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# ASSOCIATION OF SELF-REFLECTION WITH COGNITION AND BRAIN HEALTH IN COGNITIVELY UNIMPAIRED OLDER ADULTS

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## ABSTRACT

### BACKGROUND AND OBJECTIVES

Self-reflection (the active evaluation of ones thoughts, feelings, and behaviors) can confer protection against adverse health outcomes. Its effect on markers sensitive to Alzheimer disease (AD), however, is unknown. The primary objective of this cross-sectional study was to examine the association between self-reflection and AD-sensitive markers.

### METHODS

This study used baseline data from cognitively unimpaired older adults enrolled in the Age-Well clinical trial and older adults with subjective cognitive decline from the SCD-Well clinical trial. In both cohorts, self-reflection was measured via the reflective pondering subscale of the Rumination Response Scale, global cognition assessed via the Preclinical Alzheimer's Cognitive Composite 5, and a modified late-life Lifestyle-for-Brain-Health (LIBRA) index computed to assess health and lifestyle factors. In Age-Well, glucose metabolism and amyloid deposition were quantified in AD-sensitive gray matter regions via fluorodeoxyglucose- and AV45-PET scans, respectively. Associations between self-reflection and AD-sensitive markers (global cognition, glucose metabolism, and amyloid deposition) were assessed via unadjusted and adjusted regressions. Furthermore, we explored whether associations were independent of health and lifestyle factors. To control for multiple comparisons in Age-Well, false discovery rate–corrected *p* values ($p_{FDR}$) are reported.

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**RESULTS**

A total of 134 (mean age 69.3 ± 3.8 years, 61.9% women) Age-Well and 125 (mean age 72.6 ± 6.9 years, 65.6% women) SCD-Well participants were included. Across unadjusted and adjusted analyses, self-reflection was associated with better global cognition in both cohorts (Age-Well: adjusted-β = 0.22, 95% CI 0.05–0.40, $p_{FDR}$ = 0.041; SCD-Well: adjusted-β = 0.18, 95% CI 0.03–0.33, $p$ = 0.023) and with higher glucose metabolism in Age-Well after adjustment for all covariates (adjusted-β = 0.29, 95% CI 0.03–0.55, $p_{FDR}$ = 0.041). Associations remained following additional adjustment for LIBRA but did not survive false discovery rate (FDR) correction. Self-reflection was not associated with amyloid deposition (adjusted-β = 0.13, 95% CI −0.07 to 0.34, $p_{FDR}$ = 0.189).

**DISCUSSION**

Self-reflection was associated with better global cognition in 2 independent cohorts and with higher glucose metabolism after adjustment for covariates. There was weak evidence that relationships were independent from health and lifestyle behaviors. Longitudinal and experimental studies are warranted to elucidate whether self-reflection helps preserve cognition and glucose metabolism or whether reduced capacity to self-reflect is a harbinger of cognitive decline and glucose hypometabolism.

**TRIAL REGISTRATION INFORMATION**

Age-Well: NCT02977819; SCD-Well: NCT03005652.

**GLOSSARY**

**AD** = Alzheimer disease; **FDG** = fluorodeoxyglucose; **LIBRA** = Lifestyle for Brain Health; **MMSE** = Mini-Mental State Examination; **PACC5** = Preclinical Alzheimer's Cognitive Composite; **RRS** = Rumination Response Scale; **SUVR** = standard uptake value ratio.

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Alzheimer disease (AD) has an extended preclinical phase whereby subtle changes in brain pathology and cognitive function occur decades before the clinical onset.[1] In the absence of effective disease-modifying treatments, attention has shifted toward identifying risk and protective factors that might hasten or delay future AD.

Several studies have identified modifiable risk and protective factors for AD, with up to 40% of cases being attributable to modifiable factors.[2,3] However, despite evidence pointing toward the importance of psychological factors in healthy aging,[4] relatively few studies have explored associations between modifiable psychological characteristics and AD risk. Existing research in this nascent field has primarily focused on negative psychological factors (e.g., depression,[5,6] anxiety,[7] and neuroticism[8]), but evidence suggests that some psychological characteristics may confer protection against AD. For example, purpose in life[9] and the personality characteristic conscientiousness[10] have been associated with markedly reduced AD incidence. Novel neuroimaging and clinicopathologic findings have demonstrated that purpose in life[11] and conscientiousness,[12] among other psychological characteristics (e.g., resilience to stress,[13] optimism,[14] and trait mindfulness[15]), may bestow protective benefit. Specifically, higher levels of conscientiousness and trait mindfulness and greater resilience to stress have been associated with less amyloid deposition and/or tau aggregation.[10,13,15] Furthermore, although purpose in life has not been directly associated with AD pathology, it has been found to modify the association between a global measure of AD pathologic changes and cognition, with individuals reporting higher levels of purpose in life exhibiting better cognition despite greater AD pathology.[11] Extant evidence therefore indicates that benefits of positive styles of thinking may be conferred by either reducing the deleterious effects of AD pathologic changes on cognitive abilities (i.e., resilience) or via the avoidance of pathology in the first place (i.e., resistance).[16]

