Received: 13 January 2025 | Revised: 17 April 2025 | Accepted: 18 April 2025

DOI: 10.1002/trc2.70103

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Dynamic neurocognitive adaptation: A follow-up exposome investigation in aging

Filippo Cieri[1] | **Chad Lee Cross**[1,2] | **Giulia Di Francesco**[3] | **Jessica Zoe Kirkland Caldwell**[1]

[1]Department of Neurology, Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada, USA

[2]Department of Epidemiology & Biostatistics (C.L.C.), School of Public Health, University of Nevada, Las Vegas, Nevada, USA

[3]Hematology Unit, Department of Oncology-Hematology, Pescara Hospital, Pescara, Italy

Correspondence
Filippo Cieri, Department of Neurology, Cleveland Clinic Lou Ruvo Center for Brain Health, 888 W Bonneville Avenue, Las Vegas, NV 89106, USA.
Email: cierif3@ccf.org

Funding information
National Institute of General Medical Studies-supported Center of Biomedical Research Excellence, Grant/Award Number: P20 GM109025; National Institute on Aging, Grant/Award Numbers: R01-AG074392, P20-AG068053; National Institute of Neurological Disorders and Stroke, Grant/Award Number: RF1NS133812; Women's Alzheimer's Movement at Cleveland Clinic; National Institute of General Medical Sciences, Grant/Award Number: COBRE;P20GM109025

Abstract

INTRODUCTION: Forty-five percent of Alzheimer's disease (AD) cases may be preventable. Validated tools for measuring environmental factors, with precision equal to that of current biological and genetic assessment tools, are currently lacking.

METHODS: We used the dynamic Neurocognitive Adaptation (dNA) scale, our validated tool to explore protective factors in AD, in 410 older adult participants (50% women). The dNA asks participants to recall cognitive, creative, physical, and social activities that they engaged in at seven different time periods in their lives. We examined associations among engagement in these domains using distance correlations and tested differences in domain engagement over time with repeated-measures analysis of variance. We calculated within-subjects comparisons for time and all interactions among time, sex, and education. We examined between-subjects factors for sex, education, and their interaction. From these models, we constructed visualizations of estimated marginal means against time to assess potential patterns of interest.

RESULTS: Physical and creative domain engagements were significantly correlated ($p < 0.001$) in the full sample, and social engagement correlated with physical ($p < 0.001$) and creative ($p = 0.047$) domains among females. Cognitive engagement increased over time ($p < 0.001$) for the full sample, while physical and creative engagement increased from childhood to adolescence, then decreased over time ($p < 0.001$). In contrast, social engagement increased from childhood to adolescence, declined through the senior years, and then sharply increased in old age. Overall, women showed higher cognitive engagement ($p = 0.024$) and men showed higher physical engagement ($p = 0.011$). Education was positively related to higher scores in all domains.

DISCUSSION: Our scale provides new insight into the correlation of environmental factors with education, suggests areas for lifestyle intervention, and highlights the importance of sex differences and middle age as a potential transition stage.

KEYWORDS
adaptation, Alzheimer's disease, dynamic, exposome, neurocognitive, prevention, reserve, resilience, resistance, well-being

Highlights

- Physical activity decreases and cognitive activity increases through time.
- Higher involvement in physical activities is correlated with creative and social dimensions.
- Men are more involved in physical and women in cognitive activities.
- Higher education is associated with higher involvement in all the dimensions explored.

1 | BACKGROUND

The word *exposome* was introduced by Wild[1] to propose a dimension of human environmental exposure, which would complement the field of studies on the genome. As suggested by the author, the imbalance in measurement precision between genetic and environmental factors has crucial consequences, most fundamentally in limiting the ability to derive public health benefits from expenditures on the human genome and cohort studies. This is especially true in an increasingly older population with a greater number of diseases related to aging, such as Alzheimer's disease (AD). This most common cause of dementia accounts for an estimated 60% to 80% of cases.[2]

The 2024 report of the Lancet Commission on dementia prevention, intervention, and care revealed that 45% of dementia cases may be preventable.[3] This underscores the potential for significant public health impact through detailed understanding of the exposome as a risk assessment and resilience intervention target in the aging population. Our group has recently developed and validated a scale called dynamic Neurocognitive Adaptation (dNA)[4] with the aim to explore and improve the exposome approach and ultimately improve interventions in aging, especially in the context of AD, where the only available cure is prevention. The current article is a follow-up to that validation, and it is focused on three points:

1. An exposome investigation through the dNA scale, exploring changes over time and correlation with education.
2. Middle age as a potential transition stage.
3. Sex differences.

1.1 | Changes over time and correlation with education

With aging, the environment changes in many ways. Individuals undergo physiological and cognitive changes, and even gene expression is altered through epigenetic mechanisms, while the genome's structure remains largely stable over time. In this context, change itself can be considered a fundamental characteristic of the aging process. For this reason, the investigation of individual adaptation to change has a key role in aging, as a possible mechanism of plasticity, resistance, and resilience.

Aging can be seen as a physiological, predictable (in fact inevitable) complex process, full of unpredictable events. In this sense, allostasis is the ability to maintain stability, or homeostasis, through change, and it refers to the process of adaptation to stress.[5–6] If we apply the concept of allostasis to the aging process (i.e., maintaining stability through change) we can explore the way organisms actively adjust to both predictable and unpredictable events related to aging. We are not claiming that humans should be *stable* (i.e., not change through time), rather, quite the opposite, we are proposing that individuals with better adaptation will show resistance to the aging process. This can occur, for example, through consistent engagement with the environment, especially in cognitive, physical, creative, and social activity over time.

