Neuroimaging in subjective cognitive decline

Verfaillie, S.C.J.

2018

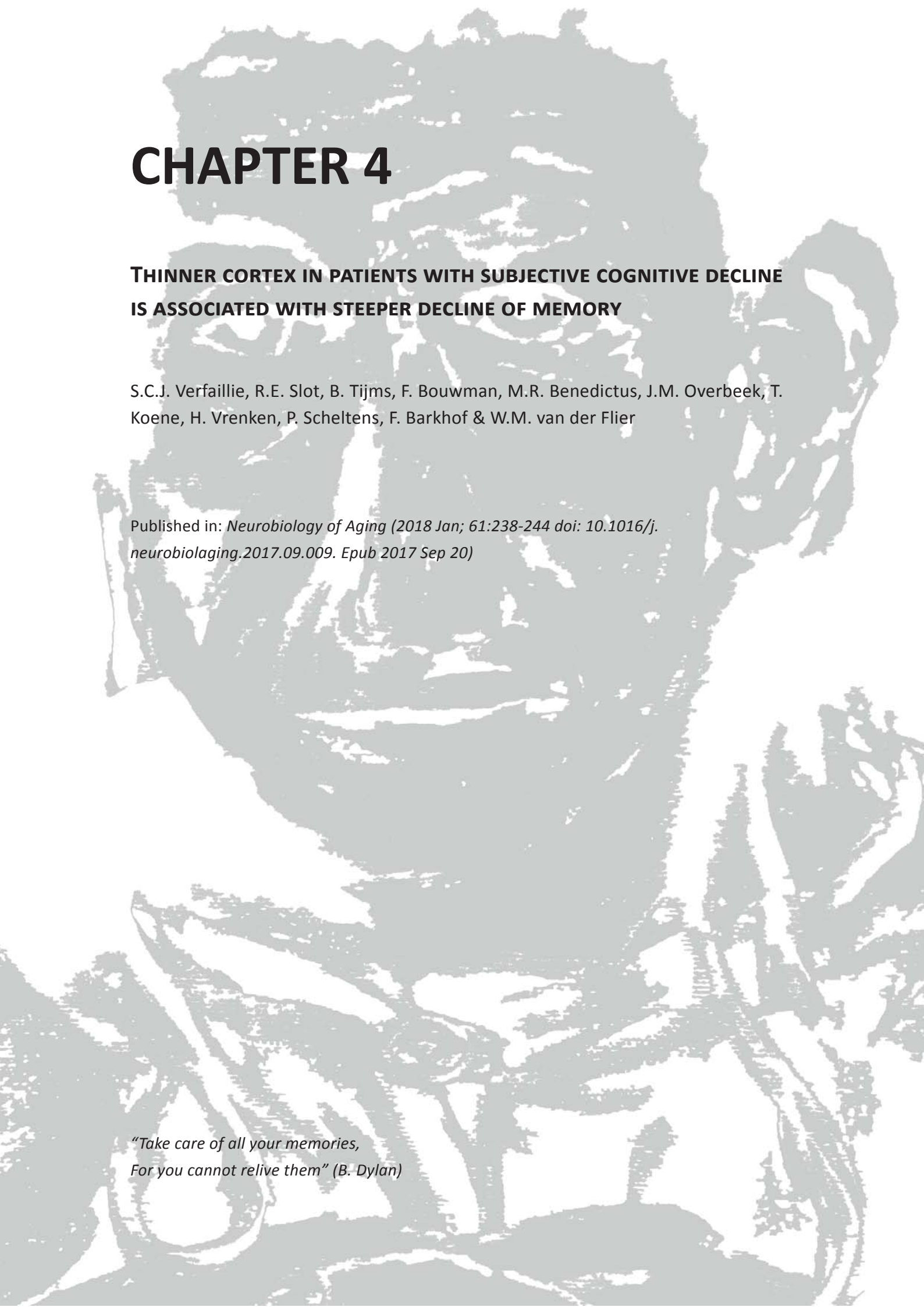
document version
Publisher's PDF, also known as Version of record

CHAPTER 4

Thinner cortex in patients with subjective cognitive decline is associated with steeper decline of memory

S.C.J. Verfaillie, R.E. Slot, B. Tijms, F. Bouwman, M.R. Benedictus, J.M. Overbeek, T. Koene, H. Vrenken, P. Scheltens, F. Barkhof & W.M. van der Flier

Published in: *Neurobiology of Aging (2018 Jan; 61:238-244 doi: 10.1016/j. neurobiolaging.2017.09.009. Epub 2017 Sep 20)*



"Take care of all your memories,
For you cannot relive them" (B. Dylan)

ABSTRACT

Background. We aimed to investigate associations between regional cortical thickness and rate of decline over time in four cognitive domains in patients with subjective cognitive decline (SCD).

Methods. We included 233 SCD patients with a total of number of 654 neuropsychological assessments (median=3, range=2-8), and available baseline MRI from the Amsterdam Dementia Cohort (125M, age: 63±9, MMSE: 28±2). We assessed longitudinal cognitive functioning at baseline and follow-up in four cognitive domains (composite z-scores): memory, attention, executive function and language. Thickness (millimetre) was estimated using Freesurfer for frontal, temporal, parietal, cingulate and occipital cortex. We used linear mixed models to estimate effects of cortical thickness on cognitive performance (dependent variables).

