RESEARCH PAPER

Do I lose cognitive function as fast as my twin partner? Analyses based on classes of MMSE trajectories of twins aged 80 and older

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Abstract

Background: Aging is associated with an increasing risk of decline in cognitive abilities. The decline is, however, not a homogeneous process. There are substantial differences across individuals although previous investigations have identified individuals with distinct cognitive trajectories. Evidence is accumulating that lifestyle contributes significantly to the classification of individuals into various clusters. How and whether genetically related individuals, like twins, change in a more similar manner is yet not fully understood.

Methods: In this study, we fitted growth mixture models to Mini Mental State Exam (MMSE) scores from participants of the Swedish OCTO twin study of oldest-old monozygotic and same-sex dizygotic twins with the purpose of investigating whether twin pairs can be assigned to the same class of cognitive change.

Results: We identified four distinct groups (latent classes) whose MMSE trajectories followed different patterns of change over time: two classes of high performing individuals who remained stable and declined slowly, respectively, a group of mildly impaired individuals with a fast decline and a small group of impaired individuals who declined more rapidly. Notably, our analyses show no association between zygosity and class assignment.

Conclusions: Our study provides evidence for a more substantial impact of environmental, rather than genetic, influences on cognitive change trajectories in later life.

Keywords: Cognitive trajectories, Growth Mixture Models, older people, Twins

Key Points

- Data Swedish oldest-old twin study
- sample classified by longitudinal MMSE scores
- results suggest the minor role of genetics

Introduction

Twins provide a unique and valuable source of information to better estimate the relative importance of genetic and environmental influences on various traits and functions. However, it is becoming increasingly apparent that the genetic setup can account only for a portion of the observed variance in most processes related to development, function and disease. Monozygotic (MZ) twin pairs, share identical DNA sequences but are often discordant, indicating that the same genotype can produce distinct phenotypes [1, 2]. This suggests the involvement of environmental influences and gene-environmental (GxE) interactions. It is, therefore, quite unlikely that the unique sequence of our genomes provides the full blueprint for observed traits and functioning.

Cognitive health and functioning are domains shown to be influenced by genetics as well as modifiable environmental risk factors. Twin studies agree that cognitive abilities are quite heritable also in later life [3, 4]. Yet, differences exist related to the specific ability under study. Analyses of subgroups defined by their actual cognitive level can present a more differential picture. For example, analyses by Petrill *et al.* [5] showed high heritability for the high end of the distribution, but very low heritability at the low-performance continuum. Longitudinal studies have shown that the E4 variant of the Apolipoprotein E allele is associated with greater cognitive decline among individuals without dementia and that those with two $\epsilon 4$ alleles are at higher risk of developing dementia [6, 7]. Furthermore, the emerging literature on genome-wide association studies extends the evidence in support of the role of genetics on AD, identifying multiple loci associated with increased risk for AD [8, 9].

Evidence shows that healthy lifestyle behaviours have a protective role. Individuals who engage in these behaviours typically have better cognition and decline at a slower rate than those with a less healthy lifestyle [10–19]. For instance, non-smokers, individuals who engage in cognitively stimulating activities and those physically active tend to lose their cognitive functions at a slower rate than smokers and those who do not engage in stimulating activities [10–19]. However, results on the role of lifestyle are not always consistent, with some other studies failing to find evidence about the protective role of healthy lifestyle behaviours on cognitive function [20].

Notably, these studies have often neglected the heterogeneity in cognitive trajectories. The question is whether a classification of individuals into different subgroups can inform about the relative contribution of environmental and genetic influences.

Several studies have employed growth mixture modelling (GMM) [21] to improve knowledge about heterogeneity in aging-related cognitive trajectories [22–25]. Yet, research efforts focusing specifically on the oldest old (i.e. those aged 80 years and older) is limited, particularly in twins.

