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The assessment of cognitive function in the German National Cohort (NAKO) – Associations of demographics and psychiatric symptoms with cognitive test performance

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ORIGINAL INVESTIGATION

The assessment of cognitive function in the German National Cohort (NAKO) – Associations of demographics and psychiatric symptoms with cognitive test performance

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ABSTRACT

Objectives: To describe the cognitive test battery of the German National Cohort (NAKO), a population-based mega cohort of 205,000 randomly selected participants, and to examine associations with demographic variables and selected psychiatric and neurological conditions.

Methods: Initial data from 96,401 participants providing data on the cognitive performance measured by a brief cognitive test battery (12-word list recall task, semantic fluency, Stroop test, digit span backwards) was examined. Test results were summarised in cognitive domain scores using exploratory and confirmatory factor analyses. Associations with sociodemographic and psychiatric factors were analysed using linear regression and generalised additive models.

Results: Cognitive test results were best represented by two domain scores reflecting memory and executive functions. Lower cognitive functions were associated with increasing age and male sex. Higher education and absence of childhood trauma were associated with better cognitive function. Moderate to severe levels of anxiety and depression, and a history of stroke, were related to lower cognitive function with a stronger effect on executive function as compared to memory. Some associations with cognition differed by German language proficiency.

Conclusions: The NAKO cognitive test battery and the derived cognitive domain scores for memory and executive function are sensitive measures of cognition.

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Cognition; German National Cohort; NAKO; depression; cognitive ageing; confirmatory factor analysis

Introduction

A lower cognitive function is associated with higher mortality (Calvin et al. 2011) and with higher risk for several diseases such as coronary heart disease, respiratory diseases, or cancer (Christensen et al. 2016; Calvin et al. 2017). Understanding the causes and determinants of these associations is an important aim of cognitive epidemiology (Deary and Batty 2007). However, the mechanisms underlying these associations are complex and are not yet completely understood.

Cognitive abilities are indicators of brain functions. Those are shaped by multiple factors throughout the lifespan that can either promote optimal functioning or lead to disability and diseases (Lubinski 2009; Deary

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2012). For instance, the cognition-disease relationship can be partially explained by a shared genetic aetiology (Deary et al. 2019) but also derives from life experiences (Lager et al. 2009) such as education or childhood maltreatment, that influence both cognition (Masson et al. 2015; Ritchie and Tucker-Drob 2018) and multiple health outcomes (Mandelli et al. 2015; Lager et al. 2017; Bailey et al. 2018; Hamad et al. 2018; Davies et al. 2019; Hamad et al. 2019). Cognitive abilities may also serve as early markers of different diseases. For instance, specific neuropsychological deficits can indicate the presence of neurodegenerative processes in clinically unimpaired individuals (Rentz et al. 2011). Similarly, cardiovascular risk factor exposure until midlife, such as blood pressure, is reflected in late-life cognitive abilities (Yaffe et al. 2014). In contrast, higher cognitive abilities are linked to more efficient neural networks mitigating the effects of neurodegenerative pathologies on brain function (Stern 2012).

Cognitive abilities can also directly contribute to the mechanisms influencing onset and progression of diseases. Higher intelligence in childhood, for example, associates with lower risk for hospitalisation due to mental disorders in adulthood (Gale et al. 2010). Similarly, higher cognitive functions in old age are associated with prolonged survival in patients with cardiovascular diseases, cancer, or stroke (Anstey et al. 2006). Herein, increased compliance to prescribed treatments (Insel et al. 2006; Stilley et al. 2010; Klepin et al. 2014) and health literacy are proposed underlying mechanisms (Bostock and Steptoe 2012; Hall and Marteau 2014; Fawns-Ritchie et al. 2018).

Understanding the mechanisms linking cognitive functions to physical and mental health requires large studies with a reliable and validated neuropsychological assessment as well as a comprehensive assessment of the disorders and risk factors of interest. To this end, the assessment of cognitive functions in NAKO offers a unique opportunity for the identification of determinants of optimal development and maintenance of brain function as well as a better understanding of cognitive contributions to the prognosis in common diseases. In this analysis, we describe the neuropsychological assessment in NAKO and demonstrate its sensitivity to potential influences of demographics such as age and sex, early life experiences such as education and childhood trauma, as well as psychiatric and neurological conditions such as depressive symptoms and stroke. Based on previous research, we expect that lower cognitive functions will be related to higher age (Wagner et al. 2018; Cornelis et al. 2019), male sex (Hayat et al. 2014; Wagner et al. 2018), lower education (Ritchie and Tucker-Drob 2018; Wagner et al. 2018), presence of childhood trauma (Masson et al. 2015) and psychiatric and neurological conditions (Castaneda et al. 2011; Cullen et al. 2015; Helmstaedter and Witt 2017; Tang et al. 2018; Wagner et al. 2018).

Methods

Sample selection

Data included in this study were derived from the German National Cohort (NAKO; German National Cohort Consortium 2014). NAKO is a population-based cohort study, examining 205,000 randomly selected participants in 18 study centres (Schipf et al. 2020). Baseline examination took place between 2014 and 2019. The current analysis includes data of the first 101,667 participants summarised in the so-called 'NAKO data freeze 100.000' (DF100K; application NAKO-399). At baseline, data was acquired at two levels: Level-1 (L1; ~3–4 h) assessment was undertaken by all participants; a subset of 20% of the subjects underwent the more detailed Level-2 assessment (L2; ~5 h). An overview of the assessment of neuropsychiatric functions and conditions (Berger et al. 2022), and detailed analyses of specific measures can be found elsewhere (Erhardt et al. 2022; Klinger-König et al. 2022; Schmiedek et al. 2022; Streit et al. 2022). Among all participants aged 18–72 in the DF100K data set, 96,401 individuals provided valid data on at least one neuropsychological test (Table 1). All participants had provided written consent for study participation. Approval had been given by all study centres' local ethics committees and the study was conducted in accordance with the Declaration of Helsinki.

Neuropsychological test battery

The NAKO neuropsychological assessment consists of a battery of six tasks that were administered to all participants (i.e. these were part of the L1 and L2 examination programmes), and two additional tests that were only performed in L2-participants, i.e. the number series task (see Schmiedek et al. 2022) and the bimanual Purdue Peg Board Test. The neuropsychological test battery was designed to assess, within a short time frame of 10–15 min, cognitive abilities known to be affected by many neurological and psychiatric conditions, in particular episodic memory, working memory, mental speed, and executive control (Table 2). The tests were selected according to a pilot study with 120 general population participants aged 20–79,

Table 1. Descriptive statistics for the Data freeze100K sample of the NAKO with valid data in at least one cognitive test.

	Mean/*N*	*SD*/%	Sample size
Age (*M*/*SD*)	51.91	12.39	96,401
Female sex (*N*/%)	51,540	53.5%	96,401
Education			
Years of education (*M*/*SD*)	15.14	2.57	94,371
Education groups (*N*/%)			95,876
Lower (ISCED-97 Level 1/2)	2287	2.4%	
Intermediate (ISCED-97 Level 3/4)	37,752	39.4%	
Higher (ISCED-97 Level 5/6)	47,988	50.1%	
Unclassified	7849	8.2%	
Cognitive tests (*M*/*SD*)			
Immediate word list recall Trial 1	6.78	1.79	95,040
Immediate word list recall Trial 2	9.48	1.77	94,858
Delayed word list recall Trial 3	8.14	2.40	94,360
Semantic fluency (animals)	25.36	6.93	96,156
Stroop task 1 (colour naming)	21.61	5.51	94,716
Stroop task 2 (incongruent condition)	42.57	14.28	94,647
Stroop effect (incongruent – colour naming)	20.98	12.26	94,633
Digit span backwards	4.79	1.31	95,756
Psychiatric scales (M/SD)			
PHQ-9 (range: 0-27)	3.88	3.71	89,590
Number of individuals with moderate to severe depressive symptoms (PHQ-9 $\geq$ 10; N/%)	6872	7.7%	89,590
Number of individuals receiving treatment of depression by physician during past 12 months	6717	7.0%	95,891
GAD7 (range: 0–21)	3.16	3.22	89,369
Number of individuals with moderate to severe anxiety symptoms (GAD7 $\geq$ 10; *N*/%)	4507	5.0%	89,369
Number of individuals receiving treatment of Anxiety or panic disorder by physician during past 12 months	3097	3.2%	96,109
CTS (range: 5–25)	7.37	2.74	81,143
Number of individuals with maltreatment in childhood (*N*/%)	22,336	27.5%	81,143
Self-reported neurologic diseases (*N*/%)			
Stroke	1679	1.7%	96,225
Temporal distance between stroke and cognitive assessment (in years)	8.58	7.84	1620
Epilepsy	1615	1.7%	96,273
Temporal distance between seizure and cognitive assessment (in years)	25.07	16.96	1586
Interviewer-rated language ability (*N*/%)			96,401
German native speaker	87,200	90.5%	
German and another language as mother tongue	2458	2.5%	
Non-native speaker: very good	2518	2.6%	
Non-native speaker: good	2462	2.6%	
Non-native speaker: average	1217	1.3%	
Non-native speaker: low	222	0.2%	
Non-native speaker: very low	30	0.0%	
Non-native speaker: unknown proficiency level	294	0.3%	

Note. For definition of maltreatment in childhood, see Glaesmer et al. (2013) and Klinger-König et al. (2022). SD: standard deviation; PHQ-9: Patient Health Questionnaire 9-item depression module; GAD7: Generalised Anxiety Disorder Screener; CTS: Childhood trauma screener.

Table 2. Description of Level 1 cognitive test battery.

	Cognitive function	Defined range of plausible values
Immediate word list recall Trial 1	Verbal episodic memory	1–12
Immediate word list recall Trial 2	Verbal episodic memory	1–12
Delayed word list recall Trial 3	Verbal episodic memory	1–12
Semantic fluency (animals)	Processing speed, semantic memory	1–79
Stroop task 1 (colour naming)	Processing speed	11–422
Stroop task 2 (incongruent)	Processing speed, inhibition	11–422
Stroop effect (incongruent – colour naming)	Executive control, inhibition	−250–360
Digit span backwards	Verbal working memory	2–9

where different traditional neuropsychological and computerised tests, nominated by experts including many of the authors, had been compared for ease of administration and scoring, acceptance by participants, and total duration.