Results. There were no associations between cortical thickness and baseline cognition, but a faster subsequent rate of memory loss was associated with thinner cortex of the frontal (β(se)=0.20 (0.07)), temporal (β(se)=0.18 (0.07)), occipital (β(se)=0.22 (0.09)) cortex (all $p<0.05_{FDR}$).

Conclusions. These findings illustrate that early cortical changes, particularly in the temporal cortex, herald incipient cognitive decline related to neurodegenerative diseases, most prominently Alzheimer's Disease.

INTRODUCTION

Alzheimer's Disease (AD) develops in the course of many years, and ultimately leads to cognitive decline and loss of independence.[1,2] Brain atrophy, especially in the cortical mantle, is a characteristic MRI finding in AD.[3,4] It has been suggested that cortical atrophy starts as early as one decade before the presentation of any objectifiable clinical symptoms.[5,6]

Community-dwelling elderly or memory clinic patients with subjective cognitive decline (SCD) have an increased risk of dementia, notably AD.[7–10] Self-perceived cognitive decline could be one of the earliest signs of AD, and SCD could be used as a framework to study the development of brain changes related to dementia.[9] However, there is a need for further harmonization and operationalization of SCD to better understand heterogeneity of outcomes,[11] for example induced by recruitment setting.[12] Cross-sectional studies have shown that compared to elderly without complaints, patients with SCD have thinner medial temporal cortex.[13–15] In addition, others demonstrated that elderly with cognitive complaints are prone to faster subsequent rate of episodic memory loss.[16] However, there is no longitudinal evidence yet of the link between cortical thinning and subsequent cognitive decline. In the current longitudinal study in patients with SCD we aimed to investigate associations between regional cortical thickness measured at baseline and subsequent rate of decline in memory, attention, language and executive functioning.

METHODS

Study population. We included 233 SCD patients with available structural MRI at baseline and repeated annual neuropsychological assessment from the Amsterdam Dementia Cohort.[17] The VU university medical Alzheimer center is a tertiary referral center and a memory clinic, and all our patients were referred by general practitioners or medical specialists (e.g. neurologist, geriatrician, psychiatrist) according to Dutch healthcare referral regulations. SCD was defined based upon a spontaneous report by patients, and there were no specific cutoffs used for subjective report measures. Patients visited our memory clinic between 2000 and 2012, and were extensively described in an earlier study.[6] At baseline, all patients underwent a standardized dementia screening, including medical history, 15-item geriatric depression scale (GDS), extensive neuropsychological assessment, physical examination, blood tests, and brain MRI.

Through multidisciplinary consensus, patients were labeled with SCD when they presented with cognitive complaints,[11] and results of clinical assessments were normal, criteria for MCI, dementia, or any other neurological or major psychiatric (e.g. major depression) disorders known to cause cognitive complaints were not met at baseline.[18–20]

Table 1. Demographic and clinical data of our group of individuals with subjective cognitive decline

Clinical/Demographic data	*(n=233)*
Male/female	125/107
Age in years	62.82 (9.18)
Education; range 1-7[47]	5.32 (1.35)
Baseline MMSE	28.35 (1.55)
Baseline GDS	2.88 (2.30)
WMH: range 1-4	2.30 (0.73)
Scanner System (GE/Impact)	108/124
Follow-up time	2.71 (2.02)
Diagnosis at last follow-up	SCD n=196, MCI n=29, probable AD n=3
	Frontotemporal dementia n=3, vascular dementia n=2
Cortical thickness estimations	
Frontal	2.21 (0.31)
Parietal	1.96 (0.31)
Temporal	2.55 (0.33)
Occipital	1.75 (0.26)
Cingulate	2.30 (0.35)
Neuropsychological Assessment	Baseline Mean (SD)
Attention	
Digit Span Forward	12.61 (3.17)
Trailmaking Test A	40.45 (16.06)
Stroop Word	46.31 (9.56)
Stroop Color	62.73 (12.10)
Executive function	
Digit Span Backward	9.35 (2.74)
Trailmaking Test B	96.33 (44.71)
Stroop Color-word	108.05 (28.17)
Memory	
Visual Association Test A	11.54 (1.05)
RAVLT (5 trials summed)	39.81 (8.74)
RAVLT Delayed Recall	8.00 (3.01)
Language	
Fluency Animals	22.23 (5.84)
Visual Association Test Naming	11.94 (0.34)

Data are presented as mean (SD). Abbreviations. AD, Alzheimer's Disease; MCI, mild cognitive impairment; MMSE, mini mental state examination; RAVLT, Dutch version of the Rey auditory verbal learning test; SCD, subjective cognitive decline; WMH, white matter hyperintensities

Because we aimed to investigate the course of cognitive functioning over time in relation to cortical thickness in normal aging and preclinical AD, we performed analyses with and without 5 additional SCD patients that developed a non-AD dementia (n=3 frontotemporal dementia, n=2 vascular dementia). Annual follow-up visits took place as part of regular health care which consisted of patient history, physical examination, and neuropsychological assessments. Follow-up duration was variable per patient and depended on the clinical decision in multidisciplinary meetings after each visit.

The medical ethics committee of the VU University Medical Center approved the study. All patients provided written informed consent for their clinical data to be used for research purposes.

