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Association of quality of life with structural, functional and molecular brain imaging in community-dwelling older adults

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ABSTRACT

Background: As the population ages, maintaining mental health and well-being of older adults is a public health priority. Beyond objective measures of health, self-perceived quality of life (QoL) is a good indicator of successful aging. In older adults, it has been shown that QoL is related to structural brain changes. However, QoL is a multi-faceted concept and little is known about the specific relationship of each QoL domain to brain structure, nor about the links with other aspects of brain integrity, including white matter microstructure, brain perfusion and amyloid deposition, which are particularly relevant in aging. Therefore, we aimed to better characterize the brain biomarkers associated with each QoL domain using a comprehensive multimodal neuroimaging approach in older adults.

Methods: One hundred and thirty-five cognitively unimpaired older adults (mean age ± SD: 69.4 ± 3.8 y) underwent structural and diffusion magnetic resonance imaging, together with early and late florbetapir positron emission tomography scans. QoL was assessed using the brief version of the World Health Organization's QoL instrument, which allows measuring four distinct domains of QoL: self-perceived physical health, psychological health, social relationships and environment. Multiple regression analyses were carried out to identify the independent global neuroimaging predictor(s) of each QoL domain, and voxel-wise analyses were then conducted with the significant predictor(s) to highlight the brain regions involved. Age, sex, education and the other QoL domains were entered as covariates in these analyses. Finally, forward stepwise multiple regressions were conducted to determine the specific items of the relevant QoL domain(s) that contributed the most to these brain associations.

Results: Only physical health QoL was associated with global neuroimaging values, specifically gray matter volume and white matter mean kurtosis, with higher physical health QoL being associated with greater brain integrity. These relationships were still significant after correction for objective physical health and physical activity measures. No association was found with global brain perfusion or global amyloid deposition. Voxel-wise

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analyses revealed that the relationships with physical health QoL concerned the anterior insula and ventrolateral prefrontal cortex, and the corpus callosum, corona radiata, inferior frontal white matter and cingulum. Self-perceived daily living activities and self-perceived pain and discomfort were the items that contributed the most to these associations with gray matter volume and white matter mean kurtosis, respectively.

Conclusions: Better self-perceived physical health, encompassing daily living activities and pain and discomfort, was the only QoL domain related to brain structural integrity including higher global gray matter volume and global white matter microstructural integrity in cognitively unimpaired older adults. The relationships involved brain structures belonging to the salience network, the pain pathway and the empathy network. While previous studies showed a link between objective measures of physical health, our findings specifically highlight the relevance of monitoring and promoting self-perceived physical health in the older population. Longitudinal studies are needed to assess the direction and causality of the relationships between QoL and brain integrity.

Introduction

Quality of life (QoL) corresponds to individuals' subjective perception of their living conditions according to their culture, value system, goals and expectations (The WHOQOL Group, 1994). This is a dynamic and multi-faceted measurement, which can be expressed under several domains that are important for older adults living at home (van Leeuwen et al., 2019). Thus, this broad ranging concept, closely related to well-being, notably encompasses physical health, psychological health, social relationships, and relationship to the environment (The WHOQOL Group, 1994). While the number and proportion of older adults increase worldwide, aging is associated with a decrease in QoL, especially in the oldest old (Brett et al., 2019; Henchoz et al., 2019; Netuveli et al., 2006). Beyond objective measures of health, QoL is an independent predictor of mortality (Idler and Benyamini, 1997; Murray et al., 2011) and represents an important factor of successful aging (Li et al., 2014). Keeping older adults healthy, especially through maintaining their QoL, is a major public health issue. In this sense, international initiatives promote economic and policy investments in health and care services to improve QoL in this growing aging population (Beard et al., 2016; Malva and Bousquet, 2016).

In the course of aging, the brain undergoes changes including decreases in gray matter (GM) volume (Fjell and Walhovd, 2010), white matter (WM) integrity (Giorgio et al., 2010) and glucose metabolism (Kalpouzos et al., 2009) especially in the frontal and temporal lobes. Increasing age is also associated with beta-amyloid accumulation in the brain, which is one of the main gateways to Alzheimer's disease (AD) (Sperling et al., 2011). Posterior cingulate and temporo-parietal hypometabolism are also characteristic of prodromal AD (Veitch et al., 2019). Structural, functional, and molecular neuroimaging allows measuring these different aspects of brain integrity and could thus be used as sensitive indices of brain aging and AD biomarkers.

Within this context, it seems of high interest to assess the links between QoL and age-related brain changes to further our understanding of the brain substrates of QoL and to help monitor interventions aimed at improving QoL in aging. We know that e.g. depression (Yüksel et al., 2018) or sleep deficits (Ju et al., 2014) might lead to brain changes and/or be modified by brain changes; in the same line, we can expect that our perception of our physical, mental, social or environmental QoL could be linked to brain health through the same mechanisms, likely to be bidirectional. Several studies have found a relationship between QoL and GM volume, mainly in the frontal cortex, cingulate cortex or insula, in young adults (Takeuchi et al., 2014), but also in patients with depression (Elderkin-Thompson et al., 2008), schizophrenia (Faget-Agius et al., 2015) or functional neurological disorder (Perez et al., 2017). Only a few studies have assessed the relationship between QoL and brain integrity specifically in older adults. They reported a positive association between general QoL and GM volume in the medial prefrontal and orbitofrontal cortex, gyrus rectus, anterior cingulate cortex, insula and/or precuneus (Hahm et al., 2019; Elderkin-Thompson et al., 2008). However, little is known about the specific relationships with the different QoL domains. It is important to further identify the QoL domain(s), and even the QoL item(s), that are the most relevant to brain health to better target interventions aimed at improving QoL in older adults. Thus, self-perceived physical health, but not mental health, was related to GM volume in medial prefrontal and anterior cingulate cortex and insula in one previous study (Hahm et al., 2019). In another study, only assessing self-perceived physical health, a link was found with frontal WM volume, but not GM volume (Elderkin-Thompson et al., 2008). These both studies used different QoL measurements (e.g. 12-item Short Form Health Survey vs 36-item Short Form Health Survey) and different imaging analyses (e.g. voxel-wise vs regions of interest) and have not specifically assessed the other QoL domains, i.e., social relationships and environment, yet. Moreover, no previous study has investigated the links between QoL domains and functional (e.g. glucose metabolism or perfusion) and molecular (e.g. amyloid deposition) neuroimaging measures.

