Abstract

Background and objectives: As the population ages, differences in cognitive abilities become more evident. We investigated key genetic and life course influences on cognitive state at age 69, building on previous work using the longitudinal MRC National Survey of Health and Development (the British 1946 birth cohort).

Methods: Multivariable regressions investigated the association between four factors :(1) childhood cognition at age 8; (2) a cognitive reserve index (CRI) composed of 3 markers: i. educational attainment by age 26, ii. engagement in leisure activities at age 43, and iii. occupation up to age 53; (3) reading ability assessed by the National Adult Reading Test (NART) at age 53 and (4) APOE genotype in relation to cognitive state measured at age 69 with Addenbrooke's Cognitive Examination third edition (ACE-III). We then investigated the modifying role of the CRI, NART, and APOE in the association between childhood cognition and the ACE-III.

Results: The analytical sample was comprised of 1,184 participants. Higher scores in childhood cognition, CRI and NART were associated with higher scores in the ACE-III. We found that the CRI and NART modified the association between childhood cognition and the ACE-III: for 30 additional points in the CRI or 20 additional points in the NART, the simple slope of childhood cognition decreased by approximately 0.10 points (CRI= 70: Marginal Effects (ME) 0.22, 95% CI 0.12-0.32, p<0.001 versus CRI= 100: ME 0.12, 95% CI 0.06-0.17, p<0.001; NART=15: ME 0.22, 95% CI 0.09-0.35, p=0.001, versus NART= 35: ME 0.11, 95% CI 0.05-0.17, p<0.001). The association between childhood cognition and the ACE-III was non-significant at high levels of the CRI or NART. Furthermore, the e4 allele of the APOE gene was associated with lower scores in the ACE-III (ß=-0.71, 95% CI -1.36 to -0.06, p=0.03) but did not modify the association between childhood cognition and cognitive state in later life.

Conclusion: The CRI and NART are independent measures of cognitive reserve since both modify the association between childhood cognition and cognitive state.

Introduction

The heterogeneity in cognitive function of older individuals might be related to the exposure and accumulation of risk and protective factors across the life course. Genetic as well as life-course factors are considered important determinants of cognitive ageing and dementia[1].

Cognitive reserve (CR) theory proposes that the knowledge and experiences individuals accumulate through their lives provide increased resilience against the clinical expression of neuropathology, helping to maintain cognitive function[2,3]. CR is thought to be developed through childhood[4,5] and further enhanced during adulthood through the interplay of various cognitively enhancing activities, including educational attainment, occupational complexity, and leisure activity engagement[6–8].

The role of childhood cognition in cognitive ageing has been widely investigated, providing support for a consistent association with later-life cognition, establishing childhood cognition as a reliable early determinant of cognitive ageing[4,9,10]. Furthermore, previous studies have shown that CR's formative variables, such as educational attainment, occupation complexity, and engagement in leisure activities, explain some of the variance in cognitive function during later life, even after accounting for early-life cognitive ability and hence, might moderate the association between childhood cognition and cognitive ageing[9,11–13]. However, it is not yet clear to what extent these environmental exposures and lifestyle choices moderate the association between early-life cognitive ability and cognitive ageing[10].

In comparison to CR's formative variables, crystallised cognitive ability, defined as knowledge acquired over time[14], has been argued to reflect CR[3,15], capturing the intellectual ability achieved that does not exclusively depend on access to and quality of formal education[5,16,17]. It has been suggested that verbal ability might have more robust positive associations with cognitive function independently of brain structure in comparison to other sociobehavioural markers, including composite proxies[13].

The apolipoprotein E (APOE) gene, which is associated with three alleles: e2, e3, and e4, is a plasma protein that plays a critical role in regulating processes that ensure brain health[18]. However, the e4 allele of the APOE gene has been associated with a faster rate of cognitive decline from midlife and a higher risk of Alzheimer's Disease (AD), positioning it as the best-known genetic risk factor for AD[19,20]. Furthermore, previous research has suggested that, despite being unassociated with early-life cognitive ability, APOE e4 is associated with lower cognitive performance in later life, predicting change in ability from youth [5,20,21].