Neuropsychological assessment. Our neuropsychological test battery included tests that measured cognitive functioning in the domains of memory, attention, executive functioning and language.[17] For the memory domain, we used: the Dutch version of the RAVLT immediate and delayed recall, and visual association task (VAT) A. For attention, we used: digit span forward, TMT-A, Stroop word naming, and Stroop color naming. For the executive function domain, we used: TMT-B, digit span backwards, Stroop color-word interference test. For the language domain, we used: Category fluency animals, VAT naming (12 items). We z-transformed each test in such a way that baseline test results had a m±sd of 0±1, and then we Z-transformed each baseline and follow-up neuropsychological score using the corresponding baseline distribution as a reference. The following scores were inverted so that lower scores reflect worse performance: TMT, and Stroop. Missing individual neuropsychological test scores were handled by multiple imputations of individual set scores.[21] Fifteen imputed data sets were created. Subsequently, composite domain scores were constructed by taking the average Z-score of tests per domain.

MRI acquisition. Structural MRI was acquired during the first visit to the memory clinic using a SignaHDxt 3.0T (n=110) (General Electric, Milwaukee, WI) and Siemens Magnetom Impact 1.0T (n=122) (Siemens, Erlangen, Germany) scanners. Sequence parameters included standardized MPRAGE for 1.0T (168 slices, matrix= 256x256, voxel size= 1x1x1.5 mm^3), and IR-FSPGR for 3.0T (176 slices, matrix= 256x256, 1x0.9x0.9 mm^3). In addition, T2-weighted and FLAIR images were acquired to classify degree of white matter hyperintensities (WMH: 0= no, 1=mild, 2=moderate, 3=severe) that were rated by an experienced neuroradiologist[7]. A standard circular head coil was used and motion was restricted using expandable foam cushions.

Image analysis. We used Freesurfer (v5.3, Harvard, MA, USA) to estimate cortical thickness in the structural MR images (v5.3, Harvard, MA, USA; https://surfer.nmr.mgh.harvard.edu). Freesurfer constructs models of the boundaries between gray and white matter as well as pial surface[22]. The distance between these surfaces gives the vertex-wise cortical thickness (i.e. the perpendicular thickness in millimeter at each location). Automated cortical parcellations were run using a default script template (recon-all).

The output was visually inspected for image and segmentation quality. Next, we ran "LobesStrict" to obtain a lobar annotation (frontal, temporal, parietal, occipital and cingulate) and consecutively imported in SPSS for further statistical analyses.

For visualization purposes, we performed a vertex-wise analysis to investigate the spatial distribution between cognitive functioning and cortical thickness in an unbiased fashion (i.e. without *a priori* defined regions). First, preprocessing was done using default settings (mris_preproc). An optimized Gaussian smoothing kernel (5mm FWHM) was used for detecting focal abnormalities.[23] To investigate cognitive change, Z-transformed cognitive scores ((last follow-up cognitive domain score – baseline cognitive domain score) / ((last follow-up date [visit] – baseline date [visit])/ 365)) were separately entered into a general linear model using glm_fit. Analyses were corrected for age, sex, education, and scanner and set on a liberal significance threshold ($p<0.001$ uncorrected). Brain region coordinates were described according to RAS coordinate system with corresponding statistical significance on a logarithmic scale (i.e. -log(10)p).

Statistical analyses. Statistical analyses were performed with SPSS version 20.0.0 (IBM Corp., Armonk New York, U.S.). To investigate demographic data, we used χ^2-tests for discrete variables, and analyses of variance (ANOVA) for continuous data.

We used linear mixed models (LMM), which account for variable follow-up duration, to estimate longitudinal changes in cognitive performance. The model included a main effect of time (in years) as a random effect, and was adjusted for age, sex and education. We also used LMM to estimate the effects of cortical thickness (in mm) on baseline and longitudinal cognitive performance (composite domain scores in separate models). Model 1 contained terms for cortical thickness, time, cortical thickness*time, and was adjusted for age, sex education, and field strength. Because field strength could bias cortical thickness estimations,[24] we additionally added "cortical thickness*time*field strength" as an interaction term. As this interaction term was not significant in any of the models, we removed it from the analyses, and kept field strength as a covariate only. In model 2 we additionally adjusted our models for WMH because we previously have found that increased WMH is associated with increased risk for clinical progression.[7] In model 3 we additionally adjusted for depressive symptoms because depressive symptoms could influence associations of cortical thickness and rate of cognitive decline.[25] In an additional set of analyses, we repeated the LMM analyses (model 1) taking progression to MCI or any type of dementia as outcome (including n=5 additional patients progressing to non-AD dementia). In addition, we stratified for patient outcome (SCD stable vs MCI/dementia) in order to investigate cortical thickness in relation to a differential course of cognitive changes (supplementary table S1). Pooled estimates (unstandardized Beta's with standard errors [SE]) based on the fifteen imputed data sets were reported. We applied the false discovery rate (FDR) procedure to correct for multiple testing.[26]

