

A Culture–Brain Link: Negative Age Stereotypes Predict Alzheimer’s Disease Biomarkers

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Although negative age stereotypes have been found to predict adverse outcomes among older individuals, it was unknown whether the influence of stereotypes extends to brain changes associated with Alzheimer’s disease. To consider this possibility, we drew on dementia-free participants, in the Baltimore Longitudinal Study of Aging, whose age stereotypes were assessed decades before yearly magnetic resonance images and brain autopsies were performed. Those holding more-negative age stereotypes earlier in life had significantly steeper hippocampal-volume loss and significantly greater accumulation of neurofibrillary tangles and amyloid plaques, adjusting for relevant covariates. These findings suggest a new pathway to identifying mechanisms and potential interventions related to the pathology of Alzheimer’s disease.

Keywords: age stereotypes, perceptions of aging, social cognition, Alzheimer’s disease, brain

Although negative age stereotypes have been found to predict a number of adverse outcomes among older individuals (e.g., Levy & Leifheit-Limson, 2009; Westerhof et al., 2014), it was unknown whether the influence of the stereotypes extended to brain structure and pathology. As premised by stereotype embodiment theory, age

stereotypes assimilated from a diversity of sources in the culture at a younger age can impact physiological and cognitive outcomes in later life when these stereotypes become self-relevant (Levy, 2009). The current study, in which the age stereotypes held by dementia-free and physically healthy participants were assessed decades before measures of brain structure and pathology, provided the first opportunity to test whether this theory applies to biomarkers of Alzheimer’s disease.

Specifically, we examined whether negative age stereotypes are a risk factor for the most frequently observed patterns of Alzheimer’s disease biomarkers: decline in the volume of the hippocampus, which is a critical brain region for maintenance of intact memory (Study 1), and the accumulation of amyloid plaques, which are protein clusters that build up between brain cells, and neurofibrillary tangles, which are twisted strands of protein that build up within brain cells (Study 2).

The identification of a culture-based environmental risk factor that contributes to Alzheimer’s disease could be particularly important because such a factor is potentially modifiable (Levy, Pilver, Chung, & Slade, 2014). The underlying assumption of the current study, that negative age stereotypes can influence the development of Alzheimer’s disease-related pathological changes in the brain, is based on research findings that support our expectation of a two-stage pathway. First, these stereotypes can contribute to stress. Second, stress can contribute to pathological changes in the brain.

Consistent with this proposed first stage, an experimental study found that older individuals who were subliminally primed with negative age stereotypes, and were then exposed to stressors, had a significant increase in cardiovascular reactivity, which is linked

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to cardiovascular events (Levy, Hausdorff, Hencke, & Wei, 2000). Additionally, the negative age stereotypes directly increased cardiovascular measures even before the stress phase of the study (Levy et al., 2000). This suggests that the negative age stereotypes both exacerbated the stress of an external challenge and acted as a direct stressor. In contrast, the positive age stereotypes appeared to have a protective effect, because the participants exposed to the positive age stereotypes did not show an increase in cardiovascular reactivity from baseline.

The internalization of negative age stereotypes makes it likely that the stressfulness they generate in the laboratory would also be found over time. This is because just as participants were experimentally primed with negative age stereotypes, older individuals in the community who hold more-negative age stereotypes tend to be subjected to what is, in effect, serial priming: Frequent-everyday-life encounters with varied forms of ageism in the environment can repetitively activate the internalized negative age stereotypes (Butler, 2008; Levy et al., 2000; Palmore, 2005). Age stereotypes encountered in the environment often fit the criteria for the types of stressors that are particularly harmful to health: (a) negative, (b) uncontrollable, (c) unpredictable, and (d) repeated over time (Williams & Mohammed, 2009).