Self-reflection, the active evaluation of one's thoughts, feelings, and behaviors, is an introspective cognitive mechanism related to many positive psychological characteristics, including purpose in life[11] and resilience to stress.[17] Despite some conflicting evidence (e.g., positive associations with depression and brooding[18]), self-reflection is primarily considered an adaptive characteristic, whereby engagement encourages awareness and evaluation of one's stress response.[19] Indeed, studies have demonstrated that adopting a self-reflective thinking style yields more adaptive stress responses, which in turn lead to better short-term and longer-term biological and psychological outcomes.[19] For instance, emerging evidence links self-reflection with reduced inflammatory responses to acute psychological stressors (e.g., interleukin-6 and cortisol),[17,20] better cardiovascular health (e.g., reduced heart rate variability),[21] and improved mental health (e.g., recovery from major depressive disorder).[22,23] Furthermore, self-reflection has been associated with positive lifestyle factors, including greater engagement in health-promoting behaviors (e.g., lower alcohol consumption and greater physical exercise)[23,24] and high openness to experience,[19] which is posited to promote more frequent and intensive engagement in stimulating leisure activities.

Despite evidence that self-reflection can confer protection against adverse health outcomes, the association between self-reflection and AD-sensitive markers is unknown. To address this gap, we

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sought to (1) determine the association between self-reflection and cognition and brain health and (2) explore whether any associations between self-reflection and AD-sensitive markers are independent of health and lifestyle factors.

# Methods

## PARTICIPANTS

### AGE-WELL

Baseline data from 134 cognitively unimpaired older adults enrolled in the Age-Well randomized clinical trial, who completed an assessment of self-reflection, were included. All participants were recruited from the general population, aged 65 years or older, native French speakers, retired for at least 1 year, received at least 7 years of education, had no evidence of major neurologic or psychiatric disorders, and performed within normal ranges on standardized cognitive tests. Detailed eligibility criteria have been previously described.[25]

### SCD-WELL

Baseline data from 125 older adults enrolled in the SCD-Well randomized clinical trial, who completed an assessment of self-reflection, were included. Participants were recruited through memory clinics at 4 European centers (London, United Kingdom; Lyon, France; Cologne, Germany; and Barcelona, Spain), met the published criteria for subjective cognitive decline (i.e., self-perceived decline in cognitive capacity but normal performance on standardized cognitive tests used to classify mild cognitive impairment or prodromal AD[26]), were aged 60 years or older, and had no evidence of major neurologic or psychiatric disorders. Further eligibility criteria are reported elsewhere.[27]

In both cohorts, age, sex, years of education, and country of residence were obtained from participants at baseline. In Age-Well, participants also provided a blood sample for *APOE* genotyping (eMethods, links.lww.com/WNL/C203), with ε4 carriers collapsed into one category.

## STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENTS

Both trials were approved by local ethics committees and were registered on ClinicalTrials.gov (Age-Well: NCT02977819; SCD-Well: NCT03005652). All participants provided written informed consent before participation.

## BEHAVIORAL MEASURES

### SELF-REFLECTION

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Participants completed the full 22-item Rumination Response Scale (RRS), with scores from the 5-item reflective pondering subscale used to assess self-reflection levels.[22] A 4-point Likert scale ranging from 1 (almost never) to 4 (almost always) was used for each item. Item scores were summed to yield a total score for each participant (possible range: 5–20), with higher scores indicating greater self-reflection levels. The RRS is widely used in clinical psychology and psychopathology research,[28] has previously been administered to older adult populations, and has displayed adequate psychometric properties.[22,29]

## PSYCHOLOGICAL DISTRESS

Brooding (i.e., passive and judgmental thoughts about one's mood) was assessed via the brooding subscale of the RRS (possible range: 5–20).[22] Depressive symptoms were measured using the Geriatric Depression Scale (possible range: 0–15).[30]