In this paper, we used data from the OCTO Twin Study, a longitudinal study of Swedish twins aged 80 and older, to examine whether: we can identify distinct classes of

individuals with similar Mini Mental State Exam (MMSE, [23]) trajectories, pairs of MZ twins are more likely than pairs of same-sex dizygotic (DZ) twins to be assigned to the same class and modifiable risk factors are associated with the assignment of individuals into various classes.

Analytical Methods

OCTO twin study

We used data from the Origins of Variance in the Old–Old: Octogenarian Twins based on the oldest cohort of the Swedish Twin Registry [26]. The sample includes 702 participants, with 351 complete twin pairs (149 identical (MZ), 202 same-sex fraternal (DZ pairs)), born in 1913 and earlier, who were, or became, 80 years of age during the first data collection wave (1991–1993) (see details in [Supplementary A2](#)).

Global cognition was assessed using the MMSE. Dementia was diagnosed according to the revised Diagnostic and Statistical Manual of Mental Disorders Third Edition [27] and by consensus from a multidisciplinary team.

Basic sociodemographic and lifestyle information was also collected. Lifestyle information included smoking, engagement in physical and cognitively stimulating activities (see details in [Supplementary A2](#)).

Statistical analysis

We fitted GMM to MMSE scores aligned as a function of years past from study entry to identify classes of individuals with similar MMSE trajectories. Class-specific intercepts and slopes were adjusted for sociodemographic factors (age, sex, education) and a dementia at baseline indicator variable. The multinomial logistic model for class probability included adjustment for sociodemographic and lifestyle variables.

We analysed the distribution of twins across classes and of pairs of twins and their zygosity by class to investigate if MZ pairs were more likely to be assigned to the same class than DZ pairs.

Results

Our analytical sample comprised of 628 individuals (220 (35%) men, 408 (64%) women). Women were older (women: 83.61 (SD = 3.17) years old vs men: 82.95 (SD = 2.76) years old, *t*-test, *P*-value = 0.007) and less educated than men (women: 6.96 (SD = 1.89), men: 7.51 (SD = 2.90), *t*-test, *P*-value = 0.01). Over 73% of the sample (*n* = 463) never developed dementia and 42 (6.7%) had been diagnosed with dementia before or at baseline; [Table 1](#) shows descriptive sample characteristics. The sample included 272 (43%) MZ and 356 (57%) DZ individuals. MZ were slightly more educated than DZ (7.50 (SE = 0.16) vs 6.89 (SE = 0.10) years of education, respectively, *t*-test, *P*-value = 0.0009) and a larger proportion of MZ was sedentary compared to DZ (63% vs 53%, chi-square test,

Table 1. Descriptive statistics of the OCTO-twin sample

Variables	<i>N</i>	Mean (SD)	Baseline characteristics	<i>N</i> (%)
MMSE 1	628	26.3 (3.9)	Monozygotic	272 (43.0)
MMSE 2	524	24.9 (6.2)	Female	408 (65.0)
MMSE 3	404	24.4 (7.1)	Smoker	248 (39.5)
MMSE 4	298	23.7 (7.5)	Stimulates the body	266 (42.4)
MMSE 5	217	22.3 (7.8)	Stimulates brain	416 (66.3)
Education (years)		7.5 (2.3)	Diagnosed with dementia at baseline	42 (6.7)

MMSE 1–5 are the MMSE scores at every follow-up. SD = standard deviation.

Table 2. Results from the 4-class growth mixture model that best fitted the OCTO-twin sample

