$, $p = .033$) were significant individual predictors. Specifically, having a child with higher adaptive functioning (OR = 1.02, 95% CI: [1.00, 1.06]); who is younger (OR = 0.95, 95% CI: [0.91, 1.00]); female (OR = 0.27, 95% CI: [0.10, 0.74]); or whose epilepsy is well-managed with medication (OR = 0.08, 95% CI OR: [0.01, 0.81]) increased the likelihood of parents under-reporting concerns at baseline. Please see Appendix IX, Tables A6a,b for full details.

Defensive reporting at follow-up

Model 1 had GAC at follow-up as the sole predictor ($b = 0.02$, $W(1) = 5.11$, $p = .024$, OR = 1.02, 95% CI OR: [1.00, 1.05]) and this model significantly predicted 70% of DR (χ^2 (1) = 5.62, $p = .018$, Cox & Snell $R^2 = 0.08$).

Model 2 also included infant's sex as a predictor (χ^2 (2) = 12.16, $p = .002$, Cox & Snell $R^2 = 0.17$) and correctly predicted 72% of cases. In this model, only sex was a significant individual predictor ($b = -1.44$, $W(1) = 6.20$, $p = .013$, OR = 0.24, 95% CI OR: [0.08, 0.74]), though GAC approached significance ($b = 0.02$, $W(1) = 3.56$, $p = .059$). As above, having a female child appeared to increase the odds of defensive reporting. Please see Appendix IX, Tables A7a,b for full details.

Discussion

Baseline parental stress was significantly increased when the child's adaptive functioning was lower, when their epilepsy was drug-resistant, and when the child was older. The first two findings are in line with previous research (Pinquart, 2018); having a child with emerging developmental issues and more complex seizure activity is associated with increased parenting stress. This is also in line with Abidin's (2012) theory of parenting stress that child characteristics play a crucial part in parenting stress as well as parent functioning and the parent-child interaction. It is furthermore well-researched that early complex epilepsy is associated with neurodevelopmental, behavioural, and emotional difficulties (Berg et al., 2012; Noebels, 2015; Symonds & McTague, 2020) and this finding was replicated in our current sample; a small-to-moderate correlation between drug-resistant epilepsy and GAC score (Table A3 in Appendix IX) was found. At follow-up, only GAC reached significance, which could be related to the drop-out rate reducing statistical power. The finding that having an older child is associated with more parental stress could be due to an increased awareness of emerging developmental issues (Macias et al., 2003), however considering the age-range of our participants it more likely reflects the finding that having a younger child is associated with increased odds of under-reporting parental stress.

The finding that a third of parents showed 'defensive responding' was interesting and unexpected. To the best of our knowledge, no previous research has investigated defensive reporting in a paediatric population apart from Abidin (2012) who noted that ≤1% of his normative paediatric sample scored within the defensive reporting range. This

finding could have some bearing on the reason why less than 5% of parents reported stress in the clinically significant range, compared to 10% in the normative sample. Abidin (2012) suggested that defensive responding could occur for three reasons: (1) the parent wants to portray themselves as highly competent; (2) the parent is not invested in their parental role and therefore does not experience stress; or (3) the parent is very competent and therefore less stressed. Unfortunately, the nature of the current analyses did not allow us to identify the reasons for defensive responding, but further insights into this would be beneficial because several studies have found higher parental stress levels in paediatric epilepsy populations even when illness severity was taken into account (Cousino & Hazen, 2013; Pinquart, 2018). Finally, our finding that a subset of parents of older, typically developing, female infants with well-managed epilepsy appear to be at particular risk of under-reporting on the PSI is worthy of further exploration and understanding. Future investigation could for example focus on using additional measures such as the Child Health Questionnaire (Landgraf, Abetz, & Ware, 1996) or assessing factors such as perceived support and adjustment.

Finally, aetiology of seizures did not appear to predict parental stress . However, as can be seen in Appendix IX (Table A3, Figure A1), aetiology of seizures was associated with drug-resistant seizures and global developmental delay with the direction of the relationship suggesting that these clinical characteristics are more common in infants with single-gene mutations. These two variables were also significantly associated with a reduction in GAC. These three factors could then mediate the relationship between

aetiology of seizures and parental self-reported stress, although further research would be required to replicate and elucidate these findings.

Limitations

One-third of parents at both baseline and follow-up showed defensive reporting. Since Abidin (2012) describes this score as a validity assessment, the current results might need to be interpreted with caution. Additionally, defensive reporting and parental stress showed opposite associations with age, DRS, and GAC and this might have overestimated the predictive value of these factors on parental stress.

Another limitation to be considered is that the time between baseline and follow-up varied between participants and it could not be ascertained from the available data how long after the outcome of genetic testing the parents were asked to complete the questionnaires. This then limits our interpretation of the current findings in terms of parental understanding of how aetiology of seizures was temporally related to parental stress in this cohort.

Finally, 55% of families included in the GACE study lived in areas of high deprivation, which is in line with existing literature that suggests that epilepsy is more common in lower socioeconomic environments (Li et al., 2008). However, our study demonstrates that families living in the most deprived areas were less likely to complete the questionnaires. It might be that the current findings do not provide a full picture of parenting stress in this population as the spread of SIMD in the regression models was

more homogenous than it was in the full GACE sample (only 21.8% fell within the bottom two quintiles at baseline, see Figure A2 in Appendix IX).

Conclusion

Parents of young children with seizures do not present with higher levels of stress when compared to normative paediatric controls, but poorly controlled seizures and lower adaptive functioning of the child can increase parental stress levels significantly. Interestingly, parents of children whose seizures are well-controlled and whose adaptive functioning is higher appeared to be more likely to report very low stress levels. Whether this reflects higher parental competence or under-reporting of concerns needs to be further researched and replicated. Nonetheless, the above factors should be considered when supporting families with a child who presents with seizures before the age of three to ensure that the families receive appropriate guidance and psychosocial support as early as possible so that negative outcomes of high parental stress are prevented.

References

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

Berg, A. T., Zelko, F. A., Levy, S. R., & Testa, F. M. (2012). Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes: A prospective cohort study. *Neurology*, *79*(13). https://doi.org/10.1212/WNL.0b013e31826c1b55

Chiou, H. H., & Hsieh, L. P. (2008). Parenting stress in parents of children with epilepsy and asthma. *Journal of Child Neurology*, *23*(3). https://doi.org/10.1177/0883073807308712

Cousino, M. K., & Hazen, R. A. (2013). Parenting stress among caregivers of children with chronic illness: A systematic review. In *Journal of Pediatric Psychology* (Vol. 38, Issue 8). https://doi.org/10.1093/jpepsy/jst049

Crum, K. I., & Moreland, A. D. (2017). Parental Stress and Children's Social and Behavioral Outcomes: The Role of Abuse Potential over Time. *Journal of Child and Family Studies*, *26*(11). https://doi.org/10.1007/s10826-017-0822-5

Hauser, W. A., Annegers, J. F., & Kurland, L. T. (1993). Incidence of Epilepsy and Unprovoked Seizures in Rochester, Minnesota: 1935–1984. *Epilepsia*, *34*(3). https://doi.org/10.1111/j.1528-1157.1993.tb02586.x

IBM Corp. Released 2020. *IBM SPSS Statistics for Windows, Version 27.0.* Armonk, NY: IBM Corp

