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Sex-specificities in anxiety and depressive symptoms across the lifespan and their links with multimodal neuroimaging

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ABSTRACT

Background: Anxiety and depressive symptoms are associated with impaired well-being, higher risk of developing psychoaffective disorders and are risk factors for Alzheimer's disease (AD). To further understand their relevance and the mechanisms underlying their link with AD, our aims were to assess how anxiety and depressive symptoms changed with age and related to AD neuroimaging biomarkers across the adult lifespan, while also exploring sex specificities.

Methods: 210 cognitively normal participants aged 19-86 years (101 men, 109 women) completed assessments of anxiety and depressive symptoms with the STAI-A and MADRS respectively, and neuroimaging measurements including structural MRI, FDG-PET and amyloid-PET. 167 of those were followed-up over 1.5–3 years. Multiple regressions were performed to assess the links between anxiety or depressive symptoms versus age, global cognition or each imaging modality, both cross-sectionally and longitudinally; and general linear models we used to test the interactive effect of sex on these associations.

Results: Depressive symptoms decreased with age, while anxiety symptoms increased only among women. Higher anxiety symptoms were associated with lower grey matter (GM) volume and glucose metabolism, with an interaction of sex, this relationship being significant only in women. Longitudinally, only low baseline GM volume predicted an increase in anxiety symptoms with time.

Limitations: Only 43% of participants reported depressive symptoms. Despite additional analyses, the low variability in the measure might have prevented us from detecting subtle changes.

Conclusions: This study emphasizes the need to consider anxiety symptoms in assessments for dementia risk, particularly in women.

1. Background

Subclinical symptoms of anxiety and depression are frequently observed in older adults (Bryant et al., 2008; Forlani et al., 2014), and are associated with a high risk of developing anxiety and depressive disorders (Chambers et al., 2004; Cuijpers and Smit, 2004; Karsten et al., 2011). Elevated levels of anxiety and depression are associated with a worsening of the quality of life of seniors, fragility, sleep problems and cognitive disorders, or even with increased rates of mortality, morbidity and disability (Bryant et al., 2008; Cuijpers and Smit, 2004; Siegel and Mathews, 2015).

Moreover, subthreshold anxiety and depressive symptoms were found to increase the risk of developing dementia (Harrington et al., 2015; Petkus et al., 2016; Singh-Manoux et al., 2017). Compared to individuals without symptoms of anxiety and depression, they were twice as likely to develop amnestic Mild Cognitive Impairment (MCI), a prodromal phase of Alzheimer's dementia, over 3–6 years (Donovan et al., 2018). Anxiety and depressive symptoms could also be a reaction

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to a perceived cognitive decline (Amieva et al., 2008) and/or a prodromal manifestation of an underlying AD pathology (Geda et al., 2013). Assessing the links between these factors and the neuroimaging markers of AD would help further understanding their relevance across the adult lifespan. More specifically, brain markers of neurodegeneration, namely grey matter (GM) volume using structural magnetic resonance imaging (MRI) and brain glucose metabolism using fluorodeoxyglucose 18F (FDG) uptake on positron emission tomography (PET), and of brain amyloidosis with PET imaging coupled with an amyloid radiotracer, would be particularly relevant (Dubois et al., 2007; Jack et al., 2018; Sperling et al., 2011).

Previous studies showed that anxiety and depressive symptoms were associated with poorer cognition or cognitive outcome (Beaudreau and O'Hara, 2009; Gallacher et al., 2009; Petkus et al., 2016; Pietrzak et al., 2015; Potvin et al., 2011; Vito et al., 2017; Wilson et al., 2011; Yochim et al., 2013). Only few studies investigated the neural correlates of subclinical anxiety and depression in cognitively normal older adults. They showed that anxiety and depressive symptoms were associated with reduced global cortical thickness (Kühn et al., 2011; Pink et al., 2017b, 2017a) and GM volume (Spampinato et al., 2009) notably in the frontal cortex. Moreover, both subclinical anxiety and depressive symptoms were associated with lower global cortical glucose metabolism (Krell-Roesch et al., 2016). Mixed results were found for amyloid load, with studies reporting a positive association between anxiety/depressive symptoms and amyloid deposition as measured with PET (Babulal et al., 2016; Hanseeuw et al., 2018; Krell-Roesch et al., 2018), while others did not find any relationship (Holmes et al., 2018). Finally, higher amyloid load was found to predict an increase in depressive symptoms (Babulal et al., 2016; Donovan et al., 2018).

Women have twice the lifetime rates of depression and most anxiety disorders, show more subclinical anxiety and depression symptoms (Altemus et al., 2014), and also have higher risk of developing dementia (Singh-Manoux et al., 2017) compared to men. Only few studies however investigated the sex-specificities in the neural substrates of anxiety and depressive symptoms. They reported conflicting results, showing that depressive symptoms were associated with decreased GM volume in the hippocampus and frontal regions only in males (Carlson et al., 2015; Spalletta et al., 2014; Taki et al., 2005), or with decreased GM volume in frontal areas only in women (Hayakawa et al., 2013). Only one study assessed the relationship of anxiety symptoms with GM volume considering possible sex-differences, and found that harm avoidance - a core feature of anxiety - was associated with reduced GM in left anterior prefrontal cortex only in women (Yamasue et al., 2008). No study assessed sex-specificities in the links of depressive and anxiety symptoms with brain glucose metabolism or amyloid load to date.

The aim of this study was to further our understanding of the relationships of anxiety and depressive symptoms to neuroimaging measures, and sex specificities, throughout the adult lifespan. Given that anxiety and depressive symptoms are modifiable risk factors through prevention and treatment (Serfaty et al., 2009; van Zoonen et al., 2014; van't Veer-Tazelaar et al., 2009), improving our understanding of their relative impact at this preclinical stage and level is particularly relevant for clinical management and risk reduction of both psychoaffective disorders and AD.

To do so, we first assessed the relationship of anxiety and depressive symptoms with age and the possible interactive effect of sex. Secondly, we investigated the links between these psychoaffective factors and global cognition and memory, as well as neuroimaging biomarkers including GM volume, glucose metabolism and amyloid deposition. We then assessed the longitudinal changes of anxiety and depressive symptoms over a 2-year follow-up period. Lastly, we assessed the predictive value of baseline psychoaffective symptoms on neuroimaging changes over time, and reversely the predictive value of baseline cognitive and neuroimaging measures on changes over time in anxiety and depressive symptoms.