Thus, the present study aims at providing a better understanding of the specific relationships between QoL domains and brain integrity in aging. For this purpose, i) we first identified the links between each QoL domain and global measures of GM volume, WM microstructural integrity, brain perfusion and amyloid deposition in cognitively unimpaired older adults; ii) for each significant relationship, we then conducted a voxel-wise analysis to identify the brain regions that were specifically involved; and iii) finally, we assessed which QoL item(s) contributed the most to these brain associations to highlight the most relevant aspect(s) of QoL in the context of brain aging. Firstly, based on the results by Hahm et al. (2019) and Elderkin-Thompson et al. (2008) mentioned above, we hypothesized that self-perceived physical health would be associated to brain integrity, at least GM volume and WM microstructural integrity as little is known about the other neuroimaging modalities and the other QoL domains. Voxel-wise analyses to identify regional relationships were more exploratory, although we expected to find brain regions involved in the salience network as reported in one previous study (Hahm et al., 2019).

Materials and methods

Participants

We included 135 cognitively unimpaired older adults (flow diagram in supplementary Figure 1S) from the baseline visit of the Age-Well randomized controlled trial (Medit-Ageing European project; Poisnel et al., 2018), sponsored by the French National Institute of Health and Medical Research (INSERM). Participants were native French speakers, mostly right-handed (93.3%), recruited from the general population, aged over 65 years old and retired for at least one year. They had at least 7 years of education, and performed within the normal range for age and educational level on standardized cognitive tests. They had no evidence of major neurological or psychiatric disorders, no history of cerebrovascular disease, chronic disease or acute unstable illness and no current medication that may interfere with cognitive functioning (Poisnel et al., 2018 for details). All participants gave their written informed consent to the study, and the Age-Well randomized clinical trial was approved by the ethics committee (CPP Nord-Ouest III, Caen; trial registration number: EudraCT: 2016- 002441-36; IDRCB: 2016-A01767-44; Clini-

Table 1
Characteristics of the study sample (n = 135).

Characteristic	Mean (SD)	Range
Demographic		
Age, years	69.4 (3.8)	65–84
Sex (female), n (%)	83 (61.5%)	
Education, years	13.2 (3.1)	7–22
Global amyloid deposition (SUVr)	1.2 (0.1)	1–1.7
Amyloid positive, n (%)[a]	28 (20.9%)	
Quality of life		
Physical health (Phy-QoL)	78.1 (13)	25–100
Psychological health (Psy-QoL)	73.3 (13.5)	37.5–100
Social (Social-QoL)	66.8 (16.9)	8.3–100
Environment (Env-QoL)	84.5 (10.2)	46.9–100
Psychoaffective measures		
State-Trait Inventory form B score	34.7 (7.1)	20–54
Geriatric Depression Scale score	1.3 (1.7)	0–11
Physical activity		
Physical Activity Scale for the Elderly	130.6 (60.6)	21.5–330.4
Objective physical health		
Body Mass Index	26.2 (4.3)	18.1–44.2
Charlson Comorbidities Index	3.1 (1.3)	2–10
Cognition		
Mini-Mental State Examination	29 (1)	26–30

Abbreviations: QoL, quality of life; SD, standard deviation; SUVR, standard uptake value ratio. [a]The threshold for amyloid positivity corresponded to the 99.9th percentile of the neocortical standard uptake value ratio distribution among 45 healthy young individuals younger than 40 years (see details in André et al., 2020).

calTrials.gov Identifier: NCT02977819). Participant characteristics are presented in the Table 1.

The world health organization's quality of life instrument (WHOQOL-BREF)

Participants filled in the French version of the WHOQOL-BREF (The WHOQOL Group, 1998) which is a self-reported questionnaire including 2 items about general QoL (not used here) and 24 items which form 4 sub-scores, i.e. one for each of the following QoL domain: physical health (Phy-QoL; 7 items), psychological health (Psy-QoL; 6 items), social relationships (Social-QoL; 3 items) and environment (Env-QoL; 8 items) (see supplementary Table S1 for details). The WHOQOL-BREF has been validated in older adults and has high test–retest reliability and validity (von Steinbüchel et al., 2006).

Participants were instructed to answer based on their experience over the last two weeks, and each question was answered using a 5-point scale, from "(1) Very poor" to "(5) Very good". Scores of items 3, 4 and 26 were reversed, so that higher scores always reflect higher QoL. As the number of items differs across QoL domains, these latter were transformed to a 0-100 scale, following the recommendations of the World Health Organization (The WHOQOL Group, 1998), using the following formula: transformed score = ((mean(items)x4)-4)x(100/16). Thus, all QoL domains were expressed on a same scale and could be entered in a same analysis.