In this paper, we focus on the L1 test battery. Herein, the following tasks were administered in the outlined order:

1. Semantic fluency task: Participants were asked to enumerate as many animal names as possible within one minute. The number of named animals was recorded. Repetitions were excluded.
2. Immediate recall of a 12-word list: Participants were asked to recall as many words as possible from a digitally recorded list of words, with one word presented every two seconds via a

loudspeaker. The word list consisted of concrete, frequent, highly imaginable, and semantically unrelated German nouns. Two such nouns were added to the 10 words of the CERAD word list (Morris et al. 1989; Berres et al. 2000), to reduce ceiling effects in younger participants. After a first recall, the same word list was presented once again followed by an additional recall. The number of correctly recalled words in both trials was recorded. Participants were then informed that they were to recall the words once again at the end of testing (see delayed recall task 6).

3. Stroop colour-word task 1: Participants were first asked to name the colour of 36 differently coloured boxes (red, green, blue, yellow), printed on a card board of 20 cm height and 30 cm width placed in front of them. In case of a mistake, participants were interrupted and instructed to correct. The time needed to name the colour of all patches was recorded as the test score.
4. Stroop colour-word task 2: Participants were presented with 36 printed names of colours, arranged on a similar card board. The colour of the ink mismatched (was incongruent with) the name of the colour (e.g. RED was printed in green colour, the correct response being 'green'). Participants were asked to name the colour of the incongruent colour name. In case of a mistake, participants were interrupted and instructed to correct. Time taken to name the ink colour of all printed words was recorded.

   Both Stroop colour-word tasks were not administered to participants with self-reported colour blindness.
5. Digit span backwards: Participants were acoustically presented with digitally recorded number sequences of increasing length, containing three to nine random single digits spoken at a rate of one second per number. Participants were instructed to recall each sequence in reverse order. If correctly recalled, a new sequence containing one more digit was presented. In case of a mistake, a second number sequence of the same length was presented. If this sequence was also incorrectly recalled no further sequences were presented. Otherwise a longer number sequence was provided.
6. Delayed free recall of the 12-words list: Participants were asked to recall the previously presented words (see immediate word list recall task 2) from memory within one minute. Correctly recalled words were counted.

In the pilot study, retest-reliability within one month ranged between .61 and .80 for single test scores of the selected tests; a global composite score (average of *z*-transformed single test scores) yielded a retest-reliability of .82.

Factors associated with levels of cognitive performance

For this study, we focussed on key sociodemographic factors known to be associated with cognition, on language proficiency as a possible limitation of test validity, and on selected mental health variables in order to demonstrate the sensitivity of the cognitive measures to concurrent psychological symptoms and recalled upbringing.

Education was assessed according to the International Standard Classification of Education 97 (ISCED-97; UNESCO 2003), and classified as described by Dragano and colleagues (Dragano et al. 2020). Education was coded as 'lower' (ISCED-97 Level 1/2: primary and lower secondary education), 'intermediate' (ISCED-97 Level 3/4: upper secondary and post-secondary non-tertiary education), and 'higher' (ISCED-97 Level 5/6: tertiary education). Participants who did not finish their education or who were not yet classified according to the International Standard Classification of Education 97 (Dragano et al. 2020) were coded as an additional group but not considered when assessing the effect size of or interactions with education.

German language proficiency was categorised according to the self-reported native language (German, German and another language, non-German native speaker). In addition, for non-native speakers, language skills were rated by the study nurse in five categories (very high, high, average, low, and very low) after testing.

Psychiatric scales assessing depressive symptoms (Patient Health Questionnaire 9-item depression module (PHQ-9; Kroenke et al. 2001; Streit et al. 2022), anxiety (Generalised Anxiety Disorder questionnaire (GAD7; Spitzer et al. 2006; Erhardt et al. 2022), and childhood trauma (childhood trauma screener (CTS); Grabe et al. 2012; Klinger-König et al. 2022) were administered.

The PHQ-9 is an established nine-item screening instrument for depression assessing the presence of depressive symptoms corresponding to Criterion A of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV; American Psychiatric Association 1994) in the last two weeks on a four-

point rating scale. Scores >=10 indicating a moderate to severe depressive symptomatology, are commonly used to index a current depressive episode. The cut-off provides a sensitivity of 88% and a specificity of 85% for a diagnosis of a major depression based on interview as suggested by recent meta-analyses (Levis et al. 2019). The GAD-7 is a seven-item anxiety questionnaire specifically linked to DSM-IV criteria (Spitzer et al. 2006). In NAKO, it assesses self-report anxiety symptoms in the last four weeks on a four-point rating scale. GAD-7 scores $\geq$10 indicate moderate to severe symptom severity and can detect a generalised anxiety disorder based on a structured clinical interview with a sensitivity of 89% and a specificity of 82% (Spitzer et al. 2006). The CTS is a five-item screening instrument assessing physical or emotional neglect and physical, emotional, and sexual abuse during childhood on a five-point Likert scale. Items were summed to index severity of childhood maltreatment. In addition, a dichotomous variable was created to indicate whether at least one CTS item was categorised as moderate to severe childhood trauma according to Glaesmer et al. (2013) (see also Klinger-König et al. 2022). Scores were included in the analyses as continuous variables (with higher score indicating more severe symptoms) and dichotomised according to cut-offs described above. In addition, the histories of the neurologic conditions stroke and epilepsy were defined as self-reported physician diagnoses. Self-reported age at diagnoses or year of diagnosis was used to compute the temporal distance to cognitive testing.

Statistical analysis

Analyses were performed with Mplus version 7.3 (Muthén and Muthén 2007) and R (R Development Core Team 2011) using the packages *mgcv* (Wood 2011) and *itsadug* (Van Rij et al. 2016). In all analyses, a two-tailed significance level of $\alpha < 0.05$ was considered statistically significant.

Derivation of cognitive domain scores

To derive cognitive domain scores, cognitive tests listed in Table 2 were considered. However, Stroop task 2 was not included as it represents the summary of cognitive abilities assessed in Stroop task 1 and the Stroop effect (colour naming-incongruent) and therefore does not add independent information to cognitive functioning. Test scores outside plausible ranges (Table 2) were set to missing. In addition, neuropsychological tests affected by organisational or technical problems during the assessment were set to missing as those could have affected the validity of the measurements. Previous research has shown that memory function in individuals with hearing problems is underestimated in case of acoustical presentation (Van Boxtel et al. 2000; Wong et al. 2019). In line with this, individuals with self-reported hearing problems ($N = 1102$, 1.1% of the total sample) showed lower scores in the acoustically presented word list recall tasks (Cohen's d: -0.343 to -0.571 indicating small to moderate effect sizes) but no significant differences in the digit span task in this sample. Test scores of the word list tasks were therefore set to missing for hearing-impaired individuals. Other sensory or motor impairments did not substantially affect any test scores and were not set to missing.

Based on prior knowledge (Table 2), cognitive domain scores were derived from individual test scores by means of confirmatory factor analysis (CFA). Notably, all task used to measure executive function cannot be considered as pure indicators of the construct. The problem of impurity of executive function tasks is a well-known problem in the literature on executive function but, importantly, the use of CFA has been proposed as a method to mitigate this problem (Miyake and Friedman 2012).

Individual test scores were modelled as categorical indicators using robust maximum likelihood estimation with the default logit link and numerical integration with 15 integration points in Mplus 7.3. To create these categorical variables, the continuous test scores were split in up to ten categories based on quantiles. This approach is in line with the graded response model from item response theory (Samejima 1969; Takane and De Leeuw 1987) which accounts for non-normal distributions and non-equal interval scaling that is often observed for neuropsychological tests (Proust-Lima et al. 2017). In addition, it can mitigate the influence of extreme and outlying individual test scores on the composite sores. This approach has already been successfully applied to large epidemiological studies and can improve the power to detect associations and the comparability of test scores across cohorts (Gross et al. 2014). The fit of a one-factor and a two-factor CFA-solution was compared based on information criteria.

In order to recheck the model structure theoretically assumed in the CFA model, the number of cognitive domains needed to represent the neuropsychological test battery was tested based on continuous test scores using parallel analysis (Horn

1965) and exploratory factor analysis (EFA) with categorical indicators and oblique geomin rotation (Asparouhov and Muthén 2009) in Mplus. We used the χ^2-difference test to compare one- and two-factor EFA models to validate the results from parallel analysis.

Missing data was handled using full information maximum likelihood (FIML; Enders 2010). As per Mplus default, cognitive domains scores derived from CFA were computed based on the expected value of the posterior distribution of the latent factors (Expected *a posteriori* (EAP) method) (Muthén and Muthén 2007) based on the results from the two-factor model. Estimated scores were set to missing if there were fewer than two tests measured per cognitive domain.

Assessment of the associations with potential determinants in cognitive performance

Association of cognitive domain scores with potential determinants of cognition was analysed using generalised additive models (GAM; Wood 2011) and ordinary linear regression (OLS). GAMs offer the advantage of analysing the non-linear relationship between variables without assuming any functional form of the association (e.g. linear or quadratic). GAMs were fitted using the maximum likelihood estimator and thin plate regression splines for continuous variables. Categorical variables were modelled as parametric terms. Models were refitted with increased basis dimensions of splines, using penalised regression instead of thin-plate splines as well as using generalised cross validation for smoothness selection. Results were compared to the associations derived from the initial model. OLS models were fitted and compared to GAM results to assess the need for modelling of non-linear relationships in the cognitive data from NAKO. Effect sizes were assessed using Cohen's f^2 (for continuous predictors; Cohen 1988; Selya et al. 2012) and Cohen's d (for dichotomous predictors; Nakagawa and Cuthill 2007). Herein, we considered commonly used cut-offs (Cohen 1988; Nakagawa and Cuthill 2007; Sawilowsky 2009; Selya et al. 2012) to classify very small ($d < 0.2$; $f^2 < 0.02$), small ($d \geq 0.2$; $f^2 \geq 0.02$), moderate ($d \geq 0.5$; $f^2 \geq 0.15$) and large ($d \geq 0.8$; $f^2 \geq 0.35$) effects.

