Genetic and Lifestyle Predictors of 15-Year Longitudinal Change in Episodic Memory

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OBJECTIVES: To reveal distinct longitudinal trajectories in episodic memory over 15 years and to identify demographic, lifestyle, health-related, and genetic predictors of stability or decline.

DESIGN: Prospective cohort study.

SETTING: The Betula Project, Umeå, Sweden.

PARTICIPANTS: One thousand nine hundred fifty-four healthy participants aged 35 to 85 at baseline.

MEASUREMENTS: Memory was assessed according to validated episodic memory tasks in participants from a large population-based sample. Data were analyzed using a random-effects pattern-mixture model that considered the effect of attrition over two to four longitudinal sessions. Logistic regression was used to determine significant predictors of stability or decline relative to average change in episodic memory.

RESULTS: Of 1,558 participants with two or more test sessions, 18% were classified as maintainers and 13% as decliners, and 68% showed age-typical average change. More educated and more physically active participants, women, and those living with someone were more likely to be classified as maintainers, as were carriers of the met allele of the catechol-O-methyltransferase gene. Less educated participants, those not active in the labor force, and men were more likely to be classified as decliners, and the apolipoprotein E ε4 allele was more frequent in decliners.

CONCLUSION: Quantitative, attrition-corrected assessment of longitudinal changes in memory can reveal substantial heterogeneity in aging trajectories, and genetic and lifestyle factors predict such heterogeneity. **J Am Geriatr Soc 2012.**

Key words: cognitive aging; assessment of cognitive disorders/dementia; attrition; cohort studies; memory

Memory and other higher-order cognitive functions decline with advancing age,[1–3] but there is considerable interindividual variability,[4] such that some elderly adults have atypically large decline, whereas others deviate by having strikingly high performance levels.[5] Accelerated decline has been much studied and linked to pathology such as dementia diseases.[6,7] By contrast, despite the fact that the concept of "successful aging" was introduced some 25 years ago,[8] factors determining well-preserved cognition in older age remain less well characterized,[9] probably because of the complexity of identifying relevant subgroups.

A cross-sectional approach to successful cognitive aging has been to select the best-performing individuals in an elderly sample,[10] but without younger individuals, this approach remains silent as to whether high-performing elderly adults have preserved levels of performance.[4] Longitudinal studies offer a more-direct assessment of preserved functioning but vary greatly in their estimates of the proportion of elderly adults who maintain high levels of cognitive performance.[4,9,11] Multiple factors might contribute to between-study discrepancies, including duration, age of participants, method of measuring cognition, and the statistical model. There is evidence of attrition causing severe positive bias,[11–14] because those remaining in the study have systematically better cognitive performance than those dropping out. Furthermore, if participants with a more-rapid decline in memory performance tend to drop out earlier from the study, the attrition is related to this progression and hence is not ignorable.[15] In contrast to prior longitudinal studies, which considered attrition to be missing at random (ignorable) when classifying individuals into groups based on their cognitive performance,[9,11] the

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approach of the current study allows for attrition to be nonignorable.

Herein are presented analyses of 15-year change in memory estimated over four measurement points. Memory was assessed using validated episodic memory tasks sensitive to mild cognitive deficits[16] rather than global screening tasks.[17] Data from a large population-based sample[16,18] were analyzed using a random-effects pattern-mixture model that considered the effect of attrition.[15,19] As a second step, multivariable logistic regressions were used, with the binary responses maintainer vs average and decliner vs average to identify demographic, lifestyle, health-related, and genetic determinants of different trajectories of age-related change in episodic memory.[9] A limited selection of genetic variants previously related to episodic memory were focused on (apolipoprotein E (APOE), kidney and brain expressed protein (KIBRA, or WW domain-containing protein 1), brain-derived neurotrophic factor (BDNF), catechol-O-methyltransferase (COMT)).[20]

METHODS

Study Population

Participants were 1,954 healthy adults (55% female) from the Betula project.[16,18] At recruitment to the study, participants were divided into 10 age cohorts at 5-year intervals (35, 40, 45, … 85). Each cohort comprised roughly 200 individuals, with the exception of the youngest (n = 100) and oldest (n = 70) cohorts. Betula participants were recruited using random selection based on the names in the population register of Umeå, a city in northern Sweden with approximately 110,000 inhabitants. Details regarding selection procedures have previously been described.[18] The participants were tested at baseline and at Years 5, 10, and 15.