This background to the relationship between negative age stereotypes and stress may help to explain the results of a longitudinal study in which the age stereotypes of participants were measured at baseline, decades before old age (Levy, Zonderman, Slade, & Ferrucci, 2009). Those holding more-negative age stereotypes had a significantly greater risk of experiencing cardiovascular events up to 38 years later, compared to those holding more-positive age stereotypes. This outcome accords with the well-established relationship of long-term stress to experiencing cardiovascular events (e.g., Steptoe & Kivimäki, 2012). It is also consistent with the higher rates of diastolic blood pressure that were found among middle-aged Black women who perceived greater day-to-day racial discrimination (Guyll, Matthews, & Bromberger, 2001).

Evidence for the second stage of the negative-age-stereotype-to-brain pathway, which involves stress influencing the brain, comes in part from research that has identified stress-hormone receptors in the hippocampus (Fenchel et al., 2015; McEwen, 1998). Although acute stress can have beneficial effects, cumulative stress can damage the brain (McEwen & Gianaros, 2011; Sapolsky, 1996). A contributor to the damage is the prolonged secretion of stress biomarkers (McEwen, 2012).

The influence of cumulative stress on Alzheimer's disease biomarkers has been demonstrated most clearly in animal research. As an example, a series of studies found that experimentally stressed mice tend to show increases in amyloid plaques and tangles, as well as decreases in hippocampal volume (Ahmadian-Attari et al., 2015; Carroll et al., 2011; Lee, Jarome, Li, Kim, & Helmstetter, 2009). In humans, those who suffer from posttraumatic stress disorder (PTSD), which is associated with cumulative stress, tend to show a significantly greater decline in hippocampal volume than do those without PTSD (Chao, Yaffe, Samuelson, & Neylan, 2014; Woon, Sood, & Hedges, 2010); older individuals with more-negative age stereotypes tend to experience higher rates of PTSD (Levy, Pilver, & Pietrzak, 2014).

This array of research findings buttresses our hypotheses that, compared with participants holding more-positive age stereotypes, those holding more-negative age stereotypes would show (a) a

steeper decline of hippocampal volume and (b) a greater accumulation of amyloid plaques and neurofibrillary tangles.

Study 1

The first study examined whether participants holding more-negative age stereotypes would have significantly greater loss of hippocampal volume over time.

Method

Participants. The cohort consisted of individuals who enrolled in the brain-neuroimaging program of the Baltimore Longitudinal Study of Aging (BLSA; Ferrucci, 2008). Enrollees received up to 10 yearly MRI scans. Inclusion criteria for this program, at time of first scan, were as follows: free of dementia as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., revised; American Psychiatric Association, 1987); physically healthy, defined as not having central-nervous-system disease, severe cardiovascular disease, severe pulmonary disease, or metastatic cancer (Driscoll et al., 2009; O'Brien et al., 2009; Resnick et al., 2000); and willingness to undergo yearly MRI scans. There were 158 participants who elected to enroll in the brain-neuroimaging program (Resnick et al., 2000).

Additional inclusion criteria for the current study were as follows: provided baseline data on age stereotypes and covariates and remained in the study until at least 60 years old. There were 52 participants who met all the inclusion criteria. The average age of the final cohort was 68.54 ($SD = 6.93$) years at the time of first MRI assessment; 92% completed high school; 31% were women; and at baseline, they tended to have high self-rated health ($M = 4.58$, $SD = 0.54$), measured on a Likert scale ranging from 1 (*very poor*) to 5 (*excellent*).

Measures.

Predictor: Negative age stereotypes. Negative age stereotypes were assessed with the 16-item age-stereotype subscale of the BLSA's Attitudes toward Old People Scale (e.g., "Old people are absent-minded"; Tuckman & Lorge, 1953), starting in 1968. Scores range from 0 to 16, with a higher score signifying more-negative age stereotypes. These subscale items were found to load on a single factor (Hatcher, 1994; Levy et al., 2009). The subscale has good reliability (Cronbach's alpha of .80) and has been found to be valid (Kline, 2000; Levy et al., 2009). It has significantly correlated in the expected direction with the Image of Aging Scale (Levy, Kasl, & Gill, 2004) and has predicted outcomes in the expected direction (Levy et al., 2009; Levy, Zonderman, Slade, & Ferrucci, 2012).