Table 2. Cognition in relation to regional cortical thickness

			Frontal		Parietal		Temporal		Occipital		Cingulate	
Attention	BL	Beta estimates (SE)	0.05	(0.18)	0.09	(0.20)	-0.03	(0.16)	-0.08	(0.30)	0.15	(0.15)
		T-values / p-values	0.53	0.72	0.36	0.72	-0.03	0.98	-0.27	0.79	1.30	0.19
	Annual	Beta estimates (SE)	0.03	(0.06)	0.04	(0.06)	0.03	(0.06)	0.05	(0.08)	0.01	(0.06)
	Slope	T-values / p-values	-0.18	0.86	0.10	0.92	-0.24	0.81	0.25	0.80	-0.85	0.40
Memory	BL	Beta estimates (SE)	0.29	(0.21)	0.35	(0.23)	0.30	(0.20)	0.51	(0.37)	0.13	(0.18)
		T-values / p-values	1.37	0.17	1.45	0.15	1.52	0.13	1.37	0.17	0.72	0.47
	Annual	Beta estimates (SE)	**0.20****	**(0.07)**	0.14	(0.07)	**0.18****	**(0.07)**	**0.22****	**(0.09)**	0.11	(0.07)
	Slope	T-values / p-values	**2.11**	**0.02**	1.92	0.05	**2.38**	**0.02**	**2.38**	**0.02**	1.57	0.12
Executive Function	BL	Beta estimates (SE)	0.12	(0.19)	0.12	(0.21)	0.04	(0.04)	-0.07	(0.31)	0.19	(0.16)
		T-values / p-values	0.66	0.51	0.55	0.58	0.28	0.78	-0.30	0.77	1.34	0.18
	Annual	Beta estimates (SE)	0.10	(0.07)	0.09	(0.07)	0.11	(0.17)	0.12	(0.09)	0.06	(0.06)
	Slope	T-values / p-values	0.68	0.50	0.69	0.50	1.05	0.30	0.94	0.35	0.14	0.89
Language	BL	Beta estimates (SE)	-0.12	(0.23)	0.05	(0.24)	-0.18	(0.22)	-0.31	(0.41)	-0.02	(0.22)
		T-values / p-values	-0.52	0.60	-0.20	0.84	-0.72	0.47	-0.76	0.45	-0.12	0.90
	Annual	Beta estimates (SE)	0.26	(0.15)	0.27	(0.15)	**0.28**	**(0.15)**	0.28	(0.19)	0.20	(0.14)
	Slope	T-values / p-values	1.70	0.09	1.56	0.12	**1.96**	**0.05**	1.48	0.14	1.58	0.12

Data are presented as unstandardized β estimates with Standard Error (S.E.). Pooled beta estimates of imputed datasets are reported with corresponding t-values and uncorrected p-values (rounded off to two decimals). β's for cortical thickness (BL) represent the estimated additional change in z-score at baseline, while β's (Annual decline) represent estimated additional change in z-score for each year of follow-up. Cognitive domains consisted of the following tests: Attention (digit span forward, TMT-A, Stroop1&2), Memory (Dutch version RAVLT immediate and delayed recall, VAT-A), Executive function (TMT-B, digit span backwards, Stroop3) and Language (Category fluency animals, VAT confrontational naming). p<.05 (in bold), **p<.05_{FDR}. Analyses were adjusted for age, sex, education and field strength.

Table 3. Cognition in relation to cortical thickness after stratification for patient outcome

			Frontal		Parietal		Temporal		Occipital		Cingulate	
Attention	BL	SCD stable	0.22	(0.20)	0.30	(0.22)	0.14	(0.18)	0.21	(0.07)	0.31	(0.17)
		MCI/AD	-0.71	(0.86)	-1.14	(0.23)	-0.77	(0.71)	-2.54	(1.10)	-0.04	(0.17)
	Annual	SCD stable	-0.09	(0.06)	-0.06	(0.06)	-0.09	(0.06)	-0.07	(0.08)	-0.09	(0.05)
	Slope	MCI/AD	0.11	(0.23)	0.14	(0.23)	0.10	(0.23)	0.09	(0.26)	-0.05	(0.17)
Memory	BL	SCD stable	**0.42**	**(0.19)**	**0.47**	**(0.21)**	**0.37**	**(0.17)**	0.42	(0.33)	0.25	(0.17)
		MCI/AD	-0.32	(1.21)	-0.31	(1.21)	-0.38	(0.93)	0.37	(1.67)	-0.58	(0.77)
	Annual	SCD stable	0.01	(0.06)	0.00	(0.06)	0.02	(0.06)	0.04	(0.08)	0.00	(0.06)
	Slope	MCI/AD	**0.50**	**(0.29)**	0.54	(0.31)	**0.57****	**(0.27)**	0.53	(0.35)	0.33	(0.26)
Executive Function	BL	SCD stable	0.22	(0.20)	0.28	(0.22)	0.16	(0.18)	0.13	(0.34)	0.27	(0.17)
		MCI/AD	-0.63	(0.99)	-0.95	(1.02)	-.97	(0.80)	-2.56	(1.31)	0.07	(0.61)
	Annual	SCD stable	-0.02	(0.07)	-0.02	(0.06)	-0.01	(0.06)	-0.01	(0.08)	-0.01	(0.06)
	Slope	MCI/AD	0.09	(0.27)	0.14	(0.27)	0.18	(0.27)	0.10	(0.31)	-0.08	(0.20)
Language	BL	SCD stable	-0.37	(0.29)	-0.31	(0.31)	-0.36	(0.27)	-0.76	(0.51)	-0.18	(0.26)
		MCI/AD	-0.63	(0.76)	-0.31	(0.33)	-0.61	(0.60)	-1.19	(1.10)	-0.17	(0.46)
	Annual	SCD stable	0.03	(0.10)	0.03	(0.10)	0.05	(0.10)	0.05	(0.13)	0.02	(0.10)
	Slope	MCI/AD	**0.29**	**(0.24)**	**0.32**	**(0.24)**	**0.41**	**(0.22)**	0.32	(0.27)	0.16	(0.19)