	High performers and stable <i>N</i> = 260 (122 MZ, 138 DZ)		High performers with slow decline <i>N</i> = 209 (82 MZ, 127 DZ)		Mildly impaired performers with fast decline <i>N</i> = 124 (48 MZ, 76 DZ)		Impaired very fast decline <i>N</i> = 35 (20 MZ, 15 DZ)	
	β (SE)	<i>P</i>	β (SE)	<i>P</i>	β (SE)	<i>P</i>	β (SE)	<i>P</i>
Fixed effects								
MMSE	28.68 (0.12)	0.00	27.29 (0.32)	0.02	25.62 (0.92)	0.00	20.78 (2.35)	0.00
Level								
Baseline	−0.10 (0.03)	0.00	−0.20 (0.08)	0.20	−0.08 (0.17)	0.68	0.28 (0.71)	0.69
age								
Education	0.05 (0.02)	0.02	0.13 (0.10)	0.20	0.37 (0.17)	0.03	0.19 (0.55)	0.72
Women	0.28 (0.13)	0.03	0.20 (0.46)	0.66	−0.57 (1.21)	0.63	0.80 (3.05)	0.79
Baseline	−0.50 (0.09)	0.02	−5.63 (2.00)	0.00	−10.34 (1.38)	0.00	7.15 (2.70)	0.00
Dementia								
Linear	−0.04 (0.04)	0.30	−0.67 (0.10)	0.00	−1.76 (0.24)	0.00	−4.00 (0.48)	0.00
Slope								
Baseline	−0.006 (0.009)	0.48	−0.04 (0.03)	0.12	0.12 (0.06)	0.85	−0.17 (0.09)	0.07
age								
Education	0.008 (0.007)	0.26	0.17 (0.02)	0.51	−0.21 (0.08)	0.00	−0.97 (0.18)	0.00
Women	0.02 (0.04)	0.69	−0.01 (0.13)	0.93	−0.44 (0.38)	0.23	−0.40 (0.50)	0.44
Baseline	−1.30 (0.24)	0.00	−2.35 (0.58)	0.00	0.16 (0.49)	0.75	0.02 (0.39)	0.95
Dementia								

Random effects: level 0.15 (0.08); linear slope 0.04 (0.01); error 0.66 (0.06). SE = standard error.

P-value = 0.02). Sixty per cent of MZ and 68% of DZ individuals were women.

A 4-class-model was identified as the best fitting model. The entropy was 0.74, which suggests a good discrimination of individuals into these four classes. (See [Supplementary A1](#) and [A2](#) for results from 1–3 and 5 class models).

MMSE trajectory classes and characteristics

First, we examined the characteristics revealed in the 4 class-model (see [Table 2](#)). See [Figure 1](#) for an illustration of observed and estimated MMSE trajectories in our sample.

High performers and stable class

The largest class included 41% of the sample (*n* = 260). A reference person (a man aged 83 years at baseline, 7 years of education) had an average baseline MMSE score of 28.68 (SE = 0.12) and did not have dementia at baseline and declined at an annual rate of −0.10 (SE = 0.04) points (non-significant estimate). Older adults had lower baseline MMSE (β = −0.10 (SE = 0.03)), education was associated with higher baseline MMSE score (β = 0.05 (SE = 0.02)), women performed better men (β = 0.28 (SE = 0.13)) and

individuals with dementia had lower baseline MMSE than individuals without dementia (β = −0.50, (SE = 0.09)). Nine incident dementia cases were assigned to this class.

High performers with slow decline class

Thirty-three per cent (33%, *n* = 209) of the sample were assigned to a class with an average baseline MMSE of 27.29 (SE = 0.32) with annual decline of −0.67 (SE = 0.10) MMSE points. Older adults at baseline had poorer baseline MMSE (β = −0.20, (SE = 0.08)), and those with dementia had poorer baseline MMSE performance (β = −5.62 (SE = 2.00)) and declined at a faster rate (β = −2.35 (SE = 0.58)) than those who were free from dementia. Only 57 incident dementia cases were assigned to this class.

Mildly impaired performers with fast decline class

Twenty per cent (20%, *n* = 124) of the sample were in a class with a lower baseline MMSE score than the other class of high-performing individuals and faster rate of decline. A reference individual in this class had an average baseline MMSE of 25.62 (SE = 0.92) with an annual decline of −1.76 (SE = 0.24) points. Individuals with dementia

Figure 1. MMSE observed and model-predicted class-specific trajectories plotted as a function of time (years past since baseline).

had considerably poorer baseline MMSE scores ($\beta = -10.34$ ($SE = 1.38$)) and those more educated had higher MMSE scores ($\beta = -0.37$ ($SE = 0.17$)) but declined faster than those less educated ($\beta = -0.21$ ($SE = 0.08$)). Only 78 individuals incident dementia cases were assigned to this class.