Based on available life course studies investigating sociobehavioural variables and verbal ability as markers of CR [4,13,22–25] and building on previous path models investigating the life-course determinants cognitive state [5,17], this study aimed to investigate the modifying role of two commonly used markers of CR and APOE genotype in the association between childhood cognition and cognitive state at age 69. The markers of CR are 1) a composite score of sociobehavioural variables (educational attainment, occupational complexity, and leisure activity engagement) assessed using the Cognitive Reserve Index (CRI)[26] and 2) reading ability at midlife assessed using the National Adult Reading Test (NART)[27]. It was hypothesised that higher scores of childhood cognition, CRI, and NART would be associated with a better cognitive state in older age, and that the CRI and NART would each predict higher cognitive state scores for individuals with lower childhood cognition scores. Furthermore, based on previous evidence we expected that the presence of the APOE e4 allele would be associated with lower cognitive state, and hypothesised that it would predict lower cognitive scores in later life, especially for individuals with low childhood cognition.

Methods

Study Population

The data were extracted from the Medical Research Council (MRC) National Survey of Health and Development (NSHD), also known as the British 1946 birth cohort. NSHD originally comprised a socially stratified sample of 5,362 individuals born within one week of March 1946, through England,

Wales, and Scotland. The study has continuously collected data on sociodemographic factors and medical, cognitive, and psychological function from birth through all the relevant developmental stages. The 24th data collection was carried out through 2014 and 2015 when participants were aged 68-69 [28].

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol received ethical approval from the Great Manchester Local Research Ethics Committee for the five English sites and Scotland Research Ethics Committee for the data collection taking place in Edinburgh. Written informed consent was obtained from the study member at each stage of data collection.

Measures

Outcome

The Addenbrooke's Cognitive Examination III (ACE-III) was administered during the nurse visits when participants were 69 years old. The ACE-III is a screen implemented test of cognitive state and has been validated as a screening tool for cognitive deficits in AD and frontotemporal dementia [29]. The ACE-III has a maximum total score of 100 and has a quasinormal distribution. The examination is comprised of five domains: Attention and Orientation (scored 0 to 18), Verbal Fluency (0 to 14), Memory (0 to 26), Language (0 to 26), and Visuospatial Function (0 to 16). A customised version of the ACE-III was administered by iPad using ACEMobile (http://www.acemobile.org). A paper version of the ACE-III was only used when the iPad screening administration was not possible.

Exposures

Childhood cognition. At the age of 8, participants took verbal and nonverbal ability tests devised by the National Foundation for Educational Research [30], which were administered by a teacher and trained personal. These tests included: (1) Reading Comprehension, (2) Word Reading, (3)

Vocabulary, and (4) Picture Intelligence. Scores from these tests were summed to create a total score ranging from 12 to 92, representing overall cognitive ability at this age.

The Cognitive Reserve Index. The CRI [26] quantifies various markers of CR, providing a standardised measure of the CR acquired during a person's lifetime. The CRI is a composite measure of educational attainment, occupational class, and leisure activities. The data for each component were extracted from various questionnaires administered to each member during their assessments at ages 26, 43 and 53. The computation of the CRI was carried out in accordance with a previous publication [26]: each component was standardised to a mean of 100 and a standard deviation of 15. To calculate the overall CRI, the three corresponding standardised scores were averaged. This average was then re-standardised and transposed to a scale with a mean of 100 and a standard deviation of 15, resulting in the CRI score.

Education. The highest educational attainment by age 26 was classified by the Burnham scale [31]. For descriptive purposes and to be consistent with the original calculation of the education component[26], we calculated the approximate number of years each qualification represents: Doctorate (20 years), Masters (17 years), Graduate degree (16 years), GCE 'A' level, Burnham B or Burnham A2 (13 years), Vocational course, sub GCE or sub-Burnham C, GCE 'O' level or Burnham C (11 years), and none attempted (10 years).