International League Against Epilepsy (ILAE) (n.d.). *Epilepsy Classification*. https://www.epilepsydiagnosis.org/epilepsy/epilepsy-classification-groupoverview [accessed 19th June 2021]

Jones, J. H., Call, T. A., Wolford, S. N., & McWey, L. M. (2021). Parental Stress and Child Outcomes: The Mediating Role of Family Conflict. *Journal of Child and Family Studies*, *30*(3). https://doi.org/10.1007/s10826-021-01904-8

Li, X., Sundquist, J., & Sundquist, K. (2008). Socioeconomic and occupational risk factors for epilepsy: A nationwide epidemiological study in Sweden. *Seizure*, *17*(3). https://doi.org/10.1016/j.seizure.2007.07.011

Macias, M. M., Saylor, C. F., Rowe, B. P., & Bell, N. L. (2003). Age-related parenting stress differences in mothers of children with spina bifida. *Psychological Reports*, *93*(3 II). https://doi.org/10.2466/pr0.2003.93.3f.1223

Mert, E., Hallioğlu, O., & Ankarali Çamdeviren, H. (2008). Turkish version of the parenting stress index short form: A psychometric study. *Turkiye Klinikleri Journal of Medical Sciences*, *28*(3).

Noebels, J. L. (2015). Single-gene determinants of epilepsy comorbidity. *Cold Spring Harbor Perspectives in Medicine*, *5*(11). https://doi.org/10.1101/cshperspect.a022756

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). https://doi.org/10.1080/15377903.2011.565267

Oakland, T., & Harrison, P. L. (2008). Adaptive Behavior Assessment System-II. In *Adaptive Behavior Assessment System-II*. https://doi.org/10.1016/B978-0-12-373586-7.X0001-X

Pastor-Cerezuela, G., Fernández-Andrés, M. I., Tarraga-Minguez, R., & Navarro-Pena, J. M. (2016). Parental Stress and ASD: Relationship With Autism Symptom Severity, IQ, and Resilience. *Focus on Autism and Other Developmental Disabilities*, *31*(4).

Pinquart, M. (2018). Parenting stress in caregivers of children with chronic physical condition—A meta-analysis. In *Stress and Health* (Vol. 34, Issue 2). https://doi.org/10.1002/smi.2780

Rivas, G. R., Arruabarrena, I., & de Paúl, J. (2021). Parenting stress index-short form: Psychometric properties of the Spanish version in mothers of children aged 0 to 8 years. *Psychosocial Intervention*, *27*(1). https://doi.org/10.5093/PI2020A14

Scottish Government (2020). *Introducing The Scottish Index of Multiple Deprivation 2020.* https://www.gov.scot/publications/scottish-index-multiple-deprivation-2020/. [Accessed on 17th June, 2021]

Symonds, J. D., & McTague, A. (2020). Epilepsy and developmental disorders: Next generation sequencing in the clinic. In *European Journal of Paediatric Neurology* (Vol. 24). https://doi.org/10.1016/j.ejpn.2019.12.008

Symonds, J. D., Zuberi, S. M., Stewart, K., McLellan, A., O'Regan, M., MacLeod, S., Jollands, A., Joss, S., Kirkpatrick, M., Brunklaus, A., Pilz, D. T., Shetty, J., Dorris, L., Abu-Arafeh, I., Andrew, J., Brink, P., Callaghan, M., Cruden, J., Diver, L. A., … Wilson, M. (2019). Incidence and phenotypes of childhood-onset genetic epilepsies: A prospective population-based national cohort. *Brain*, *142*(8). https://doi.org/10.1093/brain/awz195

Whiteside-Mansell, L., Ayoub, C., McKelvey, L., Faldowski, R. A., Hart, A., & Shears, J. (2007). Parenting stress of low-income parents of toddlers and preschoolers: Psychometric properties of a Short Form of the Parenting Stress Index. *Parenting*, *7*(1). https://doi.org/10.1080/15295190709336775

Appendices

Appendix I: Author guidelines for the journal Child Abuse and Neglect

Full guidance can be found here: https://www.elsevier.com/journals/child-abuse-and-neglect/0145-2134/guide-for-authors.

Length and Style of Manuscripts
Full-length manuscripts should not exceed 35 pages total (including abstract, text, references, tables, and figures), double spaced with margins of at least 1 inch on all sides and a standard font (e.g., Times New Roman) of 12 points (no smaller).

Article structure

Subdivision
Divide your article into clearly defined sections. Three levels of headings are permitted. Level one and level two headings should appear on its own separate line; level three headings should include punctuation and run in with the first line of the paragraph.

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Essential title page information
• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Highlights
Highlights are optional yet highly encouraged for this journal, as they increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the examples here: example Highlights.

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Abstract
Abstracts should follow a structured format of no more than 250 words including the following sections: Background, Objective, Participants and Setting, Methods, Results (giving specific effect sizes and their statistical significance), and Conclusions.

Please note: The Discussion type article requires an unstructured abstract that clearly outlines to issue or gap, the discussion approach, key messages and implications. It follows the same word length.

Keywords
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'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Figure captions
Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables
Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Reference style

Text: Citations in the text should follow the referencing style used by the American Psychological Association (view the APA Style Guide). *List:* references should be arranged first alphabetically and then further sorted chronologically if necessary.

Appendix II: Full search terms for systematic review

Medline (OVID, 1946-present, incl pre-published) (run: 23/09/2020): 166 reports

1. Economics/
2. ((econ* or "socioeconomic factors" or (econ* adj2 factors)) and ("2007" or "2008" or "2009" or "2010")).tw.
3. Economic Recession/
4. ("great recession" or ((recession or econom* ajd2 depression or (econom* adj2 crisis) or financ* ajd2 crisis) and ("2007" or "2008" or "2009" or "2010"))).tw.
5. Child Abuse/
6. (child* adj4 (abus* or neglect* or maltreat* or harm*)).tw.
7. 1 or 2 or 3 or 4
8. 5 or 6
9. 7 and 8

EMBASE (OVID, 1947-present) (run: 23/09/2020): 424 reports

1. economics/
2. ((econ* or "socioeconomic factors" or (econ* adj2 factors)) and ("2007" or "2008" or "2009" or "2010")).tw.
3. economic recession/
4. ("great recession" or ((recession or econom* ajd2 depression or (econom* adj2 crisis) or financ* ajd2 crisis) and ("2007" or "2008" or "2009" or "2010"))).tw.
5. exp child abuse/
6. (child* adj4 (abus* or neglect* or maltreat* or harm*)).tw.
7. 1 or 2 or 3 or 4
8. 5 or 6
9. 7 and 8

Web of Science, Core Collection (1900-present) (run: 23/09/2020): 141 reports

#1 TOPIC: (((econ* or "socioeconomic factors" or (econ* NEAR/2 factors)) and ("2007" or "2008" or "2009" or "2010")))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#2 TOPIC: (("great recession" or ((recession or econom* NEAR/2 depression or (econom* adj2 crisis) or financ* NEAR/2 crisis) and ("2007" or "2008" or "2009" or "2010"))))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#3 TOPIC: ((child* NEAR/4 (abus* or neglect* or maltreat* or harm*)))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#4 #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#5 #4 AND #3

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

PsychINFO (EBSCOhost, 1806-present) (run: 23/09/2020): 57 reports

S1 DE "Economics"