## HEALTH AND LIFESTYLE

The late-life Lifestyle-for-Brain-Health (LIBRA) composite[31] is a polyenvironmental risk score for cognitive functioning and dementia risk.[32] It typically comprises 10 health and lifestyle factors (i.e., depression, coronary heart disease, diabetes, hypercholesterolemia, smoking, physical inactivity, renal disease, low-to-moderate alcohol use, high cognitive activity, and healthy diet), which receive weights based on their relative risk.[33] Self-reflection is commonly confounded with psychological distress[34]; we therefore removed depression and calculated a 9-item modified LIBRA index,[33] so analyses could be adjusted for psychological distress (i.e., depression and brooding; see above). In both cohorts, weights of the remaining 9 factors were summed to yield LIBRA scores (possible range: −5.9 to 7.4), with higher scores indicating poorer health and lifestyle behaviors. See eTable 1, links.lww.com/WNL/C203, for detailed definitions and weights attributed to each factor.

## COGNITION

The Preclinical Alzheimer's Cognitive Composite 5 (PACC5) is a validated global cognitive composite sensitive to detecting and tracking preclinical AD-related decline.[35] The PACC5 includes 2 measures of episodic memory and executive function and 1 measure of global cognition. In Age-Well, all measures were available. SCD-Well had only 4 (a single measure of episodic memory); therefore, an abridged version of the PACC5 ($PACC5_{Abridged}$) was created. The specific measures included in the PACC5/$PACC5_{Abridged}$ are provided in Table 1. Briefly, PACC5/$PACC5_{Abridged}$ scores were computed in Age-Well and SCD-Well separately by converting each measure into a z-score and then taking the unweighted average (see eMethods, links.lww.com/WNL/C203, for further details).

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**Table 1** Cognitive Tests Used to Compute the PACC5/PACC5$_{Abridged}$

| | SCD-Well (PACC5$_{Abridged}$) | Age-Well (PACC5) |
|---|---|---|
| **Global memory** | Dementia Rating Scale 2 (total score) | Dementia Rating Scale 2 (total score) |
| **Executive function** | Wechsler Adult Intelligence Scale IV Coding (raw score) | Wechsler Adult Intelligence Scale IV Coding (raw score) |
| **Episodic memory** | Rey Auditory Verbal Learning Test (delayed recall score) | California Verbal Learning Test (delayed free recall score) |
| **Episodic memory** | — | Logical Memory Test (delayed recall score) |
| **Semantic memory** | Category Fluency (1 × 2 min [no. of correct animals stated]) | Category Fluency (1 × 2 min [no. of correct animals stated]) |

Abbreviation: PACC5 = Preclinical Alzheimer's Cognitive Composite 5.

## NEUROIMAGING MEASURES

Age-Well participants were scanned at the Cyceron Center (Caen, France) on the same PET (Discovery RX VCT 64 PET-CT; General Electric Healthcare) and MRI (Philips Achieva 3.0T scanner; used for PET preprocessing only) scanners. Detailed acquisition and preprocessing procedures have previously been published and are available in the eMethods, links.lww.com/WNL/C203.[25]

Participants (N = 131) underwent a florbetapir (AV45, Amyvid) PET scan to assess amyloid deposition, and a subset (N = 92) also underwent a fluorodeoxyglucose (FDG) PET scan to assess brain glucose metabolism. Standard uptake value ratios were obtained from a predetermined AD-sensitive neocortical mask for amyloid burden and the temporoparietal regions for FDG-PET, as previously defined[36] (eMethods, links.lww.com/WNL/C203). FDG-PET analyses were performed only on images corrected for partial volume effects using the 3-compartmental voxel-wise Müller-Gartner method.[37]

## STATISTICAL ANALYSES

Differences between cohorts and the associations between self-reflection and potential confounds (i.e., demographic characteristics and psychological distress) were investigated. Nonparametric tests (i.e., Spearman rho and Kruskal-Wallis) were used where data were not normally distributed.

To determine associations between self-reflection and AD-sensitive markers, we performed a series of linear regression models with each marker as the dependent variable (i.e., global cognition, glucose metabolism, and amyloid deposition) in Age-Well and SCD-Well separately. Model 1 was unadjusted, model 2 was adjusted for relevant demographic characteristics (i.e., age, sex, education, and [in SCD-Well] country of residence), and model 3 was adjusted for demographic characteristics and psychological distress (i.e., depressive symptoms and brooding levels). For analyses where glucose metabolism and amyloid deposition were the dependent variables, *APOE* ε4 status was also included as a covariate in models 2 and 3.