Occupation. Occupational class was assessed through participants' overall occupation level from age 26 to 43 and their occupation at age 53. The occupation variables were categorised into the following five groups based on the Registrar General classification: professional=5, intermediate occupations=4, skilled non-manual=3, skilled manual or partly skilled=2, and unskilled=1. The CRI computation multiples the level of occupation by the number of years spent at each job [26], hence participant's overall occupation level from ages 26 to 43 were multiplied by 20 plus their occupation at age 53 times 10, representing 30 years of work and accounting for any changes of work level at midlife.

Leisure activities. Engagement in leisure activities was measured at age 43 through a range of 14 intellectual, social, and physical activities. The selection included activities related to belonging or running to various organisations, spare time engagement in sports or artistic activities, intellectual activities, and social activities. A detailed list of the activities selected to create this component can be found in eTable 1.

National Adult Reading Test. The NART was administered to participants at age 53. This test assesses the ability to pronounce 50 words that violate conventional pronunciation rules and are unlikely to be read correctly unless the reader is familiar with them in written form rather than relying on intelligent guesswork [27]. Thus, the NART serves as a measure of crystallised cognitive ability, measuring the knowledge acquired over the life course [15]. Previous studies have suggested that the NART might represent an important marker of CR, capturing environmental enrichment afforded by lifelong learning[3,16,32]. For the analysis, the NART scale was reversed, with higher scores showing better performance; the scores range between 1 and 50.

Genetic risk was assessed using the APOE genotype as previously described for this cohort [5]. APOE was categorised as no e4 versus heterozygous e4 or homozygous e4. Due to opposing effects on cognition, participants with e2/e4 were excluded.

Covariates

We controlled for various important covariates that are related to cognitive health that were measured at age 53. As sociodemographic variables, we included sex and marital status. Marital status was dichotomised between married and not married participants; this last category included single, separated, divorced, and widowed participants. Physical health was ascertained by body mass index (BMI) and blood pressure, as well as self-reported diagnosis of a serious illness or disability. Emotional symptoms were self-reported using the General Health Questionnaire (GHQ-28), which is a validated 28 item instrument to detect symptoms of anxiety and depression and psychosocial

functioning [33]. Smoking behaviour was assessed by asking participants if they currently smoke cigarettes (yes/no).

Statistical analysis

Multivariable regression models were used to test the association between all exposures (i.e., childhood cognition, CRI, NART, and APOE) and the scores in the ACE-III. The association between the exposures and cognitive state was investigated by progressively adjusting for sex and marital status in model 1, further adjusting for physical health in model 2, GHQ-28 in model 3, and cigarette smoking in model 4. Initial investigations were carried out individually for each exposure variable and the ACE-III. We then carried the mutually adjusted association between all exposures and cognitive state. Additionally, we assessed the association between the individual childhood cognition tests (Reading Comprehension, Word Reading, Vocabulary, and Picture Intelligence) and their association with the ACE-III while accounting for the CRI, NART, genetic risk and gradually adjusting for all covariates. We also tested the association between the individual components of the CRI (education, occupation, and leisure activities) and their association with the ACE-III while accounting for childhood cognition, the CRI, NART, genetic risk and gradually adjusting for all covariates.

For the analysis of the components, education and occupation were re-categorised to ensure all levels of the variable were appropriately powered. Education was grouped into no qualification, ordinary secondary qualifications or below (vocational and 'O' levels or training equivalents), advanced secondary qualifications ('A level' and equivalent), or higher qualifications (degree or equivalent). For occupation, unskilled and partially skilled were merged, skilled manual and skilled non-manual were merged, and intermediate occupations and professional occupations were merged into a single category.

Finally, to assess the independent modifying role of the predictors in the association between childhood cognition and cognitive state in older age, we tested the interactions between childhood cognition and CRI, NART, and APOE. Marginal effect models were carried out to explore the

interactions between the continuous exposure and outcome variables. We additionally assessed the association between childhood cognition and cognitive state stratifying by the moderator variables, which were dichotomised above and below the mean.

The linearity assumption was confirmed using a scatterplot, while multicollinearity was ruled out by assessing the Variance Inflation Factor (VIF). All VIF values were small (<1.97), with a mean of 1.54. A histogram of the standardised residuals revealed a slight negative skew. However, since the sample size for this study is large, violations of the normality assumption are not expected to impact the results[34]. Furthermore, a spread-level plot suggested a mild pattern of heteroskedasticity; hence, a heteroskedasticity-consistent standard error estimator of the parameter estimates was employed in all models[35].