S2 TI ((econ* or "socioeconomic factors" or (econ* N2 factors)) and ("2007" or "2008" or "2009" or "2010")) AND AB ((econ* or "socioeconomic factors" or (econ* N2 factors)) and ("2007" or "2008" or "2009" or "2010")) AND KW ((econ* or "socioeconomic factors" or (econ* N2 factors)) and ("2007" or "2008" or "2009" or "2010"))

S3 TI (economics or "great recession" or recession or (econom* N2 depression) or (econom* N2 crisis) or (financ* N2 crisis) and ("2007" or "2008" or "2009" or "2010"))) AND AB (economics or "great recession" or recession or (econom* N2 depression) or (econom* N2 crisis) or (financ* N2 crisis) and ("2007" or "2008" or "2009" or "2010"))) AND KW (economics or "great recession" or recession or (econom* N2 depression) or (econom* N2 crisis) or (financ* N2 crisis) and ("2007" or "2008" or "2009" or "2010")))

S4 DE "Child Abuse"

S5 TI ((child* N4 (abus* or neglect* or maltreat* or harm*))) AND AB ((child* N4 (abus* or neglect* or maltreat* or harm*))) AND KW ((child* N4 (abus* or neglect* or maltreat* or harm*))

S6 S1 OR S2 OR S3

S7 S4 OR S5

S8 S6 AND S7

Appendix III: NHLBI quality assessment tool for observation cohort and cross-sectional studies

Source: 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)?			

*CD, cannot determine; NA, not applicable; NR, not reported

Appendix IV: Final approved MRP Proposal (original)

Cover page

Name of assessment	MRP proposal
Title	Social Cognition in Childhood Leukaemia Survivors
Student ID	
Date of submission	07/04/2020
Version number	4
Actual word count	3349
Maximum word count	3000

Abstract

Background.

‘Late effects’ of childhood cancer might arise due to changes in the brain as a result of the illness itself and/or because of the areas impacted by the treatment. Childhood Acute Lymphoblastic Leukaemia (ALL) is one of the more common childhood cancers and research shows that ALL treated with chemotherapy significantly impacts long-term neurocognitive functioning. There is some evidence that childhood ALL survivors present deficits in social adjustment.

Aims

This study aims to identify whether young people at least one-year post-treatment show impaired cognitive empathy when compared to healthy age-matched controls.

Methods

Participants will be recruited from tertiary oncology centres and schools in Edinburgh and Glasgow. Demographic (and clinical if applicable) information will be collected and they will be assessed with three cognitive empathy tests; the Reading The Eyes in The Mind Test, The Faux Pas Test, and ESQ questionnaire. The WASI-II and Symbol Search subtest from the WISC-V; and the Finger Tapping test will be completed to assess cognitive and psychomotor abilities. Assessments will be completed at the young people’s school or at the paediatric psychology outpatient clinic.

Application

Results from this study could inform long-term care for ALL survivors, thereby improving their psychosocial adjustment and ultimately their quality of life.

Introduction

Between 2007 and 2016, 1275 children under the age of 14 years were diagnosed with cancer in Scotland and leukaemia accounted for 31% of these diagnoses (ISD Scotland, 2019). Fortunately, medical advancement has allowed for the full recovery of over 80% of young people diagnosed with cancer (Stewart & Wild, 2014), and researchers are continuing to develop our understanding of childhood cancers. As such, some of the research perspective has shifted to instead focus on so-called 'late effects' of oncological diseases and their treatments.

Children who survived a childhood cancer have been found to be at a significantly increased risk of later cognitive, behavioural, and emotional difficulties and these difficulties have been coined late effects. These secondary difficulties might arise due to organic or functional changes in the brain as a result of the illness itself (i.e. when the central nervous system (CNS) or brain is involved in the disease) and/or because of the areas impacted by the treatment. Furthermore, the psychological impact of being diagnosed with and treated for a life-threatening illness is far reaching. For example, inpatient stays as well and poor health can limit the young person's social and educational opportunities, which can have long-term consequences for the re-integration with their peer group and their general social and cognitive development. It has also been reported that patients and their families experience high levels of stress throughout the disease process (Myers et al., 2014). This is particularly problematic when considering that high levels of stress are associated several mental health difficulties (McLaughlin, 2016). As more young people are surviving cancer, acknowledging and potentially preventing these numerous late effects is becoming more important. Although late effects are associated with all childhood cancers, only those relevant to childhood Acute Lymphoblastic Leukaemia (ALL) will now be discussed briefly due to the aim of this project.

ALL is a haematological cancer, which has chemotherapy as its first-line treatment (Cheung & Krull, 2016). Several chemotherapy agents are administered concurrently during the initial as well as the maintenance phase of the treatment of leukaemia and a

range of these agents (e.g. methotrexate, cytarabine) have been associated with late neurocognitive effects. Damage to cortical white matter as a result of CNS exposure to chemotherapy could provide an explanation for the cognitive impairments in some young people as white matter is particularly vulnerable to toxicity in the developing brain (De Luca, 2015). In addition, executive functioning (e.g. planning, behavioural inhibition, and emotional regulation) deficits are relatively common in this childhood ALL survivors, which is potentially related to structural and functional changes to the fronto-parietal attentional network (Cheung & Krull, 2015). The impact on frontal systems is particularly relevant in childhood cancers, as it is known that the frontal neurodevelopment occurs in a non-linear fashion, with peaks in development/synaptic pruning occurring during late childhood and again during post-adolescence (Blakemore & Choudhury, 2006). It is known that cranial and total body radiation can lead to cognitive decline above and beyond the effects of chemotherapy (Cheung & Krull, 2015; Willard et al., 2014) and for this reason, radiation therapy is no longer the first-line treatment for leukaemia. However, this treatment is still implemented following relapse and this project will therefore only consider young people who have been treated with chemotherapy only (i.e. have not relapsed).

A full review of neurocognitive late effects of ALL is outside the scope of this proposal, but some researchers have reported that ALL in childhood is associated with poorer social competence including maintaining peer relationships (Stam, Grootenhuis, & Last, 2001). Adolphs (2001) argues that our complex social world requires us to develop social cognition and he defines this as "the ability to construct representations of the relations between oneself and others, and to use those representations flexibly to guide social behaviour" (Adolps, 2001, p. 231). Unfortunately, literature around social adjustment in childhood ALL survivors is inconsistent and social cognition has never been directly assessed in this population. In line with a treatment related social-cognitive deficit hypothesis, however, it can be argued the negative impact of chemotherapy on the frontal lobes and its associated networks (Cheung & Krull, 2015) also explains potential poorer social functioning as the frontal areas have consistently been shown to play a role in

social cognition and emotional regulation (Blakemore & Choudhury, 2006). Similarly, Yeates and colleagues' (2007) suggest that social competence is comprised of social information processing (cognitive-executive functions, social-affective functions, and social problem-solving), social interaction (affiliative, aggressive, and withdrawn), and social adjustment (self-perceptions and perceptions of others). The argue that a brain insult, particularly in the frontotemporal and limbic regions, can therefore influence social competence as well as the relationships between the different components of their model. Finally, the relatively long treatment protocol associated with ALL potentially further endangers social development due to prolonged time away from healthy peers. The impact of ALL on social cognition should thus be studied further because humans are inherently social creatures and their quality of life is strongly connected with their ability to thrive in a social environment.