2. Methods

2.1. Participants

Two hundred and ten (101 men and 109 women) cognitively normal participants aged 19 to 86 years from the 'Imagerie Multimodale de la Maladie d'Alzheimer à un stade Précoce' (IMAP+) cohort in Caen, France, were included in the present study. Participants were recruited from the general population through advertisement or word of mouth. They had no history or clinical evidence of neurologic or psychiatric disorder, no psychotropic drug intake, and performed in the normal range in all neuropsychological tests (including tests of episodic memory, working memory, language skills, executive functions, and visuospatial abilities). Notably, none of the participants met diagnostic criteria for major depression or anxiety disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Donovan et al., 2015; Lavretsky and Kumar, 2002; Lyness et al., 2009). The IMAP+ study was approved by the local ethics committee, and written informed consent was obtained from all participants after complete description of the study. Longitudinal data was available for 167 of the participants.

2.2. Psychoaffective assessment

Depressive symptoms were assessed using the clinician-administered Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item questionnaire (Montgomery and Asberg, 1979) used to rate the severity of depressive symptoms (from 0 to 60) at the time of the evaluation. State anxiety symptoms were assessed with the Spielberger State-Trait Anxiety Inventory form Y to A (STAI-A), a 20-item self-report questionnaire (Spielberger et al., 1970), rating the severity of anxiety symptoms (from 20 to 80) at the time of the evaluation. For both scales, higher scores indicated higher levels of symptoms of anxiety and depression; yet scores remained low, as participants were screened so as not to meet diagnostic criteria for major depression or anxiety disorder. Our goal was to assess anxiety and depressive symptoms on a continuum (Altman and Royston, 2006; Laborde-Lahoz et al., 2015) so these scores were used as continuous variables.

2.3. Global cognition assessment

Global cognition was measured using the 30-point scale Mini Mental State Examination (MMSE; scores from 0 to 30)(Folstein et al., 1975) and the 144-point global score of the Mattis Dementia Rating Scale (DRS)(Mattis, 1976).

2.4. Neuroimaging data

Grey Matter (GM) volume was assessed with Magnetic Resonance Imaging (MRI), brain glucose metabolism with 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) and amyloid deposition with florbetapir-PET. Global values of GM volumes, FDG and florbetapir standardized uptake value ratios (SUVr) were obtained as described below and used as continuous variables in the following analyses. All participants underwent neuroimaging scans on the same MRI and PET scanners at the Cyceron Centre (Caen, France) within 3-month interval from the psychoaffective and cognitive assessments.

2.4.1. Neuroimaging acquisition

MRI data, high-resolution T1-weighted anatomical images, were acquired on a Philips Achieva 3.0 T scanner using a 3D fast-field echo sequence (3D-T1-FFE sagittal; repetition time = 20 ms; echo time = 4.6 ms; flip angle = 10°; 180 slices with no gap; slice thickness = 1 mm; field of view = 256 × 256 mm^2; in-plane resolution = 1 × 1mm^2).

PET scans, both FDG and florbetapir, were acquired with a Discovery RX VCT 64 PET-CT device (General Electric Healthcare) with a

resolution of 3.76 × 3.76 × 4.9 mm^3 (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 × 1.95 × 3.27 mm^3. A transmission scan was performed for attenuation correction before the PET acquisition.

FDG-PET acquisitions were performed after at least 6 h of fasting, and after 30 min at rest in a dark and quiet room. Participants were injected intravenously with ~180 MBq of FDG and after 50 min, the participants underwent a 10 min' scan. Florbetapir-PET scan was acquired for each participant during 20 min, 50 min after the intravenous injection of ~4 MBq/kg of florbetapir, except for 14 participants (8 men and 6 women) who had a 10 min (50 to 60) acquisition.

2.4.2. Neuroimaging processing

The Statistical Parametric Mapping version 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, London, UK) was used for all neuroimaging processing steps.

T1-weighted MRI images were first segmented and spatially normalized to the Montreal Neurological Institute (MNI) space. The normalized GM segments were then modulated to correct for non-linear warping effects so that values in resultant images were expressed as volume corrected for brain size, allowing us to extract values reflecting amounts of tissue corrected for individual differences in global head size (Cousijn et al., 2012; La Joie et al., 2012; Tomadesso et al., 2019).

PET images were corrected for partial volume effects using the Müller-Gärtner method, then coregistered onto their corresponding MRI, and normalized with the deformation parameters used for the MRI procedure. The cerebellar GM was then used as the reference region to quantitatively normalize the resultant images (Bejanin et al., 2019; Chételat et al., 2008; La Joie et al., 2012; Villain et al., 2008).

Total GM volume and FDG-PET global value were obtained for each participant using a binary mask of GM (including voxels with a GM probability > 30% excluding the cerebellum) on the corresponding preprocessed images. The global neocortical SUVr value was calculated from the florbetapir-PET images using a neocortex mask (including all regions but the cerebellum, hippocampus, amygdala and subcortical grey nuclei), as described in details elsewhere (La Joie et al., 2012).

2.5. Longitudinal assessment

All psychoaffective, cognitive and imaging measures described above were also obtained at follow up, i.e. after a mean duration of 2 years (± 0.12 years). Participants with follow-up measures of anxiety and depressive symptoms, and at least one of the other measures of interest, were included in the longitudinal analyses (total $n = 167$, men $n = 81$, women $n = 86$). A slope of change for each variable and each participant was calculated with simple linear regression (Chételat et al., 2005) '$y = ax + b$' (with y: score of interest; a: slope of the regression; x: number of months from the initial evaluation; b: intercept) and used in the longitudinal analyses as measures of rate of change.

2.6. Statistical analysis

2.6.1. Cross sectional data

To assess the relationship between psychoaffective factors and age, we performed multiple regressions between depressive and anxiety symptoms with age, correcting for education and anxiety symptoms or depressive symptoms respectively. Indeed, because anxiety and depression scores are expected to be related, all analyses with one of these measures was corrected for the other and inversely. To evaluate the effect of sex, we performed General Linear Models (GLMs) and tested the interactive effect of sex on the association between anxiety or depression and age (e.g. MADRS × Age × Sex). If a significant interaction was found, we repeated the multiple regressions within the subgroups of men and of women separately.