The proportion of missing data in the analytical sample ranged from 6% to 14% (see Figure 1). The main analysis was carried out using complete case analysis, and sensitivity analyses were carried out using imputed data. Missing data on predictors and covariates were estimated using multiple imputations by chained equations (MI). Analyses were conducted using Stata MP, Version 16 (Stata Corp).

Data Availability

Bona fide researchers can apply to access the NSHD data via a standard application procedure. Aggregate data are available for NSHD across 24 waves of data collection beginning in 1946. All data sharing must be within the bounds of consent given previously by study members and meet rigorous data security standards, adhering to the core principles of ethical, equitable, and efficient data sharing set out by the Medical Research Council (UK) and subject to a data-sharing agreement. Applications for data sharing can be made via established protocols outlined by the Medical Research Council Unit of Lifelong Health and Ageing at UCL (http://www.nshd.mrc.ac.uk/data/data-sharing).

Results

Of the 1,184 participants included in the analysis, 48% were female and 29% had the e4 allele of the APOE gene. At age 26, only 11% of the sample had an education above a first degree and by age 43, 38% engaged in six or more leisure activities. At age 53, 50% had a professional or intermediate occupation. Furthermore, at the last wave of data collection, the mean score in the ACE-III for the sample was 92 (SD=6), with a minimum score of 53 and a maximum score of 100 (see Table 1 for descriptive characteristics of the sample and Figure 1 for the participant flowchart).

To assess the independent influence of each exposure on cognitive state, separate models were carried out for childhood cognition, CRI, NART and APOE. Except for APOE genotype (ß=-0.60, -1.36 to 0.17), all determinants showed a significant association with cognitive state during older age. The highest regression coefficient was that of the NART (ß=0.34, 95% CI 0.30-0.38), followed by childhood cognition (ß=0.29, 95% CI 0.26-0.33), and finally, the lowest coefficient was that of the CRI (ß=0.18, 95% CI 0.16-0.20) (see eTables 2 to 5).

Mutually adjusted models

After the initial explorations, all exposures were mutually adjusted by introducing them into the same model. As presented in Table 2, it was found that for every unit increase in childhood cognition, the ACE-III score was predicted to increase by 0.10 points on average. Similarly, for every unit increase in the CRI, scores in the ACE-III increase by 0.07, and for every unit increase in the NART, the score in the ACE-III is predicted to increase by 0.22 points on average. Additionally, once childhood cognition, CRI and NART were included in the model, the presence of the e4 allele significantly predicted lower scores in the ACE-III (ß=-0.71, 95% CI -1.36 to -0.06).

The investigation of the individual cognitive tests taken at age 8 showed that all four components – Reading Comprehension, Word Reading, Vocabulary, and Picture Intelligence – significantly contributed to the variance of the ACE-III scores (Supplementary Tables 6 to 9). The effect size for all

cognitive tests was small, ranging from 0.05 to 0.08; the lowest one was for Vocabulary while the highest ones were for Reading Comprehension and Picture Intelligence.

Additional investigation of the association of the individual sub-components of the CRI and cognitive state at age 69 showed that, on average, individuals with a degree or higher qualifications scored an additional 1.22 points in the ACE-III in comparison to those with no qualifications. Individuals who engaged in 6 or more leisure activities scored 1.53 additional points in the ACE-III compared to those who engaged in 0 to 4 leisure activities. Finally, individuals with a professional or intermediate occupation scored an additional 1.50 points in the ACE-III in comparison to those with part skilled or unskilled occupations (see eTable 10).

Moderation analysis

As presented at the bottom of Table 2, we found significant interactions between childhood cognition and the CRI, as well as between childhood cognition and the NART, suggesting that the association between childhood cognition on cognitive state in older age is moderated by the CRI and by the NART.