The aim of this project is therefore to investigate the effects of leukaemia treatment on social cognition in childhood leukaemia survivors. In order to operationalise social cognition for this study, it was decided to explore cognitive empathy initially. Cognitive empathy is the ability understand one's own and others' emotional states using contextual appraisals (De Waal, 2007) and as such a key part of social cognition. This can be differentiated from the affective aspect of empathy, which involves an emotional response to the mental states of others and as such is less straightforward to assess. As this is a relatively small-scale study, it was also decided to only include ALL survivors as they constitute the largest proportion of childhood leukaemia.

Research questions

Primary research question

Do survivors of ALL show decreased cognitive empathy when compared to healthy age-matched controls?

Secondary research questions

1. Does cognitive empathy ability correlate with general intellectual ability and processing speed, and is the strength of association different for survivors of ALL?
2. Does age at diagnosis and/or time since treatment predict the impact of ALL on cognitive empathy?

Hypotheses

It is expected that childhood ALL survivors will show decreased cognitive empathy when compared to healthy age-matched controls. The secondary research questions will be of an exploratory nature and as such no hypotheses are made.

Plan of investigation

Participants

To perform a power analysis (G*Power 3.1), an effect size of $d = 0.8$ on the primary measure Reading The Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001) was used. This was based on similar research by Henry *et al*. in 2006 (Cohen's $d = 0.66$) and by Geraci *et al.* in 2010 (Cohen's $d = 1.21$). Although these studies examine cognitive empathy in an adult population and their participants had traumatic brain injuries not related to ALL, the brain damage described in these papers is likely to be similar to brain damage following paediatric ALL as described above (Cheung & Krull, 2015). Therefore, for a power level of .80 ($p < .05$, one-tailed) a minimum of 21 young people (aged 6-18) at least 1 year post-treatment and 21 age-matched healthy young people from Glasgow and Edinburgh schools will be recruited.

Following discussions with clinical teams in Edinburgh and Glasgow, it was estimated that each team will see around 30 young people a month for ALL follow-up (excluding those <1 year post-treatment). As such, recruiting 21 young people with a history of paediatric ALL seems very feasible. Please note that in order to age-match we will need to recruit more young people for the control group (estimated: 60), however we aim to assess several young people per school class to allow this and this would therefore also seem feasible.

Inclusion/exclusion criteria

Young people aged between 6 and 17 years who are at least one year post ALL treatment will be included in this study. The young people will be in or will have completed mainstream education. Young people with neurodevelopmental disorder and those in specialist education will be excluded. For the control group, healthy young people in mainstream education will be included; those with a previous life-threatening condition will be excluded from this group.

Recruitment procedures

Young people attending the leukaemia out-patient clinic will be invited to participate in the study by their clinician. Age appropriate information leaflets will be distributed, and informed consent and assent will be collected from young people and/or their parents where appropriate. For the control group, schools will be approached, and information and consent forms sent out to interested families. Data will be collected, ethics permitting, between September 2020 and April 2021.

Measures

Demographics and treatment history

Participant characteristics such as age, gender, and level of deprivation will be collected for all participants. For those in the post-treatment ALL group, clinical information will also be collected through clinical case note review by a clinician within the hospital oncology team.

Cognitive empathy

The RMET (Baron-Cohen et al., 2001) and the Faux Pas Test (FPT; Baron-Cohen et al., 1999; Gregory et al., 2002) will be administered. The RMET will allow us to assess cognitive empathy visually, whereas the FPT is a verbal assessment. The RMET child version (28 items) will be administered to young people between 6 and 11 years. The adult version 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.

Parents will also be requested to complete the Empathy Systemizing Quotient questionnaire (ESQ; Auyeung et al., 2012) to rate their child's empathy. This measure will serve as a proxy of cognitive empathy. The child (6 – 11), adolescent (12 – 15), and adult (16+) versions will be completed as appropriate. The completion time for this measure is around 10 minutes.

General intellectual ability

The Wechsler Abbreviated Scale of Intelligence, second edition, (WASI-II; Wechsler, 2011) will be used to estimate current general intellectual ability. The completion time for these tests is around 30 minutes.

Processing speed

The Symbol Search from the Wechsler Intelligence Scale for Children, fifth edition, (WISC-5; Wechsler, 2014) and the Finger Tapping Test will be used to measure processing speed. The completion time for this measure is around 10 minutes.

Impact of Covid-19 pandemic

The Covid-19 pandemic and measures imposed to halt the spread of the disease could have impacted on psychological functioning and well-being. Although a full assessment on this is beyond the scope of the current study, we wanted to consider the way the young people in this study managed the social distancing measures in an exploratory way.

To assess the impact of prolonged social distancing/isolation measures, all parents/participants will be asked to answer a short questionnaire in relation to the young person's social functioning during this period (e.g. the use of video conferencing to meet with friends) (see Appendix 1).

Design

Young people in the ALL group and their parent(s) will be invited to attend an outpatient appointment at the Royal Hospital for Children in Glasgow to complete neuropsychological assessment. This assessment will last approximately one hour and 10

minutes. Parents will be asked to complete the ESQ during this time. Control participants will be assessed in their school. Questionnaires for the parents in this group will be send to their home with a pre-stamped envelope.

Research procedures

Collected data will be stored on secure NHS computers for a period of three years. Data will be anonymised for analyses and dissemination.

Data analysis

Primary analysis

To answer the primary question whether ALL survivors differ on a measure of social cognition when compared to a matched healthy control group, a t-test for independent samples with the score on the RMET as the dependent variable and group as the independent variable will be used. The RMET was chosen as the primary measure as this task has been widely used by researchers assessing social cognition (e.g. Dorris et al, in prep; Geraci *et al*, 2010).

Secondary analyses

As this study will not be adequately powered for below analyses, these will be of an exploratory nature.

A MANCOVA with group as independent variable, direct cognitive empathy measures (i.e. scores on the RMET and FPT) as dependent variables and general intellectual ability and processing speed as covariates is proposed to examine whether ALL impacts

cognitive empathy. An ACOVA with above independent variable and covariates, but with ESQ rating as dependent variable is also suggested.

To examine whether age at diagnosis predicts the impact of ALL on cognitive empathy, age will be divided in three brackets ([6-9], [10-12], [13-17]) in accordance with literature around the development of social cognition (Blakemore & Choudhury, 2006; Dorris et al, in prep). A MANCOVA with age range as independent variable, and direct cognitive empathy measures as dependent variables, and with the same covariates as above would be conducted.

Settings and equipment

Young people will attend an approximately one-hour session to complete the described tests at either their school or at the paediatric psychology out-patient units in Edinburgh or Glasgow. A NHS encrypted laptop will be acquired for data collection.

Health and safety issues

No health and safety concerns are raised at this time for either the researcher or the participants.