Impaired very fast decline class

Finally, 6% ($n = 35$) of the sample was in a class characterized by low baseline scores and a very substantial decline. Their average baseline MMSE was 20.78 ($SE = 2.35$), with an annual decline of -4.00 ($SE = 0.48$) points. Individuals who received a diagnosis of dementia had better baseline MMSE performance, compared with those without dementia ($\beta = 7.17$ ($SE = 2.70$)) and those with more education declined at a faster rate than less-educated individuals ($\beta = -0.97$ ($SE = 0.19$)). Only 19 individuals incident dementia cases were assigned to this class.

Risk factors and class assignment probability

We analysed the effect of risk factors in relation to the above classification (see Table 3). Compared with the high performing and stable class, as expected, older baseline age was associated with higher odds of being in the class of impaired performers with very fast decline. This was also the case in the class of high performing individuals with fast decline. Women had lower odds of being in the class of mildly impaired performers with fast decline individuals, than in the high performers and stable class of individuals. More educated individuals also had lower odds of being

in the classes of mildly impaired performers with a fast decline and impaired with a very fast decline than in the high performers and stable class. Individuals who did not engage in physical activity were more likely to be in the mildly impaired performers with fast decline class, compared with the high performing and stable class of individuals, a finding that suggests a partial protective effect of education and physical activity.

Distribution of twins across classes

Of the 260 individuals in the high performing and stable class, 122 (46%) were MZ and 138 (54%) were DZ individuals, whereas of the 209 individuals in the class of high performers with slow decline 82 (39%) were MZ and 127 (51%) were DZ. Of the 124 individuals assigned to the mildly impaired performers with fast decline class, 48 (39%) were MZ and 76 (51%) were DZ individuals and finally, 20 (57%) of the individuals in the Impaired with fast decline group were MZ whereas 15 (43%) were DZ individuals.

A posteriori, we analysed whether zygosity was associated with the likelihood of being assigned to an MMSE trajectory class (see Figure 2). We failed to find evidence in support of an association ($X^2_{(3)} = 6.59$, $P = 0.08$) between class and zygosity.

Notably, of all MZ individuals, 50% ($n = 63$) was assigned to the same class as their co-twin whereas the other 50% of the total number of MZ individuals were assigned to a different class than their co-twin. Thirty-seven per cent (37%, $n = 59$) of DZ were assigned to the same class as

Table 3. Odds ratio results from multinomial model for class assignment with reference to the high performers and stable class

	High performers with slow decline		Mildly Impaired performers with fast decline		Impaired very fast decline	
	OR (SE)	P	OR (SE)	P	OR (SE)	P
Baseline age	1.09 (0.04)	0.05	1.14 (0.05)	0.01	1.08 (0.10)	0.39
Education	0.92 (0.05)	0.11	0.75 (0.09)	0.02	0.79 (0.11)	0.03
Women	0.88 (0.28)	0.56	0.45 (0.18)	0.002	0.45 (0.37)	0.21
Smoking	0.91 (0.25)	0.75	0.59(0.24)	0.09	3.22 (2.68)	0.48
Stimulates the body	1.01 (0.27)	0.94	2.42 (0.69)	0.04	3.54 (2.06)	0.22
Stimulates the brain	1.50 (0.36)	0.18	2.76 (1.08)	0.10	2.48 (1.37)	0.39

OR = odds ratio; SE = standard error.

Figure 2. Distribution of monozygotic and DZ individuals across classes.

their cotwin whereas 63% ($n = 99$) were assigned to a class different from their co-twin's.

Discussion

In the present study, we investigated the heterogeneity of MMSE trajectories in a sample of oldest-old and same-sex Swedish MZ and DZ and tested their distribution across classes.