Although the study was based on a random sample, attrition was expected to be nonignorable with respect to memory (see Table 1 for statistics on attrition), and that had to be addressed in the statistical analysis. Reasons for attrition were death, withdrawal, moving out of the area, sickness and dementia, no contact, and unknown or unspecified reasons.

The Regional Ethical Vetting Board at Umeå University approved this study (approval no. 870303, 97–173, 221/97, 97–173, 03–484, 01–008, 169/02, 02–164, 03–484, 05–082M and 08–132M). Written informed consent was obtained from all participants.

Cognitive Measure

The episodic memory measure was a composite of five tasks: immediate free recall of 16 visually and orally presented short sentences, delayed cued recall of nouns from the previously presented sentences, immediate free recall of 16 enacted sentences, delayed cued recall of nouns from the enacted sentences, and immediate free recall of a list of 12 orally presented nouns. Two alternate sets of sentences and nouns were used in the first four measures, and four sets were used in the fifth measure. The procedures and tests have been fully described previously.[18] The episodic memory test score can a priori range between 0 and 76, with a higher score indicating better episodic memory.

Baseline Characteristics

Baseline demographic characteristics were age and sex. Self-reported lifestyle characteristics were years of education, labor force participation, and whether the participant was living with someone. Baseline health characteristics were self-reported health (feeling well) and whether the participant had engaged in some physical activities during the previous 3 months. Finally, participants were categorized according to memory-relevant genetic information: APOE genotype (presence or absence of the ε4 allele), KIBRA genotype (categorized as T-allele carriers or CC genotype carriers), BDNF genotype (categorized as met allele carriers or val/val homozygotes), and COMT genotype (categorized as met allele carriers or val/val homozygotes). A summary of all baseline characteristics is shown in Table 1.

Table 1. Characteristics of Study Population According to Dropout Pattern

Characteristic	Group 1, n = 396	Group 2, n = 372	Group 3, n = 315	Group 4, n = 871
Episodic memory score, mean ± SD				
Year 0	24.8 ± 11.0	30.0 ± 10.5	33.0 ± 10.2	38.3 ± 8.8
Year 5	–	26.7 ± 11.8	32.8 ± 10.9	39.3 ± 9.2
Year 10	–	–	29.4 ± 12.1	39.0 ± 9.7
Year 15	–	–	–	36.8 ± 11.2
Age, mean ± SD	69.2 ± 13.8	65.9 ± 12.9	60.9 ± 13.4	51.8 ± 10.8
Education, mean ± SD	8.2 ± 4.7	8.7 ± 3.5	9.6 ± 3.8	11.2 ± 4.0
Female, n (%)	226 (57)	190 (51)	170 (54)	488 (56)
Feeling well, n (%)	258 (65)	276 (74)	248 (79)	696 (80)
Not working, n (%)	274 (69)	220 (59)	151 (48)	159 (18)
Living with someone, n (%)	222 (56)	251 (67)	237 (75)	725 (83)
Physical activity, n (%)	273 (69)	323 (87)	282 (90)	814 (93)
Apolipoprotein E, ε4, n (%)	102 (26)	108 (29)	98 (31)	248 (28)
Kidney and brain expressed protein, t-carrier, n (%)	128 (32)	179 (48)	153 (49)	451 (52)
Brain-derived neurotrophic factor, val/val, n (%)	159 (40)	233 (63)	190 (60)	540 (62)
Catechol-*O*-methyltransferase, met-carrier, n (%)	179 (45)	268 (72)	225 (71)	667 (77)

Participants were stratified into four groups on the basis of their last available measurement: Group 1, participants dropping out after the first test wave; Group 2, after the second; Group 3, after the third; and Group 4, participants continuing through the fourth test wave.
SD = standard deviation.