The substrates of psychoaffective factors were assessed using multiple regressions, between psychoaffective measures (i.e. depressive symptoms and anxiety symptoms) on the one hand, and global cognition and imaging data (i.e. GM volume, glucose metabolism and amyloid load) on the other hand. Results are presented with correction for level of education and anxiety symptoms for correlations with depressive symptoms, and for level of education and depressive symptoms for correlations with anxiety symptoms, to independently evaluate the links of those psychoaffective symptoms with cognition and brain parameters along the ageing process. We then performed GLMs to evaluate the possible interactive effects of sex on these associations (e.g. MADRS × Global DRS × Sex) and repeated the multiple regressions within the subgroups of men and of women separately if the interaction was significant. Age was not included as a covariate in our main analyses because we were specifically interested in assessing the age-related relation between anxiety and depressive symptoms with global cognition and neuroimaging markers. However, all analyses were repeated, and results were also reported with age as a covariate, to check whether possible relationships where entirely driven by age. Pairwise deletion was used in case of missing data and all statistical analyses were performed using the STATISTICA software (v13.0, StatSoft Inc., Tulsa, OK).

2.6.2. Longitudinal data

The slopes of change of psychoaffective factors were compared to zero with one sample t-tests to assess whether they changed over time. We then compared the slopes of change of psychoaffective factors between men and women with ANCOVA, correcting for education, to assess sex-specificities. We then performed multiple regressions between baseline psychoaffective measures and slopes of change in global cognition and imaging data, and then between baseline cognition and imaging data and slopes of change in psychoaffective measures, correcting for baseline education and baseline anxiety symptoms or depressive symptoms depending of the analysis. When specified, baseline age was also included in the model as a covariate to assess the links independently from age effects. Lastly, we performed GLMs to evaluate the interactive effect of sex in the predictions (e.g. Baseline MADRS × slope of Global DRS × Sex), and repeated the multiple regressions in subgroups of men and of women separately when the interactive effect of sex was significant. Pairwise deletion was used in case of missing data and all statistical analyses were performed using the STATISTICA software (v13.0, StatSoft Inc., Tulsa, OK).

2.6.3. Supplementary analyses

Since neither the anxiety nor the depressive score showed a normal distribution, correlation analyses were repeated with non-parametric Spearman's correlation tests. Also, as an important floor effect was observed on MADRS data with a large number of participants having a score of zero, we repeated all analyses with depressive symptoms excluding these participants, i.e. within a subgroup of participants with at least one depressive symptom ($n = 89$). The cross-sectional and longitudinal multiple regressions between depressive symptoms and age, cognition and brain parameters were assessed in this subgroup, correcting for level of education and anxiety symptoms, and when specified, for age. The interactive effect of sex was also tested in this subsample in order to check that the results were consistent and not driven by the floor effect.

3. Results

3.1. Description of the population

The demographics of the study participants are listed in Table 1 (see age distribution in supplementary Fig. 1) and in supplementary Table 5 for the participants included in the longitudinal analyses. Amongst the 210 cognitively unimpaired adults, 48% were women. There was no difference between men and women in age, education, or anxiety symptoms and depressive symptoms. However, we found lower GM volume and higher glucose metabolism in women. Additionally, as

Table 1
Cross-sectional study sample characteristics.

	Total population	n	Men	n	Women	n	ANOVA
Age	48.41 ± 18.99	210	47.51 ± 19.32	101	49.25 ± 18.73	109	0.508
Level of education	13.18 ± 3.16	210	13.33 ± 3.43	101	13.05 ± 2.89	109	0.521
Depressive symptoms (MADRS; range: [0–15])	1.44 ± 2.52	210	1.61 ± 2.98	101	1.29 ± 2.02	109	0.367
Anxiety symptoms (STAI A; range: [20–57])	26.73 ± 7.04	198	26.24 ± 7.23	96	27.20 ± 6.85	102	0.341
Cognition (MMSE; range: [25–30])	29.26 ± 0.90	210	29.28 ± 0.81	101	29.24 ± 0.98	109	0.782
Global cognition (DRS; range: [130–144])	141.81 ± 2.56	209	141.65 ± 2.84	100	141.96 ± 2.27	109	0.378
GM volume	671.49 ± 79.06	207	712.98 ± 69.39	98	634.18 ± 68.04	109	**0.000**
Glucose metabolism	1.16 ± 0.10	189	1.15 ± 0.10	91	1.18 ± 0.11	98	**0.048**
Amyloid load	0.91 ± 0.11	138	0.90 ± 0.11	70	0.91 ± 0.11	68	0.321

Values indicate mean ± standardized deviation. Values in bold correspond to significant ANOVA comparing men and women, p values ($p < 0.05$). DRS Dementia Rating Scale, MADRS Montgomery-Åsberg Depression Rating Scale, MMSE Mini Mental State Examination, STAI A Spielberger State-Trait Anxiety Inventory state form.

expected, anxiety and depression scores were correlated (non-parametric $p = 0.001$).

3.2. Psychoaffective associations with age

We found a decrease in depressive symptoms with age, while anxiety symptoms did not significantly change with age (Table 2 and Fig. 1). This result did not hold in non-parametric analyses ($p = 0.191$; Supplementary Tables 1 and 2).

Regarding sex-differences in age-related associations with psychoaffective factors, we found no moderating effect of sex on depressive symptoms, and a trend on anxiety symptoms (Table 2 and Fig. 1). Analyses within each sex subgroup revealed that anxiety symptoms significantly increased with age in women but not in men (Table 2 and Fig. 1). Non-parametric analyses showed similar results (Supplementary Table 1).

Findings for depressive symptoms in the subgroup with at least one depressive symptom were similar but less significant (Supplementary Table 3).

Table 2
Cross-sectional relationships of psychoaffective factors to global cognition and neuroimaging measures and interaction with sex.

Depressive symptoms (MADRS)	Total group	Interactions with sex	Men	Women
Age	0.049 (−0.141)	0.613	-	-
Global cognition (DRS)	0.423 (−0.060)	0.895	-	-
GM volume	0.388 (0.062)	0.233	-	-
Glucose metabolism	0.069 (0.135)	0.307	-	-
Amyloid load	0.940 (0.006)	0.865	-	-
Anxiety symptoms (STAI A)	Total group	Interactions with sex	Men	Women
Age	0.252 (0.083)	0.082	0.667 (−0.046)	0.045 (0.200)
Global cognition (DRS)	0.712 (−0.027)	0.854		
GM volume	0.072 (−0.128)	0.014	0.543 (0.064)	0.006 (−0.272)
Glucose metabolism	0.033 (−0.157)	0.049	0.821 (−0.025)	0.002 (−0.314)
Amyloid load	0.182 (0.116)	0.238	–	–

Values indicate p (r) values of the multiple linear regressions between depressive or anxiety symptoms on the one hand, and the corresponding cognitive or neuroimaging variables on the other hand. All analyses with depressive symptoms were corrected for level of education and anxiety symptoms, while all analyses with anxiety symptoms were corrected for level of education and depressive symptoms. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). DRS Dementia Rating Scale, MADRS Montgomery-Åsberg Depression Rating Scale, STAI A Spielberger State-Trait Anxiety Inventory state form.