In exploratory analyses, we tested whether the presence of amyloid pathology altered associations between self-reflection and global cognition and glucose metabolism by including a self-reflection-by-amyloid deposition interaction. Furthermore, in Age-Well, where *APOE* data were available, we

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included *APOE* ε4 status as an additional covariate in models 2 and 3, when assessing the association between self-reflection and cognition.

Finally, to explore the potential mechanism linking self-reflection with AD-sensitive markers, we examined the relationship between self-reflection and LIBRA in a series of unadjusted and adjusted regressions (i.e., models 1, 2, and 3). In further exploratory analyses, LIBRA was then added as an additional covariate in analyses investigating associations between self-reflection and each AD-sensitive marker (i.e., model 4: demographic characteristics, psychological distress, and LIBRA).

There is an ongoing debate surrounding the utility of correcting for multiple comparisons.[38,39] We therefore report the number of analyses performed and provide both unadjusted and adjusted *p* values to facilitate interpretations regarding the strength of evidence. Specifically, Benjamini-Hochberg–adjusted *p* values, which control the false discovery rate (FDR), are reported for the Age-Well analyses. All analyses were conducted using R, version 4.0.2, and used 2-tailed hypothesis tests with $\alpha = 0.05$.

### DATA AVAILABILITY

The Age-Well and SCD-Well study protocols, including summary statistical analysis plans, have previously been published.[25,27] The Material can be mobilized, under the conditions and modalities defined in the Medit-Ageing Charter by any research team belonging to an Academic, for carrying out a scientific research project relating to the scientific theme of mental health and well-being in older people. The Material may also be mobilized by nonacademic third parties, under conditions, in particular financial, which will be established by separate agreement between Inserm and the said third party.

## Results

### PARTICIPANT CHARACTERISTICS

Demographic characteristics for each cohort are provided in Table 2. Participants in Age-Well were younger ($W = 6{,}016$, $p < 0.001$) and had better cognition ($t[264.70] = 5.07$, $p < 0.001$) and lower levels of brooding ($W = 7{,}190$, $p = 0.047$) relative to SCD-Well participants. In both cohorts, self-reflection was positively associated with brooding levels (Age-Well: $r_s[134] = 0.49$, $p < 0.001$; SCD-Well: $r_s[125] = 0.36$, $p < 0.001$) and depressive symptoms (Age-Well: $r_s[134] = 0.22$, $p = 0.011$; SCD-Well: $r_s[125] = 0.21$, $p = 0.021$). Self-reflection was additionally negatively associated with age ($r_s[134] = -0.25$, $p = 0.004$) and positively associated with education ($r_s[134] = 0.19$, $p = 0.027$) in Age-Well, and country of residence ($H[3] = 9.81$, $p = 0.020$, with levels higher in Germany relative to all the countries) in SCD-Well.

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**Table 2** Demographic, Clinical, and Biological Characteristics of the SCD-Well and Age-Well Cohorts

| Characteristics | SCD-Well (N = 125) | Age-Well (N = 134) |
|---|---|---|
| **Demographics** | | |
| **Age, y** | 72.6 (6.9) | 69.3 (3.8) |
| **Female sex, no. (%)** | 82 (65.6%) | 83 (61.9%) |
| **Education, y** | 13.5 (3.8) | 13.1 (3.1) |
| **White race, no. (%)** | 121 (96.8%) | — |
| ***APOE* ε4 carriers, no. (%)** | — | 35 (26.7%)[b] |
| **Trial site, no. (%)** | | |
| **Caen, France** | — | 134 (100.0%) |
| **Barcelona, Spain** | 40 (32.0%) | — |
| **Cologne, Germany** | 21 (16.8%) | — |
| **London, United Kingdom** | 28 (22.4%) | — |
| **Lyon, France** | 36 (28.8%) | — |
| **Self-reflection** | | |
| **RRS reflective pondering score** | 8.5 (2.8) | 8.9 (3.2) |
| **Psychological distress** | | |
| **RRS brooding score** | 8.7 (2.6) | 8.1 (2.3) |
| **GDS depression score** | 2.6 (2.3) | 1.3 (1.7) |
| **Global cognition** | | |
| **$PACC5_{Abridged}$/PACC5** | 0.0 (1.0) | 0.0 (1.0) |
| **Neuroimaging AD markers** | | |
| **Global glucose metabolism, FDG SUVR** | — | 1.2 (0.1)[c] |
| **Global amyloid, florbetapir SUVR** | — | 1.2 (0.2)[d] |
| **Amyloid positive, no. (%)** | — | 28 (21.1%)[d] |
| **Health and lifestyle** | | |
| **LIBRA** | −0.82 (2.5)[a] | −0.41 (1.9) |