We identified four distinct subgroups of individuals with similar change trajectories. The majority of individuals was classified into two groups with MMSE baseline scores above impairment levels who showed a more preserved cognition or a decline at relatively slow annual rate. A third class was also identified with MMSE scores showing mild impairment but with the faster decline and a fourth small class of individuals with low baseline MMSE score and who thereafter declined at a very fasterate. The overall MMSE score for the entire sample was 26.3 ($SD = 3.9$), which suggests that many individuals had a fairly good global cognition when they entered the study.

Previous studies have reported the existence of groups of individuals whose MMSE trajectories follow different patterns of change [28–31]. However, differences in study designs and features of the samples tend to make comparisons difficult. Despite these differences, studies provide evidence of multiple and distinct patterns of MMSE change over time.

Noteworthy, our findings about the distribution of twins across the four classes showed no association between zygosity and class assignment and that the majority of twins were not assigned to the same class as their co-twin. This provides evidence in support of a greater role for lifestyle and environmental exposures, and not genetics, in late-life cognitive change. A large effect of genetics would otherwise had resulted in MZ and DZ twins assigned to the same class. Our findings are, therefore, in support of a nurture rather than a nature effect. Yet, given the relatively small sample and the inclusion only oldest-old individuals in our study, further research is necessary to better understand the relative contributions of genetic and environmental influences on late-life cognitive change.

Furthermore, the effect of examined risk factors on class-specific level and rate of change varied across classes. Baseline dementia showed almost consistent effects across the classes. In the three larger classes (94% of the sample), individuals with a diagnosis of dementia performed poorer in the MMSE at baseline but not in the class of impaired and high performers stable class, where similar individuals had higher scores than those without dementia. This finding is likely to be explained by a delayed diagnosis of dementia of individuals in that class. Furthermore, an a-posteriori analysis of individuals in this smaller class, showed that only five individuals assigned to that class had been diagnosed with dementia at study entry and 19 (54%) of individuals in this class developed dementia later, which may explain this result. Similarly, in the two larger classes where dementia at baseline emerged as significantly associated with the rate of change, the association was negative. In the other two classes, the estimates did not reach statistical significance, likely due to the small number of individuals with dementia who were assigned to these classes (22 in the Mildly Impaired performers with a fast decline and five in the Impaired very fast decline class, respectively).

Older baseline age emerged as negatively associated with MMSE performance only in the high performers and stable class. Education was consistently found to be positively associated with baseline MMSE performance across the four classes, although the estimate was only significant in the best performing classes where it was also found to be associated with slower decline. In the two fast declining classes more educated individuals exhibited faster decline than less educated individuals. These findings are partly supportive of the theory of cognitive reserve [32] suggesting that individuals with higher educational attainment will perform at a higher cognitive level as they age given their greater baseline cognitive reserve, although they decline at a faster rate once brain pathologies start to manifest clinically. It is possible that individuals in the mildly impaired and impaired fast decliners are on or after the inflection point and hence, education is no longer protective.

Our results about the effect of lifestyle factors on the probability of class assignment provide limited support to the hypothesis that lifestyle factors have a protective effect on cognitive function. The findings that being physically active increases the probability of being assigned to the high performers and stable class, compared to the class of mildly impaired performers with a fast decline, but not to the impaired decliners or high performers with slow decline is somehow unexpected. Our measure of physical activity was limited as the question unfortunately does not capture frequency or intensity. Evidence on mechanisms by which physical activity may have a protective effect on cognitive function in old age shows variations by dose, mode and cognitive function evaluated [33].

Our study also has some other limitations. We failed to estimate models with a larger number of classes and assumed random missing data, an assumption that may not

be realistic. Also, our questions about engagement in physical and cognitively are far from optimal. However, this study was initiated in 1991, when research about their effect on cognitive health was still in the early stages.

In sum, this first investigation based on a classification of a twin sample into distinct groups and of similarities and differences between MZ and same-sex DZ twin pairs suggests a more minor role of genetic effects in late-life cognitive change.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

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