Psychoaffective measures

Anxiety and depressive symptoms were assessed using the Spielberger State-Trait Anxiety Inventory (STAI-B) (Spielberger et al., 1970) and the short-form (15 items) of the Geriatric Depression Scale (GDS) (Yesavage and Sheikh, 1986), respectively. Participants were screened for the lack of clinical anxiety or depression disorders, so that higher scores indicated higher anxiety or depression at the sub-clinical level.

Objective physical health and physical activity

Two measures were used to reflect objective physical health: the body mass index (BMI), known to be associated with all-cause mortality (Angelantonio et al., 2016), and the Charlson Comorbidities Index (CCI) (Charlson et al., 1987) that quantifies an individual's burden of disease and corresponding 1-year mortality risk. The BMI was calculated as weight in kilograms divided by height in meters squared, objectively obtained during the medical interview. The CCI was calculated by a medical doctor based on blood sample analyses and the medical interview. The CCI was adjusted for the age of the participant and computed, so that higher score indicated more comorbidities (e.g. hypertension, cholesterol…). Physical activity was assessed, over a one-week period, using the Physical Activity Scale for the Elderly (PASE) (Washburn et al., 1993) which was filled by participants. Six participants did not fully complete the PASE, resulting in 6 missing data. Higher score indicated greater physical activity.

Neuroimaging data acquisition

All participants were scanned at the Cyceron Center (Caen, France) on the same magnetic resonance imaging (MRI; Philips Achievia 3.0T scanner) and positron emission imaging (PET; Discovery RX VCT 64 PET-CT scanner, General Electric Healthcare) cameras.

MRI data: A high-resolution T1-weighted structural image using a three-dimensional fast-field echo sequence (sagittal; repetition time, 7.1 ms; echo time, 3.3 ms; flip angle, 6°; field of view, 256 × 256 mm^2, 180 slices, voxel size: 1 × 1 × 1 mm^3) and a three-dimensional fluid-attenuated inversion recovery (FLAIR; sagittal; repetition time, 4800 ms; echo time, 272 ms; inversion time, 1650 ms; flip angle, 40°; field of view, 250 × 250 mm^2, 180 slices, voxel size: 0.98 × 0.98 × 1 mm^3) were acquired. Then, an echo-planar imaging/spin echo diffusion weighted sequence (DKI) was performed at multiple shells: 3b-values (0, 1000, 2000 s/mm^2) (axial; 30 directions; repetition time, 6100 ms; echo time, 101 ms; flip angle, 90°; field of view, 216 × 216 mm^2, 48 slices, voxel size: 2.7 × 2.7 × 2.7 mm^3) and additional blips images with b=0 s/mm^2 (number of signal averages, 9) were acquired in reverse phase encoding direction for susceptibility distortion.

PET data: florbetapir-PET scans were acquired with a resolution of 3.76 × 3.76 × 4.9 mm^3 (field of view, 157 mm). For each PET-scan, forty-seven plans were obtained with a voxel size of 1.95 × 1.95 × 3.2 mm^3. A transmission scan was performed for attenuation correction before the PET acquisition. Each participant underwent a 10 min PET scan beginning at the intravenous injection of ≈ 4MBq/Kg of florbetapir to measure brain perfusion, and a 10-minute PET scan beginning 50 min after the intravenous injection, to measure amyloid deposition. Dual-phase PET imaging has recently emerged as a promising technique to provide both FDG-like information on neurodegeneration (Hsiao et al., 2012; Kuo et al., 2017; Lin et al., 2016) and information on amyloid deposition from a single PET-tracer injection (Florek et al., 2018; Garibotto et al., 2016). The early PET-scan was reconstructed from 1 to 8 min and the late PET-scan was reconstructed from 50 to 60 min.

Neuroimaging preprocessing

T1-weighted images were segmented using FLAIR images. GM segments were spatially normalized to the Montreal Neurological Institute (MNI) template and modulated to correct for non-linear warping so that values in resultant images are expressed as volume corrected for brain size, using the Statistical Parametric Mapping (SPM12) software's multiple channels segmentation procedure (http://www.fil.ion.ucl.ac.uk/spm/software/spm12).

DKI images were corrected for susceptibility, eddy current distortions and subject motion using Functional Magnetic Resonance of the Brain (FMRIB) diffusion toolbox (FSL 5.0.9, http://www.fmrib.ox.ac.uk/fsl). Then, DKI data were processed using Matlab R2012b (MathWorks, Natick, Massachusetts) and the Diffusional Kurtosis Estimator software (DKE: Version 2.6; http://nitrc.org/projects/dke) for estimating the diffusional kurtosis tensor (Tabesh et al., 2011). Images were smoothed with a 3.375 × 3.375 × 3.375 mm FWHM Gaussian filter to reduce the

impact of noise and misregistration. Mean kurtosis parameter maps, reflecting WM microstructural integrity including the number, density, orientation, and degree of organization of WM microstructures (Falangola et al., 2008), were then extracted from the diffusional kurtosis estimator. These maps were then coregistered to their corresponding T1-weighted MRI and normalized to the MNI template by applying the deformation parameters from the corresponding T1-weighted MRI.

Florbetapir-PET images were coregistered onto their corresponding T1-weighted MRI and normalized to the MNI template by applying the deformation parameters from the corresponding T1-weighted MRI images. Resulting images were scaled using the GM cerebellum as the reference region (André et al., 2020; La Joie et al., 2012), resulting in standardized uptake value ratio (SUVR) maps.