All analyses included age, sex, education, and German language proficiency (native speaker, German and another language as mother tongue, non-native speaker) as covariates. In OLS models, age^2 was included to account for known non-linear age associated trends in cognition (Wagner et al. 2018) without using more complex analysis approaches such as GAM. This allowed for a comparison of the results of the two statistical approaches with regard to the effect size of the association of age and cognitive function. Two-way interactions of age, sex, and education were assessed. In addition, interactions of German language proficiency with the three aforementioned variables as well as all self-reported neurologic conditions and psychiatric scales were examined. Associations of cognitive domain scores and individual neuropsychological tests with ratings of German language skills (native speaker, German and another language as mother tongue, five–category rating of skills for non-native speakers, see above) were assessed using OLS regression adjusting for age, sex, and education. The effect sizes of the differences to native speakers were expressed as Cohen's *d*.

Results

Cognitive domain score computation

A two-factor CFA model with a memory factor derived from the word list tasks (immediate recall trial 1, immediate recall trial 2 and delayed recall trial 3) and an executive function factor (derived from semantic fluency task, Stroop task 1, Stroop effect (task 2–1), digit span backwards task) showed significantly better fit than a one-factor model ($AIC_{1factor} = 2567482.3$, $BIC_{1factor} = 2568106.7$, $AIC_{2factor} = 2550789.1$, $BIC_{2factor} = 2551443.0$). Loadings of the individual tests on the respective factor are displayed in Supplementary Table 1. As expected from these results, parallel analysis on continuous indicators suggested that a two-factor model was best suited to describe the NAKO neuropsychological test data as only the eigenvalue of the first and second factor was above the upper limit of the 95%-confidence interval (CI) of the eigenvalue obtained from parallel analysis ($Eigenvalue_{factor2} = 1.034$ $Eigenvalue_{Parallel\_analysis\_factor2} = 1.007$ (upper 95%CI = 1.011)). Similarly, an EFA using categorical indicators suggested a better fit for a two factor model (χ^2-difference (6)=19616.65, $p < 0.001$). Main loadings of the EFA confirmed the theoretically assumed model structure of the CFA. After analysis, valid domain scores were available for 94,637 participants on memory and for 94,862 participants on executive function.

Associations with demographic variables

Mean unadjusted cognitive scores differed between study centres, with effect sizes considered very small to small according to previously defined cut-offs

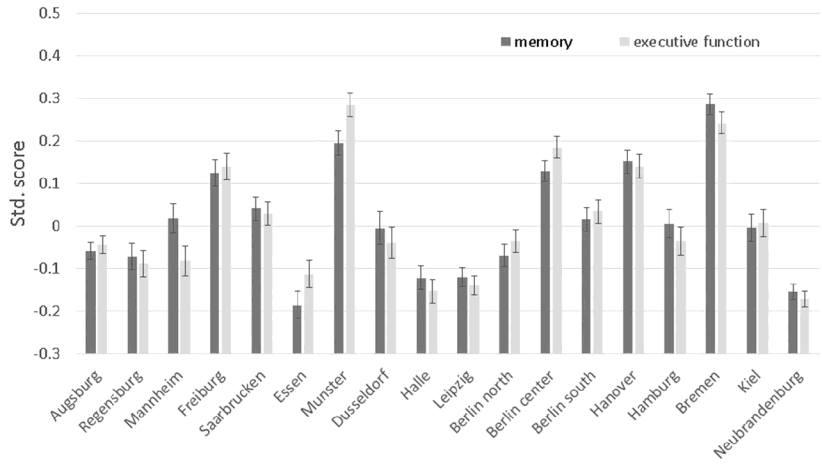

Figure 1. Unadjusted means and 95%-confidence intervals of memory and executive function domain scores per study centre. Std: standardised.

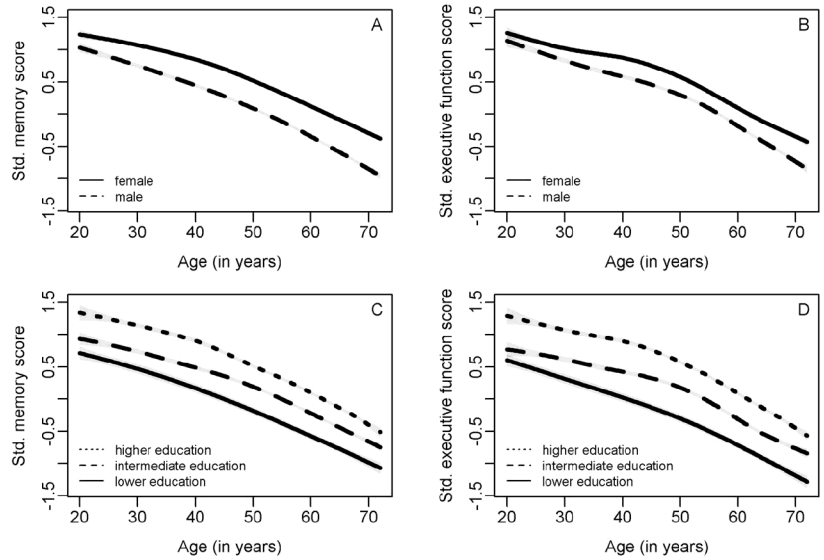

Figure 2. Association of demographic variables with memory and executive function Note. Estimated associations from generalised additive models including age, sex, education and German language proficiency as covariates are displayed. Shaded areas mark 95%-confidence intervals. (A) Estimates for standardised memory score by age and sex; (B) Estimates for standardised executive function score by age and sex; (C) Estimates for standardised memory score by age and education; (D) Estimates for standardised executive function score by age and education. Std: standardised.

(Figure 1; memory f^2=0.017; executive function f^2=0.020). Scores of memory and executive function showed strong associations with age, sex, and education in the GAM analyses (Supplementary Tables 2 and 3). Among all variables, age showed the strongest single effect on cognition (memory f^2=0.285; executive function f^2=0.308). Females showed higher cognitive abilities in both domain scores (Figure 2), with a slightly higher effect size in memory (f^2=0.067) compared to executive function (f^2=0.028). Higher education was associated with higher cognitive domain scores (Figure 2) with a slightly stronger effect on executive function (f^2=0.067) as compared to memory (f^2=0.044). All two-way interactions between the three variables were statistically significant but showed a negligible effect size (Supplementary Tables 4 and 5). Results from OLS regression were almost identical.

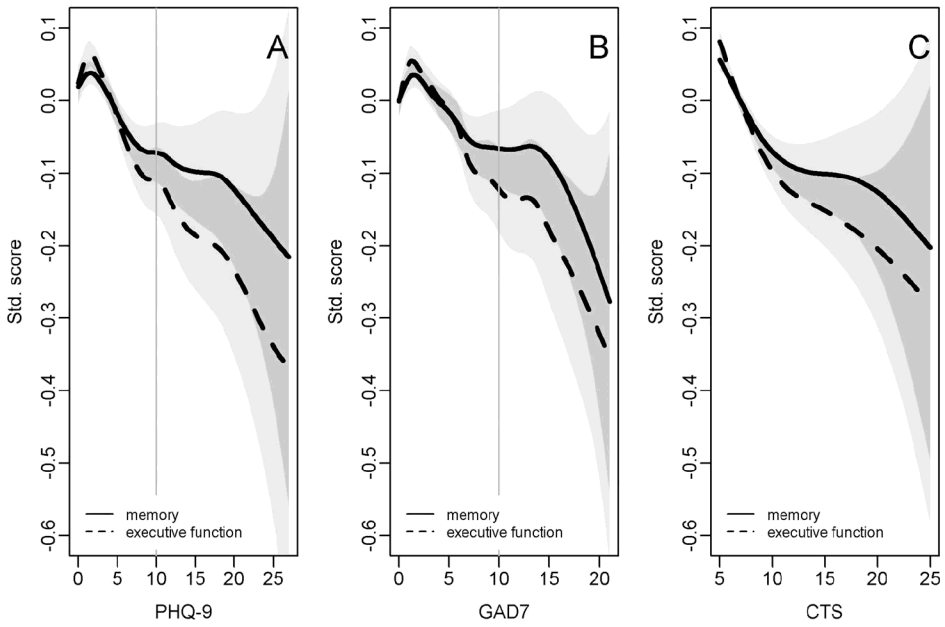

Figure 3. Depressive and anxiety symptoms and childhood trauma are associated with memory and executive function. *Note.* Estimates are derived from generalised additive models adjusted for age, sex, education and German language proficiency. Shaded areas mark 95% confidence intervals. Both memory and executive function score are associated with the respective psychiatric scale below clinically relevant levels (vertical line). Above clinically relevant levels, the association seems to be stronger for executive function compared to memory indicating a stronger sensitivity of executive function to disturbances of brain function by psychiatric disorders. (A) Association of the memory and executive function score with the Patient Health Questionnaire 9 -item depression module (PHQ-9) that measures depressive symptoms; (B) Association of the memory and executive function score with the Generalised Anxiety Disorder Screener (GAD7) measuring anxiety symptoms; (C) Association of the memory and executive function score with the Childhood trauma screener (CTS) assessing self-reported exposure to traumatic experiences during childhood. Grey vertical lines indicate cut-offs for moderate to severe symptoms levels on the respective scale. Std.: standardised.