Ethical considerations

Ethical approval for this project will be sought from the Ethics Committee, the Caldicott Guardian, and the Scottish government for the inclusion of healthy school pupils. We will request sponsorship from NHS R&D. We will liaise with SCOTCRN and Young Patient Group Advisory to maximise the benefit/value of this study and to ensure our information and consent forms are appropriate. We will provide a brief report of

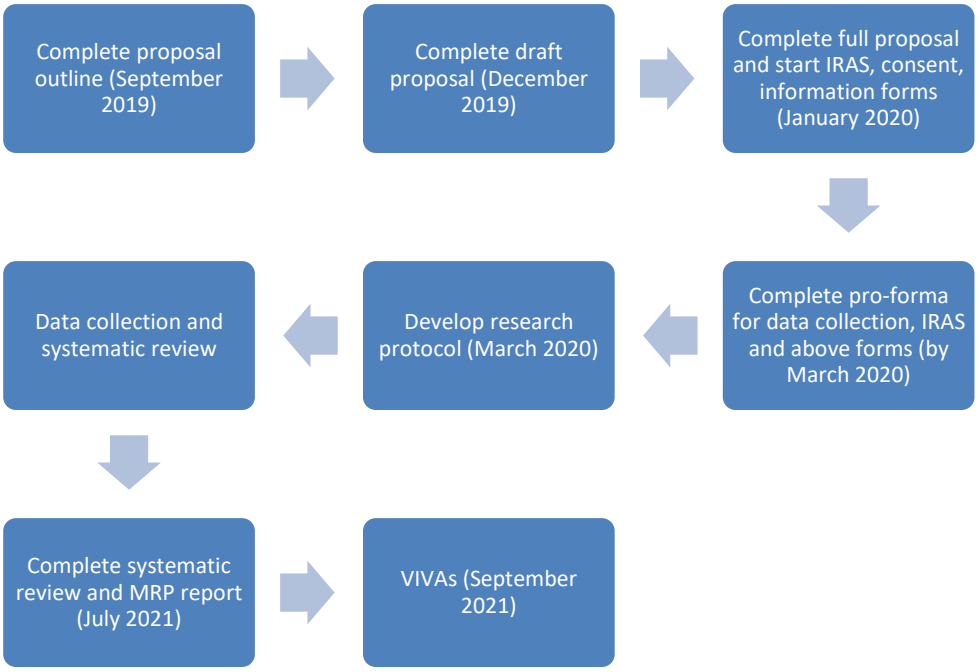
neuropsychology findings to patients and to those in the control group where we identified significant difficulties. Young people in the control group will receive a summary of the study's findings due to practical constraints otherwise.

Informed consent will be sought from young people over the age of 12 and from the parents of younger children. From these younger children, assent will be sought to ensure that the young persons' wishes are respected. Consent/assent will be sought through teachers and oncologists as appropriated.

Financial issues

No issues identified and the expenses form is attached elsewhere.

Timetable



Practical applications

Results from this study could inform long-term care for ALL survivors, thereby improving their psychosocial adjustment and ultimately their quality of life. This study might, for example, feed into the standard follow-up care of paediatric ALL survivors by assessing for social deficits post-treatment and offering early intervention where appropriate, which in turn might improve some of these deficits before they impact significantly and the young person's social functioning. Other research has suggested, for instance, that interventions aimed at increasing parental nurturance can improve social outcomes in children with traumatic brain injuries (Deighton et al., 2019).

References

American Childhood Cancer Organisation. (September, 2017). Drugs: Chemotherapy Drugs and Other Pharmaceuticals. Retrieved from: http://www.acco.org/drugs-chemotherapy-drugs-and-other-pharmaceuticals/

Adolphs, R. (2001). The neurobiology of social cognition. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/S0959-4388(00)00202-6

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*. 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. *Learning*.

Blakemore, S. J., & Choudhury, S. (2006). Development of the adolescent brain: Implications for executive function and social cognition. In *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/j.1469-7610.2006.01611.x

British Psychological Society (2020). https://www.bps.org.uk/sites/www.bps.org.uk/files/Member%20Networks/Divisions/DoN/DON%20guidelines%20on%20the%20use%20of%20tele-neuropsychology%20%28April%202020%29.pdf

Cheung, Y. T., & Krull, K. R. (2015). Neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia treated on contemporary treatment protocols: A systematic review. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2015.03.016

De Luca, C. (2015). *A compendium of evidence and framework for neuropsychological services in paediatric cancer*. Retrieved from: https://pics.org.au/health-professionals/useful-resources-and-links/

De Waal, F. B. M. (2008). Putting the altruism back into altruism: The evolution of empathy. *Annual Review of Psychology*. https://doi.org/10.1146/annurev.psych.59.103006.093625

Deighton, S., Durish, C. L., Taylor, H. G., Rubin, K., Dennis, M., Bigler, E. D., Vannatta, K., Gerhardt, C. A., Stancin, T., & Yeates, K. O. (2019). Theory of Mind and Parental Nurturance as Predictors of Peer Relationships After Childhood Traumatic Brain Injury: A Test of Moderated Mediation. *Journal of the International Neuropsychological Society*. https://doi.org/10.1017/S135561771900064X

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

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*. https://doi.org/10.3109/02699052.2010.487477

Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., & Hodges, J. R. (2002). Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: Theoretical and practical implications. *Brain*. https://doi.org/10.1093/brain/awf079

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*. https://doi.org/10.1016/j.neuropsychologia.2006.03.020

Information Services Division (ISD) Scotland (2019). *Children and Young People with Cancer in Scotland: 2007-2016.* Retrieved from: https://www.isdscotland.org/Health-Topics/Cancer/Publications/

McLaughlin, K. A. (2016). Future Directions in Childhood Adversity and Youth Psychopathology. *Journal of Clinical Child and Adolescent Psychology*. https://doi.org/10.1080/15374416.2015.1110823

Myers, R. M., Balsamo, L., Lu, X., Devidas, M., Hunger, S. P., Carroll, W. L., Winick, N. J., Maloney, K. W., & Kadan-Lottick, N. S. (2014). A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: A report from the Children's Oncology Group. *Cancer*. https://doi.org/10.1002/cncr.28578

Stam, H., Grootenhuis, M., & Last, B. (2001). Social and emotional adjustment in young survivors of childhood cancer. In *Supportive Care in Cancer*.

https://doi.org/10.1007/s005200100271

Stewart, B. and Wild, C.P. (eds.), International Agency for Research on Cancer, WHO. (2014) World Cancer Report 2014 [Online]. Available from: http://www.thehealthwell.info/node/725845 [Accessed: 23rd February 2017].

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., Leung, W., Huang, Q., Zhang, H., & Phipps, S. (2014). Cognitive outcome after pediatric stem-cell transplantation: Impact of age and total-body irradiation. *Journal of Clinical Oncology*. https://doi.org/10.1200/JCO.2014.56.2223

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*. https://doi.org/10.1037/0033-2909.133.3.535

Appendix V: Impact of Covid-19 questionnaire for children and young people

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 how many hours per week?

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

4. Did your child have social contact with *other family* (not in their home) through social media where they 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 your child have social contact with *friends* through social media where they 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 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, how many hours per day 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 how many hours per week?

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

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 VI: Author guidelines for the journal Developmental Medicine and Child Neurology

Full guidance can be found here:
https://onlinelibrary.wiley.com/page/journal/14698749/homepage/forauthors.html#_Toc511662550

b) Reporting guidelines

For all Original Articles, Systematic Reviews, Meta-analyses, Scoping Reviews, Clinical Practice Guidelines, and Case Series the Editors and Editorial Board require that authors follow the guidelines of the Equator network when reporting research methods and findings (http://www.equator-network.org/library/).

We require that authors conduct all original research, Systematic Reviews, and Scoping Reviews based on an appropriate pre-established protocol.

Submissions must be accompanied by the appropriate checklist, fully completed with page numbers where applicable. Please select the most suitable checklist from the following and download the appropriate checklist, for example:

Observational studies (i.e. most Original Articles): STROBE checklist

Systematic Reviews or Meta-analyses: PRISMA 2020 checklist (for all systematic reviews) and AMSTAR-2 checklist (for systematic reviews of interventions)

Scoping reviews: PRISMA-ScR

Randomized controlled trials: CONSORT guidelines

Clinical practice guidelines: AGREE II

Case series: CARE

Other types of study e.g. Diagnostic Accuracy: please visit the Equator website http://www.equator-network.org/library/

While completing the checklist(s), authors should consult the relevant guidance document to ensure the checklist is reported as accurately as possible. Failure to address all items leads to poorly synthesised evidence and misleading conclusions.