3.3. Psychoaffective associations with cognition

Neither depressive symptoms nor anxiety symptoms were associated with global cognition (Table 2). We found the same results, in the subgroup with at least one depressive symptom, and/or when also correcting for age (Supplementary Tables 1–4). There was no moderating effect of sex in any of these analyses (Table 2; Supplementary Tables 1, 3 and 4).

3.4. Psychoaffective associations with brain parameters

Depressive symptoms showed no association with either GM volume, or amyloid deposition, and only a trend for brain glucose metabolism which tended to increase as depressive symptoms increased (Table 2). No moderating effect of sex was observed (Table 2). Results were similar with non-parametric analyses, in the subgroup with at least one depressive symptom, and/or when also correcting for age (Supplementary Tables 1–4).

Anxiety symptoms were associated with lower brain glucose metabolism, weakly associated with lower GM volume, and not associated with amyloid (Table 2 and Fig. 2). Sex moderated relationships with glucose metabolism and GM volume such that higher anxiety symptoms were associated with lower GM volume and brain glucose metabolism only in women (Table 2 and Fig. 2).

Non-parametric analyses showed the same moderating effects of sex and the same findings within each sex group (Supplementary Table 1). Effects were attenuated when correcting for age but findings remained similar (Supplementary Table 4).

3.5. Longitudinal changes and links of psychoaffective factors with cognition and brain parameters

There was no significant change over time in psychoaffective factors, cognitive measures and glucose metabolism. GM volume decreased over time and amyloid deposition increased over time (Supplementary Table 5). When comparing the slopes of change of the different measures over time between men and women, we only found a trend for amyloid load, and one-sample t-test in each sub-group showed an increase in amyloid load only in women (Supplementary Table 5).

Baseline psychoaffective factors did not predict slopes of change in

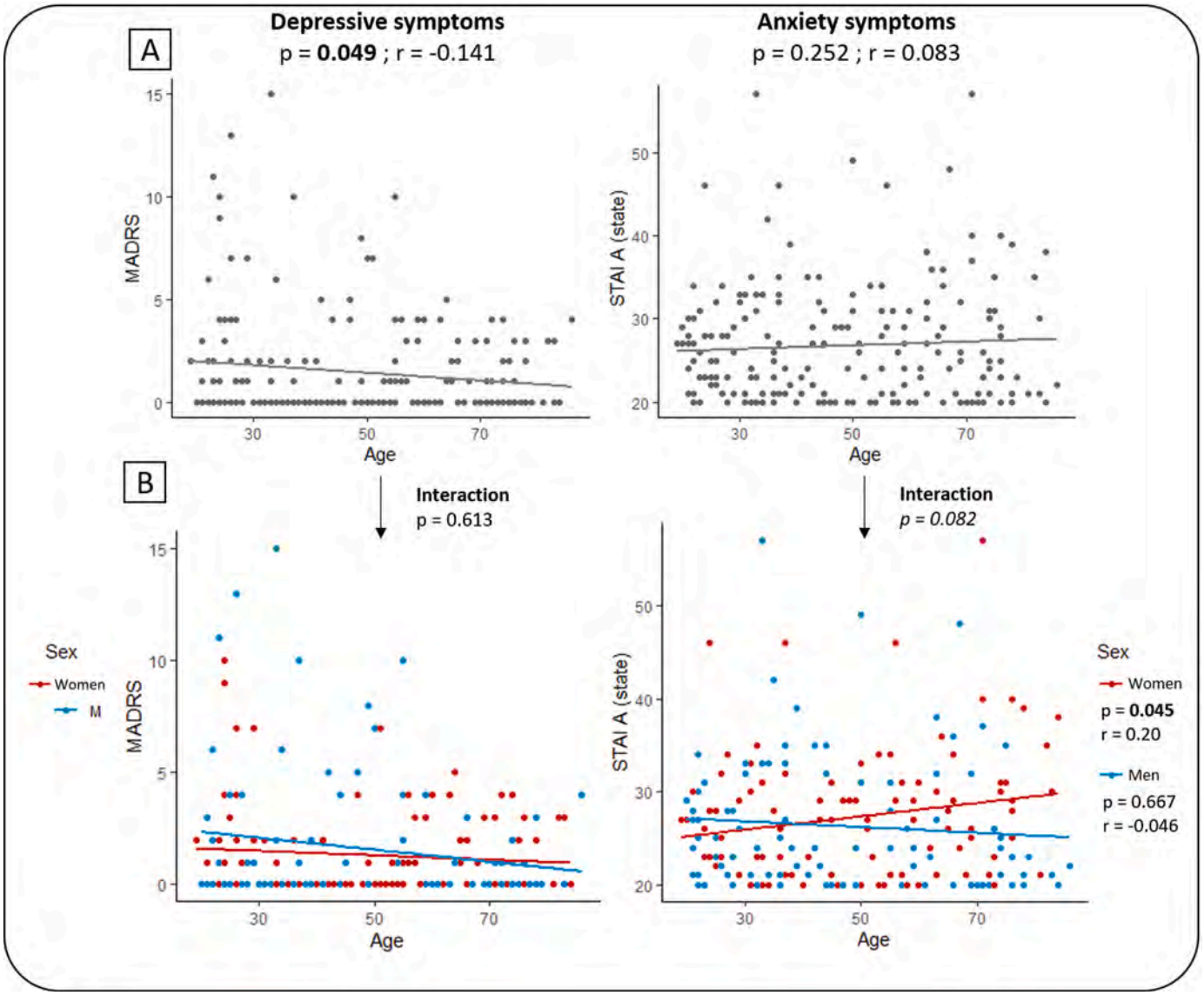

Fig. 1. Multiple regressions of psychoaffective factors with age and interactions with sex. Graphs indicate *p* and *r* values of multiple regressions. A: Multiple regression of depressive symptoms or anxiety symptoms with age, corrected for the level of education and anxiety symptoms or depressive symptoms respectively. B: Interactive effects of sex on the multiple regression of depressive symptoms or anxiety symptoms with age, corrected for the level of education and anxiety symptoms or depressive symptoms respectively, in the group of Men and Women separately. Values in bold correspond to significant *p* values ($p < 0.05$) and values in italic correspond to trends ($0.01 < p < 0.05$). MADRS Montgomery-Asberg Dementia Rating Scale, *p* value, *r* value, STAI A Spielberger State-Trait Anxiety Inventory state form.

cognition or brain measures in the main analyses (Table 3), with non-parametric analyses (Supplementary Table 6), in the subgroup with at least one depressive symptom (Supplementary Table 3) and/or after correcting for age (Supplementary Table 7).