Associations with psychiatric scales and self-reported neurological diseases

More depressive (PHQ-9) and anxiety (GAD7) symptoms were associated with lower cognitive functions (Figure 3; Supplementary Tables 6 and 7). GAM analyses revealed that below the cut-off demarcating moderate to severe symptom levels (<10 points) that could be clinically relevant, memory and executive functions showed similarly steep slopes for the association with both psychiatric scales. In individuals with moderate to severe symptom levels, in contrast, a stronger slope for the association of symptom levels with executive functions was found. A similar pattern was observed for more severe childhood trauma (CTS). Differences in memory and executive functions between individuals with and without moderate to severe symptom levels showed very small to small effect sizes in memory (PHQ-9: $d = -0.104$; GAD7: $d = -0.105$; CTS: $d = -0.088$) and executive function (PHQ-9: $d = -0.197$; GAD7: $d = -0.204$; CTS: $d = -0.131$). All scales were independently related to cognitive function as indicated by a multivariate analysis including all three scales as predictors in a single model.

Self-reported stroke ($N = 1679$) and epilepsy ($N = 1615$) were associated with lower memory (stroke: $d = -0.252$; epilepsy: $d = -0.229$) and executive function (stroke: $d = -0.389$; epilepsy: d=-0.246) scores (Figure 4; Supplementary Tables 6 and 7).

Association of German language proficiency with cognitive scores

All individual cognitive test scores and the memory and executive domain scores were lower in non-native German speakers and native speakers with an additional mother tongue compared with German native speakers (Supplementary Figure 1). Lower interviewer-rated language skills were associated with a lower cognitive performance. Associations were less pronounced with the digit span backwards, Stroop effect, and the difference of the immediate word list recall (trial 2) and the word list delayed recall (trial 3).

In addition, associations of age, education, and CTS with cognitive functions differed by German language proficiency (German native speaker, German and

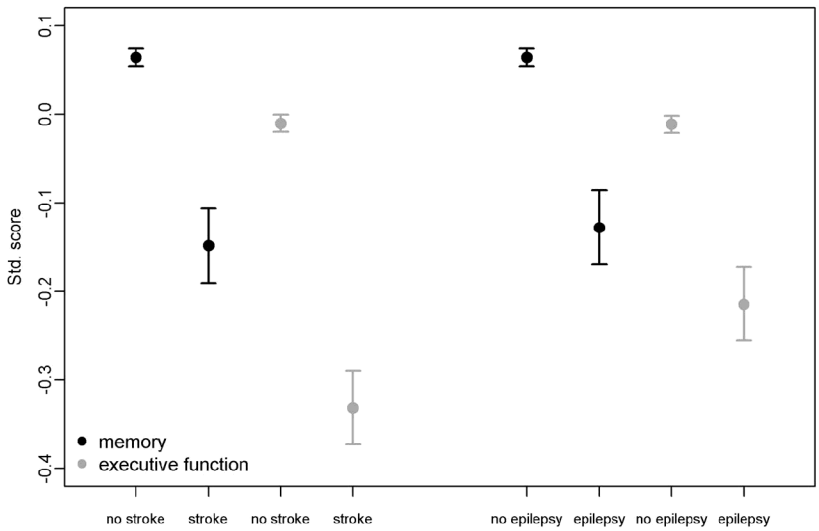

Figure 4. Association of self-reported neurological diseases with memory and executive function *Note*. Estimates and 95% confidence intervals are derived from generalised additive models adjusted for age, sex, education and German language proficiency. Std.: standardised.

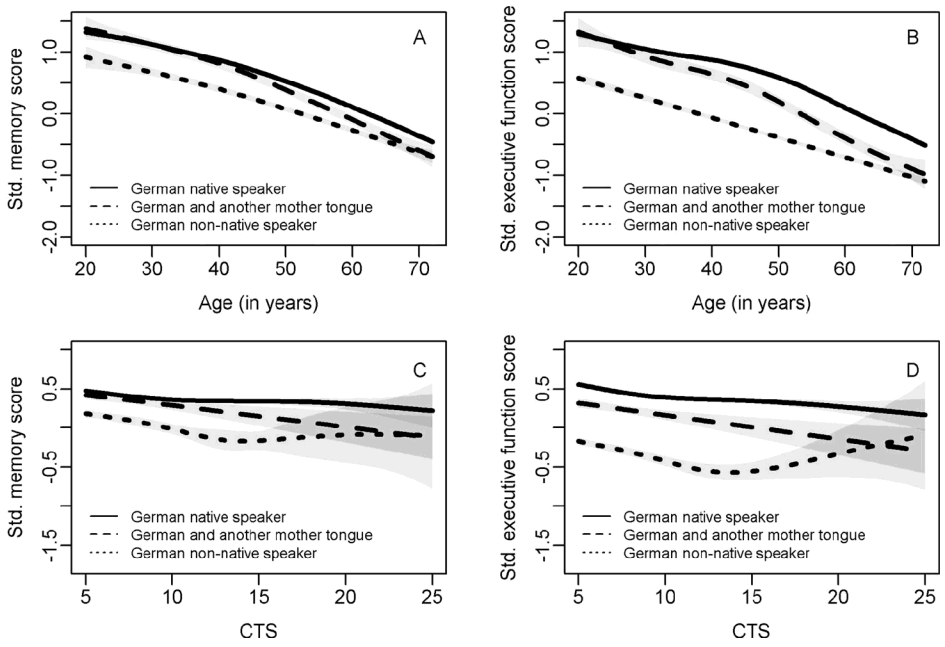

Figure 5. Association of age and CTS with memory and executive function depending on German language proficiency. *Note*. The association of the memory and executive function score with age and Childhood trauma screener (CTS) depend on German language proficiency. German native speakers with an additional mother tongue and non-native German speakers (dotted lines) show lower cognitive scores overall. In addition, the association of cognition with age is weaker in native speakers compared to the other two groups as indicated by lower slopes of the displayed trajectories. Similarly, the slopes of the association of the CTS with cognition differed depending on German language proficiency. (A) standardised memory score by age and language; (B) standardised executive function score by age and language; (C) standardised memory score by Childhood trauma screener (CTS) and language; (D) standardised executive function score by Childhood trauma screener (CTS) and language. Std: standardised.

another mother tongue, German non-native speaker; Figure 5; Supplementary Tables 8–11). There was no interaction between German language proficiency and sex, depressive symptoms (PHQ-9), anxiety (GAD7), or self-reported neurologic conditions, respectively (Supplementary Tables 8–13).

In order to illustrate the distribution of selected neuropsychological tests in the NAKO data freeze

100 K data, percentiles for Stroop task 2 and delayed word list recall stratified by age and sex are presented in Supplementary Tables 14 and 15, respectively. The Stroop task 2 was selected as it summarises processing speed, executive control, and inhibition ability. The delayed word list recall test was chosen as it represents a summary of learning and long-term memory retrieval of newly learned material.

Discussion

We calculated and tested cognitive domain scores for memory and executive function from the neuropsychological test battery of NAKO using the DF100K dataset. We found associations of higher scores for both cognitive domains with younger age, female sex, and higher education. In addition, lower cognitive scores were associated with more childhood trauma, depressive and anxiety symptoms, as well as a history of stroke or epilepsy. The observations are consistent with previous studies on factors associated with cognitive function in the general population (Castaneda et al. 2008, 2011; Hayat et al. 2014; Cullen et al. 2015; Wagner et al. 2018; Cornelis et al. 2019).

Descriptive analyses suggest that there are some differences in cognitive performance between NAKO study centres. Causes and mediators of these differences, such as regional socioeconomic differences, should be further explored in the complete NAKO sample. As expected, age was the single most important correlate of cognitive functions. The non-linear association indicates stronger age-related differences above the age of 50. The cross-sectional age differences will, in part, reflect age-related intra-individual cognitive changes; for example, a lower processing speed in older age (Salthouse 1996), or increasing levels of brain pathology. But only follow-up data that are currently being collected in NAKO will allow differentiating such intra-individual changes from inter-individual differences (e.g. cohort effects related to environmental and societal changes). Of note, linear regression analyses including a quadratic effect of age yielded almost identical results and effect sizes compared to the more complex GAM analyses, suggesting the former is a valid approach to examine and adjust for age-related effects in upcoming analyses of cognitive data in NAKO.

Female sex was associated with higher function in memory and, to a smaller degree, also in executive function. This is in line with previous reports from population-based studies (Hayat et al. 2014; Wagner et al. 2018). The direction of these sex differences could partially depend on the modality of assessment. While women usually show better verbal abilities, men often have better visuospatial abilities (Pauls et al. 2013). In line with this, men seem to perform slightly better in the L2-test of numerical reasoning in NAKO (Schmiedek et al. 2022). These modality-dependent cognitive sex differences stress the importance of sex as a covariate in analyses of cognitive functions.

Inter-individual differences were also found with regard to early life factors. Higher education was associated with better cognitive functions. Effects of education were slightly stronger for executive functions than for memory abilities. When growing up, cognitive abilities and education reciprocally influence each other (Lövdén et al. 2020). Of note, education level was associated to the cognitive domain scores with only a small to moderate effect size.

Besides factors associated with better cognitive function, the domain scores also showed associations with presumably detrimental conditions affecting early development. More reported traumatic experiences during childhood were associated with lower cognitive functions, even after controlling for current depressive and anxiety symptoms. Understanding the mechanisms contributing to this finding will be an aim of further research in NAKO. However, the effect size of the association was very small (f^2=0.004, d= −0.09) suggesting that the detected differences are most likely minor and do not have a noticeable effect on cognition on the individual level. Nevertheless, our findings demonstrate that early life experiences influence the cognitive function measured in adulthood and that the derived cognitive domain scores in NAKO are sensitive indicators for those influences.

The presence of depression and anxiety symptoms were associated with lower cognitive functions in NAKO. However, the effect sizes of cognitive differences between individuals with and without levels of depression or anxiety above cut-offs indicating moderate to severe symptom levels were very small to small and may not account for a considerable part of inter-individual differences in cognition on the population level. Although this is in line with previous reports from population-based studies (Castaneda et al. 2008, 2011; Cullen et al. 2015; Wagner et al. 2018), these results are also surprising given the considerably stronger effects reported in clinical samples (Rock et al. 2014). It might be explained by higher symptom severity in clinical samples. In addition, the simplistic application of a uniform cut-off to define clinically relevant symptom levels might yield more false positive classifications as compared to more elaborated

psychiatric diagnosis leading to a dilution of group contrasts. Further research in the NAKO sample will aim to shed light on our initial findings by studying the different available diagnostic approaches and the effects of cognitive function on the disabilities induced by psychiatric disorders.