For Editorials, Commentaries, Book Reviews, Invited Reviews, Case Series, and Letters, no checklist is required.

c) Original articles

Articles should comprise an introductory section (but not headed ‘Introduction’), followed by ‘Method’ (with optional subheadings, such as ‘Participants’ [rather than ‘Subjects’] and ‘Statistical analysis’), ‘Results’, and ‘Discussion’ sections. The Discussion section should include the limitations of the study. Subheadings should otherwise be kept to a minimum.

Authors are encouraged to submit video material supporting their papers, where appropriate, for publication in the journal.

Papers longer than 3000 words, such as those reporting randomized controlled trials, may be published at the Editors’ discretion.

In the Method section, authors should state which pre-established protocol was followed for the study. Randomized controlled trials should include a short trial protocol as supplementary information. Please refer to the ‘Reporting guidelines’ section for reporting guidelines and protocol registration.

We encourage the inclusion of a graphical abstract which captures the content of the article for readers at a single glance.

h) References

The Vancouver style is used, as recommended by the International Committee of Medical Journal Editors. Cite using a superscript number in the text, with a numerical list of references at the end of the paper presented in order of citation. Cite only peer-reviewed, published material. The journal does not recognize abstracts or submitted (as opposed to accepted, or ‘forthcoming’) papers as proper citations; such material should not be listed with the references but cited only in text, followed by ‘(personal communication)’.

List all authors unless more than six, in which case list the first three followed by ‘et al.’, using Index Medicus abbreviations for journal names (see www.nlm.nih.gov/tsd/serials/lji.html). Order and punctuate bibliographic information as follows, omitting issue month and number unless needed to distinguish issues. For additional citation formats, adapt appropriate examples from the NLM’s Citing Medicine (www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=citmed).

i) Figures and tables

Note that the Editors may decide that large figures or tables should be published online-only.

Tables, figure legends and short appendices Set out on separate pages at the end of (and as part of) the main document, after the references.

Tables and appendices to be published online only Present as separate files in Microsoft Word or Rich Text format.

Figures (e.g. illustrations, charts and photographs) Present electronically as separate files (not in the main text of the article). Guidelines about acceptable file formats and illustration preparation are provided at
authorservices.wiley.com/bauthor/illustration.asp

Please label radiographs, CT, or MRI scans with left [L] and right [R], and if appropriate with anterior [A] and posterior [P]. Areas of interest should be marked with an arrow. For EEGs please indicate the gain, timescale, and lead position.

Graphs should be as simple as possible, not three-dimensional, and not framed. Shading should be white, black, or strong hatching, not grey. No background lines should be used (except for bars and axes).

Authors are encouraged to consider gender equality and ethnic diversity when preparing images of children, young people, or adults, whether real (photographs) or line drawings. Individuals shown should ideally be representative of all members of the global community and not just from one homogenous group.

Figures of inclusion/exclusion criteria and flow diagrams of the study recruitment process will go online only, as supporting material.

Figures should be numbered in order in the text. A caption must be supplied for each figure. The caption should not repeat what is written in the text material and should follow the Journal style (please refer to recent issues for examples). All captions should be placed in a list at the end of the main document. Please remember to supply captions for figures that will be published electronically. The caption must describe all labels in a figure. For images, the caption should include the type of image, its plane, whether or not contrast material was used, the pulse sequence information for MR images and the features to be observed by the reader. However, full details of the MR sequences should be described in the methods section, not in the caption.

j) Statistical reporting

The Editors advise reading “Statistical recommendations for papers submitted to Developmental Medicine & Child Neurology” (Rigby AS, Dev Med Child Neurol 2010; 52: 299–304) for guidelines on appropriate use and reporting of statistical analyses. Authors are recommended to work with a statistician where appropriate.

Appendix VII: Proof of ethical approval to analyse GACE study data

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 VIII: Clinical proforma 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

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

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		

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

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 IX: Supplementary information for Chapter 3

Table A1: Differences between those who completed any questionnaires and those who did not for clinical and demographic variables

Variable	*N*	χ^2 (df)	*p*-value
SIMD quintile	289	10.09 (4)	.039
Infant's sex	301	1.53 (1)	.248
Global Developmental Delay	301	0.04 (1)	.848
Drug-Resistant Seizures	301	0.47 (1)	.494
Aetiology of Seizures	295	4.21 (2)	.122
Epilepsy Diagnosis	301	2.69 (1)	.101
		***F*(df)**	***p*-value**
Age at first seizure	300	0.99 (1, 298)	.322

NB. SIMD = Scottish Index of Multiple Deprivation

Table A2a: Differences between those who completed follow-up and those who did not for categorical predictor variables

Variable	*N*	χ^2 (df)	*p*-value
SIMD	274	14.17 (4)	.007
Infant's Sex	285	0.39 (1)	.534
Global Developmental Delay	285	1.05 (1)	.306
Drug-Resistant Seizures	285	0.01 (1)	.938
Aetiology of Seizures	279	6.11 (2)	.047

NB. SIMD = Scottish Index of Multiple Deprivation.
Epilepsy diagnosis was not included in the regression analyses as a predictor variable.

Table A2b: Differences between those who completed follow-up and those who did not for continuous predictor variables

Variable	*N*	*F*(df)	*p*-value
Age at baseline	132	0.00 (1,130)	.983
Age at first seizure	284	0.19 (1,282)	.664
GAC at baseline	120	2.47 (1,118)	.118
TS at baseline	125	0.33 (1,123)	.568

NB. GAC = General Adaptive Composite on ABAS-2; TS = Total Stress on PSI-4-SF.

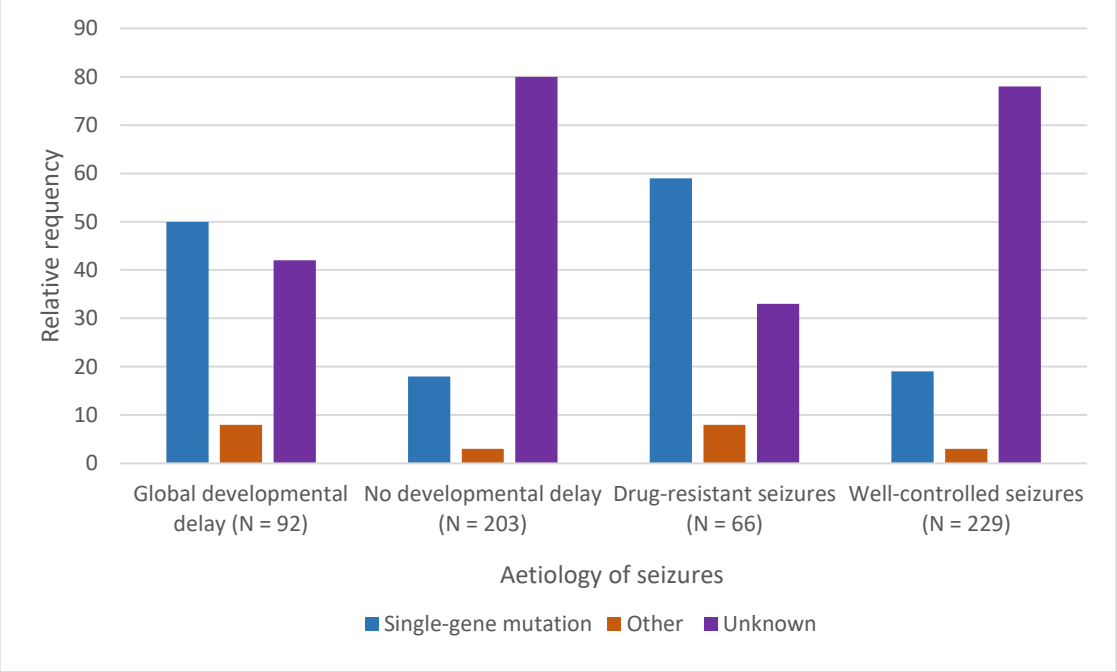


Figure A1: Aetiology of seizures spread as a factor of global developmental delay and drug-resistant epilepsy in percentages. Other aetiology of seizures included: infectious; metabolic; and structural.