Education is the most commonly used proxy of cognitive reserve. It may simply correlate with a more general and dynamic adaptation to the environment, or alternatively may facilitate, mediate, or even cause that adaptation. For example, IQ and education duration are positively correlated, which can be interpreted either as students with greater propensity for intelligence going on to complete more education, or a longer education increasing intelligence.[7,8] Similarly, people with higher education are more likely to know the benefits of an active life and so may be more cognitively and physically active. On the other hand, studies in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort have found no support for the hypothesis that education is a protective factor against brain pathology.[9]

Our scale proposes an investigation of a broader set of protective activities, beyond IQ and years of education, that may contribute dynamically to maintaining a younger neurocognitive system, and may build resistance to AD pathology, such as amyloid aggregation and neuroinflammation, though neurocognitive adaptation.

1.2 | Middle age as a transition stage

Recent evidence has confirmed the importance of the transition from middle to older age[10,11] as a time of non-linear and dynamic change,[12,13] which does not proceed at the same rate throughout the body and over time.[14,15] For instance, non-linear changes in RNA and protein expression related to aging have been recently reported,[16,17] as have non-linear changes in methylation intensity, which seems to follow a power law pattern.[18] Because individual longitudinal trajectories of cognitive change during middle age are highly variable and partially independent of early-life and congenital factors,[19] midlife may be a critical transition stage for intervention.

Fluid intelligence, processing speed, and memory performance all show significant decline during middle age,[20] further demonstrating this stage of life as a point when individual differences in future cognitive trajectories begin to emerge.[20] These differences relate in part to the first symptoms of mild cognitive impairment (MCI) as a preclinical stage of AD.

From a neuroscientific perspective, most fasciculi (particularly the associational fibers) display inverted U-curve relationships across the lifespan, with turning points between the ages of 40 and 50 years.[21] In accordance with these structural changes, the average strength and number of functional connections appear to decline after the age of 50 years, and long-range functional connections are lost.[10,22] During this period, we also observe a phenomenon called *dedifferentiation*, which consists of reduced segregation between neural networks, especially in higher associational systems, and subsequent loss of functional specialization.[23] This segregation loss appears to be non-linear—with a breakpoint at ≈ 50 years–compared, for instance, to a linear trend for the sensorimotor systems, and to significant interindividual variability. Finally, with aging our brain also loses its ability to anticorrelate the activation of task-negative (default network) and task-positive networks (dorsal attention and frontoparietal control networks), and this decline is exacerbated in cognitively pathological aging, such as MCI.[24]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Higher involvement in physical and cognitive activities has a protective role against neurodegeneration. Although this is an accepted idea in the field, the relationship between different activities, their change through time, and differences between women and men are less investigated. These aspects are appropriately explored by the authors.
2. **Interpretation**: These findings propose a comprehensive assessment of lifetime adaptive behaviors, which can be applied in research on Alzheimer's disease (AD) risk reduction and in clinical practice. Moreover, these results suggest a focus on a specific transition stage as a suitable stage for intervention. Finally, because women are two thirds of AD patients, differences between men and women should not be underestimated.
3. **Future directions**: The article proposes a framework for the involvement in different activities as protective factors against neurodegeneration. Further research using this tool may extend reserve, resilience, and resistance approaches, involving different activities, their changes through time, and specific time windows for risk reduction interventions. Furthermore, more studies should explore correlation of a more adaptive lifestyle with neuropsychological, neurophysiological, and neuroimaging measures.

1.3 | Sex differences

The mentioned middle age changes in trends and trajectories show interindividual variability, non-linearity, and significant sex differences. These differences between women and men in the cognitive neuroscience of aging are well known, especially in MCI and AD.[25–29]

In women, some changes specifically related to the midlife transition stage may be due to menopause;[30] during that same middle age we observe accelerating brain structural and functional changes in both sexes.[31] Nonetheless, menopause increases epigenetic aging, as measured in female blood samples.[32] Its age of onset has a genetic architecture that mainly involves the DNA damage response,[33] which could drive aging of the body, brain, and cognition through epigenomic information loss.[34]

In this article we used the dNA scale to explore some of these behavioral differences. We examined cognitive, physical, creative, and social engagement over time; association of this engagement with education (as a proxy of cognitive reserve); the role of middle age as a transition stage; and potential differences between women and men. Our hypotheses are that all types of engagement will change over time in a non-linear fashion. We expect a positive correlation between the degree of involvement in different activities and education. We also expect a sex difference in the physical dimension, in which men usually show a greater involvement compared to women. We are interested, in a more exploratory way, in the effect of middle age in our sample.

2 | METHODS

2.1 | Participants

For the use of the dNA scale and its validation, an ethical approval was obtained from the institutional review board (IRB) of the Cleveland Clinic (IRB number #22310) and informed consent for publication was obtained from the study participants. The total sample included 815 participants (50% women); minimum age 65 years old; mean participant age was 72.80 (standard deviation [SD]: 5.35; see Table S1 in supporting information for details and to read the validation paper[4]). The total sample used for the validation included two subsamples: one used for an initial exploratory factor analysis (EFA; $N = 405$), and a second for subsequent cross-validation ($N = 410$), performed via confirmatory factor analysis (CFA). The sample size was determined according to convention[35] and verified experimentally. For this study we have used the sample from the CFA (410 subjects).

Data collection used survey measures administered via Qualtrics. All subjects were required to be fluent English speakers and US residents. All enrolled study participants provided demographic information, including age in years, sex, gender identity, level of education attainment (e.g., diploma or degree type), number of years of education, marital status, and number of children and grandchildren. Participants were excluded if they reported age < 65 years, living outside the United States, or not fluent in English.

Each domain of engagement was assessed separately for seven decades across the life course: childhood (0–10 years), adolescence (11–20 years), youth (21–30 years), adulthood (31–40 years), middle age (41–50 years),; senior age (50–64 years), old age (65+ years). Items are introduced with the statement, "The following questions ask about your involvement in.…" Each question instructed participants to identify the best answer. For example, "How often did you read, or do you currently read books/e-books/audiobooks?" represents a typical item (see supporting information to visualize the dNA scale). All information about the sample and the specific psychometric features of the scale are available in our validation article.[4] All data modeling and procedures specifically related to the validation were performed by two different authors (G.d.F.; F.C.) using standard software packages (Stata Statistical Software, version. 18.0; StataCorp.; and SPSS, version 23).