Statistical Analysis

The purpose was to classify individuals into groups based on baseline level and estimated rate of change for the episodic memory composite and to find predictors for group membership. A pattern mixture modeling approach, which uses random coefficients to take into account nonignorable dropout, was used to address attrition.[15] As a first step, participants were combined into four groups on the basis of their last available measurement: Group 1 with pattern {1,0,0,0}; Group 2 with pattern {1,1,0,0}; Group 3 with patterns {1,1,1,0} or {1,0,1,0}; and Group 4 with patterns {1,1,1,1}, {1,0,1,1}, {1,1,0,1}, or {1,0,0,1}, where 0 indicates missing and 1 indicates observed for each of the four time points of observation. This resulted in four groups representing a monotone missing-data pattern. (It was assumed that intermittent missing observations are missing at random.) An intercept and a linear slope regressing episodic memory score against time were further estimated using ordinary least squares for each of the 1,558 participants with more than one observation, because an estimate of the rate of change requires at least two observations.

The overall average rate of change in episodic memory, taking into consideration nonignorable dropout, which is a weighted average of the expected slope for each of the missing data patterns, was of primary interest. The estimated individual slopes were modeled as a linear function of dropout group, age (modeled as a continuous variable), and baseline episodic memory score; interaction effects between dropout group and age and between dropout group and baseline episodic memory score were also allowed for. Because of differences in variances between dropout patterns, the parameters in this model were estimated using weighted least squares and were all found significant ($P < .001$). A formal presentation of the model and estimated model parameters are presented in Appendix S1.

Based on the above analysis corrected for attrition, three groups of participants were defined based on how their baseline episodic memory score and estimated rate of change in episodic memory compared with those of an average participant. A maintainer was defined as a participant with a moderate to high baseline score and a better-than-average rate of change, and vice versa for a decliner. Predicted final score (estimated memory score at Year 15), defined as baseline score plus rate of change multiplied by 15, was considered for this purpose. Individual final score was also compared with the final score of a participant with average baseline score and average overall rate of change within a given age cohort. Average baseline scores were estimated using all available baseline scores, including scores from participants dropping out at the second test wave. Individuals exceeding the predicted final score by one standard deviation (SD) (different SDs are used for the different dropout patterns) were classified as maintainers (≥ 1 SDs above) or decliners (≥ 1 SDs above). Participants not classified as maintainers or decliners were classified as average.

In the second step of the analysis, predictors of belonging to the groups of maintainers or decliners were identified. For this purpose, multivariable logistic regressions were performed with the responses maintainer vs average and decliner vs average and the covariates listed in Table 1. Participants with missing covariates were omitted. No interactions between age and not working or between age and living with someone were found, so they were excluded from subsequent analyses. Odds ratios with corresponding 95% confidence intervals were estimated. All analyses were performed using software R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Dropout Groups 2 and 3 had significantly more negative rate of change than participants with complete data in the pattern mixture model, indicating that attrition was not ignorable. Moreover, dropout group interacted with age and baseline episodic memory score such that, for older participants with a low baseline score, the dropout effect was stronger and related to a more-negative rate of change in episodic memory, whereas for younger participants with higher baseline scores, the dropout effect was related to minor decline or even a positive rate of change (results available in Appendix S1).

Of the 1,558 participants with two or more measures, 285 (18%) were classified as maintainers and 209 (13%) as decliners, leaving 1,064 (68%) in the average group. Average memory scores at the four measurement occasions are shown in Figure 1A; SDs varied only a little (~10) between groups and over time. The attrition-corrected analysis classified 21% as maintainers and only 10% as decliners in participants with complete data. This can be compared with an analysis using only complete cases, which yields 15% maintainers and 15% decliners; see Figure 1B for a comparison of the two analyses. By taking into account attrition, asymmetry was obtained in the amount of maintainers and decliners because the correction shifts the overall rate of change.