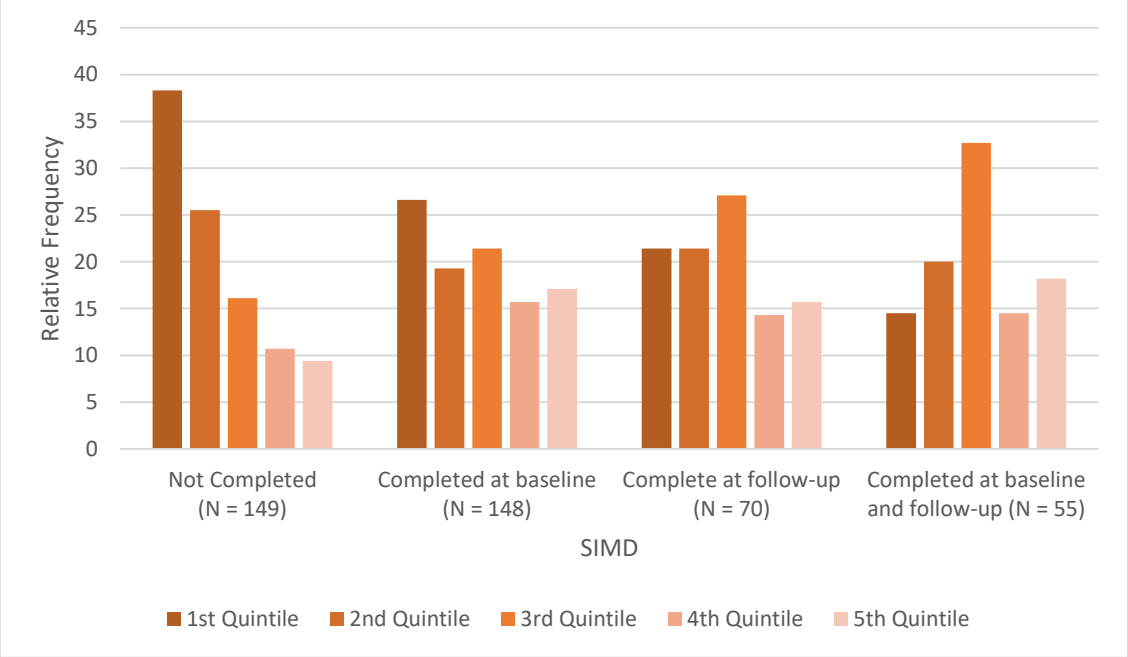


Figure A2: Spread of Scottish Index of Multiple Deprivation (SIMD) quintiles across those who completed the questionnaires and those who did not, in percentages (missing data not included).

Table A3: Pearson's *R* (when at least one variable is continuous) and *Phi* (when both variables are categorical) coefficients for all variables. *N* ranged from 52 to 301.

	1‡	**2†‡**	**3‡**	**4‡**	**5‡**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15‡**	**16**	**17**	**18**	**19**	**20‡**
2‡	*0.18*																			
3‡	*0.07*	*0.40* **																		
4‡	*0.11*	*0.37* **	*0.61* **																	
5‡	*0.14*	*0.02*	*0.01*	*-0.01*																
6	0.02	-0.26 **	-0.17	-0.02	0.03															
7	-0.06	-0.22	-0.25 *	-0.15	0.05	0.76 **														
8	-0.03	-0.26 **	-0.25 **	-0.16 **	0.05	0.73 **	0.76 **													
9	0.09	-0.11	-0.19 *	-0.36 **	-0.26 **	-0.24 **	-0.21	-0.15												
10	0.47 **	-0.08	-0.49 **	-0.61 **	-0.19	-0.07	0.02	0.08	0.62 **											
11	-0.18	0.08	0.26 **	0.18	0.22 *	0.14	0.32 *	0.19 *	-0.30 **	-0.04										
12	-0.10	0.14	0.32 **	0.22 *	0.13	0.27 **	0.23	0.23 **	-0.62 **	-0.44 **	0.66 **									
13	-0.20 *	0.02	0.19 *	0.15	0.17	0.38 **	0.34 **	0.31 **	-0.57 **	-0.41 **	0.65 **	0.84 **								

	1‡	**2**‡	**3**‡	**4**‡	**5**‡	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**‡	**16**	**17**	**18**	**19**	**20**‡
14	-0.16	0.11	0.32 **	0.21 *	0.21 *	0.29 **	0.33 *	0.26 **	-0.56 **	-0.35 *	0.85 **	0.92 **	0.92**							
15‡	*0.07*	*-0.04*	*-0.22* *	*-0.15*	*-0.26* **	-0.21 *	-0.21	-0.16	0.31 **	0.05	-0.71 **	-0.44 **	-0.45 **							
16	-0.20	0.08	0.19	0.23 *	0.29 *	0.12	0.16	0.17	-0.32 *	-0.37 **	0.73 **	0.52 **	0.62 **	-0.60 **						
17	-0.40 **	0.11	0.39 **	0.38 **	0.27 *	0.05	0.05	0.05	-0.54 **	-0.58 **	0.45 **	0.73 **	0.58 **	0.74 **	-0.56 **					
18	-0.37 **	-0.03	0.06	0.14	0.22	0.10	0.16	0.18	-0.42 **	-0.46 **	0.49 **	0.54 **	0.60 **	0.68 **	-0.37 **	0.71 **				
19	-0.32 *	0.03	0.25 *	0.25 *	0.28 *	0.09	0.13	0.17	-0.46 **	-0.49 **	0.64 **	0.65 **	0.67 **	0.63 **	-0.23	0.70 **	0.74 **			
20‡	*0.05*	*-0.04*	*-0.12*	*-0.12*	*-0.34* **	-0.10	-0.14	-0.09	-0.30 *	0.29 *	-0.48 **	-0.42 **	-0.34 *	0.77 **	-0.42 **	0.90 **	0.89 **	0.89 **		
21‡	*0.22* **	*0.26* **	*0.34* **	*0.37* **	*-0.02*	-0.02	-0.12	-0.14 *	-0.22 *	-0.23	0.07	0.17	0.23 **	-0.51 **	*0.45* **	-0.74 **	-0.60 **	-0.53 **	-0.71 **	*0.01*

* $p < .05$, two-tailed

** $p < .01$, two-tailed

† for the purpose of correlational analyses, aetiology of seizures was divided into known and unknown