2.2 | Statistical analysis

We analyzed the data using several approaches. First, correlations among mean engagement scores across the seven timepoints for cognitive, physical, creative, and social domains were assessed using distance correlations, a set of measures that examines potential relationships among vectors without the assumptions necessary for classical product-moment correlations, and hence remain valid under multiple conditions, including when variables have an implicit assumption of temporality that may violate assumptions of traditional coefficients.[36,37] Significance values for these correlations were calculated using $n = 10{,}000$ Monte Carlo resamples of the vectors using the <energy> package in R (v. 4.4.1). Second, noting that the data were temporally balanced among subjects, we further examined the four domains separately across the seven time periods using repeated-measures analysis of variance with Greenhouse–Geisser sphericity corrections in SPSS (v. 29). We included in the models within-subjects comparisons for time and all interactions among time, sex, and education attainment and between-subjects factors for sex, education, and their interaction. Third, we calculated planned contrasts within domains for pairwise time comparisons and interactions if these factors were significant in the model. Next, we examined Bonferroni–Holm–corrected exploratory pairwise comparisons among levels of education attainment. Finally, from these models, we constructed visualizations of estimated marginal means against time to assess potential patterns of interest. Herein we use a significance threshold of 0.05.

TABLE 1 Distance-based correlations among the four domains.

	Cognitive	Physical	Creative
Combined sample			
Physical	0.53 (0.430)[a]		
Creative	0.62 (0.393)	**0.91 (< 0.001)**	
Social	0.48 (0.645)	0.70 (0.128)	0.63 (0.221)
Female sample			
Physical	0.60 (0.420)		
Creative	0.67 (0.255)	**0.82 (0.044)**	
Social	0.63 (0.352)	**0.99 (< 0.001)**	**0.81 (0.047)**
Male sample			
Physical	0.51 (0.458)		
Creative	0.47 (0.671)	**0.92 (0.001)**	
Social	0.52 (0.454)	0.74 (0.107)	0.59 (0.325)

Note: *P* values are based on $n = 10{,}000$ Monte Carlo resamples to construct a bootstrap distribution.
[a]Data are presented as coefficient (*p* value); significant correlations are in bold.

3 | RESULTS

3.1 | Associations among domains

In both the pooled and sex-stratified samples, the cognitive domain was not significantly correlated with any of the other three domains (all $p >$ 0.05). The physical and creative domains were significantly correlated ($p < 0.001$), and this same association was independently significant for both females and males ($p = 0.044$ and $p = 0.001$, respectively). Additionally, the social domain was significantly correlated with both the physical ($p < 0.001$) and creative ($p = 0.047$) domains among females but not for males (both $p > 0.05$; Table 1).

3.2 | Temporal evaluation of domains

For the cognitive domain, there was an overall increase in scores as a function of time ($p < 0.001$), but there were no significant interactions of sex or education with time (Figure 1, Table 2). Specifically, within-subjects contrasts for time were significant ($p < 0.05$) for child versus adolescent, youth versus adult, and senior versus old (Table 3). When examining between-subjects effects, both sex ($p = 0.024$) and education ($p < 0.001$) showed significant differences, but their interaction did not ($p = 0.467$). Specifically, scores were higher for females compared to males (Figure 1), and scores trended higher with higher education attainment (Figure 2), but differently by education grouping, with high school education having the lowest scores (Table 4).

For the physical domain, there was an overall increase from childhood to adolescence followed by a decrease in scores as a function of time ($p < 0.001$), and time and sex had a significant interaction ($p = 0.015$; Figure 1, Table 2). Specifically, within-subjects contrasts for time were significant ($p < 0.05$) for all pairwise age categories