The images resulting from the preprocessing procedure described above for each neuroimaging modality were used both to obtain global neuroimaging values and for the voxel-wise analyses, as described below.

Calculation of global neuroimaging values

Averaged global neuroimaging values were obtained by applying a binary mask of either GM or WM depending on the neuroimaging modality, on the corresponding preprocessed images. More specifically, to obtain global values of GM volume, brain perfusion and amyloid deposition, a mask of total GM including voxels with a GM probability > 60% (average of the GM segments of all participants thresholded at 0.6 and binarized) and excluding the cerebellum, was applied to the GM segments, early and late florbetapir-PET SUVR images, respectively, to exclude non-GM voxel and reduce the probability of overlap with other tissue classes. To obtain global values of WM mean kurtosis, a mask of total WM including voxels with a WM probability > 60% (average of the WM segments of all participants thresholded at 0.6 and binarized) and excluding the cerebellum, was applied to the mean kurtosis maps to exclude non-WM voxel and reduce the probability of overlap with other tissue classes.

Additional processing steps for voxel-wise analyses

The images obtained from the neuroimaging preprocessing steps described above (Section 2.6.) were further smoothed and masked before being entered in voxel-wise analyses. GM segments were smoothed with an 8 × 8 × 8 mm full-width at half-maximum (FWHM) Gaussian filter. A 6.7 × 6.7 × 6.7 mm FWHM Gaussian filter was applied on the mean kurtosis maps so that the final smoothness of the images was equivalent to that of GM volume images. PET images were smoothed with an 8 × 8 × 8 mm full-width at half-maximum (FWHM) Gaussian filter. GM volume and PET images were masked with the same GM mask as described in the previous section, while mean kurtosis images were masked with the same WM mask as mentioned above.

Statistical analyses

First, to assess whether there was a specific association between the QoL domains and each neuroimaging modality, multiple linear regressions were performed using each global neuroimaging value as a dependent variable, the QoL domains as independent variables and demographics (age, sex, education) as covariates (model 1). The same analyses were repeated including depressive and anxiety symptom scores (model 2) or excluding participants exhibiting depressive symptoms higher than a typical cutoff (i.e., GDS>5) (Wancata et al., 2006). Multiple linear regressions were performed using the R software (R Core Team, 2019), and were considered significant at $p < 0.0125$ (Bonferroni correction for multiple comparisons with a p value of 0.05/4 for the four QoL domains).

In a second step, when a significant link was found between a QoL domain and the global value for a specific neuroimaging modality, the corresponding analysis was repeated voxel-wise using SPM12 (controlling for the same covariates) to further assess the regional specificity of the association. A voxel-level p(uncorrected)<0.005 threshold with a cluster-level threshold of p<0.05 corrected for family-wise errors (FWE) was applied for all voxel-wise analyses.

Finally, to further identify which item(s) of the WHOQOL-BREF contributed the most to the previously identified associations, averaged regional neuroimaging values were extracted from the preprocessed images (before the smoothing step) in the significant clusters of the previous analyses (i.e., the voxel-wise analyses, model 1). Then, forward stepwise linear regressions were performed with each averaged regional neuroimaging value as a dependent variable and the items of the corresponding QoL domain as independent variables. Demographics (i.e., age, sex and education) as well as the other QoL domains were controlled for by forcing their inclusion into the model ("step 0"). The p-value to enter in the model was set to 0.05. These regression analyses were performed using the "stepwise" function (https://rubin.msu.domains/code/stepwise_demo.nb.html) and the "stats" package in R (R Core Team, 2019).

Results

Effect of demographics and covariates on QoL domains

Relationships between QoL domains, demographic variables and covariates are reported in Fig. 1. In brief, an effect of sex on QoL scores was found only for the Phy-QoL ($p = 0.03$) with men showing higher scores than women. Phy-QoL, Psy-QoL and Env-QoL, but not Soc-QoL were positively associated with education ($p = 0.04$; 0.04 and 0.005 and 0.88 respectively). All QoL domains were strongly negatively associated with anxiety and depressive symptom scores (all p values ≤ 0.005). Only Phy-QoL was negatively associated with CCI ($p = 0.01$) and positively associated with PASE ($p = 0.01$).

Associations between QoL domains and global neuroimaging values

The results of the multiple linear regression between the QoL domains and global neuroimaging values are presented in Table 2 (model 1) and supplementary Table S2 (model 2). Positive associations were found between the Phy-QoL and both global GM volume (standardized β coefficients=0.26, p=0.004) and global WM mean kurtosis (standardized β coefficients=0.29, p=0.003). Scatterplots of these associations are represented in Fig. 4A. No other associations were found with the other QoL domains (i.e., Psy-QoL, Soc-QoL and Env-QoL) or the other global neuroimaging values (i.e., brain perfusion and amyloid deposi-

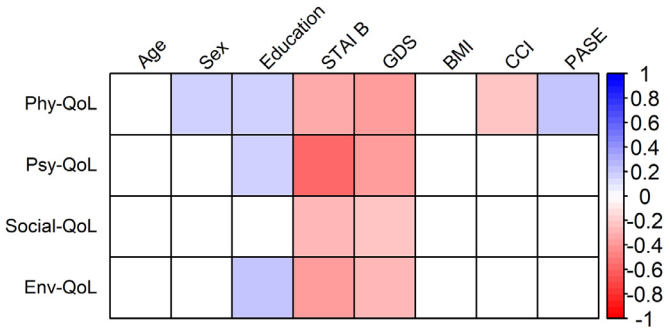

Fig. 1. Pearson's correlation matrix between quality of life domains and demographics and covariates. Pearson's coefficients are indicated in blue (positive) or red (negative) or white when $p > 0.05$. Abbreviations: Phy-QoL, Physical health quality of life; Psy-QoL, Psychological health quality of life; Social-QoL, Social quality of life; Env-QoL, Environment quality of life; STAI B, State-Trait Inventory form B score; GDS, Geriatric Depression Scale score; BMI, Body Mass Index; CCI, Charlson Comorbidities Index; PASE, Physical Activity Scale for Elderly.