Data are presented as β estimates with Standard Error (S.E.). β's for cortical thickness (BL) represent the estimated additional change in z-score at baseline, while β's (Annual decline) represent estimated additional change in z-score for each year of follow-up. Cognitive domains consisted of the following tests: Attention (digit span forward, TMT-A, Stroop1&2), Memory (Dutch version RAVLT immediate and delayed recall, VAT-A), Executive function (TMT-B, digit span backwards, Stroop color-word) and Language (Category fluency animals, VAT confrontational naming). p<.05 (in Bold), **$p<0.05_{FDR}$. All models were adjusted for age, sex, education, field strength.

RESULTS

Demographic and clinical data are presented in table 1. After an average follow-up of (mean±SD) 3±2 years 196 SCD patients remained stable, while 32 progressed to MCI (n=29, of which n=25 amnestic, n=2 multi-domain, n=1 non-amnestic neuropsychological profiles) or AD dementia (n=3). In general, language functioning (β(SE)= -0.14(0.05), $p<0.05_{FDR}$) decreased over time, whereas memory (β(SE)= -0.01(0.02) p=0.88), attention (β(SE)= -0.03(0.02) p=0.60) and executive functioning (β(SE)= -0.01(0.02) p=0.28) did not change significantly over time. If we stratified for incident clinical progression we found a decrease in language function over time (β(SE)= -0.07(0.02)) in SCD stable, while SCD patients with future clinical progression showed decreased memory (β(SE)= -0.21(0.07)), executive function (β(SE)= -0.14(0.04)) and language (β(SE)= -0.44(0.10)) (all $p<0.05_{FDR}$).

Associations between cortical thickness and cognition are summarized in table 2. At baseline, there were no associations between cortical thickness and any of the cognition domains after adjusting for age, sex, education and scanner (all $p>0.05_{FDR}$; model 1). By contrast, frontal (β(se)=0.20 (0.07)), temporal (β(SE)= 0.18 (0.07)), and occipital (β(SE)= 0.22 (0.09)) cortex were associated with steeper rate of decline of memory (all $p<0.05_{FDR}$; model 2; table 2). There were no associations between cortical thickness and language, attention or executive functioning over time (all $p>0.05_{FDR}$). After additionally adjusting for WMH and GDS (models 2&3; supplementary table S1), associations between temporo-occipital cortex and memory remained essentially unchanged, but associations between frontal cortex and memory disappeared after GDS adjustment. When we repeated the LMM analyses including n=5 additional patients progressing to non-AD dementia, we found that cortical thickness in all lobes was associated with rate of memory decline (supplementary table S2), but not with other cognitive domains. Subsequently, for visualization purposes vertex-wise analyses were done to explore local associations with memory functioning across the cortical mantle (figure 1). These analyses showed that thinner cortex of the left hemispheric insular (-log(10)p= 3.35, 13/34/-21), lateral orbitofrontal (-log(10)p= 3.89, -4/77/-43), superior temporal (-log(10) p= 3.03, -39/6/-41), middle temporal (-log(10)p=3.14, -41/-14/-46), inferior parietal (-log(10)p= 3.32, -27/-61/-4) gyri, and right hemispheric middle temporal gyrus (-log(10)p= 3.13, 32/23/-59), and rostral anterior cingulate cortex (-log(10) p= 4.59, 32/80/-2) were associated with decline of memory function.

Associations between cortical thickness and cognition stratified for final patient outcome (stable vs progression to MCI or AD) are summarized in table 3. In SCD patients who finally developed MCI/AD, thinner temporal cortex was related to a steeper decline of memory ($p<0.05_{FDR}$), while such an effect was not observed in patients who remained stable. When we repeated the LMM analyses including n=5 additional patients progressing to non-AD dementia, we found that frontal, parietal, temporal and occipital cortex was associated with rate of memory decline (all $p>0.05_{FDR}$), but not with other cognitive domains.

DISCUSSION

We found that widespread cortical thinning in SCD patients was associated with faster subsequent decline in memory over time, but not related to concurrent cognitive function. These findings suggest that subtle cortical changes could precede measurable cognitive decline.

We studied patients who visited a memory clinic because they perceived deficits in their cognitive functioning. Such cognitive complaints in elderly could be caused by a myriad of factors, including normal aging, preclinical AD, cerebrovascular disease, or psychological factors such as mood disorders.[25,27–29] Although SCD patients typically complain about their memory, early cognitive decline may also affect other cognitive domains. We showed that language functioning decreased over time across the entire group of SCD patients, which illustrates that cognitive complaints could also originate from poorer language performance.