The results of the multivariable analysis, controlled for age, are summarized in Table 2. Education, physical activity, sex, living status and COMT-met carrier were found to be significant predictors when contrasting maintainers with average participants. In particular, participants who were more educated, more physically active, female, and living with someone were more likely to be classified as maintainers, as were carriers of the met allele of the COMT gene. Participants who were less educated, not active in the labor force, and male were more likely than average participants to be classified as decliners. Also, participants with the APOE ε4 allele were more likely to be decliners.

A sensitivity analysis was performed to test the robustness of the results to the thresholds used for classification. Thresholds were set to 0.8 SDs and 1.2 SDs, yielding 23% and 14%, respectively, in the maintainer group and 18% and 10%, respectively, in the decliner group. The more-liberal thresholds caused physical activity and COMT-met carrier to become nonsignificant when comparing maintainers with average; similar results for decliners vs average were found. For the stricter thresholds, sex was no longer significant for decliners vs average, otherwise similar results were found.

DISCUSSION

These results provide evidence for substantial heterogeneity in how episodic memory changes over a 15-year period.

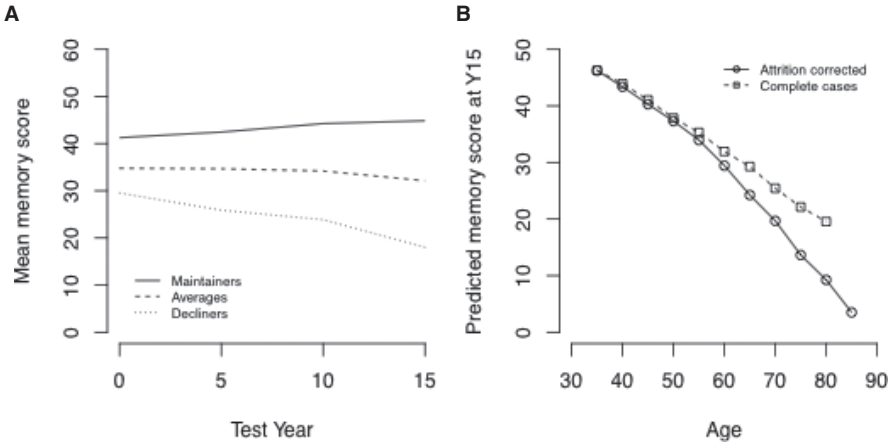

Figure 1. (A) Average test scores for 1,558 participants: maintainers, average performers, and decliners. Missing values after dropout are predicted using individual baseline test score and average slope for the memory performance group they belong to. (B) Comparison of predicted episodic memory score at Year 15 for complete cases, with and without attrition correction.

Table 2. Multivariable Logistic Regression Analyses with All Characteristics Listed When Controlling for Age

	Maintainers vs Average	Decliners vs Average
Characteristic	Odds Ratio (95% Confidence Interval) *P*-value	
Education	1.15 (1.09–1.20) <.001	0.91 (0.86–0.96) <.001
Male	0.43 (0.32–0.64) <.001	1.53 (1.08–2.16) .02
Feeling well	1.05 (0.69–1.59) .81	0.79 (0.54–1.17) .24
Not working	0.71 (0.36–1.04) .17	1.72 (1.04–2.84) .04
Lives with someone	1.73 (1.15–2.62) .009	0.74 (0.49–1.13) .16
Physical activity	2.19 (1.21–5.93) .02	0.98 (0.55–1.75) .96
Apolipoprotein E, ε4	1.12 (0.92–1.86) .50	1.84 (1.30–2.59) <.001
Kidney and brain expressed protein, t-carrier	0.87 (0.65–1.24) .37	0.98 (0.70–1.36) .89
Brain-derived neurotrophic factor, val/val	1.25 (0.90–1.72) .18	0.87 (0.62–1.23) .44
Catechol-*O*-methyltransferase, met-carrier	1.78 (1.17–2.69) .007	1.00 (0.67–1.49) >.99