Abbreviations: AD = Alzheimer disease; FDG = fluorodeoxyglucose; GDS = Geriatric Depression Scale; LIBRA = Lifestyle for Brain Health; MMSE = Mini-Mental State Examination; PACC5 = Preclinical Alzheimer's Cognitive Composite; RRS = Rumination Response Scale; SUVR = standard uptake value ratio.
Data are presented as mean (SD) of participants unless otherwise indicated.
[a] N = 113.
[b] N = 131.
[c] N = 92.
[d] N = 133.

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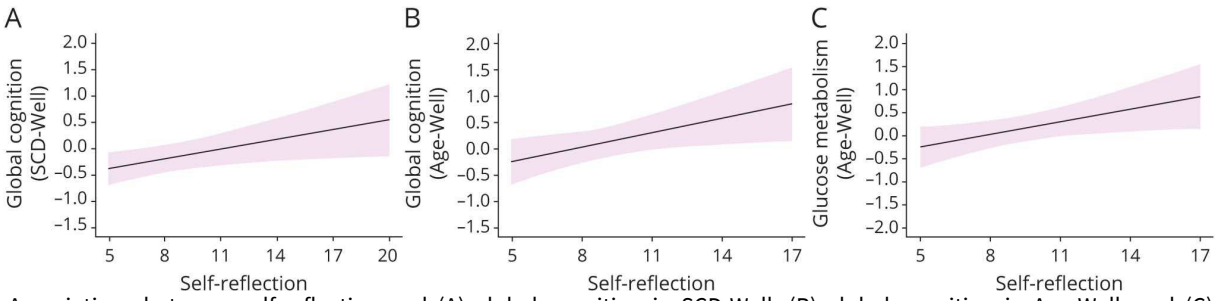
## ASSOCIATIONS BETWEEN SELF-REFLECTION AND AD-SENSITIVE MARKERS

Results from the multiple linear regressions between self-reflection and AD-sensitive markers are presented in Figure 1 and Table 3 and described below.

***Figure 1.*** *Association Between Self-reflection and Global Cognition and Glucose Metabolism in SCD-Well and Age-Well*




Associations between self-reflection and (A) global cognition in SCD-Well, (B) global cognition in Age-Well, and (C) glucose metabolism in Age-Well. The illustrated associations are derived from model 3 adjusted linear regression and represent estimates for the average participant in each cohort (e.g., SCD-Well: female participant from the Barcelona site with mean values for age [72.6], education [13.5], depression symptoms [2.6], and brooding levels [8.7]; Age-Well: female participant, with mean values for age [69.3], education [13.1], depression symptoms [1.3], and brooding levels [8.1]).

**Table 3** Association Between Self-reflection and AD-Sensitive Markers in SCD-Well and Age-Well

| | SCD-Well | | Age-Well | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Global cognition (N = 125) | | Global cognition (N = 134) | | | Glucose metabolism (N = 92)[a] | | | Amyloid deposition (N = 133)[b] | | |
| | Coefficient (95% CI) | *p* Value | Coefficient (95% CI) | *p* Value | $p_{FDR}$ | Coefficient (95% CI) | *p* Value | $p_{FDR}$ | Coefficient (95% CI) | *p* Value | $p_{FDR}$ |
| **Model 1** | 0.23 (0.05 to 0.40) | 0.012 | 0.28 (0.12 to 0.45) | <0.001 | 0.003 | 0.17 (−0.03 to 0.37) | 0.101 | 0.152 | 0.06 (−0.11 to 0.23) | 0.479 | 0.479 |
| **Model 2** | 0.15 (0.01 to 0.29) | 0.042 | 0.16 (0.00 to 0.32) | 0.044 | 0.111 | 0.18 (−0.04 to 0.40) | 0.111 | 0.111 | 0.15 (−0.03 to 0.33) | 0.104 | 0.111 |
| **Model 3** | 0.18 (0.03 to 0.33) | 0.023 | 0.22 (0.05 to 0.40) | 0.014 | 0.041 | 0.29 (0.03 to 0.55) | 0.027 | 0.041 | 0.13 (−0.07 to 0.34) | 0.189 | 0.189 |