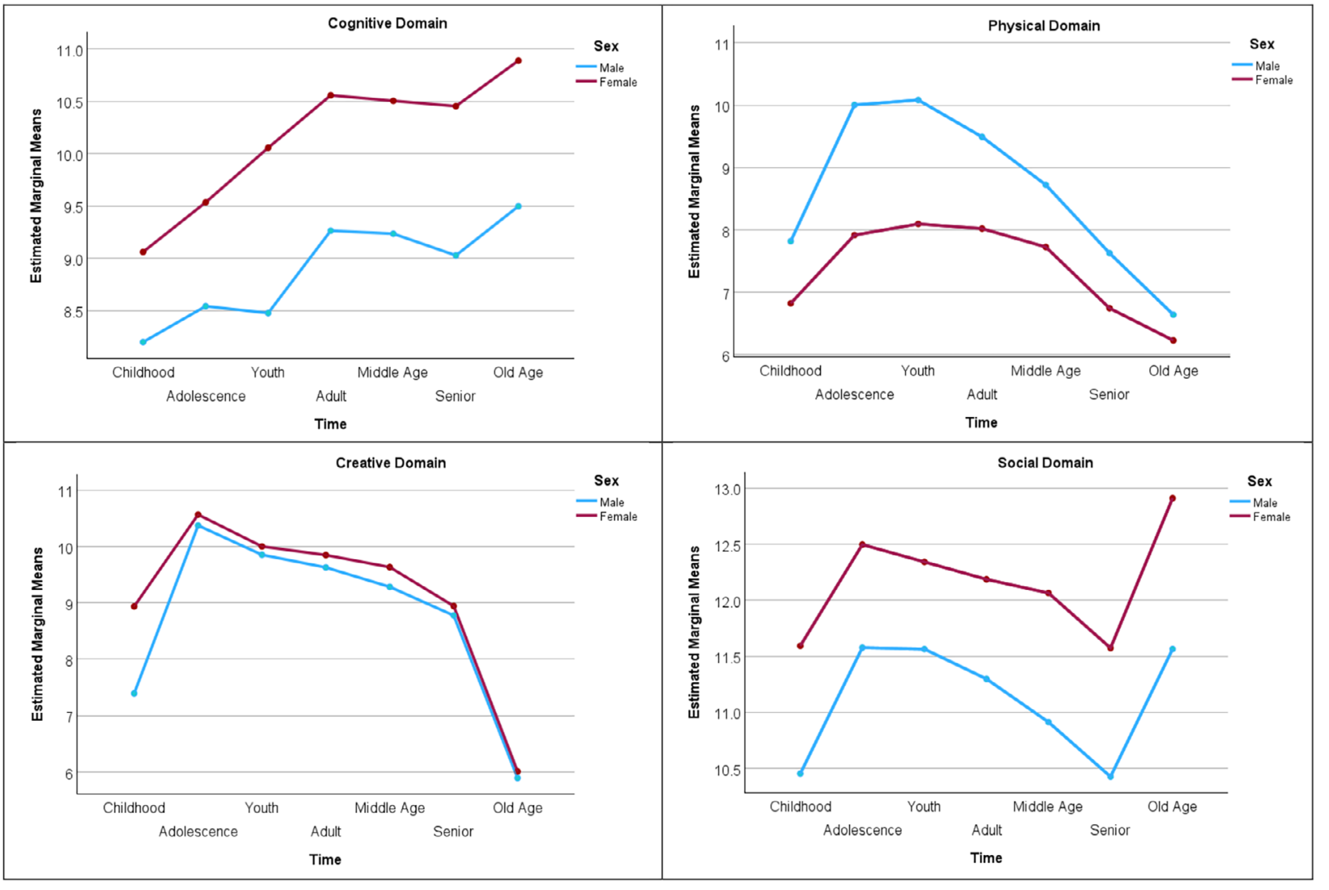

FIGURE 1 Score versus time (age group) by sex for each domain

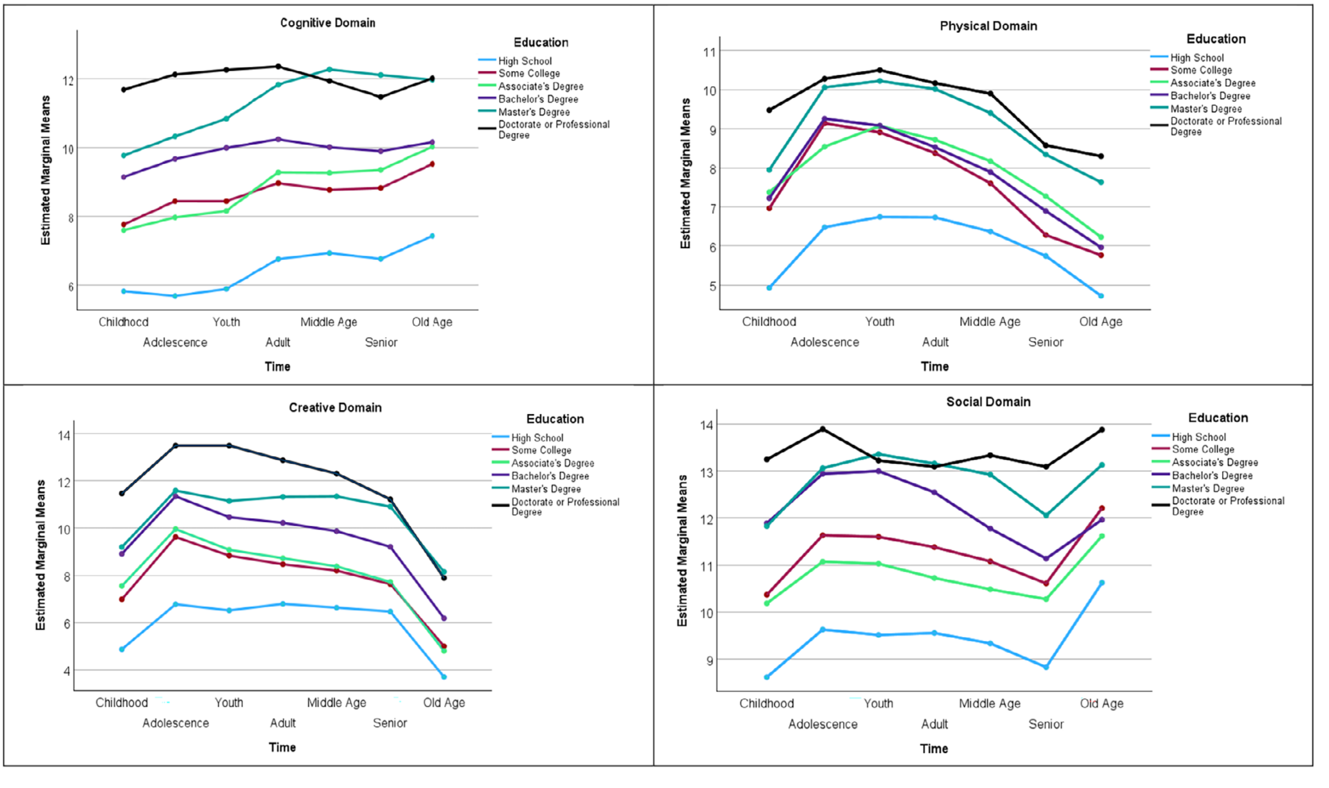

FIGURE 2 Score versus time (age group) by education attainment for each domain

TABLE 2 Tests of within- and between-subjects factors by domain.