As for the relationships between baseline cognition or brain measures and slope of change in psychoaffective factors, low GM volume at baseline predicted increase in anxiety symptoms over time (Table 3) with a trend for an interaction with sex indicating that this relationship was found in women, but not in men (Table 3). Non-parametric analyses and those correcting for age showed similar results (Supplementary Tables 6 and 7).

4. Discussion

To our knowledge this is the first study to assess the links of anxiety and depressive symptoms with cognition and multiple neuroimaging biomarkers (i.e. GM volume, glucose metabolism and amyloid deposition), together with sex-specificities, across the adult lifespan. We showed that depressive symptoms decreased with age, but were not associated with cognitive or neuroimaging measures. We showed sex-specific effects with anxiety symptoms, in that they increased with age, and were associated with lower GM volume and brain glucose metabolism, only in women.

4.1. Psychoaffective factors associations with age

When assessing the link with age in the whole sample, we found no change in anxiety symptoms, but an age-related decrease in depressive symptoms. This trend remained after removing participants who scored 0 in the cross-sectional analysis. Consistently, we also found a trend for a decrease in depressive symptoms in our longitudinal analysis. Our results are supported by those from previous studies who reported a decrease in the prevalence of mood disorders (Teachman, 2006) or negative affect (Charles et al., 2001) with age. This decrease is thought

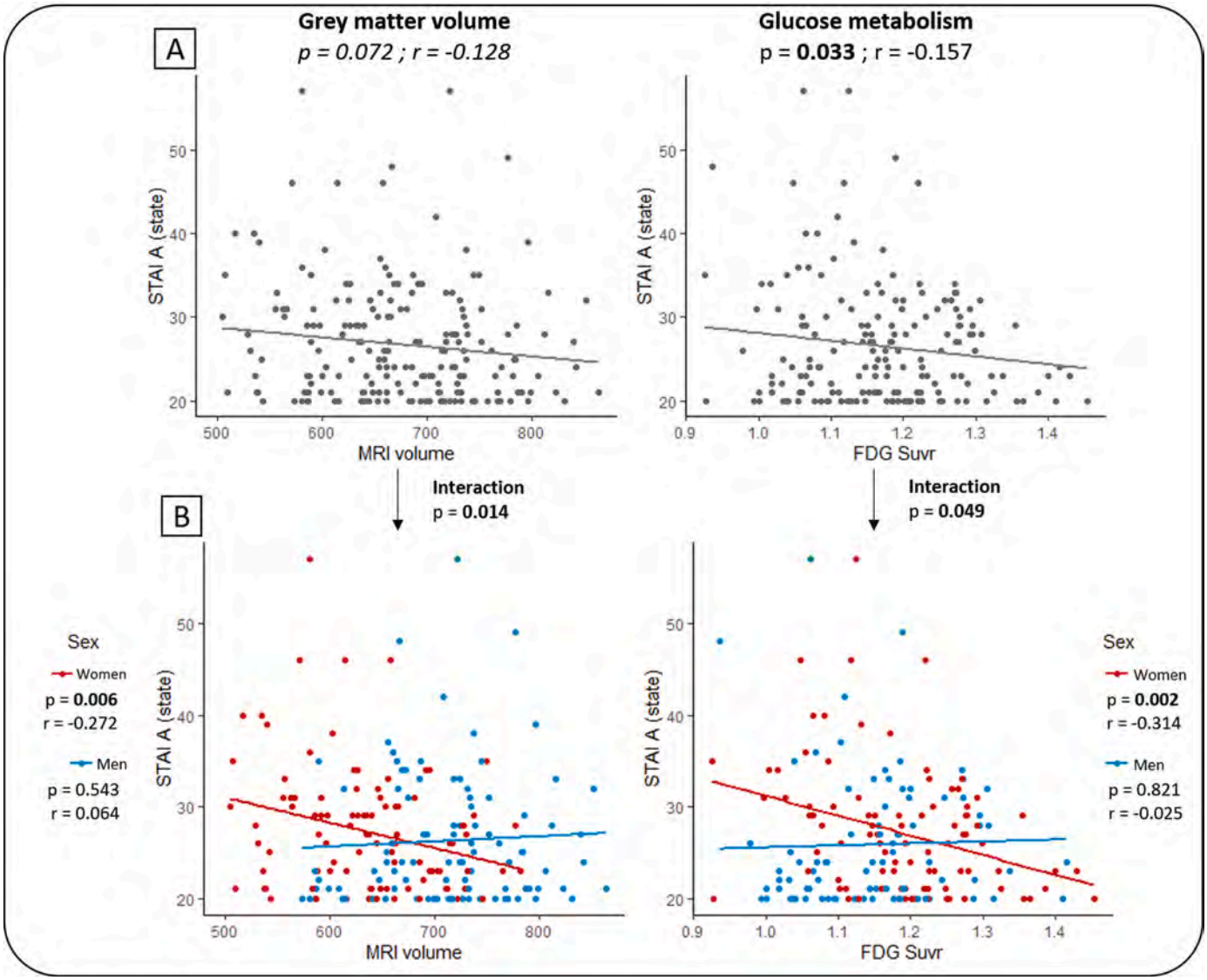

Fig. 2. Sex-specific relationships between psychoaffective factors and neuroimaging measures. Graphs indicate *p* value and *r* value of multiple regressions. A: Multiple regression of grey matter volume and glucose metabolism with depressive symptoms or anxiety symptoms, corrected for level of education and anxiety symptoms or depressive symptoms respectively. B: Interactive effects of sex on the links between anxiety symptoms, and grey matter volume or glucose metabolism, corrected for level of education and depressive symptoms, showing a negative relationship in women only. Values in bold correspond to significant *p* values ($p < 0.05$) and values in italic correspond to trends ($0.01 < p < 0.05$). FDG Fluorodeoxyglucose, MADRS Montgomery-Asberg Dementia Rating Scale, MRI Magnetic Resonance Imaging, *p* value, *r* value, STAI A Spielberger State-Trait Anxiety Inventory state form.

to reflect better coping skills in older adults, with avoidance of negative interactions, and/or lower physiological arousal in response to emotional events (Charles et al., 2001). The lack of association between age and anxiety symptoms might reflect the lower sensitivity of anxiety to age effects and/or methodological choices such as the anxiety scale or the population.