The top section of Table 3 presents the simple slopes of childhood cognition at mean levels of the CRI and above and below two standard deviations of the mean, each representing low and high levels of the CRI. After adjusting for all covariates, including the NART, it was found that for 30 additional points in the CRI, the slope of childhood cognition decreased by approximately 0.10 points, indicating that, when compared to individuals with high childhood cognition, the CRI had a stronger association with cognitive state for individuals with low childhood cognition (see Figure 2). Similarly, stratified regressions showed that, when compared to individuals who scored above the mean in the CRI, the coefficient of the association between childhood cognition and cognitive state was significant and higher for individuals who scored below the mean in the CRI (0.15 versus 0.08) (Table 4).

The bottom section of Table 3 presents the simple slopes of childhood cognition at mean scores of the NART and two standard deviations above and below the mean, each representing low and high scores in the NART. After adjusting for all covariates, including the CRI, it was found that for 20 additional points in the NART, the slope of childhood cognition decreases by approximately 0.11 points, indicating that, when compared to individuals with high childhood cognition, the NART had a stronger association with cognitive state for individuals with low childhood cognition (see Figure 3). Stratified regressions showed that, compared to individuals who scored higher in the NART, the regression coefficient for the association between childhood cognition and cognitive state was higher for those who scored below the mean in the NART (0.17 versus 0.15) (Table 4).

Furthermore, the interaction between childhood cognition and APOE was non-significant (see Table 2), suggesting that APOE genotype does not modify the association between childhood cognition and cognitive state in older age. However, the stratified analysis in Table 4 showed that for individuals who scored above the mean in the CRI or NART, the APOE e4 allele predicted lower scores in the ACE-III. On the other hand, the association between APOE genotype and the ACE-III was non-significant for individuals who scored below the mean in the CRI or NART.

Sensitivity analyses

All analyses carried out using imputed data (N=1,762) confirmed the findings from the complete case analyses (eTables 11 and 12).

Discussion

This study investigated the modifying roles of CR measures and APOE genotype on the association between childhood cognition and cognitive state in older age in the British 1946 birth cohort. Both the formative and reflective measures of CR—here indexed using the CRI and NART respectively—were found to modify the association between childhood cognitive ability and cognitive state, whereby increased scores in either measure resulted in better cognitive performance than what

would have been predicted by childhood cognition alone. APOE genotype did not modify the association between childhood cognition and cognitive state.

This study corroborates previous findings highlighting the malleable nature of cognitive function [10,12,36] and adds to the literature by suggesting that, for individuals with low childhood cognitive ability, lifestyle and environmental factors play a greater role in determining cognitive state in old age. Hence, this study provides support to the hypothesis that older age cognition is the result of the interaction of childhood cognitive ability and CR enhancing factors throughout the life course, which accumulate over time and have the potential to modify the rate of cognitive decline[3,9,10,12,37].

Evidence from the Lothian birth cohorts (LBC) has suggested that the greatest factor influencing cognitive differences in older age is childhood cognitive ability[11]. However, a recent systematic review assessing nine studies using data from LBC and NSHD found inconsistent results for the association between childhood cognition and cognitive decline, suggesting that the relationship might be moderated by unknown factors [10]. The current findings complement the literature by attributing differences between these two stages to mid-life intellectual enrichment measured using the CRI or NART and suggesting that childhood cognition influences late-life cognitive state only for individuals with low CR during adulthood. Hence, the results contribute to the understanding of the mechanisms through which early and mid-life environmental lifestyle factors affect cognitive ageing and support the relevance of a lifelong investment in the accumulation of CR.

In this study, the composite index of reserve showed a significant association with cognitive state during older age. These findings are in accordance with previous studies investigating the association between composite socio-behavioural markers of CR and cognitive decline or dementia [6,22,38]. Furthermore, consistent with the findings of previous epidemiological studies investigating the role of education and occupation on cognitive function and dementia[17,39,40], as well as previous analysis carried out in this cohort[5], the sub-component analysis of the CRI showed that higher educational attainment and occupation predicted higher scores in the ACE-III. It has been argued that variables

such as education and occupation contribute to the continuity and even improvement of cognitive skills, as well as the development of other important skills such as motivation, social integration, self-efficacy, and self-regulation all of which predict better cognitive ageing[17,41].