Table 2
Multiple linear regressions between the QoL domains and global neuroimaging values adjusted for age, sex, education and the other QoL domains (model 1)

	Global neuroimaging values (structural)					
	Gray matter volume (n=135)			White matter mean kurtosis (n=134)		
	standardized β coefficients	t value	p value	standardized β coefficients	t value	p value
Phy-QoL	**0.26**	**2.9**	**0.004**	**0.29**	**3.02**	**0.003**
Psy-QoL	0.14	1.42	0.16	-0.25	-2.42	0.02
Social-QoL	0.01	0.12	0.9	0.04	0.43	0.67
Env-QoL	-0.21	-2.13	0.04	-0.07	-0.71	0.48
	Global neuroimaging values (functional & molecular)					
	Brain perfusion (n=133)			Amyloid deposition (n=134)		
	standardized β coefficients	t value	p value	standardized β coefficients	t value	*p* value
Phy-QoL	-0.06	-0.6	0.55	-0.18	-1.75	0.08
Psy-QoL	0.17	1.57	0.12	0.07	0.69	0.49
Social-QoL	-0.06	-0.59	0.56	-0.04	-0.39	0.7
Env-QoL	0.02	0.22	0.82	0.14	1.31	0.19

Note: Results, in bold, were considered significant at $p<0.0125$, after applying a Bonferroni correction for multiple testing (p=0.05/4 for the four QoL domains). Abbreviations: Phy-QoL, Physical health quality of life; Psy-QoL, Psychological health quality of life; Social-QoL, Social quality of life; Env-QoL, Environment quality of life

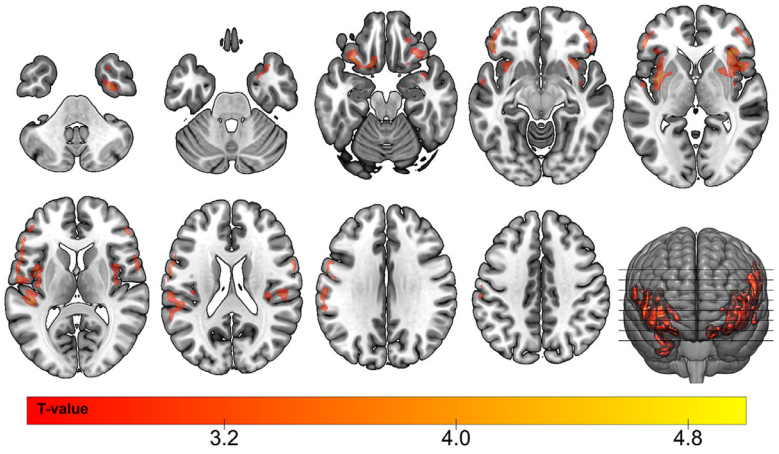

Fig. 2. Positive associations between the physical health quality of life (Phy-QoL) and gray matter volume adjusted for age, sex, education and the other quality of life domains (model 1). Results were thresholded at the voxel level with p(uncorrected)<0.005 and at the cluster level with p(FWE-corrected)<0.05 and overlaid on an MNI-normalized template brain using MRIcroGL.

tion). Results remained unchanged after further adjustment for anxiety and depressive symptom scores (model 2) or excluding participants with GDS>5 (see supplementary Table S3). To check whether these relationships with the Phy-QoL were independent from objective measures of physical health and physical activity, analyses were also repeated with the BMI, CCI and PASE as additional covariates. Results remained unchanged ($p = 0.017$ for global GM volume and $p = 0.032$ for global WM mean kurtosis).

Voxel-wise associations between Phy-QoL and neuroimaging

Based on the previous results, voxel-wise analyses were carried out to assess the regional specificity of the relationships between Phy-QoL on the one hand, and whole-brain GM volume and WM mean kurtosis on the other hand.

A positive association between Phy-QoL and GM volume was found in the anterior insula, ventrolateral prefrontal cortex (encroaching the postcentral gyrus, gyrus rectus and orbitofrontal cortex), bilaterally, and in the left superior temporal cortex (encroaching the entorhinal cortex). The T-value maps and significant clusters are represented in Fig. 2 and scatterplot is represented in Fig. 4B. Peak statistics and coordinates of significant clusters are detailed in supplementary Table S4.

As for WM mean kurtosis, a positive association with Phy-QoL was found in the corpus callosum (frontal part) and corona radiata (encroaching the superior longitudinal fasciculus), the inferior frontal gyrus WM and the cingulum, bilaterally. T-value maps and significant clusters are represented in Fig. 3 and scatterplot is represented in Fig. 4B. Peak statistics and coordinates of significant clusters are detailed in supplementary Table S4.

Voxel-wise analyses with Phy-QoL were repeated with the BMI, CCI and PASE as additional covariates to assess the specific relationships with self-perceived physical health, independently from objective measures of physical health and physical activity. Results remain overall the same although they were less statistically significant (supplementary Figure S2).