4.2. Cognitive correlates of psychoaffective symptoms

In this study we found no links between anxiety or depressive symptoms and global cognitive performance. This is at odds with previous studies that reported a relationship between increased anxiety and depressive symptoms and decreased global cognition and memory performance in elders (Beaudreau and O'Hara, 2009; Gallacher et al., 2009; Pietrzak et al., 2015; Wilson et al., 2011; Yochim et al., 2013). This might be due to the fact that previous studies focused on elderly population while we cover the entire adult age range, and that we assessed cognition as a whole, with a low variability on the MMSE, as the population was cognitively normal. The limited range of this scale, related to both the scale itself and the population assessed, might have prevented us from discovering subtle differences. Also, previous studies focused on trait anxiety (i.e. a personality trait), while we assessed state anxiety, suggesting that only the former would influence cognitive performance (Gallacher et al., 2009; Pietrzak et al., 2015; Potvin et al., 2011; Vito et al., 2017; Wilson et al., 2011). This is in line with a previous study also showing that state anxiety in older adults was not deleterious for cognitive performance and can even be beneficial, depending on the cognitive domains (Potvin et al., 2013).

4.3. Neuroimaging correlates of psychoaffective symptoms

Depressive symptoms were not associated with neuroimaging markers (i.e. GM volume, glucose metabolism, and amyloid load) in this study, either cross-sectionally or longitudinally. Previous studies regarding this matter showed mixed results, some reporting an association of depressive studies with brain parameters (Babulal et al., 2016;

Table 3
Relationships between baseline psychoaffective measures and slopes of change in cognition and neuroimaging measures and reversely.

		Global cognition (DRS) slope of change	GM volume slope of change	Glucose metabolism slope of change	Amyloid load slope of change
Baseline depressive symptoms (MADRS)	Total group	0.323 (0.081)	0.169 (−0.111)	0.699 (0.037)	0.176 (−0.174)
	Interaction of sex	0.396	0.824	0.588	0.670
Baseline anxiety symptoms (STAI A)	Total group	0.206 (−0.103)	0.293 (0.085)	0.721 (−0.034)	0.345 (0.121)
	Interaction of sex	0.650	0.882	0.955	0.107
		Depressive symptoms (MADRS) slope of change			
Baseline predictor		Total group	Interaction of sex	Men	Women
Global cognition (DRS)		0.356 (0.07)	0.068	0.547 (−0.072)	0.082 (0.193)
GM volume		0.142 (−0.117)	0.114	–	–
Glucose metabolism		0.108 (−0.150)	0.256	–	–
Amyloid load		0.936 (0.009)	0.838	–	–
		Anxiety symptoms (STAI A) slopes of change			
Baseline predictor		Total group	Interaction of sex	Men	Women
Global cognition (DRS)		0.700 (−0.032)	0.713	-	
GM volume		0.040 (−0.170)	0.097	0.939 (−0.009)	0.044 (−0.234)
Glucose metabolism		0.440 (0.079)	0.777	-	-
Amyloid load		0.542 (−0.075)	0.674	-	-

Values indicate p (r) values of the multiple linear regressions between baseline or slopes of changes in depressive symptoms or baseline or slopes of changes in anxiety symptoms on the one hand, and the corresponding baseline or slopes of changes in cognitive or neuroimaging variables on the other hand. All analyses with baseline or slopes of changes in depressive symptoms were corrected for the level of education and baseline anxiety symptoms while all the analyses with baseline or slopes of anxiety symptoms were corrected for the level of education and baseline depressive symptoms. Values in bold correspond to significant p values ($p < 0.05$) and values in italic correspond to trends ($0.01 < p < 0.05$). DRS Dementia Rating Scale, MADRS Montgomery-Åsberg Depression Rating Scale, STAI A Spielberger State-Trait Anxiety Inventory state form.

Donovan et al., 2015; Dotson et al., 2009; Krell-Roesch et al., 2018, 2016; Pink et al., 2017a; Taki et al., 2005), while others did not (Blackmon et al., 2011; Hayakawa et al., 2013). This might be related to the age range considered, as all studies assessing the same large age range than in the present study, covering the full adult life span, did not find an association (range 21–62 years (Blackmon et al., 2011); range 37–71 (Hayakawa et al., 2013)); while all the studies that found a link assessed only elderly (Babulal et al., 2016; Donovan et al., 2015; Dotson et al., 2009; Krell-Roesch et al., 2018, 2016; Pink et al., 2017a; Taki et al., 2005). It is thus possible that this link is specific to the elderly, or that those associations are different depending on age.

In contrast, we found anxiety symptoms to be associated with lower GM volume and glucose metabolism, which is consistent with previous studies in young and elderly adults (Krell-Roesch et al., 2016; Kühn et al., 2011; Pink et al., 2017b; Spampinato et al., 2009). This link was found specifically with neurodegeneration, while no relationship was found with amyloid load, suggesting that it is not directly related to this AD pathological change. Only one study found an association but only in subcortical studies that were not assessed here (Hanseeuw et al., 2018). Decrease in GM volume, cortical thickness, brain activity, and glucose consumption is observed in ageing and still more in AD (Perna et al., 2016; Yankner et al., 2008). The fact that anxiety symptoms were associated with neurodegeneration biomarkers suggest that individuals with anxiety undergo more severe brain aging and/or are more vulnerable to age-related neurodegenerative changes, which might in turn reduce brain reserve and increased risk of developing dementia.

4.4. Longitudinal relationships

However, our longitudinal analyses showed that low baseline GM volume predicted an increase in anxiety symptoms, while baseline anxiety did not predict any change in cognitive or neuroimaging variables. This finding suggest that neurodegeneration/structural changes precede and possibly lead to anxiety symptoms, rather than the reverse (Geda et al., 2017). However, an additional risk factor may synergistically interact with neurodegeneration, or may lead to neuropsychiatric symptoms with a cofounder such as age (Pink et al., 2017b). This might not exclude other possible mechanisms, such as anxiety/depression being responsible for neurodegenerative processes and/or amyloid deposition – even if we failed to find evidence in support of these alternative hypotheses. Importantly, the different neuropsychiatric symptoms might have distinct causal relationships with brain integrity and dementia/Alzheimer's disease, which would stress the relevance to assess them each separately instead of as a global measure of neuropsychiatric symptoms.