‡ categorical variable

Phi coefficients in *italics*

Legend

1. Scottish Index of Multiple Deprivation quintile (1-5)
2. Aetiology of seizures (0 = unknown, 1 = known)
3. Drug-resistant epilepsy (0 = no, 1 = yes)
4. Global development delay (0 = no, 1 = yes)
5. Infant's sex (0 = female, male = 1)
6. Age at baseline
7. Age at follow-up
8. Age at first seizure
9. General Adaptive Composite at baseline
10. General Adaptive Composite at follow-up
11. Parental Distress at baseline
12. Parent-Child Dysfunctional Interaction at baseline
13. Difficult Child at baseline
14. Total Stress at baseline
15. Defensive reporting at baseline (0 = no, 1 = yes)
16. Parental Distress at follow-up
17. Parent-Child Dysfunctional Interaction at follow-up
18. Difficult Child at follow-up
19. Total Stress at follow-up
20. Defensive reporting at T2 (0 = no, 1 = yes)
21. Epilepsy diagnosis (0 = no, 1= yes)

Table A4a: multiple stepwise regression for parenting stress at baseline (models)

Model		df	*F*	*p*	R^2
1	Regression	2	25.17	.000	0.31
	Residual	110			
	Total	112			
2	Regression	6	13.08	.000	0.43
	Residual	106			
	Total	112			

Table A4b: multiple stepwise regression for parenting stress at baseline (coefficients)

		Unstandardized Coefficients				95% CI for B	
Model		*B*	*SE*	*t*	*p*	Lower	Upper
1	(Constant)	130.86	9.67	13.54	.000	111.71	150.02
	GAC at baseline	-0.69	0.10	-6.99	.000	-0.89	-0.50
	Aetiology	-1.42	2.11	-0.67	.502	-5.61	2.77
2	(Constant)	102.07	12.31	8.29	.000	77.67	126.47
	GAC at baseline	-0.52	0.10	-5.08	.000	-0.72	-0.32
	Aetiology	-0.45	2.20	-0.21	.838	-4.80	3.90
	Age at baseline	0.49	0.16	2.99	.003	0.17	0.82
	SIMD	-1.92	1.26	-1.52	.132	-4.42	0.59
	DRS	15.77	4.74	3.33	.001	6.34	25.16
	SEX	4.06	3.65	1.11	.268	-3.17	11.29

NB. SE = Standard Error; GAC = Global Adaptive Composite; SIMD = Scottish Index of Multiple Deprivation; DRS = Drug-Resistant Seizures.

Table A5a: multiple stepwise regression for parenting stress at follow-up (models)

Model		*df*	*F*	*p*	R^2
1	Regression	1	19.81	.000	0.24
	Residual	62			
	Total	63			
2	Regression	4	6.15	.000	0.29
	Residual	59			
	Total	63			

Table A5b: multiple stepwise regression for parenting stress at follow-up (coefficients)

		Unstandardized Coefficients				95% CI for B	
Model		*B*	*SE*	*t*	*p*	Lower	Upper
1	(Constant)	105.41	8.25	12.78	.000	88.93	121.90
	GAC at follow-up	-0.43	0.10	-4.45	.000	-0.62	-0.24
2	(Constant)	95.53	11.28	8.47	.000	72.95	118.10
	GAC at follow-up	-0.31	0.13	-2.32	.024	-0.57	-0.04
	SIMD	-2.45	2.17	-1.13	.262	-6.79	1.88
	DRS	3.81	7.44	0.51	.611	-11.08	18.69
	SEX	9.69	5.29	1.83	.072	-0.90	20.28

NB. SE = Standard Error; GAC = Global Adaptive Composite; SIMD = Scottish Index of Multiple Deprivation; DRS = Drug-Resistant Seizures

Table A6a: Multiple stepwise logistic regression for defensive reporting at baseline (models)

Omnibus Tests of Model Coefficients

Model		χ^2	df	*p*	Cox & Snell R^2
1	Step	0.41	3	.012	
	Block	0.41	3	.012	
	Model	0.41	3	.012	0.13
2	Step	29.20	10	.001	
	Block	29.20	10	.001	
	Model	29.61	12	.003	0.24

Table A6b: Multiple stepwise logistic regression for defensive reporting at baseline (coefficients)

							95% CI OR		
Variables in the Equation		*B*	*SE*	*Wald*	df	*p*	OR	Lower	Upper
Model 1	GAC at baseline	0.04	0.01	8.84	1	.003	1.04	1.01	1.07
	Aetiology			0.03	2	.984			
	Aetiology(1)	-0.22	1.24	0.03	1	.860	0.80	0.07	9.19
	Aetiology(2)	-0.02	0.48	0.00	1	.972	0.98	0.38	2.54
	Constant	-4.24	1.27	11.08	1	.001	0.01		
Model 2	GAC at baseline	0.03	0.02	3.92	1	.048	1.03	1.00	1.06
	Aetiology			0.50	2	.780			
	Aetiology(1)	-0.95	1.38	0.47	1	.492	0.39	0.03	5.81
	Aetiology(2)	-0.24	0.63	0.15	1	.703	0.79	0.23	2.71

SIMD			1.39	4	.845			
SIMD(1)	0.51	0.77	0.44	1	.507	1.67	0.37	7.56
SIMD(2)	0.77	0.75	1.04	1	.308	2.15	0.49	9.39
SIMD(3)	-0.01	0.74	0.00	1	.993	0.99	0.23	4.27
SIMD(4)	0.28	0.75	0.14	1	.709	1.32	0.31	5.74
Age at baseline	-0.05	0.02	3.92	1	.048	0.95	0.91	1.00
SEX(1)	-1.31	0.51	6.55	1	.010	0.27	0.10	0.74
DRS(1)	-2.59	1.22	4.56	1	.033	0.08	0.01	0.81
Constant	-1.62	1.69	0.92	1	.336	0.20		

NB. SE = Standard Error; OR = Odds Ratio; GAC = Global Adaptive Composite; SIMD = Scottish Index of Multiple Deprivation; DRS = Drug-Resistant Seizures; GDD = Global Developmental Delay

Table A7a: Multiple logistic regression for defensive reporting at follow-up (models)

Omnibus Tests of Model Coefficients

Model		χ^2	df	*p*	Cox & Snell R^2
1	Step	5.62	1	.018	
	Block	5.62	1	.018	
	Model	5.62	1	.018	0.08
2	Step	6.54	1	.011	
	Block	6.54	1	.011	
	Model	12.16	2	.002	0.17

Table A7b: Multiple stepwise logistic regression for defensive reporting at follow-up (coefficients)

Variables in the Equation		*B*	*SE*	*Wald*	df	*p*	95% CI OR		
							OR	Lower	Upper
Model 1	GAC at follow-up	0.02	0.01	5.11	1	.024	1.02	1.00	1.05
	Constant	-2.77	0.98	8.03	1	.005	0.06		
Model 2	GAC at follow-up	0.02	0.01	3.56	1	.059	1.02	1.00	1.05
	SEX(1)	-1.44	0.58	6.20	1	.013	0.24	0.08	0.73
	Constant	-1.75	1.04	2.83	1	.093			

NB. SE = Standard Error; OR = Odds Ratio; GAC = Global Adaptive Composite; SIMD = Scottish Index of Multiple Deprivation; DRS = Drug-Resistant Seizures; GDD = Global Developmental Delay