	F	*p*	Partial η^2
Cognitive domain			
Within subjects			
Time	10.653	**<0.001**	0.026
Time × sex	0.541	0.626	0.001
Time × education	1.094	0.332	0.014
Time × sex × education	0.719	0.743	0.009
Between subjects			
Sex	5.140	**0.024**	0.013
Education	10.397	**<0.001**	0.116
Sex × education	0.922	0.467	0.012
Physical domain			
Within subjects			
Time	41.034	**<0.001**	0.094
Time × sex	3.672	**0.015**	0.009
Time × education	1.125	0.331	0.014
Time × sex × education	0.717	0.755	0.009
Between subjects			
Sex	6.490	**0.011**	0.016
Education	5.191	**<0.001**	0.062
Sex × education	0.859	0.509	0.011
Creative domain			
Within subjects			
Time	91.687	**<0.001**	0.188
Time × sex	2.640	**0.015**	0.007
Time × education	1.525	0.091	0.019
Time × sex × education	1.001	0.451	0.012
Between subjects			
Sex	0.717	0.398	0.002
Education	15.265	**<0.001**	0.162
Sex × education	1.121	0.349	0.014
Social domain			
Within subjects			
Time	15.665	**<0.001**	0.038
Time × sex	0.634	0.562	0.002
Time × education	1.904	**0.029**	0.023
Time × sex × education	0.507	0.914	0.006
Between subjects			
Sex	5.740	**0.017**	0.014
Education	8.869	**<0.001**	0.101
Sex × education	1.250	0.285	0.016

Note: Bold value indicates $p < 0.05$.

TABLE 3 Planned contrasts by domain for those with significant within-subject effects (Table 1).

	F	*p*	Partial η^2
Cognitive domain			
Time			
Child versus adolescent	5.120	**0.024**	0.013
Adolescent versus youth	2.115	0.147	0.005
Youth versus adult	17.557	**<0.001**	0.042
Adult versus middle age	0.132	0.716	0.000
Middle age versus senior	0.973	0.325	0.002
Senior versus old	6.930	**0.009**	0.017
Physical domain			
Time			
Child versus adolescent	83.534	**<0.001**	0.174
Adolescent versus youth	0.858	0.355	0.002
Youth versus adult	8.303	**0.004**	0.021
Adult versus middle age	24.966	**<0.001**	0.059
Middle age versus senior	68.520	**<0.001**	0.148
Senior versus old	15.871	**<0.001**	0.039
Time × sex			
Child versus adolescent	9.247	**0.003**	0.023
Adolescent versus youth	0.130	0.719	0.000
Youth versus adult	4.998	**0.026**	0.012
Adult versus middle age	4.935	**0.027**	0.012
Middle age versus senior	0.206	.650	0.001
Senior versus old	1.562	0.212	0.004
Creative domain			
Time			
Child versus adolescent	127.137	**<0.001**	0.243
Adolescent versus youth	10.269	**0.001**	0.025
Youth versus adult	2.613	0.107	0.007
Adult versus middle age	6.033	**0.014**	0.015
Middle age versus senior	31.620	**<0.001**	0.074
Senior versus old	279.831	**<0.001**	0.414
Time × sex			
Child versus adolescent	10.937	**0.001**	0.027
Adolescent versus youth	0.017	0.896	0.000
Youth versus adult	0.093	0.760	0.000
Adult versus middle age	0.322	0.571	0.001
Middle age versus senior	0.725	0.395	0.002
Senior versus old	0.022	0.881	0.000
Social Domain			
Time			
Child versus adolescent	54.834	**<0.001**	0.122
Adolescent versus youth	0.562	0.454	0.001
Youth versus adult	4.300	**0.039**	0.011

(Continues)

TABLE 3 (Continued)

	F	p	Partial η^2
Adult versus middle age	9.440	**0.002**	0.023
Middle age versus senior	25.724	**<0.001**	0.061
Senior versus old	98.081	**<0.001**	0.199
Time × education			
Child versus adolescent	0.439	0.822	0.006
Adolescent versus youth	0.785	0.561	0.010
Youth versus adult	0.815	0.539	0.010
Adult versus middle age	2.659	**0.022**	0.032
Middle age versus senior	1.250	0.285	0.016
Senior versus old	2.823	**0.016**	0.034

Note: Bold value indicates $p < 0.05$.

except adolescent versus youth (p = 0.355), and interaction of time and sex was significant for child versus adolescent (p = 0.003), youth versus adult (p = 0.026), and adult versus middle age (p = 0.027; Table 3). Between-subjects differences were significant for both sex (p = 0.011) and education (p < 0.001), but not for their interaction (p = 0.509). Scores were always higher for males compared to females at all ages (Figure 1), and scores were higher as a function of education attainment (Figure 2), but differently by education grouping, with high school education with the lowest scores (Table 4).

For the creative domain, there was an overall increase in scores from childhood to adolescence followed by a moderate monotonic decline through senior age and then a precipitous drop to old age (p < 0.001); time and sex had a significant interaction (p = 0.015; Figure 1, Table 2). Pairwise within-subjects contrasts were significant (p < 0.05) for all pairwise age categories except for youth versus adult (p = 0.107; Table 3). Between-subjects differences were significant only for education (p < 0.001), with male and female scores very similar across age (Figure 1). Scores were always higher for those with education attainment greater than high school (Figure 2), with significantly higher scores at later ages for those with graduate-level education attainment (p < 0.05; Table 4).

Finally, for the social domain, there was an overall score increase from childhood to adolescence followed by a decline through the senior years and then a steep increase in old age (Figure 1). Additionally, there was a significant effect of time (p < 0.001) and for the interaction of time and education (p = 0.029; Table 2). Pairwise within-subjects contrasts were significant (p < 0.05) for all pairwise age categories except for youth versus adult (p = 0.454; Table 3). Between-subjects differences were noted for both sex (p = 0.017) and education (p < 0.001), but not for their interaction (p = 0.285). Female scores were uniformly higher than male (Figure 1). Again, scores were always higher for those with education attainment exceeding high school, with the patterns in score behavior generally similar (Figure 2).

4 | DISCUSSION

Aging is influenced by genetic factors,[38] but < 10% of differences in longevity between individuals can be attributed to inherited genes.[39] Environmental factors are therefore critical determinants of aging processes.[40] In this article we applied our dNA scale for an exposome investigation in a population of US residents > 65 years old, as a follow-up to our validation study.[4] We wanted to explore the correlation of our scale with education (as one of the most used proxies of reserve), the importance of the middle age with respect to environmental engagement, and relative sex differences, given women's higher vulnerability to AD pathology.