Outcome: Hippocampal volume. Hippocampal volume was assessed yearly by MRIs for up to 10 years (for details on image quantification, see Driscoll et al., 2009). Our study participants had a total of 364 MRI assessments, with an average of seven per participant. Because longitudinal trajectories did not significantly differ for the right and left hippocampal volumes in the cohort, $t(94) = 1.13$, $p > .250$, $d = 0.21$, 95% confidence interval (CI) $[-.16, .57]$, we averaged the hippocampal volumes at each time point. MRI scans took place an average of 25.08 ($SD = 5.18$) years after the baseline-age-stereotype measure.

Covariates. The covariates considered have been found to relate to the predictor and/or the outcome in previous research

(Driscoll et al., 2009; Levy, 1996, 2009; Resnick et al., 2000). These covariates consisted of demographics (i.e., age, sex, and education) and health at time of baseline-age-stereotype assessment, that is, number of chronic conditions on the basis of medical records; well-being as measured by a subset of the Chicago Attitude Inventory (Burgess, Cavan, & Havighurst, 1948); and self-rated health. Additional covariates were neuroticism, measured by the neuroticism dimension of the NEO Personality Inventory (Costa & McCrae, 1992), and cognitive performance, measured by the Benton Visual Retention Test (BVRT; Benton, 1974). The well-being measure (Burgess et al., 1948) has good test-retest reliability and has been validated in a number of studies with older individuals (Costa, McCrae, & Norris, 1981; Larson, 1978; Shock, 1952). The BVRT was selected because it measures visual recall, which is sensitive to decline with age (Lamar, Zonderman, & Resnick, 2002), and has been found to be valid with older individuals (Giambra, Arenberg, Zonderman, Kawas, & Costa, 1995). We also included intracranial volume as a covariate to ensure that hippocampal-volume findings were above and beyond individual differences in overall brain volume (Driscoll et al., 2009; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003).

Statistical analyses. To examine whether those holding more-negative age stereotypes had a significantly steeper decline in hippocampal volume, we conducted a multivariate model, with the interaction of time and negative age stereotypes as the predictor of hippocampal volume over time. Both variables were continuous. Nonlinearity was checked by adding an age-squared term to the model. The term was not significant ($F = 0.51, p > .25, d = 0.077, 95\% \text{ CI} [-.135, .290]$). Hence, we used a linear mixed-effects regression model. In the model, a one-tailed test of significance was used to reflect the predicted pattern of results of age stereotypes, on the basis of previous studies of the adverse effect of negative age stereotypes on other outcomes (Levy, 2009; Levy, Slade, Murphy, & Gill, 2012; Meisner, 2012; Sargent-Cox, Anstey, & Luszcz, 2012; Westerhof et al., 2014).

To maintain power in the models, we created a parsimonious model by backward elimination, which removed the covariates that did not reach significance, after the forced inclusion of the demographic and health variables, ($p < .05$, two-tailed; Harrell, 2001).

To make sure that the models were not influenced by extreme observations, we conducted two outlier analyses. We examined whether any observation was more than three standard deviations from the regression line of the final model and whether any observation was more than one Cook's distance (Cook & Weisberg, 1982).

Internal validation was conducted using bootstrap modeling, a resampling with replacement procedure (Efron & Tibshirani, 1986). To be conservative, we selected 10,000 samples, each consisting of 74 observations, the same as in the original model (Efron & Tibshirani, 1998; Pattengale, Alipour, Bininda-Emonds, Moret & Stamatakis, 2010). We checked whether the parameter estimate of age stereotypes on hippocampal volume from the original model was within the 95% confidence interval of the median-parameter estimate of age stereotypes on hippocampal volume from the bootstrap procedure.