Interestingly, both cognitive domain scores also seemed to be similarly sensitive to subclinical levels of these symptoms. This finding indicates that, even without levels of psychopathology that could be considered clinically relevant (i.e. below cut-offs indicating moderate to severe symptoms in PHQ-9 and GAD7), mood is linked to the levels of cognitive abilities. Cognitive functions may therefore form an integral part of human health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (World Health Organization 1946, p. 1). This supports previous claims (Deary and Batty 2007; Lubinski 2009) that understanding the determinants and effects of cognition could contribute to the identification of relevant factors and measures promoting health in the general population.

NAKO participants with moderate to severe levels of depression and anxiety had stronger decreases in executive function as compared to memory function. This is in line with previous meta-analyses (Castaneda et al. 2011; Ferreri et al. 2011; Lee et al. 2012; Rock et al. 2014) and shows that different brain functions indexed by the two cognitive domain scores are differentially affected by mental disorders. Similarly, a history of stroke was associated with larger impairments in executive functions than in memory, while impairments in the two domains were almost equally strong in individuals with a history of epilepsy. In consequence, cognitive functions, especially in the context of specific disorders, might not always constitute a uniform construct but can be characterised by specific impairments that are detectable by the NAKO cognitive domain scores. Despite this, a global cognitive composite score derived from all cognitive L1-tasks may be useful for some analytic purposes (e.g. when cognitive abilities are considered as a covariate), and the mean of executive function and memory domain scores can then be used to summarise cognitive function.

We found an association of lower cognitive performance with reports of a history of stroke or epilepsy as expected from previous research (Helmstaedter and Witt 2017; Tang et al. 2018). Further studies are required to determine modifying factors of the association between cognition and these conditions, such as, for instance, disease duration and severity, temporal distance to the event and medication effects. Building upon the results presented here, future research using NAKO data will investigate the association of cognition with other neurological conditions, such as Parkinson's disease or migraine.

Our analyses also revealed that the associations reported here might not be uniform across all subgroups of individuals within the NAKO study population. For instance, we showed that German language proficiency was strongly associated with the assessed cognitive scores and also influenced the associations of cognition with age, education, and childhood trauma. The main reason for this finding might be the importance of language comprehension for task performance, reaching beyond the mere understanding of test instructions. Lower language proficiency will render it more difficult to name animals during one minute, while making it possibly easier to name the colour of words in the Stroop interference trial, due to reduced automatic processing of the word meaning. Therefore, true cognitive function will likely be underestimated for non-native speakers of German. The slightly lower cognitive function in individuals reporting German and another language as their mother tongue most likely derives from associated confounding factors, like immigration history and resulting social disparities, and not from the fact that multiple languages are fluently spoken by these individuals.

Consequently, in future analysis, it will be important to include language proficiency as a covariate and, additionally, to check for effect modification. Otherwise, if the exposure of interest is related to language proficiency, there will be a risk for language-dependent bias in the examined associations. In case the exposure of interest is strongly correlated with language proficiency, it is advisable to focus on specific neuropsychological tests that are less strongly related to language proficiency.

Strength and limitations

A major strength is the large sample from the general population in multiple regions in Germany. In addition, the use of validated neuropsychological tests allows for a sensitive assessment of factors influencing cognition. Furthermore, advanced statistical techniques to take into account methodological problems (such as missing data, extreme values, and possible violation of interval scaling) were used to summarise cognitive function within each domain. Also, the comparison of results from GAM and linear regression

models allowed demonstrating the robustness of the identified findings from different model assumptions that may guide further analytic choices for NAKO cognition data. A limitation is the verbal assessment modalities for cognitive function that limits the validity for German non-native speakers. In addition, selective participation in the NAKO DF100K sample and the response proportion of ~18% (Schipf et al. 2020) could limit the generalisability of the presented results. Furthermore, when assessing the association of cognition with psychiatric and neurological conditions, we cannot ensure that the association derives from the condition itself. Instead, it is possible that the associations derived, for instance, from side effects of medical treatments and medication.

Conclusions

The NAKO neuropsychological test battery and the derived cognitive domain scores for memory and executive function are sensitive measures of cognition throughout the lifespan. Examining cognition in the NAKO baseline assessment and the upcoming follow-up will provide a valuable opportunity to determine the contribution and consequence of cognition for health in the general population. The presented analyses stress the importance of language proficiency, sex, and non-linear associations of age with cognition for use in future evaluations of cognitive function.

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Supplementary Material

The assessment of cognitive function in the German National Cohort (NAKO) – Associations of demographics and psychiatric symptoms with cognitive test performance

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Supplementary Table 1. Factor loadings from exploratory and confirmatory factor analysis

Neuropsychological test	Exploratory factor analysis (EFA)				Confirmatory factor analysis (CFA)			
	Loading memory factor		Loading executive factor		Loading memory factor		Loading executive factor	
	Est	SE	Est	SE	Est	SE	Est	SE
Immediate word list recall trial 1	0.725	0.004	0.099	0.005	2.340	0.013	-	-
Immediate word list recall trial 2	0.906	0.001	0.007	<0.001	4.047	0.029	-	-
Delayed word list recall trial 3	0.916	0.003	-0.046	0.004	3.319	0.020	-	-
Semantic fluency (animals)	0.011	0.002	0.590	0.004	-	-	1.307	0.011
Stroop task 1	0.089	0.006	-0.683	0.006	-	-	-1.291	0.011
Stroop effect (Stroop task2-task1)	-0.132	0.006	-0.408	0.006	-	-	-1.150	0.010
Digit span backwards	0.018	0.006	0.492	0.007	-	-	1.075	0.010

Note. In EFA both factors showed a correlation of 0.646, in the CFA model the correlation was 0.667. Est: Estimate; SE: standard error.

Supplementary Table 2. Associations of demographic variables with the memory score

	Generalized additive models (GAM)				Linear regression (OLS)			
Age (GAM: f^2=0.285; OLS: f^2=0.285)	edf	ref. df	F	p	Est	SE	t	p
Age	5.99	7.51	3578.72	<2.2E-308	0.00	0.00	-0.95	3.4E-01
Age²	-	-	-	-	0.00	0.00	-22.11	5.1E-108
	Est	SE	t	p	Est	SE	t	p
Sex (GAM: f^2=0.067; OLS: f^2=0.067)	-0.44	0.01	-79.35	<2.2E-308	-0.44	0.01	-79.35	<2.2E-308
Education (GAM: f^2=0.044; OLS: f^2=0.044)	Est	SE	t	p	Est	SE	t	p
Intermediate education	0.34	0.02	18.24	3.3E-74	0.34	0.02	18.23	3.8E-74
Higher education	0.67	0.02	36.72	3.9E-293	0.67	0.02	36.72	4.2E-293

Note. edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error.

Supplementary Table 3. Associations of demographic variables with the executive function score

	Generalized additive models (GAM)				Linear regression (OLS)			
Age (GAM: f^2=0.309; OLS: f^2=0.307)	edf	ref. df	F	p	Est	SE	t	p
Age	7.79	9.74	2981.37	<2.2E-308	0.02	0.00	10.93	8.6E-28
Age²	-	-	-	-	0.00	0.00	-34.67	9.2E-262
	Est	SE	t	p	Est	SE	t	p
Sex (GAM: f^2=0.028; OLS: f^2=0.028)	-0.28	0.01	-51.59	<2.2E-308	-0.28	0.01	-51.64	<2.2E-308
Education (GAM: f^2=0.067; OLS: f^2=0.067)	Est	SE	t	p	Est	SE	t	p
Intermediate education	0.41	0.02	22.51	6.6E-112	0.41	0.02	22.49	1.1E-111
Higher education	0.82	0.02	45.49	<2.2E-308	0.82	0.02	45.38	<2.2E-308

Note. edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error.

Supplementary Table 4. Interaction effects of demographic variables on the memory score

	Generalized additive models				Linear regression			
Interaction education x sex								
	Est	SE	t	p	Est	SE	t	p
Sex	-0.42	0.02	-24.39	5.1E-131	-0.42	0.02	-24.40	4.2E-131
Intermediate education	0.36	0.02	18.19	8.9E-74	0.36	0.02	18.18	9.4E-74
Higher education	0.67	0.02	34.22	5.3E-255	0.67	0.02	34.21	5.6E-255
Intermediate education x sex	-0.05	0.02	-2.76	5.7E-03	-0.05	0.02	-2.77	5.6E-03
Higher education x sex	0.00	0.02	0.07	9.5E-01	0.00	0.02	0.07	9.4E-01
	df1	df2	F	p	df1	df2	F	p
Interaction (GAM: f^2=0.0002; OLS: f^2=0.0002)	94322.09	1.98	11.57	1.0E-05	94328	2	11.60	9.2E-06
Interaction age x sex								
	Est	SE	t	p	Est	SE	t	p
Sex	-0.44	0.01	-79.44	<2.2E-308	-0.10	0.07	-1.38	1.7E-01
	edf	ref. df	F	p	Est	SE	t	p
Age	5.89	7.39	1688.90	<2.2E-308	1.2E-03	2.1E-03	0.54	5.9E-01
Age²	-	-	-	-	-3.6E-04	2.2E-05	-16.43	1.4E-60
Age x sex	2.62	3.28	45.31	1.1E-30	-8.0E-03	3.2E-03	-2.53	1.2E-02
Age² x sex	-	-	-	-	2.8E-05	3.2E-05	0.85	3.9E-01
	df1	df2	F	p	df1	df2	F	p
Interaction (GAM: f^2=0.002; OLS: f^2=0.002)	94319.19	4.89	30.84	7.3E-31	94328	2	72.14	4.9E-32
Interaction age x education								
	Est	SE	t	p	Est	SE	t	p
Intermediate education	0.34	0.02	18.25	3.0E-74	0.50	0.19	2.61	9.00E-03
Higher education	0.67	0.02	18.25	2.8E-291	0.91	0.20	4.64	3.57E-06
	edf	ref. df	F	p	Est	SE	t	p
Age	4.68	5.86	605.00	<2.2E-308	-1.3E-02	3.8E-03	-3.55	3.8E-04
Age²	-	-	-	-	-2.3E-04	4.1E-05	-5.59	2.3E-08
Age x Intermediate education	2.97	3.71	5.11	7.4E-04	1.6E-02	4.6E-03	3.45	5.6E-04
Age x Higher education	4.27	5.35	3.30	4.1E-03	1.3E-02	4.5E-03	2.93	3.4E-03
Age² x Intermediate education	-	-	-	-	-1.5E-04	4.9E-05	-3.01	2.6E-03
Age² x High education	-	-	-	-	-1.5E-04	4.8E-05	-3.20	1.4E-03
	df1	df2	F	p	df1	df2	F	p
Interaction (GAM: f^2=0.001; OLS: f^2=0.001)	94314.07	10.01	7.05	3.5E-11	94326	4	14.51	7.5E-12

Note. edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; df1: nominator degrees of freedom; df2: denominator degrees of freedom.