We found that in the cognitive dimension, there is an overall increase in scores as a function of time. This is consistent with our dynamic view of the cognitive dimension, compared to the static application of years of education. In other words, on one hand the education attainment is unlikely to change after the age of 25 to 30, while involvement in cognitive activities can change and, in our sample, did consistently change over time. This is also consistent with the idea that some cognitive functions (fluid intelligence, processing speed, and memory performance) can decrease with time, especially in middle age, but some other functions, such as crystallized intelligence, continue to increase in adulthood.[20] Higher involvement in cognitive activities correlates with higher education attainment, with high school education showing the lowest cognitive engagement scores. This result should open a further exploration of the investigation of education as a variable favoring or mediating other factors such as greater involvement in other protective activities.

Overall, our results confirm the importance of education, pointing out that people with higher education are more likely to be more involved in cognitive, physical, creative, and social activities.[41] Salient points by domain included: (1) In the physical domain, we found an increase in engagement from childhood to adolescence followed by a steady decrease as a function of time. Physical engagement scores were also higher as a function of education attainment, and individuals with high school education showed the lowest scores in group comparisons. (2) For the creative domain, there was an overall increase in involvement from childhood to adolescence followed by a moderate monotonic decline through senior age, and then a precipitous drop to old age. Again, higher education was associated with higher creative involvement. (3) For the social domain, we found an overall engagement increase from childhood to adolescence followed by a consistent decline through the senior years, and then a steep increase in old age. We found a significant effect of time and a significant interaction of time and education. As with physical and creative activity, involvement in social activity was higher for those with greater than high school education.

Our second interest was focused on the importance of middle age. During this stage our sample had a consistent decrease in involvement in every domain, including in the cognitive domain, where there is otherwise a consistent increase over time. This is quite consistent with our current cultural–economic system, in which

TABLE 4 Corrected pairwise between-subjects post hoc tests for education attainment for domains with a significant education effect.

Education attainment pairwise comparison	p^a Cognitive domain	Physical domain	Creative domain	Social domain
High school versus some college	**0.007**	**0.037**	**0.004**	**0.002**
High school versus associate degree	**0.032**	**0.037**	**0.010**	0.306
High school versus bachelor degree	**<0.001**	**0.002**	**<0.001**	**<0.001**
High school versus master's degree	**<0.001**	**<0.001**	**<0.001**	**<0.001**
High school versus doctorate or professional degree	**<0.001**	**0.015**	**<0.001**	**0.008**
Some college versus associate degree	1.000	1.000	1.000	1.000
Some college versus bachelor degree	1.000	1.000	**0.073**	1.000
Some college versus master's degree	**0.006**	**0.345**	**<0.001**	**0.142**
Some college versus doctorate or professional degree	**0.143**	1.000	**0.002**	1.000
Associate degree versus bachelor degree	1.000	1.000	**0.703**	**0.429**
Associate degree versus master's degree	**0.048**	1.000	**0.007**	**0.038**
Associate degree versus doctorate or professional degree	**0.261**	1.000	**0.008**	**0.625**
Bachelor degree versus master's degree	**0.195**	1.000	**0.807**	1.000
Bachelor degree versus doctorate or professional degree	**0.683**	1.000	**0.213**	1.000
Master's degree versus doctorate or professional degree	1.000	1.000	1.000	1.000

Note: Bold value indicates $p < 0.05$.

[a]All *P* values are Bonferroni–Holm corrected to protect Type 1 error rate. *P* values calculated as "1" occur owing to the correction for Type 1 error and simply indicate non-significance, not an actual value of "1."

midlife often represents the most competitive and time-demanding career stage. During this stage there is a greater workload, associated with family and professional responsibilities, which could leave less time for other activities, such as physical or social. Interestingly, for the cognitive domain, we found a decrease in engagement from adult to middle age and from middle age to senior age, with all the other transitions showing increased involvement. In all other dimensions, we observe decreased involvement in activities between 40 and 50 years old, confirming the necessity of a specific investigation and potentially a specific intervention during this stage of life.

Finally, differences between men and women should be explored in detail because women make up two thirds of AD cases. As mentioned, the general decrease found in both sexes can be increased in females, specifically related to a biological transition stage related to menopause. We found the physical domain particularly interesting, with a decreased involvement after adolescence as a function of time, with time and sex interacting significantly. Females showed lower physical activity involvement compared to males at all ages. Related to these results, both animal and clinical studies have shown that physical activity can alleviate symptoms of neurodegenerative diseases and delay pathological progression,[42] and have confirmed a close connection between exercise and the immune system.[43] Moreover, involvement in this specific kind of activity is correlated with improving musculoskeletal health and function, preventing cognitive decline, reducing symptoms of depression and anxiety, and helping maintain a healthy weight.[44–47]

Consistent with our results, a recent study[48] described an increase in physical inactivity with a prevalence 5% greater among women than men. The study found this pattern increased in people aged ≥ 60 years, in both sexes. The authors of this research concluded that if the 2010 to 2022 trends continue, the global target of a 15% relative reduction in physical inactivity between 2010 and 2030 will not be met (posterior probability < 0.01). These latter results confirm a trend of a global pandemic of physical inactivity[49] with a total of 5.3 million deaths per year associated with inactivity.[50] Lower physical activity, associated with menopause, could contribute to the female's higher vulnerability to AD.[51]

Our study has limitations: this project was initiated during the COVID-19 pandemic; therefore, we have used a sample virtually collected by Qualtrics. Virtual recruitment also could lack sample diversity and generalizability. Virtual data collection may introduce selection bias, as only individuals with internet access can participate. We are currently collecting additional data (e.g., biomarkers, neuropsychological, neuroimaging) at our site to address this weakness. In addition to these points, we acknowledge that the dNA asks participants to report on their activity engagement in a retrospective fashion and so results depend on participant recall. Ideal investigation of this kind should use longitudinal data to track changes over time, instead of being retroactively based.