Phy-QoL items contributing to the associations with regional neuroimaging values

In order to determine which items of Phy-QoL contributed the most to the associations with neuroimaging data highlighted above, regional

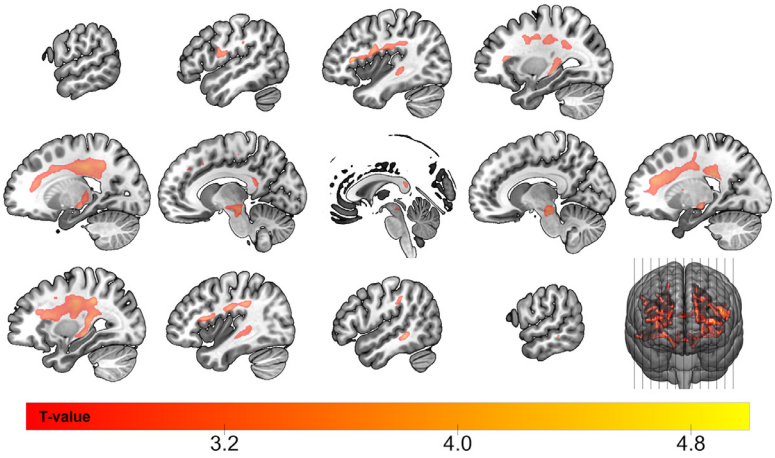

Fig. 3. Positive associations between the physical health quality of life (Phy-QoL) and white matter mean kurtosis adjusted for age, sex, education and the other quality of life domains (model 1). Results were thresholded at the voxel level with p(uncorrected)<0.005 and at the cluster level with p(FWE-corrected)<0.05 and overlaid on an MNI-normalized template brain using MRIcroGL.

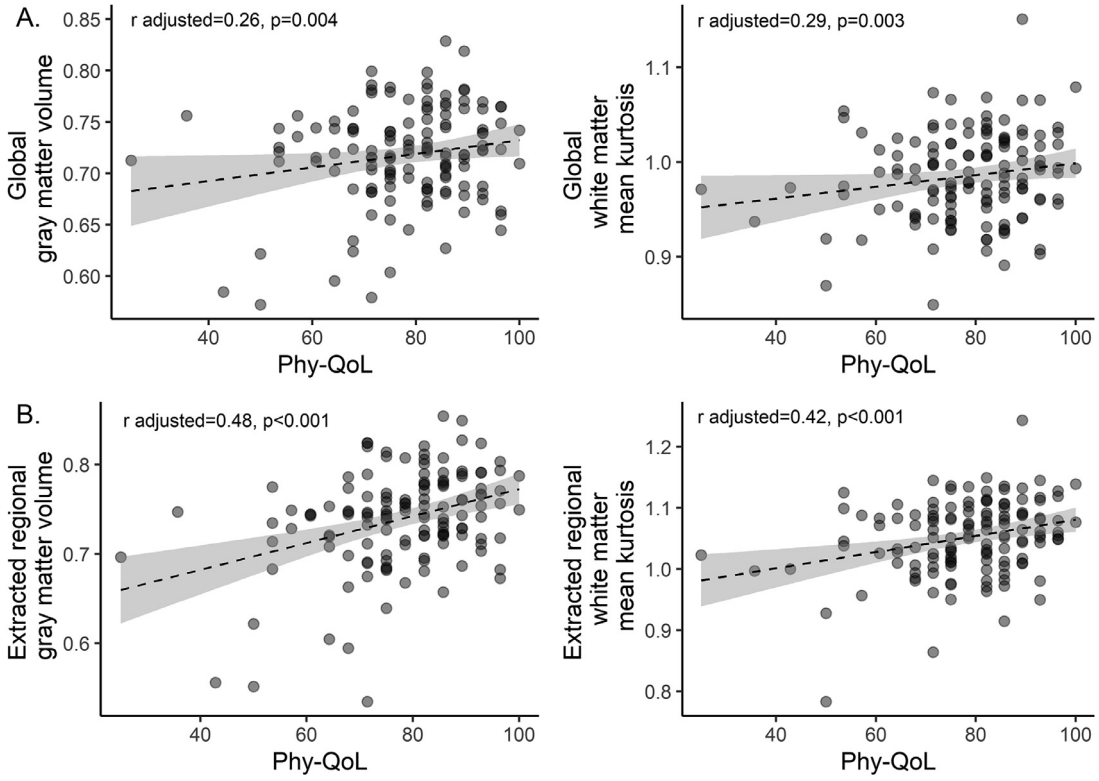

Fig. 4. Scatterplots of positive associations between physical health quality of life (Phy-QoL) and both global (A) and extracted regional (B) gray matter volume and white matter mean kurtosis. Raw data (i.e., unadjusted) are plotted. Statistical values were obtained using models controlling for age, sex, education and the other quality of life domains (model 1).

GM volume and WM structural integrity were extracted from significant clusters of the previous voxel wise analyses and forward stepwise linear regressions were performed (Table 3).

The best predictors of regional GM volume were item 17 (self-perceived daily living activities; i.e., *"how satisfied you are with your ability to perform your daily living activities"*), explaining 11% of the variance, followed by item 4 (self-perceived dependence on medicinal substances and medical aids; i.e., "*how much do you need any medical treatment to function in your daily life*"), explaining 4% of the variance and item 15 (self-perceived mobility; i.e., "*how well are you able to get around*"), explaining 4% of the variance. No other items entered the model, so that 38% of the variance was explained by the final model including the covariates (forced into the model) and these 3 predictive variables (step 3).