To present the age-stereotype groups for illustration in Figure 1, the sample was dichotomized into those below and those at or above the age-stereotype-measure mean of seven. In the multivar-

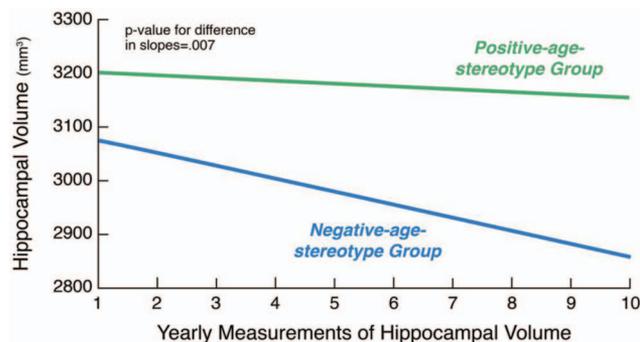


Figure 1. Association of age stereotypes with hippocampal-volume decline over time. The figure is based on a model that adjusted for covariates.

iate models, however, the age-stereotype measure was examined as a continuous variable.

Results

As predicted, participants holding more-negative age stereotypes, compared to those holding more-positive age stereotypes, had a significantly steeper decline in hippocampal volume in the full model ($F = 6.24, p = .007, d = 0.29$), adjusting for age, sex, education, self-rated health, well-being, number of chronic conditions, and intracranial volume.

The rate of hippocampal-volume decline in the negative-age-stereotype group was three times the rate of decline in the positive-age-stereotype group (see Figure 1). That is, participants holding more-negative age stereotypes tended to have the same hippocampal-volume decline in 3 years that participants holding more-positive age stereotypes tended to have in 9 years.

We determined that the association of negative age stereotypes with greater hippocampal volume was not caused by outliers. All observations of hippocampal volume were within three standard deviations of the regression line, and all but one observation had a Cook's distance less than the cutoff criterion of one for outliers (Cook & Weisberg, 1982). When we removed this observation that was considered an outlier, it was found that negative age stereotypes continued to predict a decline in hippocampal volume over time ($F = 4.78, p = .0148, d = 0.25$).

The results of the bootstrap analysis, with 10,000 samples of 74 participants each, showed that the parameter estimate for age stereotypes on hippocampal volume from the original-model was stable and robust (Pattengale et al., 2010). This original-age-stereotype-parameter estimate did not differ significantly from the median-parameter estimate for age stereotypes on hippocampal volume that was generated by the bootstrap analysis, because the original parameter estimate was within the 95% confidence interval of the bootstrapped-median-parameter estimate (Efron & Tibshirani, 1998).

Study 2

The second study examined whether participants holding more-negative age stereotypes would have significantly greater accumulation of amyloid plaques and neurofibrillary tangles.

Method

Participants. All BLSA participants were invited to join the brain-autopsy program. It aims to compare structural changes due to normal aging with those due to disease (Dolan et al., 2010; O'Brien et al., 2009). Our participants met the following criteria in addition to having a brain autopsy: remained in the study until at least 60 years old and provided baseline data on age stereotypes and covariates. There were 74 participants who met all the inclusion criteria. The average age of the final cohort was 88.75 ($SD = 6.45$) years at the time of autopsy; 96% completed high school; 26% were women; and at baseline, they tended to have high self-rated health ($M = 4.51$, $SD = .51$).

Measures.

Predictor: Negative age stereotypes. The predictor was the same one used in Study 1. It was examined as a continuous variable.

Outcome: Composite-plaques-and-tangles score. For the primary outcome, we used a composite-plaques-and-tangles score that has been validated in previous studies, and which is useful for quantitating the combined effects of amyloid plaques and neurofibrillary tangles in relation to cognitive impairment (Dolan et al., 2010; Troncoso et al., 2008). Investigators at the Johns Hopkins University Alzheimer's Disease Research Center, without knowledge of participants' age-stereotype scores, identified amyloid plaques and neurofibrillary tangles in five brain regions: superior/middle temporal gyrus, medial frontal lobe, inferior parietal cortex, orbitofrontal cortex, and occipital cortex (Troncoso et al., 2008). Amyloid plaques were graded according to the criteria of the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) and were then divided into three groups: 1 = zero or mild; 2 = moderate; and 3 = frequent (Mirra et al., 1991). Neurofibrillary tangles were graded according to Braak criteria (Braak & Braak, 1991) and then divided into three groups: 1 = preclinical (Braak Stages 0, I, and II); 2 = moderate (Braak Stages III and IV); and 3 = severe (Braak Stages V and VI; Shoghi-Jadid et al., 2002). The amyloid plaques and neurofibrillary tangles were assessed an average of 28.49 ($SD = 6.03$) years after the baseline-age-stereotype measurement.