Our study also has strengths: we are presenting a new and empirically validated scale, designed to measure engagement in lifetime brain-healthy activity. Our scale allows a more dynamic investigation of these activities, with a granular time distinction, and has promise for recommending clinical lifestyle interventions, especially during middle age. Our results underscore the need to pair basic indicators of reserve, such as education, with more complex assessment of individual involvement in the environment. This broader approach will help us to understand exposome-based mechanisms of adaptation to aging and AD.

ACKNOWLEDGMENTS

The authors have nothing to report. This work was supported by the National Institute of General Medical Studies-supported Center of Biomedical Research Excellence (COBRE; P20 GM109025); the National Institute on Aging (R01-AG074392 and P20-AG068053), The National Institute of Neurological Disorders and Stroke (RF1NS133812), and the Women's Alzheimer's Movement at Cleveland Clinic.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent.

REFERENCES

1. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev*. 2005;14(8):1847-50. doi: 10.1158/1055-9965.EPI-05-0456
2. Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. *Alzheimers Dement*. 2024;20(5):3708-3821.
3. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404(10452):572-628. doi: 10.1016/S0140-6736(24)01296-0
4. Cieri F, Di Francesco G, Cross CL, Bender A, Caldwell JZK. Dynamic Neurocognitive Adaptation in aging: development and validation of a new scale. *Alzheimer and Dementia*. 2025 In Production.
5. Sterling P, Eyer J. Allostasis: A new paradigm to explain arousal pathology. In Fisher S, Reason J, (eds), *Handbook of Life Stress, Cognition and Health*. John Wiley and Sons; 1988 pp 629-649
6. Sapolsky RM. Why stress is bad for your brain. *Science*. 1996;273: 749-750
7. Brinch CN, Galloway TA. Schooling in adolescence raises IQ scores. *Proc Natl Acad Sci*. 2012;109(2):425-30. doi: 10.1073/pnas.1106077109
8. Ritchie SJ, Tucker-Drob EM. How Much Does Education Improve Intelligence? A Meta-Analysis. *Psychol Sci*. 2018;29(8):1358-1369. doi: 10.1177/0956797618774253
9. Bauer CE, Brown CA, Gold BT; Alzheimer's Disease Neuroimaging Initiative. Education does not protect cognitive function from brain pathology in the ADNI 2 cohort. *Neurobiol Aging*. 2020;90:147-149. doi: 10.1016/j.neurobiolaging.2019.11.017
10. Dohm-Hansen S, English JA, Lavelle A, Fitzsimons CP, Lucassen PJ, Nolan YM. The 'middle-aging' brain. *Trends Neurosci*. 2024;47(4):259-272. doi: 10.1016/j.tins.2024.02.001
11. Shen X, Wang C, Zhou X, *et al*. Nonlinear dynamics of multi-omics profiles during human aging. *Nat Aging*. 2024;4:1619–1634. doi: 10.1038/s43587-024-00692-2
12. Ahadi S, Zhou W, Schüssler-Fiorenza Rose SM, et al. Personal aging markers and ageotypes revealed by deep longitudinal profiling. *Nat Med*. 2020;26:83-90
13. Li X, Ploner A, Wang Y, et al. Longitudinal trajectories, correlations and mortality associations of nine biological ages across 20-years follow-up. *eLife*. 2020;9:e51507
14. Schaum N, Lehallier B, Hahn O, et al. () Ageing hallmarks exhibit organspecific temporal signatures. *Nature*. 2020;583:596-602
15. Wagner V, Kern F, Hahn O, et al. Characterizing expression changes in noncoding RNAs during aging and heterochronic parabiosis across mouse tissues. *Nat Biotechnol*. 2023;42:109-118
16. Fehlmann T, Lehallier B, Schaum N, et al. Common diseases alter the physiological agerelated blood microRNA profile. *Nat Commun*. 2023;11:5958.
17. Shavlakadze T, Morris M, Fang J, et al. Age-related gene expression signature in rats demonstrate early, late, and linear transcriptional changes from multiple tissues. *Cell Rep*. 2019;28:3263-3273.
18. Vershinina O, Bacalini MG, Zaikin A, Franceschi C, Ivanchenko M. Disentangling age-dependent DNA methylation: deterministic, stochastic, and nonlinear. *Sci Rep*. 2021;11:9201.
19. Elliott ML, Caspi A, Houts RM, et al. Disparities in the pace of biological aging among midlife adults of the same chronological age have implications for future frailty risk and policy. *Nat Aging*. 2021;1:295-308
20. Zimprich D, Mascherek A. Five views of a secret: does cognition change during middle adulthood? *Eur J Ageing*. 2010;7:135-146
21. Yeatman JD, Wandell BA, Mezer AA. Lifespan maturation and degeneration of human brain white matter. *Nat Commun*. 2021;5:4932
22. Ma L, Tian L, Hu T, Jiang T, Zuo N. () Development of individual variability in brain functional connectivity and capability across the adult lifespan. *Cereb Cortex*. 31, 3925-3938
23. Chan MY, Park DC, Savalia NK, Petersen SE, Wig GS. Decreased segregation of brain systems across the healthy adult lifespan. *Proc Natl Acad Sci U S A*. 2014;111:E4997–E5006
24. Esposito R, Cieri F, Chiacchiaretta P, et al. Modifications in resting state functional anticorrelation between default mode network and dorsal attention network: comparison among young adults, healthy elders and mild cognitive impairment patients. *Brain Imaging Behav*. 2018;12(1):127-141. doi: 10.1007/s11682-017-9686-y
25. Caldwell JZK, Cummings JL, Banks SJ, Palmqvist S, Hansson O. Cognitively normal women with Alzheimer's disease proteinopathy show relative preservation of memory but not of hippocampal volume. *Alzheimers Res Ther*. 2019;11(1):109. doi: 10.1186/s13195-019-0565-1
26. Cieri F, Yang Z, Cordes D, Caldwell JZK; Alzheimer's Disease Neuroimaging Initiative. 2022. Sex Differences of Brain Functional Topography Revealed in Normal Aging and Alzheimer's Disease Cohort. *J Alzheimers Dis*. 2021;80(3):979-984. doi: 10.3233/JAD-201596
27. Cieri F, Zhuang X, Cordes D, Kaplan N, Cummings J, Caldwell J; Alzheimer's Disease Neuroimaging Initiative (ADNI) 2022b. Relationship of sex differences in cortical thickness and memory among cognitively healthy subjects and individuals with mild cognitive impairment and Alzheimer disease. *Alzheimers Res Ther*. 2022;14(1):36. doi: 10.1186/s13195-022-00973-1
28. Cieri F, Giriprakash PP, Nandy R, et al. Functional connectivity differences of the olfactory network in Parkinson's Disease, mild cognitive impairment and cognitively normal individuals: A resting-state fMRI study. *Neuroscience*. 2024;559:8-16. doi: 10.1016/j.neuroscience.2024.08.031
29. Yang Z, Cieri F, Kinney JW, Cummings JL, Cordes D, Caldwell JZK; Alzheimer's Disease Neuroimaging Initiative. Brain functional topology differs by sex in cognitively normal older adults. *Cereb Cortex Commun*. 2022;3(3):tgac023. doi: 10.1093/texcom/tgac023
30. Caldwell JZK, Isenberg N. The aging brain: risk factors and interventions for long term brain health in women. *Curr Opin Obstet Gynecol*. 2023;35(2):169-175. doi: 10.1097/GCO.0000000000000849