The best predictors of regional WM mean kurtosis were item 3 (self-perceived pain and discomfort; i.e., *"to what extend you feel that physical pain prevents you from doing what you need to do"*), explaining 12% of the variance, followed by item 18 (self-perceived work capacity; i.e., "*how satisfied are you with your capacity for work*"), explaining 3% of the variance. No other items entered the model, so that 21% of the variance was explained by the final model including the covariates (forced into the model) and these 2 predictive variables (step 2).

Discussion

The main objective of this study was to identify the specific relationships of different QoL domains and different markers of brain integrity using multimodal neuroimaging. We showed that only Phy-QoL,

Table 3
Forward linear regressions showing the items of the physical health QoL (Phy-QoL) that were significantly associated with regional neuroimaging values (from significant clusters of Figs. 2 and 3)

Factor	Standardized β coefficient	R^2	p value
Gray matter volume			
Step 0		0.19	<0.001 (F=5.11)
Step 1		0.3	<0.001 (F=7.59)
Item 17	0.36	0.11*	<0.001
Step 2		0.34	<0.001 (F=8.18)
Item 17	0.31	-	<0.001
Item 4	0.23	0.04*	0.003
Step 3 (full model)		0.38	<0.001 (F=8.448)
Item 17	0.24	-	0.007
Item 4	0.21	-	0.006
Item 15	0.22	0.04*	0.008
White matter mean kurtosis			
Step 0		0.06	0.208 (F=1.431)
Step 1		0.18	<0.001 (F=3.842)
Item 3	0.35	0.12*	<0.001
Step 2 (full model)		0.21	<0.001 (F=4.189)
Item 3	0.32	-	<0.001
Item 18	0.23	0.03*	0.019

Note: Variables forced into the model: age, sex, education and the other quality of life domains (step 0). α to enter = 0.05.
* Unique R^2 contribution of the item

reflecting self-perceived physical health, was associated with GM volume, mainly within anterior (frontal and insula) brain areas, and with WM microstructural integrity, mainly in long-distant fronto-parietal and parieto-temporal WM tracts. No associations were found between QoL domains and brain perfusion or amyloid deposition. Daily living activities, and pain and discomfort, were the Phy-QoL items contributing the most to these measures of GM volume and WM microstructural integrity, respectively.

Overall, our finding of a link between QoL and GM volume is consistent with previous studies in older adults (Elderkin-Thompson et al., 2008; Hahm et al., 2019) but also in patients with depression (Elderkin-Thompson et al., 2008), schizophrenia (Faget-Agius et al., 2015), and functional neurological disorder (Perez et al., 2017). We found a specific relationship between higher self-perceived physical health and both greater GM volume and greater WM integrity. Consistently, the only two studies assessing QoL domains have also reported a relationship between Phy-QoL and GM (Hahm et al., 2019) or WM (Elderkin-Thompson et al., 2008) volumes. However, they did not assess all QoL domains, so that the specificity of these relationships is highlighted for the first time in the present study. Moreover, no previous study assessed the links with WM integrity using diffusion imaging data, while this technique is particularly sensitive to microstructural WM changes with age (Fjell et al., 2008; Giorgio et al., 2010; Westlye et al., 2010). The observed association with self-perceived physical health found here suggests that this QoL domain is particularly relevant to brain health (at least GM volume and WM microstructural integrity) in cognitively unimpaired older adults. It is possible that the other QoL domains, namely psychological health, social relationships and environment, would be more strongly related to brain health in other populations, such as patients with depression or dementia.

We found that Phy-QoL was mainly associated with GM volume in the anterior insula, ventrolateral prefrontal and superior temporal cortex and WM integrity in the corpus callosum (rostrum and genu), the corona radiata (encroaching on the superior longitudinal fasciculus), the inferior frontal WM and the cingulum. This is overall consistent with previous studies also showing that higher self-perceived physical health was associated with greater GM volume in the frontal cortex and insula (Hahm et al., 2019), and WM volume in fronto-parietal WM tracks (Elderkin-Thompson et al., 2008), although with subtle differences as they highlighted the orbital part of the frontal cortex, and also involved the anterior cingulate cortex. These findings seem consistent as regard to self-perceived physical health because such brain areas, e.g. the insula involved in socio-emotional and sensorimotor processing (Uddin et al., 2017), might help people to perceive their physical health. Taken together, these GM regions and WM fibers associated with self-perceived physical health are parts of the salience network (Barrett and Satpute, 2013; Uddin, 2015) and the empathy network (Engen and Singer, 2013; Moore et al., 2015; Shamay-Tsoory, 2011) which might be relevant here for the cognitive process needed for self-perception, and the pain pathway (Bushnell et al., 2013; Lieberman et al., 2014) which is expected to be involved given that pain perception is a relevant aspect of self-perceived physical health. Overall, these networks are involved in self-cognitive processes such as self-awareness, interoception, emotion or cognitive mentalizing, which are needed for the subjective assessment of health (Jylhä, 2009).