Supplementary Table 5. Interaction effects of demographic variables on the executive function score

	Generalized additive models				Linear regression			
Interaction education x sex								
	est	se	t	p	est	se	t	p
Sex	-0.23	0.02	-13.81	2.5E-43	-0.24	0.02	-14.01	1.5E-44
Intermediate education	0.44	0.02	23.14	3.8E-118	0.44	0.02	23.07	2.0E-117
Higher education	0.82	0.02	42.65	<2.2E-308	0.81	0.02	42.49	<2.2E-308
Intermediate education x sex	-0.10	0.02	-5.36	8.4E-08	-0.10	0.02	-5.19	2.1E-07
Higher education x sex	-0.02	0.02	-0.83	4.1E-01	-0.01	0.02	-0.64	5.2E-01
	df1	df2	F	p	df1	df2	F	p
Interaction (GAM: f^2=0.001; OLS: f^2=0.001)	94091.91	2.00	32.26	1.0E-14	94100	2	31.90	1.4E-14
Interaction age x sex								
	est	se	t	p	est	se	t	p
Sex	-0.28	0.01	-51.62	<2.2E-308	-0.07	0.07	-0.94	3.5E-01
	edf	ref. df	F	p	est	se	t	p
Age	7.91	9.88	1449.02	<2.2E-308	1.9E-02	2.1E-03	9.02	2.0E-19
Age²	-	-	-	-	-5.6E-04	2.2E-05	-25.85	8.9E-147
Age x sex	4.70	5.90	13.80	2.2E-15	-5.3E-03	3.1E-03	-1.69	9.1E-02
Age² x sex	-	-	-	-	2.2E-05	3.2E-05	0.68	5.0E-01
	df1	df2	F	p	df1	df2	F	p
Interaction (GAM: f^2=0.001; OLS: f^2=0.001)	94087.37	6.55	13.42	1.9E-16	94100	2	26.71	2.5E-12
Interaction age x education								
	est	se	t	p	est	se	t	p
Intermediate education	0.41	0.02	22.49	9.8E-112	-0.39	0.10	-3.79	1.5E-04
Higher education	0.82	0.02	45.29	<2.2E-308	0.09	0.10	0.93	3.5E-01
	edf	ref. df	F	p	est	se	t	p
Age	5.45	6.82	572.92	<2.2E-308	-8.7E-03	3.7E-03	-2.33	2.0E-02
Age²	-	-	-	-	-2.9E-04	4.1E-05	-7.23	4.7E-13
Age x Intermediate education	5.14	6.44	9.58	5.7E-11	3.2E-02	4.5E-03	7.10	1.2E-12
Age x Higher education	4.23	5.29	7.30	5.0E-07	3.2E-02	4.4E-03	7.29	3.1E-13
Age² x Intermediate education	-	-	-	-	-3.0E-04	4.8E-05	-6.33	2.5E-10
Age² x Higher education	-	-	-	-	-3.3E-04	4.7E-05	-7.06	1.7E-12
	df1	df2	F	p	df1	df2	F	p
Interaction (GAM: f^2=0.001; OLS: f^2=0.001)	94083.72	10.19	9.37	5.4E-16	94098	4	25.56	3.4E-21

Note. edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; df1: nominator degrees of freedom; df2: denominator degrees of freedom.

Supplementary Table 6. Associations of self-reported neurologic diseases and psychiatric scales with the memory score

	Generalized additive models					Linear regression					
Psychiatric scales: Univariate analysis											
	edf	ref. df	F	p	f2	Est	SE	t	p	d	n
PHQ-9	6.44	7.97	26.61	2.6E-41	0.002	-0.09	0.01	-8.22	2.0E-16	-0.104	87868
GAD7	6.80	8.23	17.27	2.7E-26	0.002	-0.09	0.01	-6.77	1.3E-11	-0.105	87660
CTS	3.54	4.35	70.28	1.5E-62	0.004	-0.07	0.01	-11.04	2.4E-28	-0.088	79675
Psychiatric scales: Multivariate analysis											
	edf	ref. df	F	p	f2	Est	SE	t	p	d	n
PHQ-9	4.01	5.08	11.04	9.1E-11	0.001	-0.05	0.01	-3.95	7.8E-05	-0.054	78992
GAD7	5.85	7.17	3.77	4.8E-04	0.000	-0.04	0.02	-2.47	1.3E-02	-0.041	78992
CTS	3.39	4.18	52.50	3.0E-45	0.003	-0.07	0.01	-9.77	1.6E-22	-0.078	78992
Neurological disorders											
	Est	SE	t	p	f2	Est	SE	t	p	d	n
stroke	-0.21	0.02	-10.01	1.4E-23	0.001	-0.21	0.02	-9.99	1.7E-23	-0.252	94172
epilepsy	-0.19	0.02	-8.99	2.6E-19	0.001	-0.19	0.02	-9.00	2.3E-19	-0.229	94220

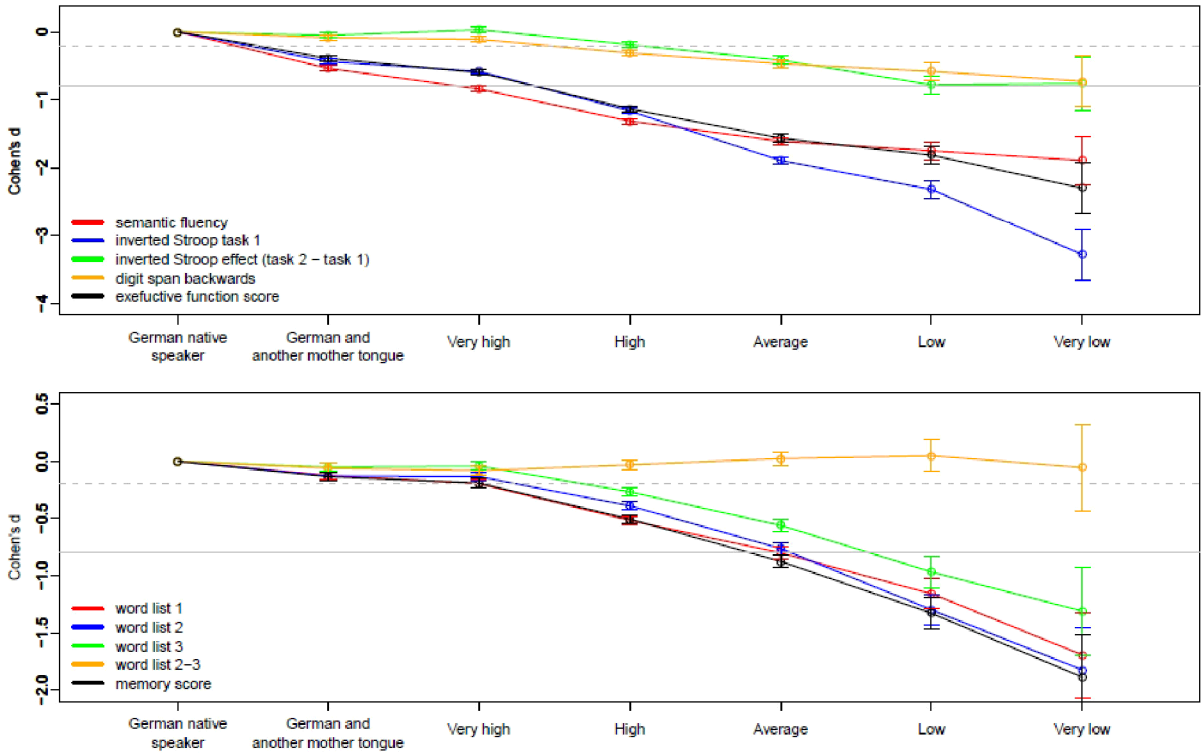
Note. Generalized additive models analysed the continuous relationship between the scales and cognitive scores. In linear regression models, scales were dichotomized according to established cut-offs (i.e. 10 for all scales, see method section). edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; f2: Cohen's f^2; d: Cohen's d; n: sample size; PHQ-9: Patient Health Questionnaire 9-item depression module; GAD7: Generalized Anxiety Disorder Screener; CTS: Childhood trauma screener.