Two recent cross-sectional studies on cognitively intact and mildly cognitively impaired elderly demonstrated that thinner temporal, precuneus and occipital cortex were associated with impaired episodic memory.[30,31] In contrast, we did not find any associations between cortical thickness and poorer concurrent memory performance. We extend on the former studies, as we found associations between fronto-temporo-occipital cortical thinning and future decline in memory. Our exploratory vertex-wise analyses further corroborate predominant lateral temporal cortex involvement in relation to memory decline. Our findings are in line with literature showing that temporal lobes are important for memory (dys)function in non-demented individuals[32–34] as well as in AD patients.[3,35] Notwithstanding, when we repeated the analyses including SCD patients with future progression to MCI or any type of dementia, we found that cortical thickness in all lobes were associated with memory decline. The previous could be explained by different pathophysiological mechanisms involved in other types of dementias affecting also parietal and cingulate cortices. Others found that patients with SCD and concomitant depressive symptoms have pronounced fronto-striatal, and to a lesser extent temporo-occipital brain abnormalities.[28,36–38] In addition, elderly with subclinical depressive symptoms showed poorer performance on memory, processing speed and executive functioning compared to elderly without symptoms.[39] In the current study, we excluded patients with a major psychiatric disorder such as depression. Associations between temporo-occipital cortex and memory decline remained unchanged after adjusting for (subclinical) depressive symptoms, while associations between frontal cortex and memory disappeared. This fits with the notion that depressive symptoms are related to thickness of the frontal lobe.

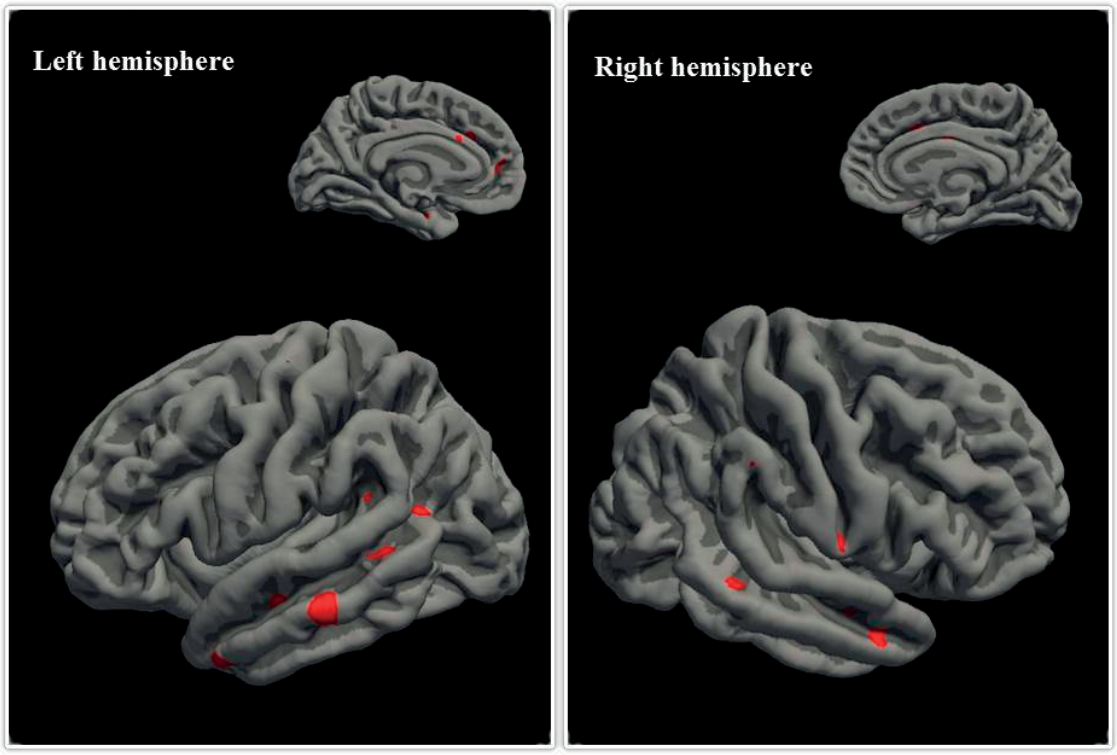


Figure 1. Vertex-wise associations with memory performance over time in SCD. Red reflects positive correlations between memory decline and cortical thickness (p<0.001 uncorrected).

We observed that executive functioning decreased annually in SCD patients with future clinical progression, but this did not seem to be related to reduced cortical thickness. In contrast, others have found associations between fronto-parietal thickness and task accuracy during a card sorting task in cognitively intact elderly.[40] Discrepancies could be explained by the fact that in the present study divided attention, working memory and interference were lumped together as a broad reflection of executive functioning. The advantage of a composite score over a single neuropsychological test is that it robustly reveals associations with the cognitive domain under study, while including many individual tests increases the risk of false positive findings due to multiple testing.

Among the strengths of our study was our unique sample of cognitively normal elderly at high risk for AD with spontaneous self-reported cognitive decline and medical help seeking behavior. Several potential limitations need to be considered. Our SCD patients all visited a memory clinic, and received variable follow-up duration based on clinical indications. For this reason, it is unclear to which extent our results can be extrapolated to the general population. Nonetheless, our results are highly relevant for cognitively normal patients in memory clinics. Of note, referred SCD patients could be a clinically relevant group for future preventive trials as they self-perceive cognitive decline. In addition, others have shown that in comparison to SCD in the general population, memory clinic SCD is associated with additional subclinical depressive symptomatology and atrophy.[12] While

there might have been subclinical depressive symptoms in our SCD sample, these did not seem to affect associations between cortical thickness and memory. Second, we have used two scanner systems for estimating cortical thickness, each operating at different magnetic field strengths, which could have influenced our associations. Notwithstanding, there were no significant interactions between scanner and cortical thickness, suggesting that scanner did not influence associations between cortical thickness and trajectories of cognitive decline. Third, our results could have been influenced by practice effects with different patterns and cognitive trajectories depending on the cognitive domain[41]. While subtle practice effects may have occurred, we expect that these effects were especially present in stable SCD patients, and less so in patients with future progression. It has recently been demonstrated that preclinical AD reduces the magnitude of gain from retesting, especially with regard to episodic memory.[42] Finally, we have used domains scores composed of several neuropsychological tests. For example, language consisted of confrontational naming and semantic fluency, but the latter also depends on executive functioning. Specific linguistic characteristics in relation to brain imaging should be investigated more precisely in future studies.