3.5. Sex differences

Studies have shown that women tend to show more anxiety and depressive symptoms than men (Altemus et al., 2014), and that their risk to develop AD is also higher (Singh-Manoux et al., 2017). In addition, the brain is in constant remodeling, showing different age-related brain changes between men and women, notably in the cerebellum and frontal regions (Delvecchio et al., 2021; Guo et al., 2016; Ritchie et al., 2018). We thus aimed to assess the effect of sex on age-related changes in psychoaffective factors and on their links with cognition and neuroimaging measures. Interestingly, we showed sex-specificities in anxiety symptoms with age across the adult lifespan, and in their links with neuroimaging biomarkers. More specifically, we found anxiety symptoms to increase with age only among women, and to be associated with neurodegeneration (being GM volume loss or glucose hypometabolism) also in women only. These findings are in line with previous studies reporting higher anxiety levels in elderly women compared to elderly men (Bergua et al., 2012), and decreased frontal GM volume associated with higher anxiety-related personality traits only in women (Yamasue et al., 2008). Here we extend the finding of specific anxiety-related brain changes in women to brain function (glucose metabolism) as well. It is possible that women are more vulnerable to anxiety symptoms than men, which could be at least partly related to hormonal differences. Indeed, the difference in prevalence of anxiety symptoms between men and women arise at puberty, and the menstrual cycle, pregnancy and menopause are triggers for onset, recurrence and exacerbation of affective disorders (Altemus et al., 2014). The higher level of anxiety symptoms in women, which is associated with neurodegeneration, could partly explains their higher risk of developing AD.

4.6. Limitations and perspectives

In line with previous studies (Beekman et al., 2000; Lenze, 2003), anxiety symptoms and depressive symptoms are interrelated. Yet we were able to evidence specific relationships with brain measures as the relationships between anxiety and neurodegeneration biomarkers remained significant when correcting for depression. This emphasizes the differences between these two measures as actually reflecting distinct psychoaffective factors, that show different sensitivity to age and independent relationships with neuroimaging data, highlighting the relevance to assess and account for them both (Potvin et al., 2011).

One of the limitations of our study refers to the small number of participants reporting depressive symptoms (43%) and limited range of the depression, anxiety and cognitive measures. This was expected as all our participants were cognitively healthy community-dwelling participants selected for the lack of clinically significant anxiety or depression. However, this limited the variability of the measure and thus the sensitivity (power) of our statistical tests when assessing the effect of age or links with cognition/neuroimaging. To limit this bias and verify the validity of our findings, we repeated all analyses with non-parametric tests, as well as in a subgroup only including individuals with at least one depressive symptom, and findings were considered as relevant only if they remained significant in this subgroup. However, we cannot exclude the fact that this floor effect and related low variability in the measure prevented us from detecting slight changes in depressive or anxiety symptoms with age and/or subtle links with cognition/neuroimaging. More specifically, the range of anxiety/depression scales were limited, which might have underpowered the analyses. Further studies with larger range might allow to detect more subtle relationships; yet, in the present study, the limited range was inherent to the population i.e. the fact that we were specifically interested in subclinical levels of anxiety and depression. Moreover, we did not correct for multiple comparisons, as it would have prevented us from detecting subtle changes targeted at this asymptomatic stage. Additionally, the mean duration of the follow-up period in our longitudinal analyses was 2.4 years, which might not be enough to capture protracted age-related (and/or preclinical-AD related) processes associated with very subtle changes. Moreover, our study focused on a sample of highly educated cognitively normal participants with subclinical anxiety and depression, so our results could not be generalized to the global population. Additionally, one of the limitation is the lack of information on handedness, tobacco smoking, or other lifestyle factors to better describe the population, that could impact the representativeness of the sample. Future work could investigate anxiety and depressive symptoms in a larger spectrum of adults in terms of cognition and psychoaffective state, with a longer follow-up. Ideally, interventional studies would allow researchers to assess the impact of reducing anxiety and depressive symptoms on cognition, brain integrity, and risk of AD.

5. Conclusion

Our results showed, using multimodal neuroimaging, a link between anxiety symptoms and lower GM volume and glucose metabolism. They also suggest that the rate of change in anxiety symptoms depends on GM volume, but it is also possible that neurodegeneration results from greater anxiety. Importantly, we highlighted sex-specificities as these relationships were only found in women. Thus, women showed age-related increase in anxiety, and anxiety was specifically related to neurodegeneration in women. This study highlights the relevance of assessing anxiety symptoms early as part of dementia screening measures, especially in women.

Declarations of Competing Interest

No competing interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.10.004.

References

Altemus, M., Sarvaiya, N., Neill Epperson, C., 2014. Sex differences in anxiety and depression clinical perspectives. Front. Neuroendocrinol. 35, 320–330. https://doi.org/10.1016/j.yfrne.2014.05.004.

Altman, D.G., Royston, P., 2006. The cost of dichotomising continuous variables. BMJ 332, 1080. https://doi.org/10.1136/bmj.332.7549.1080.

Amieva, H., Goff, M.L., Millet, X., Orgogozo, J.M., Pérès, K., Barberger-Gateau, P., Jacqmin-Gadda, H., Dartigues, J.F., 2008. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann. Neurol. 64, 492–498. https://doi.org/10.1002/ana.21509.

Babulal, G.M., Ghoshal, N., Head, D., Vernon, E.K., Holtzman, D.M., Benzinger, T.L.S., Fagan, A.M., Morris, J.C., Roe, C.M., 2016. Mood changes in cognitively normal older adults are linked to Alzheimer disease biomarker levels. Am. J. Geriatr. Psychiatry 24, 1095–1104. https://doi.org/10.1016/j.jagp.2016.04.004.

Beaudreau, S.A., O'Hara, R., 2009. The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. Psychol. Aging 24, 507–512. https://doi.org/10.1037/a0016035.

Beekman, A.T., de Beurs, E., van Balkom, A.J., Deeg, D.J., van Dyck, R., van Tilburg, W., 2000. Anxiety and depression in later life: co-occurrence and communality of risk factors. Am. J. Psychiatry 157, 89–95. https://doi.org/10.1176/ajp.157.1.89.

Bejanin, A., La Joie, R., Landeau, B., Belliard, S., de La Sayette, V., Eustache, F., Desgranges, B., Chételat, G., 2019. Distinct interplay between atrophy and hypometabolism in Alzheimer's versus semantic dementia. Cereb. Cortex 29, 1889–1899. https://doi.org/10.1093/cercor/bhy069. N. Y. N 1991.