Supplementary Table 7. Associations of self-reported neurologic diseases and psychiatric scales w the executive function score

	Generalized additive models					Linear regression					
Psychiatric conditions: Univariate analysis											
	edf	ref. df	F	p	f2	Est	SE	t	p	d	n
PHQ-9	8.32	10.12	58.79	3.0E-120	0.007	-0.16	0.01	-15.53	2.7E-54	-0.197	87630
GAD7	9.05	10.98	35.78	4.2E-77	0.005	-0.17	0.01	-13.22	7.3E-40	-0.204	87419
CTS	3.79	4.63	143.68	4.8E-136	0.008	-0.11	0.01	-16.45	9.9E-61	-0.131	79441
Psychiatric conditions: Multivariate analysis											
	edf	ref. df	F	p	f2	Est	SE	t	p	d	n
PHQ-9	6.08	7.57	20.73	1.5E-29	0.002	-0.10	0.01	-7.55	4.5E-14	-0.103	78756
GAD7	7.81	9.59	7.35	3.2E-11	0.001	-0.09	0.02	-5.62	1.9E-08	-0.092	78756
CTS	3.73	4.57	100.47	1.7E-93	0.006	-0.09	0.01	-14.27	3.6E-46	-0.114	78756
Neurological disorders											
	Est	SE	t	p	f2	Est	SE	t	p	d	n
stroke	-0.32	0.02	-15.38	2.4E-53	0.088	-0.32	0.02	-15.40	1.9E-53	-0.389	93950
epilepsy	-0.20	0.02	-9.71	2.9E-22	0.086	-0.20	0.02	-9.68	3.8E-22	-0.246	93991

Note. Generalized additive models analysed the continuous relationship between the scales and cognitive scores. In linear regression models, scales were dichotomized according to established cut-offs (i.e. 10 for all scales, see method section). edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; f2: Cohen's f^2; d: Cohen's d; n: sample size; PHQ-9: Patient Health Questionnaire 9-item depression module; GAD7: Generalized Anxiety Disorder Screener; CTS: Childhood trauma screener.

Supplementary Figure 1. Effect size of the association of German language proficiency with individual neuropsychological test and memory and executive function scores



Note. Effect size illustrate the difference in neuropsychological test scores between native speakers and either individuals with additional native languages (German and another mother tongue) or non-native German speakers with different degrees of German language proficiency shown on the x-axis. The plot in the top row shows test and scores assessing executive function, plot on the bottom shows tests assessing memory. Grey line indicate a large effect size (d=0.8), grey dotted line a small effect size (d=0.2). Effect sizes for the Stroop task were inverted so that negative Cohen's d values represent lower levels of performance.

Supplementary Table 8. Interaction effect of language abilities and demographic variables on the memory score

	generalized additive models				linear regression			
language x age								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.14	0.02	-7.76	8.5E-15	0.13	0.20	0.65	5.2E-01
non-native speaker	-0.41	0.01	-36.15	3.9E-284	-0.24	0.15	-1.57	1.2E-01
	edf	ref. df	F	p	Est	SE	t	p
age	6.07	7.61	3224.14	<2.2E-308	-2.8E-04	1.7E-03	-0.17	8.7E-01
age²					-3.7E-04	1.7E-05	-21.83	2.0E-105
age x German and another mother tongue	1.01	1.03	24.03	7.9E-07	-3.4E-03	9.0E-03	-0.38	7.0E-01
age x non-native speaker	2.03	2.55	9.16	4.5E-05	-1.2E-02	6.5E-03	-1.91	5.6E-02
age² x German and another mother tongue					-3.2E-05	9.7E-05	-0.34	7.4E-01
age² x non-native speaker					1.7E-04	6.7E-05	2.51	1.2E-02
	edf	ref. df	F	P	df1	df2	F	p
Interaction	94319.12	4.96	10.41	6.2E-10	94326	4	12.54	3.3E-10
language x sex								
	Est	SE	t	p	Est	SE	t	p
sex	-0.44	0.01	-75.63	<2.2E-308	-0.44	0.01	-75.62	0.0E+00
German and another mother tongue	-0.11	0.02	-4.74	2.1E-06	-0.11	0.02	-4.73	2.2E-06
non-native speaker	-0.42	0.01	-28.79	2.0E-181	-0.42	0.01	-28.76	3.6E-181
sex x German and another mother tongue	0.00	0.03	0.03	9.7E-01	0.00	0.03	0.04	9.7E-01
sex x non-native speaker	0.01	0.02	0.39	6.9E-01	0.01	0.02	0.39	7.0E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	94322.08	2.00	0.08	9.2E-01	94328	2	0.07	9.3E-01
language x education								
	Est	SE	t	p	Est	SE	t	p
Intermediate education	0.33	0.02	17.23	2.0E-66	0.33	0.02	17.22	2.4E-66
high education	0.66	0.02	34.25	1.7E-255	0.66	0.02	34.25	1.9E-255
German and another mother tongue	-0.09	0.04	-1.96	5.0E-02	-0.09	0.04	-1.97	4.9E-02
non-native speaker	-0.45	0.03	-16.59	9.7E-62	-0.45	0.03	-16.57	1.3E-61
Intermediate education x German and another mother tongue	-0.09	0.05	-1.81	7.0E-02	-0.09	0.05	-1.80	7.2E-02
Intermediate education x non-native speaker	-0.02	0.03	-0.58	5.6E-01	-0.02	0.03	-0.57	5.7E-01
high education x German and another mother tongue	0.02	0.05	0.47	6.4E-01	0.02	0.05	0.49	6.3E-01
high education x non-native speaker	0.08	0.03	2.51	1.2E-02	0.08	0.03	2.51	1.2E-02
	edf	ref. df	F	p	df1	df2	F	p
Interaction	94320.05	4.03	6.78	1.8E-05	94326	4	6.78	1.9E-05

Note. Generalized additive models analysed the continuous relationship between the scales and cognitive scores. In linear regression models, scales were dichotomized according to established cut-offs (i.e. 10 for all scales, see method section). edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; df1: nominator degrees of freedom; df2: denominator degrees of freedom.

Supplementary Table 9. Interaction effect of language abilities and psychiatric scales on the memory score

	generalized additive models				linear regression			
language x PHQ-9								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.09	0.02	-4.63	3.7E-06	-0.09	0.02	-4.44	9.0E-06
non-native speaker	-0.37	0.01	-30.71	4.8E-206	-0.37	0.01	-29.53	9.1E-191
	edf	ref. df	F	p	Est	SE	t	p
PHQ-9	6.45	7.98	23.09	1.7E-35	-0.08	0.01	-7.26	3.9E-13
PHQ-9 x German and another mother tongue	1.01	1.03	1.91	1.7E-01	-0.07	0.06	-1.32	1.9E-01
PHQ-9 x non-native speaker	1.01	1.02	0.27	6.0E-01	-0.02	0.04	-0.63	5.3E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	87842.04	2.30	0.99	3.8E-01	87856	2	1.02	3.6E-01
language x GAD7								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.09	0.02	-4.79	1.6E-06	-0.10	0.02	-5.31	1.1E-07
non-native speaker	-0.37	0.01	-30.72	4.4E-206	-0.37	0.01	-29.91	1.5E-195
	edf	ref. df	F	p	Est	SE	t	p
GAD7	6.81	8.23	14.87	2.8E-22	-0.09	0.01	-6.13	9.1E-10
GAD7 x German and another mother tongue	1.02	1.03	0.85	3.5E-01	0.08	0.07	1.09	2.8E-01
GAD7 x non-native speaker	1.00	1.01	1.02	3.2E-01	-0.05	0.04	-1.19	2.3E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	87633.80	2.28	0.87	4.3E-01	87648	2	1.39	2.5E-01
language x CTS								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.07	0.02	-3.46	5.4E-04	-0.06	0.02	-2.46	1.4E-02
non-native speaker	-0.33	0.01	-25.07	4.0E-138	-0.30	0.02	-18.91	1.3E-79
	edf	ref. df	F	p	Est	SE	t	p
CTS	3.64	4.47	54.46	3.3E-49	-0.07	0.01	-9.35	9.2E-21
CTS x German and another mother tongue	1.01	1.02	3.53	6.0E-02	-0.05	0.04	-1.21	2.3E-01
CTS x non-native speaker	3.45	4.25	5.85	7.5E-05	-0.11	0.03	-4.18	2.9E-05
	edf	ref. df	F	p	df1	df2	F	p
Interaction	79648.00	7.47	4.42	4.0E-05	79663	2	9.28	9.3E-05

Note. Generalized additive models analysed the continuous relationship between the scales and cognitive scores. In linear regression models, scales were dichotomized according to established cut-offs (i.e. 10 for all scales, see method section). edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; df1: nominator degrees of freedom; df2: denominator degrees of freedom; PHQ-9: Patient Health Questionnaire 9-item depression module; GAD7: Generalized Anxiety Disorder Screener; CTS: Childhood trauma screener.

Supplementary Table 10. Interaction effect of language abilities and neurologic disorders on the memory score

	generalized additive models				linear regression			
language x stroke								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.11	0.02	-6.26	4.0E-10	-0.11	0.02	-6.24	4.5E-10
non-native speaker	-0.42	0.01	-37.88	1.3E-311	-0.42	0.01	-37.87	1.9E-311
stroke	-0.21	0.02	-9.73	2.4E-22	-0.21	0.02	-9.71	2.9E-22
stroke x German and another mother tongue	-0.08	0.15	-0.57	5.7E-01	-0.08	0.15	-0.58	5.6E-01
stroke x non-native speaker	0.06	0.10	0.64	5.2E-01	0.06	0.10	0.64	5.2E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	94154.06	2.00	0.38	6.8E-01	94160	2	0.39	6.8E-01
language x epilepsy								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.11	0.02	-6.48	9.4E-11	-0.11	0.02	-6.46	1.1E-10
non-native speaker	-0.42	0.01	-38.03	4.5E-314	-0.42	0.01	-38.03	5.0E-314
epilepsy	-0.20	0.02	-8.99	2.5E-19	-0.20	0.02	-9.01	2.2E-19
eplilepsy x German and another mother tongue	0.05	0.14	0.36	7.2E-01	0.05	0.14	0.37	7.1E-01
eplilepsy x non-native speaker	0.13	0.10	1.26	2.1E-01	0.13	0.10	1.26	2.1E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	94202.00	2.00	0.84	4.3E-01	94208	2	0.85	4.3E-01

Note. edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; df1: nominator degrees of freedom; df2: denominator degrees of freedom.