The majority of individuals (greater than two-thirds of the examined sample) showed a pattern of decline typical for their age group according to the applied statistical threshold; 18% of the remaining participants were classified as maintainers, with high, stable memory performance over time, and 13% as decliners, with faster memory decline than the mean of their age groups. The observation that 18% of the examined participants were classified as maintainers indicates that previous definitions of successful aging as the upper 30% of a sample[9] may be overly liberal. Still, 18% is considerably higher than some previous estimates.[4] The proportion of decliners found is similar to proportions found in previous longitudinal studies. Although the frequency of maintainers and decliners is in any study bound to be dependent on the cognitive test used and the choice of an arbitrary threshold, the approach used in the current study to define maintaining (and declining) memory ability takes into account baseline performance and change over time. Although it might appear from Figure 1A that maintainers differed from the average group mainly in that they have a higher baseline memory ability, this is because all age cohorts were averaged in the figure. In the younger cohorts, maintainers had a more-positive slope than the average group, whereas in the older cohorts, average participants had a more-declining slope than maintainers (results available upon request from authors). Attrition was found to be substantial over the 15-year period examined. This longitudinal study allowed for nonignorable attrition. The attrition correction shifted the overall rate of change, which yielded a higher estimated proportion of maintainers than of decliners. It was found that the attrition effect was stronger in older, lower-performing participants, whereas younger, higher-performing participants showed less strong effects, which is consistent with previous research.[11,12] These differences might be explained as different missing data patterns caused by differences in reasons for nonparticipation. The proposed model can be implemented using standard statistical software and can be used for other cognitive domains and applied to other episodic tasks.

The analysis of predictors of group status identified significant factors for maintained performance and accelerated decline. Maintainers had a higher level of education than average participants. Education is typically a strong predictor of memory performance,[4] and it has been suggested that education may convey some form of "cognitive reserve" that serves as a buffer against decline.[21] There was a higher proportion of women in the maintainer group, which is in accordance with previous cross-sectional findings.[22] The basis for the female memory superiority remains unclear, but might be related to many aspects of central nervous system functioning.[23] The maintainers reported being more physically active, which is consistent with reports that physically fit older adults have better cognition[24] and less age-related brain change.[25] Maintainers were also more likely to be living with someone, which may reflect the positive influence of social stimulation on neurocognitive functioning.[26] Finally, of the genetic polymorphisms examined, there were more COMT-met carriers in the maintainer group. This observation is indicative of a role of dopamine

in successful episodic memory aging.[27] Low education and male sex predicted being classified as a decliner, which complements the findings related to success. Another predictor of decline was not being active in the labor force. Finally, there was an overrepresentation of APOE ε4 carriers in the declining group, which is consistent with previous findings.[28] To the degree that accelerated episodic memory decline, as identified here, relates to forthcoming dementia, the higher proportion of ε4 carriers may reflect the role of APOE ε4 as a genetic risk factor for Alzheimer's disease.[29] Some characteristics (subjective well-being, KIBRA, BDNF) did not predict group status. There are several potential explanations for the negative findings, including power concerns, because previous work indicates that isolated genes have modest effect sizes.[20]

A potential limitation of this study is that change in episodic memory was assumed to be a linear function of time. In many cases, this is a reasonable assumption, but nonlinear relationships are also of relevance and are something the model did not take into consideration.

CONCLUSION

In summary, using a large sample of randomly selected, representative individuals, the present work provides evidence of substantial heterogeneity in aging trajectories. The identification of individuals who maintain good episodic memory over time may contribute to the study of protective factors (e.g., physical activity was identified here), and the identification of predictors of decline may have implications for attempts at early diagnosis of age-related diseases such as dementia.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. The Model and Classification Procedure.