Model 1: unadjusted.
Model 2: adjusted for age, sex, education, and (in SCD-Well) country of residence. For glucose metabolism and amyloid deposition analyses, *APOE* ε4 status was included as an additional covariate.
Model 3: adjusted for depressive symptoms and brooding levels along with all model 2 covariates.
[a] N = 89 included in models 2 and 3.
[b] N = 130 included in models 2 and 3.

### GLOBAL COGNITION

In Age-Well, self-reflection was positively associated with PACC5 in the unadjusted model (model 1: standardized estimate = 0.28, 95% CI 0.12–0.45, $p$ <0.001; $p_{FDR}$ = 0.003) and following adjustment for demographic characteristics (model 2: standardized estimate = 0.16, 95% CI 0.00–0.32, $p$ = 0.044; $p_{FDR}$ = 0.111); although the latter association did not survive multiple comparison correction. Following additional adjustment for psychological distress, a positive association, which survived multiple comparison correction, was observed (model 3: standardized estimate = 0.22, 95% CI 0.05–0.40, $p$ = 0.014, $p_{FDR}$ = 0.041). There was no evidence that psychological distress levels were associated with global cognition (*p's* > 0.25; eTable 2, links.lww.com/WNL/C203). In exploratory analyses, neither the inclusion of *APOE* ε4 status as an additional covariate nor a self-reflection-by-amyloid deposition interaction affected results (eTable 3, links.lww.com/WNL/C203).

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The associations between self-reflection and global cognition were replicated in SCD-Well. Specifically, self-reflection was positively associated with $PACC5_{Abridged}$ in unadjusted (model 1: standardized estimate = 0.23, 95% CI 0.05–0.40, $p$ = 0.012) and adjusted analyses (model 2: standardized estimate = 0.15, 95% CI 0.01–0.29, $p$ = 0.042; model 3: standardized estimate = 0.18, 95% CI 0.03–0.33, $p$ = 0.023). Furthermore, there was no evidence that psychological distress levels contributed to model 3 ($p's$ > 0.17; eTable 2, links.lww.com/WNL/C203).

### BRAIN GLUCOSE METABOLISM

There was no evidence of an association between self-reflection and glucose metabolism in either the unadjusted model or the model adjusted for demographic characteristics ($p's$ > 0.101). However, following adjustment for psychological distress, a positive relationship between self-reflection and glucose metabolism emerged (model 3: standardized estimate = 0.29, 95% CI 0.03–0.55, $p$ = 0.027, $p_{FDR}$ = 0.041). Although there was no evidence that depressive symptoms contributed to the model, brooding was negatively associated with glucose metabolism (standardized estimate = −0.26, 95% CI −0.51 to −0.01, $p$ = 0.045 [eTable 2, links.lww.com/WNL/C203]). The association between brooding and glucose metabolism, however, did not survive correction for multiple comparisons ($p_{FDR}$ = 0.135). Inclusion of a self-reflection-by-amyloid deposition interaction did not affect results (eTable 4, links.lww.com/WNL/C203).

### AMYLOID DEPOSITION

We found no evidence of a relationship between self-reflection and amyloid deposition in any analyses ($p's$ > 0.10). Further, results did not change when using florbetapir-PET images corrected for partial volume effects.

## HEALTH AND LIFESTYLE

In both cohorts, self-reflection was negatively associated with LIBRA in all unadjusted and adjusted analyses ($p's$ < 0.02; eTable 4, links.lww.com/WNL/C203). Inclusion of LIBRA as an additional covariate (model 4; eTable 2, links.lww.com/WNL/C203) did not alter associations between self-reflection and either global cognition (Age-Well: standardized estimate = 0.21, 95% CI 0.02–0.39, $p$ = 0.028; SCD-Well: standardized estimate = 0.17, 95% CI 0.01–0.32, $p$ = 0.033) or glucose metabolism (standardized estimate = 0.27, 95% CI 0.01–0.54, $p$ = 0.046). Associations in Age-Well, however, did not survive correction for multiple comparisons (global cognition: $p_{FDR}$ = 0.069; glucose metabolism: $p_{FDR}$ = 0.069).