Global brain atrophy is common in AD, but also occurs with normal aging[43,44] and both can evoke cognitive complaints.[45] In a former study following participants over a period of 10 years, those who remained cognitively intact (i.e. normal aging), showed brain volume decreases in the frontal lobes and superior parietal regions, whereas those who progressed to MCI, showed accelerated volume loss in temporal regions.[46] Our findings also point towards involvement of temporal cortical regions in relation to memory decline. Thinner temporal cortex could be an early reflection of AD, more specifically since some of the SCD patients finally progressed to MCI or AD dementia during the course of the study, and these findings were particularly attributable to this subgroup.

SUPPLEMENTARY MATERIALS

https://www.sciencedirect.com/science/article/pii/S0197458017303020?via%3Dihub

This article was published in Neurobiology of Aging, Jan, 61, 238-244, Copyright Elsevier (2018). Re-printed with permission.

REFERENCES

1. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367(9):795-804. doi:10.1056/NEJMoa1202753.
2. Scheltens P, Blennow K, Breteler MMB, et al. Alzheimer's disease. *Lancet (London, England)*. 2016;6736(15):1-13. doi:10.1016/S0140-6736(15)01124-1.
3. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry*. 1992;55:967-972. doi:10.1136/jnnp.55.10.967.
4. Spulber G, Niskanen E, MacDonald S, et al. Evolution of Global and Local Grey Matter Atrophy on Serial MRI Scans During the Progression from MCI to AD. *Curr Alzheimer Res*. 2012;9(4):516-524. doi:10.2174/156720512800492486.
5. Dickerson BC, Stoub TR, Shah RC, et al. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. *Neurology*. 2011;76:1395-1402. doi:10.1212/WNL.0b013e3182166e96.
6. Verfaillie SCJ, Tijms B, Versteeg A, et al. Thinner temporal and parietal cortex is related to incident clinical progression to dementia in patients with subjective cognitive decline. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2016;5. doi:10.1016/j.dadm.2016.10.007.
7. Benedictus MR, van Harten AC, Leeuwis AE, et al. White Matter Hyperintensities Relate to Clinical Progression in Subjective Cognitive Decline. *Stroke*. 2015. doi:10.1161/STROKEAHA.115.009475.
8. Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry*. 2010;67:414-422. doi:10.1001/archgenpsychiatry.2010.30.
9. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's Dement*. 2014:1-9. doi:10.1016/j.jalz.2014.01.001.
10. Schmand B, Jonker C, Hooijer C, Lindeboom J. Subjective memory complaints may announce dementia. *Neurology*. 1996;46(1):121-125. doi:10.1212/WNL.46.1.121.
11. Molinuevo JL, Rabin LA, Amariglio R, et al. Implementation of subjective cognitive decline criteria in research studies. *Alzheimer's Dement*. 2017;13(3):296-311. doi:10.1016/j.jalz.2016.09.012.
12. Perrotin A, La Joie R, de La Sayette V, et al. Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimer's and Dementia*. 2016.
13. van der Flier WM, van Buchem MA, Weverling-Rijnsburger AWE, et al. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. *J Neurol*. 2004;251(6):671-675. doi:10.1007/s00415-004-0390-7.
14. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology*. 2006;67(5):834-842. doi:10.1212/01.wnl.0000234032.77541.a2.
15. Meiberth D, Scheef L, Wolfsgruber S, et al. Cortical thinning in individuals with subjective memory impairment. *J Alzheimers Dis*. 2015;45(1):139-146. doi:10.3233/JAD-142322.
16. Scheef L, Spottke A, Daerr M, et al. Glucose metabolism, gray matter structure, and memory decline in subjective memory impairment. *Neurology*.

2012;79(13):1332-1339. doi:10.1212/WNL.0b013e31826c1a8d.