The subjective assessment of QoL as performed here is likely influenced by several parameters including psychological factors and subjective appraisal together with physical, environmental and social conditions. Indeed, we found all QoL domains to be associated with anxiety and depressive symptom scores which is in line with several studies showing influence of depression (Sivertsen et al., 2015) and anxiety (Brett et al., 2012) on QoL in older adults. Our analyses with brain integrity were yet adjusted for anxiety and depressive symptom scores, and repeated in a subsample excluding participants exhibiting a high score of depressive symptoms (i.e., GDS>5). Results remained unchanged, indicating that the relationships found between QoL and brain integrity was independent from the influence of these factors on QoL. We also found Phy-QoL to be associated with an objective measure of physical health (the CCI) and physical activity, which is in line with several studies (Bayliss et al., 2005; Rejeski and Mihalko 2001; Wu et al., 2013). A few studies have shown lower self-perceived physical health in older adults who were obese compared to those who had normal weight (Bottone et al., 2013; Zawisza et al., 2019). In contrast, we did not find association between Phy-QoL and BMI, another measure of objective physical health, which could be explained by the low rate of obese in our sample. Furthermore, it is well known that brain integrity, as reflected in GM volume and WM volume or microstructural integrity for instance, is related to objective physical health (Bolzenius et al., 2015; Kharabian Masouleh et al., 2016) and physical activity (Erickson et al., 2014; Sexton et al., 2016, for review). We thus adjusted for these variables to assess whether the links we found with Phy-QoL reflected the same process. The fact that we still found Phy-QoL to be associated with GM volume and WM microstructural integrity when controlling for the effects of BMI, CCI and PASE showed that this link was specific to the subjective assessment of physical health and at least partly independent from these measures of objective physical health and physical activity.

To further understand the meaning of our findings and identify which specific aspect(s) of self-perceived physical health is involved, we performed complementary item analyses. Self-perceived daily living activities were identified as the strongest contributors to the associations with GM volume and pain and discomfort as the strongest contributors to the associations with WM microstructural integrity. While they should be considered with caution given the low variability of each item, these findings suggest that, in a clinically unimpaired population, daily living activities and pain are the most relevant QoL determinants of brain integrity. Daily living activities and pain have already been highlighted as particularly relevant QoL determinants in older adults (Molzahn et al., 2010). Our findings might reflect the fact that, as their brain ages, older adults have a general decrease in several cognitive functions including for instance processing speed and executive functions (Harada et al., 2013), which, they feel, mainly impact, in terms of QoL, their daily living activity and their feeling of pain and discomfort. While daily living activity is actually expected to be impaired by decreased brain (and cognitive) integrity, and more particularly gray matter volume, the link with pain and discomfort might be less direct, possibly reflecting the fact that, as they get older, people are more and

more subject to pain and discomfort and they consider this as a significant burden for their QoL. Overall, our findings thus suggest that self-perceived physical health, and especially self-perceived daily living activities and pain and discomfort, are the most relevant factors of QoL related to brain health – more specifically to GM volume and WM microstructural integrity in older adults. These findings are interesting for interventional studies as they provide more concrete understanding of which specific aspects underline self-perceived physical health here.

No association was found between QoL and functional (i.e., brain perfusion) or molecular (i.e., amyloid deposition) neuroimaging. This suggests that QoL is mainly associated with structural changes, while perfusion and amyloid deposition changes are not paralleled with QoL changes, at least at this stage (i.e., in cognitively unimpaired older adults). However, this does not exclude that associations with other modalities may exist in specific regions that would be highlighted with a regional-specific (or voxel-wise) approach. Indeed, a previous study found a relationship between higher social QoL and decreased parietal functional connectivity in healthy working female managers (Kraft et al., 2018), suggesting that QoL could be related with other (e.g. functional) markers of brain integrity in other populations or using a different approach (i.e., regional-specific or voxel-wise).

The main strengths of our study include the use of complementary multimodal neuroimaging with voxel-wise analyses and the assessment of distinct aspects of QoL, which allowed better characterization of the brain substrates of specific QoL domains in cognitively unimpaired older adults. Our studies also have several limitations. Firstly, although we adjusted our main results for BMI, CCI and PASE to account for objective physical health and physical activity, more detailed or specific measures (e.g. cortisol, actigraphy, hand grip strength…) could be used in future studies to better dissociate (and possibly as well to compare) the respective contribution of subjective physical health, objective physical health and physical activity, to brain integrity in general and GM volume and WM microstructural integrity in particular. Secondly, other measures of brain integrity (e.g. functional connectivity) could be included, and comparisons with other populations (e.g. subjective cognitive decline) would be interesting to highlight the specificity of our findings to cognitively unimpaired older adults. Thirdly, the cross-sectional design of our study is a limitation as it prevented us from determining the direct causality of the association between self-perceived physical health and brain structural integrity. Further work is needed, including longitudinal observational, but also interventional studies, to investigate the causality of the relationships between QoL and brain changes, and if these changes are reversible. Finally, we only considered the different neuroimaging modalities separately; future studies could further look at the specificity of these neuroimaging modalities through direct inter-modality comparisons.

Conclusion

This is the first study to address the links between distinct QoL domains and multimodal neuroimaging in cognitively unimpaired older adults. Our data revealed that QoL, and more specifically self-perceived physical health, was positively related to global GM volume mainly within anterior (frontal and insula) brain areas and to global WM microstructural integrity mainly in long-distance fronto-parietal and parieto-temporal WM tracts, but not to global brain perfusion or global amyloid deposition. Future interventional studies designed to improve QoL might focus on daily living activities and pain and discomfort, together with the personal appraisal of these items, and test the effects on brain health and the causality of the relationship between QoL and brain integrity in cognitively unimpaired older adults.

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Data and code availability statement

Data and code are made available on request following a formal data sharing agreement and approval by the consortium and executive committee (https://silversantestudy.eu/2020/09/25/data-sharing). 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 non-academic third parties, under conditions, in particular financial, which will be established by separate agreement between Inserm and by the said third party. Data sharing policies described in the Medit-Ageing charter are in compliance with our ethics approval and guidelines from our funding body.

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Credit authorship contribution statement

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.117819.

Appendix

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