The sum of the modified CERAD and Braak scores yielded a composite-plaques-and-tangles score ranging from 2 to 6, with a higher score indicating a more-advanced condition (Dolan et al., 2010; Troncoso et al., 2008).

Covariates. The covariates considered have been found to relate to the predictor and/or the outcome in previous research (Driscoll et al., 2009; Levy, 1996, 2009; Resnick et al., 2000). These covariates consisted of demographics (i.e., age, sex, and education) and health at time of baseline-age-stereotype assessment, that is, number of chronic conditions on the basis of medical records, well-being (Burgess et al., 1948), and self-rated health. Additional covariates were neuroticism, as measured by the neuroticism dimension of the NEO Personality Inventory (Costa & McCrae, 1992), and cognitive performance, as measured by the BVRT (Benton, 1974).

Statistical analyses. To examine whether those holding more-negative age stereotypes had higher composite-plaques-and-tangles scores, we conducted a generalized linear model with the negative-age-stereotype measure included as a continuous variable and the composite-plaques-and-tangles score as the

outcome. A one-tailed test of significance was used to reflect the predicted pattern of how negative age stereotypes were likely to exert their impact (e.g., Levy, 2009; Levy, Slade, et al., 2012; Meisner, 2012; Sargent-Cox et al., 2012; Westerhof et al., 2014).

To maintain power in the models, we created a parsimonious model by backward elimination, which removed the covariates that did not reach significance, after the forced inclusion of the demographic and health variables, ($p < .05$, two-tailed; Harrell, 2001).

To make sure that the models were not influenced by extreme observations, we conducted two outlier analyses. We examined whether any observation was more than three standard deviations from the regression line of the final model and whether any observation was more than one Cook's distance (Cook & Weisberg, 1982).

Internal validation was conducted using bootstrap modeling (Efron & Tibshirani, 1986). To be conservative, we selected 10,000 samples, each consisting of 52 observations, the same as in the original model (Efron & Tibshirani, 1998; Pattengale et al., 2010). We checked whether the parameter estimate of age stereotypes on the composite-plaques-and-tangles score from the original model was within the 95% confidence interval of the median-parameter estimate of age stereotypes on the composite-plaques-and-tangles score from the bootstrap procedure.

Results

As predicted, participants holding more-negative age stereotypes, compared to those holding more-positive age stereotypes, had significantly higher composite-plaques-and-tangles scores, $t(1, 59) = 1.71$, $p = .046$, $d = 0.45$, adjusting for age, sex, education, self-rated health, well-being, and number of chronic conditions (see Figure 2).

The association of negative age stereotypes with higher composite-plaques-and-tangles scores was not caused by outliers. We found that all of the scores were within three standard deviations of the regression line, and all scores were less than the Cook's distance cutoff of one for outliers (Cook, & Weisberg, 1982).

The results of the bootstrap procedure showed that the parameter estimate for age stereotypes on the composite-plaques-and-tangles scores from the original model was stable and robust (Pattengale et al., 2010). This original-age-stereotype-parameter estimate did not differ significantly from the median-parameter estimate for age stereotypes on the composite-plaques-and-tangles scores that were generated by the bootstrap analysis, because the original parameter estimate was within the 95% confidence interval of the bootstrapped median-parameter estimate (Efron & Tibshirani, 1998).

General Discussion

As predicted, participants holding more-negative age stereotypes had a significantly steeper decline of hippocampal volume than did those holding more-positive age stereotypes. Also as predicted, participants holding more-negative age stereotypes had a significantly greater accumulation of amyloid plaques and neurofibrillary tangles, compared to those holding more-positive age stereotypes.