Supplementary Table 11. Interaction effect of language abilities and demographic variables on the executive function score

	generalized additive models				linear regression			
language x age								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.38	0.02	-20.93	4.5E-97	0.53	0.19	2.72	6.6E-03
non-native speaker	-0.84	0.01	-76.04	<2.2E-308	0.22	0.15	1.50	1.3E-01
	edf	ref. df	F	p	Est	SE	t	p
age	7.97	9.96	2668.90	<2.2E-308	0.02	0.00	13.32	1.8E-40
age²					0.00	0.00	-35.95	3.7E-281
age x German and another mother tongue	1.01	1.02	84.02	3.9E-20	-0.03	0.01	-2.93	3.4E-03
age x non-native speaker	4.30	5.40	19.47	2.4E-20	-0.05	0.01	-8.30	1.0E-16
age² x German and another mother tongue					0.00	0.00	1.62	1.0E-01
age² x non-native speaker					0.00	0.00	8.96	3.3E-19
	edf	ref. df	F	P	df1	df2	F	p
Interaction	94086.80	7.11	27.67	7.2E-39	94098	4	46.46	4.5E-39
language x sex								
	Est	SE	t	p	Est	SE	t	p
sex	-0.28	0.01	-49.59	<2.2E-308	-0.28	0.01	-49.66	<2.2E-308
German and another mother tongue	-0.36	0.02	-15.53	2.6E-54	-0.36	0.02	-15.55	1.9E-54
non-native speaker	-0.87	0.01	-60.50	0.0E+00	-0.87	0.01	-60.75	0.0E+00
sex x German and another mother tongue	0.08	0.03	2.34	1.9E-02	0.08	0.03	2.32	2.1E-02
sex x non-native speaker	0.01	0.02	0.48	6.3E-01	0.01	0.02	0.55	5.8E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	94091.92	1.99	2.81	6.1E-02	94100.	2	2.78	6.2E-02
language x education								
	Est	SE	t	p	Est	SE	t	p
intermediate education	0.42	0.02	21.85	1.4E-105	0.42	0.02	21.83	2.3E-105
high education	0.82	0.02	43.34	<2.2E-308	0.82	0.02	43.25	<2.2E-308
German and another mother tongue	-0.24	0.04	-5.56	2.7E-08	-0.24	0.04	-5.51	3.6E-08
non-native speaker	-0.85	0.03	-32.05	3.6E-224	-0.85	0.03	-32.15	1.5E-225
intermediate education x German and another mother tongue	-0.15	0.05	-2.86	4.2E-03	-0.15	0.05	-2.94	3.3E-03
intermediate education x non-native speaker	-0.04	0.03	-1.31	1.9E-01	-0.04	0.03	-1.23	2.2E-01
high education x German and another mother tongue	-0.05	0.05	-0.99	3.2E-01	-0.05	0.05	-1.05	2.9E-01
high education x non-native speaker	0.00	0.03	0.15	8.8E-01	0.00	0.03	0.15	8.8E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	94089.90	4.01	3.62	5.9E-03	94098	4	3.63	5.9E-03

Note. edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; df1: nominator degrees of freedom; df2: denominator degrees of freedom.

Supplementary Table 12. Interaction effect of language abilities and psychiatric scales on the executive function score

	generalized additive models				linear regression			
language x PHQ-9								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.28	0.02	-15.34	5.0E-53	-0.29	0.02	-15.15	9.0E-52
non-native speaker	-0.80	0.01	-68.94	<2.2E-308	-0.82	0.01	-67.17	<2.2E-308
	edf	ref. df	F	p	Est	SE	t	p
PHQ-9	8.02	9.78	54.84	3.3E-107	-0.16	0.01	-14.86	7.3E-50
PHQ-9 x German and another mother tongue	1.02	1.03	0.11	7.6E-01	0.01	0.05	0.10	9.2E-01
PHQ-9 x non-native speaker	5.67	7.06	1.47	1.7E-01	0.04	0.04	1.09	2.8E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	87590.61	11.68	1.37	1.7E-01	87618	2	0.60	5.5E-01
language x GAD7								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.28	0.02	-15.47	6.6E-54	-0.29	0.02	-15.81	3.2E-56
non-native speaker	-0.81	0.01	-69.32	0.0E+00	-0.82	0.01	-68.36	0.0E+00
	edf	ref. df	F	p	Est	SE	t	p
GAD7	8.05	9.54	37.78	2.3E-70	-0.18	0.01	-13.01	1.1E-38
GAD7 x German and another mother tongue	1.02	1.04	0.03	8.4E-01	0.08	0.07	1.24	2.1E-01
GAD7 x non-native speaker	1.00	1.00	0.71	4.0E-01	0.07	0.04	1.59	1.1E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	87389.67	2.27	0.39	7.0E-01	87407	2	1.92	1.5E-01
language x CTS								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.24	0.02	-12.87	7.3E-38	-0.25	0.02	-10.96	6.3E-28
non-native speaker	-0.76	0.01	-59.84	<2.2E-308	-0.74	0.02	-47.83	<2.2E-308
	edf	ref. df	F	p	Est	SE	t	p
CTS	3.91	4.76	118.69	4.8E-116	-0.10	0.01	-14.72	5.5E-49
CTS x German and another mother tongue	1.01	1.02	1.17	2.8E-01	-0.01	0.04	-0.15	8.8E-01
CTS x non-native speaker	3.61	4.43	5.78	6.9E-05	-0.11	0.03	-4.02	5.8E-05
	edf	ref. df	F	p	df1	df2	F	p
Interaction	79412.97	6.49	4.79	3.9E-05	79429	2	8.08	3.1E-04

Note. edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; df1: nominator degrees of freedom; df2: denominator degrees of freedom; PHQ-9: Patient Health Questionnaire 9-item depression module; GAD7: Generalized Anxiety Disorder Screener; CTS: Childhood trauma screener.

Supplementary Table 13. Interaction effect of language abilities and neurologic scales on the executive function score

	generalized additive models				linear regression			
language x stroke								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.32	0.02	-18.71	5.6E-78	-0.32	0.02	-18.76	2.3E-78
non-native speaker	-0.86	0.01	-79.95	<2.2E-308	-0.87	0.01	-80.25	<2.2E-308
stroke	-0.33	0.02	-15.15	8.9E-52	-0.33	0.02	-15.18	5.9E-52
stroke x German and another mother tongue	-0.07	0.15	-0.46	6.4E-01	-0.07	0.15	-0.48	6.3E-01
stroke x non-native speaker	0.16	0.10	1.61	1.1E-01	0.17	0.10	1.67	9.5E-02
	edf	ref. df	F	p	df1	df2	F	p
Interaction	93929.92	2.00	1.43	2.4E-01	93938	2	1.53	2.2E-01
language x epilepsy								
	Est	SE	t	p	Est	SE	t	p
German and another mother tongue	-0.33	0.02	-19.02	1.8E-80	-0.33	0.02	-19.07	6.9E-81
non-native speaker	-0.86	0.01	-79.83	<2.2E-308	-0.87	0.01	-80.12	<2.2E-308
epilepsy	-0.21	0.02	-9.74	2.2E-22	-0.21	0.02	-9.71	2.7E-22
epilepsy x German and another mother tongue	0.23	0.14	1.65	1.0E-01	0.23	0.14	1.65	1.0E-01
epilepsy x non-native speaker	0.06	0.10	0.64	5.2E-01	0.06	0.10	0.67	5.1E-01
	edf	ref. df	F	p	df1	df2	F	p
Interaction	93970.86	2.00	1.52	2.2E-01	93979	2	1.54	2.1E-01

Note. edf: effective degrees of freedom; ref. df: reference degrees of freedom; p: p-value; Est: Estimate; SE: standard error; df1: nominator degrees of freedom; df2: denominator degrees of freedom.

Supplementary Table 14. Percentiles of word list delayed recall (trial 3; number of recalled words) score by sex and age group.

Sex / Age group		Delayed recall performance relative to age- and sex matched peers						
		≥2.5%	≥10%	≥25%	≥50%	≥75%	≥90%	≥97.5%
		Percentile of raw scores (words)						
		2.5th	10th	25th	50th	75th	90th	97.5th
Men	N							
20-29	2919	5	7	8	10	11	12	12
30-39	4122	5	6	8	9	11	12	12
40-49	9272	4	5	7	8	10	11	12
50-59	12434	3	5	6	8	9	10	12
60-72	14904	2	3	5	6	8	9	11
Women	N							
20-29	3897	6	8	9	11	12	12	12
30-39	4961	6	7	9	10	12	12	12
40-49	11448	5	7	8	10	11	12	12
50-59	14922	4	6	7	9	10	11	12
60-72	15481	3	4	6	8	9	10	12

Note. Higher raw scores in this task reflect better memory performance. Example: a woman age 55 able to recall 6 out of 12 words performs same or better than the lower 10% of women of her age group. The median performance is the 50th percentile.

Supplementary Table 15. Percentiles of the Stroop task 2 (seconds needed to complete the incongruent condition, that is naming the ink colour of 36 incongruently printed colour words) by sex and age group.

Sex / Age group		Stroop incongruent word-colour naming performance relative to age- and sex-matched peers						
		≥2.5%	≥10%	≥25%	≥50%	≥75%	≥90%	≥97.5%
		Percentile of raw scores (seconds)						
		97.5th	90th	75th	50th	25th	10th	2.5th
Men	N							
20-29	2902	54	44	38	33	29	25	22
30-39	4059	59	48	41	35	31	27	24
40-49	9171	67	52	44	38	33	29	25
50-59	12279	72	56	48	41	35	31	27
60-72	15088	101	68	56	47	40	36	31
Women	N							
20-29	3906	51	42	37	32	28	25	22
30-39	4995	56	46	39	34	30	27	24
40-49	11493	60	49	42	36	31	28	25
50-59	14981	69	54	46	39	34	30	27
60-72	15773	90	63	53	45	39	34	30

Note. Higher raw scores in this task reflect lower (worse) performance. Example: a woman age 55 needing 30 seconds performs same or better than 90% of all women of her age group. The median performance is the 50th percentile.