Furthermore, our findings for the leisure activity subscale are in accordance with a previous study in this sample which assessed the longitudinal association between leisure activity engagement and cognition at midlife[8] and with two systematic reviews that found that engagement in cognitive, physical, or other leisure activities was associated with lower risk of cognitive decline [7,42]. Cognitive decline in older life can have various causes, including genetic predispositions, physical inactivity, and chronic conditions, such as depression and heart disease, each of these associated with different risk and protective factors which might be modified by a wide variety of lifestyle choices[42–44].

When assessed in adulthood, the NART might provide a reliable marker of CR[3,15] representing environmental enrichment beyond sociodemographic estimates such as years of education[16,45] and capturing mature ability[36]. As Cattell argued, the development of crystallised ability is the result of the engagement in a variety of activities, the time and energy devoted to the activities, and the individual's motivation, all of which can take an infinite variety [46]. Based on this theory, and building on the findings of a previous path analysis carried out with this cohort[5], the NART was included in our models as an independent marker reflecting CR since the CRI, which can be argued to constitute a formative model, may not always fully reflect the degree of intellectual ability achieved [47]. However, after comparing the role of formative versus reflective measures of CR, our findings suggest that both measures independently modify the association between childhood cognition and cognitive state at age 69 with very similar effect sizes.

The investigation of the association between APOE genotype on cognitive state showed that, consistent with previous investigations, the APOE e4 allele predicts lower late-life cognition scores, albeit with a small effect size[5,48]. Possibly due to the small effect of APOE on the ACE, this association was only evident when a larger proportion of the variance was accounted for by childhood cognition,

CRI, and NART. However, contrary to our hypothesis, the interaction analysis suggested that APOE e4 does not modify the association between childhood cognition and cognitive state. Previous evidence from this cohort has suggested that the adverse effects of APOE e4 tend to manifest in later stages in life, potentially starting at age 69[20], and therefore, moderation investigations using data from older individuals are needed to clarify these findings. Furthermore, in contrast to previous moderation investigations that have suggested that the association between APOE e4 and cognition is more noticeable in individuals with lower CR[49,50], the stratified analysis in this study indicated that the APOE e4 allele significantly predicted lower scores in the ACE-III for individuals with higher CR. This finding might be due to a larger range of ACE-III scores for individuals with the e4 allele when compared to those without (53-100 vs. 64-100) in this sample or it might suggest an interaction between APOE and CR. Hence, future work could help elucidate this finding.

This study built upon previous findings of life course determinants of cognitive ageing[5,17] to assess and compare the moderating role of two commonly used measures of CR in the association between childhood cognition and cognitive state. All predictors and the outcome were measured with widely accepted scales and reliable measures across the life course. Furthermore, for a birth cohort with such an extended follow-up period (70 years), this study had a relatively large sample size. However, despite the lack of pronounced ceiling effects found with some cognitive tests, scores in the ACE-III were negatively skewed, limiting the ability of the CRI and NART to predict improvement for those with high childhood cognition. Despite this, the marked increase in cognitive state scores driven by CR for individuals with low childhood was clearly captured. Additionally, some important limitations for this study are related to selective attrition over time. As previously reported [5], the sample of NSHD participants who were interviewed at age 69 was comprised of the cohort survivors who are more likely to be healthier, to have better cognitive function, and to be more socially advantaged than those not followed up; therefore the potential of survivor and attrition bias needs to be considered. These biases might affect the external validity of the study, and therefore, replication in other populations is necessary to confirm the results.

In conclusion, our study suggests that the association between childhood cognitive ability and cognitive state in older age is moderated by an intellectually enriching lifestyle, indicating that cognitive ability is subject to environmental influences throughout the life course and that CR can offset the negative influence of low childhood cognition. The present study also underlines the role of the CRI and NART as measures of reserve since both measures independently modify the association between childhood cognition and cognitive state. Finally, from a policy perspective, the results highlight the importance of CR factors for cognitive maintenance and enhancement through adulthood to prevent old-age cognitive decline, particularly for individuals who might not have benefited from an enriching childhood.

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