17. Van Der Flier WM, Pijnenburg YAL, Prins N, et al. Optimizing patient care and research: The Amsterdam dementia cohort. *J Alzheimer's Dis*. 2014;41:313-327. doi:10.3233/JAD-132306.
18. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56:303-308. doi:10.1001/archneur.56.3.303.
19. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7:263-269. doi:10.1016/j.jalz.2011.03.005.
20. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on. *Alzheimer's …*. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008.The.
21. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59(10):1087-1091. doi:10.1016/j.jclinepi.2006.01.014.
22. Fischl B, Van Der Kouwe A, Destrieux C, et al. Automatically Parcellating the Human Cerebral Cortex. *Cereb Cortex*. 2004;14(1):11-22. doi:10.1093/cercor/bhg087.
23. Lerch JP, Evans AC. Cortical thickness analysis examined through power analysis and a population simulation. *Neuroimage*. 2005;24(1):163-173. doi:10.1016/j.neuroimage.2004.07.045.
24. Han X, Jovicich J, Salat D, et al. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. *Neuroimage*. 2006;32(1):180-194. doi:10.1016/j.neuroimage.2006.02.051.
25. Comijs HC, Deeg DJH, Dik MG, Twisk JWR, Jonker C. Memory complaints; The association with psycho-affective and health problems and the role of personality characteristics: A 6-year follow-up study. *J Affect Disord*. 2002;72(2):157-165. doi:10.1016/S0165-0327(01)00453-0.
26. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency By Yoav Benjamini 1 and Daniel Yekutieli 2. *Ann Stat*. 2001;29(4):1165-1188. doi:10.1214/aos/1013699998.
27. Deligkaris P, Panagopoulou E, Montgomery AJ, Masoura E. Job burnout and cognitive functioning: A systematic review. *Work Stress*. 2014;28(2):107-123. doi:10.1080/02678373.2014.909545.
28. Enache D, Cavallin L, Lindberg O, et al. Medial temporal lobe atrophy and depressive symptoms in elderly patients with and without Alzheimer disease. *J Geriatr Psychiatry Neurol*. 2015;28(1):40-48. doi:10.1177/0891988714541873.
29. Geerlings MI, Den HT, Koudstaal PJ, Hofman A, Breteler MM. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. *Neurology*. 2008;70(15):1258-1264.
30. Doré V, Villemagne VL, Bourgeat P, et al. Cross-sectional and longitudinal analysis of the relationship between Aβ deposition, cortical thickness, and memory in cognitively unimpaired individuals and in Alzheimer disease. *JAMA Neurol*. 2013;70(7):903-911. doi:10.1001/jamaneurol.2013.1062.
31. Villeneuve S, Reed BR, Wirth M, et al. Cortical thickness mediates the effect of β-amyloid on episodic memory. *Neurology*. 2014;82(9):761-767. doi:10.1212/WNL.0000000000000170.
32. Ojemann GA, Creutzfeldt O, Lettich E, Haglund MM. Neuronal activity in human

lateral temporal cortex related to short-term verbal memory, naming and reading. *Brain*. 1988;111(Pt 6):1383-403.

33. Scoville WB, Milner B. Loss of recentmemory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry*. 1957;20(1):11-21. doi:10.1136/jnnp.20.1.11.
34. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. *Science (80-)*. 1991;253(5026):1380-1386. doi:10.1126/science.1896849.
35. Jack CR, Petersen RC, Xu YC, et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology*. 1997;49:786-794. doi:10.1212/WNL.49.3.786.
36. Grieve SM, Korgaonkar MS, Koslow SH, Gordon E, Williams LM. Widespread reductions in gray matter volume in depression. *NeuroImage Clin*. 2013;3:332-339. doi:10.1016/j.nicl.2013.08.016.
37. Verfaillie SCJ, de Wit SJ, Vriend C, Remijnse PL, Veltman DJ, van den Heuvel OA. The course of the neural correlates of reversal learning in obsessive-compulsive disorder and major depression: A naturalistic follow-up fMRI study. *J Obsessive Compuls Relat Disord*. 2016;9. doi:10.1016/j.jocrd.2016.02.004.
38. von Gunten a, Fox NC, Cipolotti L, Ron M a. A volumetric study of hippocampus and amygdala in depressed patients with subjective memory problems. *J Neuropsychiatry Clin Neurosci*. 2000;12(4):493-498. doi:10.1176/appi.neuropsych.12.4.493.
39. Shimada H, Park H, Makizako H, Doi T, Lee S, Suzuki T. Depressive symptoms and cognitive performance in older adults. *J Psychiatr Res*. 2014;57(1):149-156. doi:10.1016/j.jpsychires.2014.06.004.
40. Burzynska AZ, Nagel IE, Preuschhof C, et al. Cortical thickness is linked to executive functioning in adulthood and aging. *Hum Brain Mapp*. 2012;33(7):1607-1620. doi:10.1002/hbm.21311.
41. Machulda MM, Pankratz VS, Christianson TJ, et al. Practice Effects and Longitudinal Cognitive Change in Normal Aging vs. Incident Mild Cognitive Impairment and Dementia in The Mayo Clinic Study of Aging. *Clin Neuropsychol*. 2013;27(8):1247-1264. doi:10.1080/13854046.2013.836567.
42. Hassenstab J, Ruvolo D, Jasielec M, Xiong C, Grant E, Morris JC. Absence of practice effects in preclinical Alzheimer's disease. *Neuropsychology*. 2015;29(6):940-948. doi:10.1037/neu0000208.
43. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci*. 2003;6(3):309-315. doi:10.1038/nn1008.
44. Fjell AM, Walhovd KB, Fennema-Notestine C, et al. One-year brain atrophy evident in healthy aging. *J Neurosci*. 2009;29(48):15223-15231. doi:10.1523/JNEUROSCI.3252-09.2009.
45. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. *Int J Geriatr Psychiatry*. 2000;15(11):983-991. doi:10.1002/1099-1166(200011)15:11<983::aid-gps238>3.0.co;2-5.
46. Driscoll I, Davatzikos C, An Y, et al. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*. 2009;72(22):1906-1913. doi:10.1212/WNL.0b013e3181a82634.
47. Verhage F. Intelligence and age in a dutch sample. *Hum Dev*. 1965;8(4):238-245. doi:10.1159/000270308.