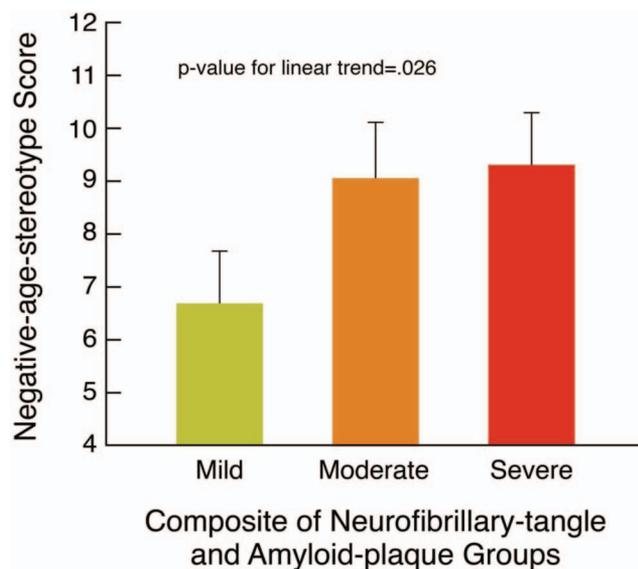


Figure 2. More-negative age stereotypes associated with severity of neurofibrillary-tangle and amyloid-plaque pathology. The mean negative-age-stereotype scores and standard error of the means bars are adjusted for covariates. The groups are based on the composite-plaques-and-tangles scores of 2 or 3 = Mild, 4 = Moderate, and 5 or 6 = Severe.

The robustness of the findings is indicated by the disparateness of the methods used to measure the outcomes: Longitudinal MRI scans for hippocampal volume in the first study, whereas the second study relied on brain autopsies to generate the composite measure of amyloid plaques and neurofibrillary tangles. Additional indications of this robustness include the following: Negative age stereotypes predicted the biomarkers in the two studies, even though the samples differed in their average ages by 20 years; these results were not due to the influence of extreme values; and the internal validation procedure of bootstrapping replicated the results from the original models with both hippocampal volume and the composite measure of amyloid plaques and neurofibrillary tangles as the outcomes.

Several factors support our assumption that negative age stereotypes contributed to the Alzheimer's disease biomarkers, rather than the reverse direction. First, the baseline measurement of stereotypes occurred more than 20 years before the measurement of hippocampal volume as well as plaques and tangles. Second, all participants were dementia-free at baseline, and members of the neuroimaging subsample were dementia-free at the initial MRI scans (O'Brien et al., 2009). Third, previous studies have demonstrated that negative age stereotypes increased stress, but the reverse did not occur; the negativity of age stereotypes held by older individuals did not significantly change over a 10-year period, despite encounters with highly stressful life events (Levy et al., 2000; Levy, Slade, Chung, & Gill, 2014).

A limitation of the otherwise comprehensive data available for our cohort is that it did not include a perceived-stress measure. Perhaps future research will examine stress as a mediator of the relationship of age stereotypes on Alzheimer's disease biomarkers.

Our finding that negative age stereotypes held earlier in life predicted brain pathology in later life may shed light on a prior

finding that those holding more-negative age stereotypes before old age experienced significantly greater memory-performance decline in later life (Levy, Slade, et al., 2012). (The potential role of brain pathology was not considered in that study.)

The current study is the first to demonstrate that a culture-based risk factor predicts the development of Alzheimer's disease-related pathological changes in the brain. This finding provides a basis for reinterpreting Alzheimer's disease data. To illustrate, diet, a previously established environmental factor (Mattson, 2004), has been posited as an explanation for why the rate of Alzheimer's disease in the United States is five times that of India (Grant, Campbell, Itzhaki, & Savory, 2002). Alternatively, this discrepancy might be explained by a comparison of those two cultures from which age stereotypes are derived: India has a tradition of venerating elders (Bhat & Dhruvarajan, 2001), whereas the United States has a prevalence of negative age stereotypes (Butler, 2008; Levy, Slade, Kunkel, & Kasl, 2002). By expanding the boundaries of known environmental influences on amyloid plaques, neurofibrillary tangles, and hippocampal volume, our results suggest a new pathway to identifying mechanisms and potential interventions related to Alzheimer's disease.

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