31. Bethlehem RAI, Seidlitz J, White SR, et al.; 3R-BRAIN; AIBL; Alzheimer's Disease Neuroimaging Initiative; Alzheimer's Disease Repository Without Borders Investigators; CALM Team; Cam-CAN; CCNP; COBRE; cVEDA; ENIGMA Developmental Brain Age Working Group; Developing Human Connectome Project; FinnBrain; Harvard Aging Brain Study; IMAGEN; KNE96; Mayo Clinic Study of Aging; NSPN; POND; PREVENT-AD Research Group; VETSA. Brain charts for the human lifespan. *Nature*. 2022;604(7906):525-533. doi: 10.1038/s41586-022-04554-y
32. Levine ME, Lu AT, Chen BH, et al. Menopause accelerates biological aging. *Proc Natl Acad Sci*. 2016;113:9327-9332
33. Ruth KS, Day FR, Hussain J, et al. Genetic insights into biological mechanisms governing human ovarian ageing. *Nature*. 2021;596:393-397
34. Yang J-H, Hayano M, Griffin PT, et al. Loss of epigenetic information as a cause of mammalian aging. *Cell*. 2023;186:305-326.e27
35. Comrey AL, Lee HB. *A first Course in Factor Analysis*. Erlbaum; 1992.
36. Szekely GJ, Rizzo ML. Brownian distance covariance. *Annals of Applied Statistics*. 2009;3(4):1236-1265.
37. Szekely GJ, Rizzo ML, Bakirov NK. Measuring and testing dependence by correlation of distances. *Annals of Statistics*. 2007;35(6):2769-2794.
38. Melzer D, Pilling LC, Ferrucci L. The genetics of human ageing. *Nat Rev Genet*. 2020;21(2):88-101.
39. Ruby JG, Wright KM, Rand KA, et al. Estimates of the heritability of human longevity are substantially inflated due to assortative mating. *Genetics*. 2018;210(3):1109-1124. doi: 10.1534/genetics.118.301613
40. Kalia V, Belsky DW, Baccarelli AA, Miller GW. An exposomic framework to uncover environmental drivers of aging. *Exposome*. 2022;2(1):osac002. doi: 10.1093/exposome/osac002
41. Liu Y, Lachman ME. Education and cognition in middle age and later life: the mediating role of physical and cognitive activity. *J Gerontol B Psychol Sci Soc Sci*. 2020;75(7):e93-e104. doi: 10.1093/geronb/gbz020
42. Mahalakshmi B, Maurya N, Lee SD, Bharath Kumar V. Possible neuroprotective mechanisms of physical exercise in neurodegeneration. *Int J Mol Sci*. 2020;21(16):5895. doi: 10.3390/ijms21165895
43. Walsh NP, Gleeson M, Shephard RJ, et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev*. 2011;17:6-63.
44. WHO. *Global Recommendations on Physical Activity For Health*. World Health Organization; Geneva: 2010. https://apps.who.int/iris/bitstream/handle/10665/272722/9789241514187-eng.pdf
45. WHO. *Seventy-first World Health Assembly A71/18*. Physical Activity for Health. 2018. doi: https://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_18-en.pdf
46. Kohl HW, Craig CL, Lambert EV, et al. The pandemic of physical inactivity: global action for public health. *Lancet*. 2012;380:294-305.
47. Sallis JF, Bull F, Guthold R, et al. Progress in physical activity over the olympic quadrennium. *Lancet*. 2016;388:1325-1336.
48. Strain T, Flaxman S, Guthold R, et al.; Country Data Author Group. National, regional, and global trends in insufficient physical activity among adults from 2000 to 2022: a pooled analysis of 507 population-based surveys with 5·7 million participants. *Lancet Glob Health*. 2024;12(8):e1232-e1243. doi: 10.1016/S2214-109X(24)00150-5
49. WHO. More active people for a healthier world. *Global Action Plan on Physical Activity 2018-2030*. WHO 2018.
50. Althoff T, Sosič R, Hicks JL, King AC, Delp SL, Leskovec J. Large-scale physical activity data reveal worldwide activity inequality. *Nature*. 2017;547(7663):336-339. doi: 10.1038/nature23018
51. Simmons N, Ruiz MR, Ronca F. Perimenopausal physical activity and dementia risk: a systematic review. *Int J Sports Med*. 2024;45(9):637-658. doi: 10.1055/a-2307-8122

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Cieri F, Cross CL, Francesco GD, Caldwell JZK. Dynamic neurocognitive adaptation: A follow-up exposome investigation in aging. *Alzheimer's Dement*. 2025;11:e70103. https://doi.org/10.1002/trc2.70103