# Discussion

The present study examined the relationship between self-reflection and markers sensitive to AD. We found that higher levels of self-reflection were associated with better global cognition in 2 independent cohorts of cognitively unimpaired older adults. Furthermore, we found evidence of a

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relationship between self-reflection and glucose metabolism in AD-sensitive neocortical regions. We did not observe associations with amyloid deposition.

Self-reflection has been associated with openness to experience and posited to promote intellectual curiosity, both of which are thought to lead to a lifetime of stimulating activities and learning of new information.[40,41] Prior investigations have demonstrated that factors promoting greater lifetime cognitive activity (e.g., occupational complexity) and openness to experience can bestow cognitive advantages later in life.[42,43] Comparable cognitive advantages have also been reported for positive psychological characteristics, including optimism[14] and trait mindfulness.[15] In the present study, self-reflection was associated with better global cognition, as measured via a cognitive composite sensitive to tracking AD-related decline (i.e., PACC5).[35] Although we propose that engagement in self-reflection helps preserve cognition, the converse relationship must also be acknowledged. Self-reflection involves high-level cognitive functions (e.g., problem-solving); thus, individuals with better cognitive ability may be more able to engage in self-reflection.

Self-reflection was also positively associated with brain glucose metabolism. Furthermore, we observed a negative association between brooding and glucose metabolism. This aligns with literature reporting associations between neuropsychiatric symptoms and glucose hypometabolism in cognitively normal older adults.[44] Together, these opposing associations support the differentiation of self-reflection and brooding as adaptive and maladaptive ruminative styles, respectively.[22] To expand, self-reflection (i.e., the active evaluation of one's thoughts, feelings, and behaviors), but not brooding (i.e., circular, nonpurposeful, and judgmental thinking), is generally considered adaptive because of its association with increased resilience to stress[45] and markers of good mental health (e.g., well-being[46] and recovery from depression[23]). However, it is important to note that although extant literature typically supports an adaptive conceptualization of self-reflection, contrary findings have been reported (e.g., associations with greater suicidal ideation).[18] There is currently no clear explanation to account for these conflicting findings, but it seems likely that the relative adaptiveness of self-reflection may depend on other individual state or trait characteristics (e.g., depression severity).[40] In particular, research has assessed the effect of brooding on the adaptiveness of self-reflection. Despite being distinct constructs, associated with markedly different outcomes, self-reflection, and brooding commonly co-occur.[18,20,22,40] Notably, engaging in self-reflection has been found to predict brooding (but not vice versa), with previous research suggesting that self-reflection becomes brooding when attempts to find solutions to problems are unsuccessful.[40] It has therefore been proposed that a failure to account for brooding in analyses may result in the positive function of self-reflection being masked.[22] In agreement with the above, we found that self-reflection and brooding were positively correlated in both cohorts, and a positive association between self-reflection and glucose metabolism was observed only following adjustment for brooding and depressive symptoms (i.e., psychological distress). These findings highlight that the relative adaptiveness of the self-reflective process can be easily hampered in the presence of (even subclinical) psychological distress levels. Important avenues for future research include investigating under what circumstances self-reflection turns to brooding and whether the associations we observed between self-reflection and AD-sensitive markers are present in psychiatric populations.

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Notably, in the current study, self-reflection was not related to fibrillar amyloid, as measured by PET imaging. Prior studies have reported complementary findings; for example, although purpose in life has been shown to reduce the negative effect of AD pathology on cognition, direct associations with AD pathology (i.e., amyloid and tau) have not been observed.[11] Of interest, the ability to find purpose in life and a developed sense of direction requires engagement in self-reflective practices.[11,47] Together, it is conceivable that, instead of preventing the accumulation of pathologic changes (i.e., providing resistance[16]), self-reflection may contribute to the development of efficient neural systems that allow one to maintain cognition even in the face of accumulating amyloid pathology (i.e., resilience[16]). Indeed, in our exploratory analyses', associations between self-reflection and global cognition and glucose metabolism remained largely unchanged following inclusion of self-reflection-by-amyloid deposition interactions.

The systematic self-reflection model of resilience-strengthening proposes that everyday stressors are pertinent to the development of resilient capacities when scaffolded in self-reflective practices.[19] For example, initial responses to stressors may increase distress levels. However, engagement in self-reflection can facilitate the search for better coping strategies. On re-exposure to similar stressors, an individual's resilience, developed through self-reflection, may then promote better psychological and physiologic outcomes.[19] Although relatively little data are available on the association between self-reflection and physiologic outcomes, emerging evidence indicates that self-reflection is associated with important health-related biomarkers. For example, self-reflection has been negatively associated with cortisol[17] and interleukin-6 levels[20] in older adults. Furthermore, self-reflection has been associated with better cardiovascular health,[21] recovery from psychological ill-health,[22,23] and healthier lifestyles.[48] Stress responses, health, and lifestyle factors are associated with AD risk[2]; thus, self-reflection may affect AD-sensitive markers via one of these pathways. To this end, we investigated the association between self-reflection and health and lifestyle behaviors that have been associated with cognitive functioning and AD risk (i.e., LIBRA) and in exploratory analyses assessed whether self-reflection affects AD-sensitive markers independently of these behaviors.[31,33] Aligning with existing literature, self-reflection was associated with better health and lifestyle behaviors in both cohorts. Of interest, associations between self-reflection and cognition and glucose metabolism remained even after LIBRA was included as an additional covariate. Self-reflection, however, may affect AD-sensitive markers via other factors (e.g., associations with other psychological constructs, stress response, neuroendocrine functions, and inflammatory markers), which we were not able to test in the current study. Future studies, powered to conduct mediation analyses, are required to determine whether health and lifestyle behaviors and/or other factors mediate associations between self-reflection and AD-sensitive markers.

This study has some notable strengths. We replicated the association between self-reflection and global cognition in 2 independent cohorts of cognitively unimpaired older adults, including 1 multicentric study, and additionally characterized these associations using multimodal neuroimaging in the other study. Furthermore, we explored a potential mechanism that might link self-reflection with AD-sensitive markers.

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We must also acknowledge the limitations. First, despite replicating findings in 2 separate cohorts that differed in recruitment population, age, cognition, and brooding levels, the selective nature of the Age-Well and SCD-Well cohorts may limit the generalizability of our findings—participants were highly educated and were screened for the absence of serious physical and mental illnesses. Research conducted in more diverse samples is therefore required to assess the generalizability of our findings. Furthermore, it would be reasonable to surmise that individuals with higher self-reflection levels would be more likely to participate in clinical trials, which include a meditation-based intervention such as Age-Well and SCD-Well. However, self-reflection levels in both cohorts do not appear to be higher than those commonly reported in the literature.[49,50] Second, although the association between self-reflection and brain glucose metabolism survived (an albeit liberal) correction for multiple comparisons, the association was assessed in only one cohort (i.e., Age-Well). Furthermore, exploratory analyses in Age-Well assessing whether associations between self-reflection and AD-sensitive markers are independent of health and lifestyle factors did not survive correction. The exploratory analyses in particular should be interpreted cautiously, with studies including larger sample sizes required to confirm (or refute) our findings. Third, although we adjusted for a wide array of potential confounders (including psychological distress), other variables (e.g., brain atrophy and vascular disease) known to influence our AD-sensitive outcomes were not examined. Finally, the cross-sectional design precludes us from determining causality. For example, although we propose that engagement in self-reflection helps preserve cognitive function and glucose metabolism, the opposite may also be true—preclinical AD alterations and/or symptoms could lead to reduced capacity for self-reflection. Investigations using data from longitudinal cohorts or intervention studies targeting self-reflection would help address this issue. Crucially, evidence suggests that self-reflection is modifiable and that improvement in self-reflection is associated with better health-related outcomes. For example, an intervention designed to promote self-reflection in older adults demonstrated sustained improvements in positive affect, perceived resilience, and physiologic stress responses.[45] The majority of adults can engage in self-reflection to some degree (e.g., irrespective of socioeconomic status and physical health); thus, interventions that focus on promoting self-reflection could be conducted in a large swathe of the population and have wide-reaching positive effects. Both Age-Well and SCD-Well are randomized clinical trials that include meditation interventions and comprehensive AD marker assessments.[25,27] Findings from these studies will indicate whether meditation interventions can promote self-reflection and whether greater engagement in self-reflective practices is associated with changes in AD-sensitive markers.

Self-reflection is associated with cognition and brain health, which may provide protection against AD. The identification of factors that protect against or delay the onset of AD may help combat the large and rapidly increasing public health challenge that this disease possesses. Although it is not yet known whether promoting self-reflection could reduce AD risk, the findings here indicate that this is an avenue worth exploring.

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## Disclosure

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