Bergua, V., Meillon, C., Potvin, O., Bouisson, J., Le Goff, M., Rouaud, O., Ritchie, K., Dartigues, J.F., Amieva, H., 2012. The STAI-Y trait scale: psychometric properties and normative data from a large population-based study of elderly people. Int. Psychogeriatr. 24, 1163–1171. https://doi.org/10.1017/S1041610212000300.

Blackmon, K., Barr, W.B., Carlson, C., Devinsky, O., DuBois, J., Pogash, D., Quinn, B.T., Kuzniecky, R., Halgren, E., Thesen, T., 2011. Structural evidence for involvement of a left amygdala-orbitofrontal network in subclinical anxiety. Psychiatry Res. 194, 296–303. https://doi.org/10.1016/j.pscychresns.2011.05.007.

Bryant, C., Jackson, H., Ames, D., 2008. The prevalence of anxiety in older adults: methodological issues and a review of the literature. J. Affect. Disord. 109, 233–250. https://doi.org/10.1016/j.jad.2007.11.008.

Carlson, J.M., Depetro, E., Maxwell, J., Harmon-Jones, E., Hajcak, G., 2015. Gender moderates the association between dorsal medial prefrontal cortex volume and depressive symptoms in a subclinical sample. Psychiatry Res. Neuroimag. 233, 285–288. https://doi.org/10.1016/j.pscychresns.2015.06.005.

Chambers, J.A., Power, K.G., Durham, R.C., 2004. The relationship between trait vulnerability and anxiety and depressive diagnoses at long-term follow-up of generalized anxiety disorder. J. Anxiety Disord. 18, 587–607. https://doi.org/10.1016/j.janxdis.2003.09.001.

Charles, S.T., Reynolds, C.A., Gatz, M., 2001. Age-related differences and change in positive and negative affect over 23 years. J. Pers. Soc. Psychol. 80, 136–151.

Chételat, G, Desgranges, B., Landeau, B., Mézenge, F., Poline, J.B., de la Sayette, V., Viader, F., Eustache, F., Baron, J.C., 2008. Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. Brain J. Neurol. 131, 60–71. https://doi.org/10.1093/brain/awm288.

Chételat, G, Eustache, F., Viader, F., De La Sayette, V., Pélerin, A., Mézenge, F., Hannequin, D., Dupuy, B., Baron, J.C., Desgranges, B., 2005. FDG-PET measurement is more accurate than neuropsychological assessments to predict global cognitive deterioration in patients with mild cognitive impairment. Neurocase 11, 14–25. https://doi.org/10.1080/13554790490896938.

Cousijn, J., Wiers, R.W., Ridderinkhof, K.R., van den Brink, W., Veltman, D.J., Goudriaan, A.E., 2012. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. Neuroimage 59, 3845–3851. https://doi.org/10.1016/j.neuroimage.2011.09.046.

Cuijpers, P., Smit, F., 2004. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. Acta Psychiatr. Scand. 109, 325–331. https://doi.org/10.1111/j.1600-0447.2004.00301.x.

Delvecchio, G., Maggioni, E., Pigoni, A., Crespo-Facorro, B., Nenadić, I., Benedetti, F., Gaser, C., Sauer, H., Roiz-Santiañez, R., Poletti, S., Rossetti, M.G., Bellani, M., Perlini, C., Ruggeri, M., Diwadkar, V.A., Brambilla, P., 2021. Sexual regional dimorphism of post-adolescent and middle age brain maturation. A multi-center 3T MRI study. Front. Aging Neurosci. 13, 622054 https://doi.org/10.3389/fnagi.2021.622054.

Donovan, N.J., Hsu, D.C., Dagley, A.S., Schultz, A.P., Amariglio, R.E., Mormino, E.C., Okereke, O.I., Rentz, D.M., Johnson, K.A., Sperling, R.A., Marshall, G.A., 2015. Depressive symptoms and biomarkers of Alzheimer's disease in cognitively normal older adults. J. Alzheimers Dis. JAD 46, 63–73. https://doi.org/10.3233/JAD-142940.

Donovan, N.J., Locascio, J.J., Marshall, G.A., Gatchel, J., Hanseeuw, B.J., Rentz, D.M., Johnson, K.A., Sperling, R.A., 2018. Longitudinal association of amyloid beta and anxious-depressive symptoms in cognitively normal older adults. Am. J. Psychiatry 175, 530–537. https://doi.org/10.1176/appi.ajp.2017.17040442.

Dotson, V.M., Davatzikos, C., Kraut, M.A., Resnick, S.M., 2009. Depressive symptoms and brain volumes in older adults: a longitudinal magnetic resonance imaging study. J. Psychiatry Neurosci. Jpn. 34, 367–375.

Dubois, B., Feldman, H.H., Jacova, C., Dekosky, S.T., Barberger-Gateau, P., Cummings, J., Delacourte, A., Galasko, D., Gauthier, S., Jicha, G., Meguro, K., O'brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway, S., Stern, Y., Visser, P.J., Scheltens, P., 2007. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 6, 734–746. https://doi.org/10.1016/S1474-4422(07)70178-3.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.

Forlani, C., Morri, M., Ferrari, B., Dalmonte, E., Menchetti, M., De Ronchi, D., Atti, A.R., 2014. Prevalence and gender differences in late-life depression: a population-based study. Am. J. Geriatr. Psychiatry 22, 370–380. https://doi.org/10.1016/j.jagp.2012.08.015.

Gallacher, J., Bayer, A., Fish, M., Pickering, J., Pedro, S., Dunstan, F., Ebrahim, S., Ben-Shlomo, Y., 2009. Does anxiety affect risk of dementia? Findings from the caerphilly prospective study. Psychosom. Med. 71, 659–666. https://doi.org/10.1097/PSY.0b013e3181a6177c.

Geda, Y.E., Krell-Roesch, J., Sambuchi, N., Michel, B.F., 2017. Neuropsychiatric Symptoms and neuroimaging biomarkers in Alzheimer disease: "which is the cart and which is the horse? Am. J. Geriatr. Psychiatry 25, 694–696. https://doi.org/10.1016/j.jagp.2017.03.007.

Geda, Y.E., Schneider, L.S., Gitlin, L.N., Miller, D.S., Smith, G.S., Bell, J., Evans, J., Lee, M., Porsteinsson, A., Lanctôt, K.L., Rosenberg, P.B., Sultzer, D.L., Francis, P.T., Brodaty, H., Padala, P.P., Onyike, C.U., Ortiz, L.A., Ancoli-Israel, S., Bliwise, D.L., Martin, J.L., Vitiello, M.V., Yaffe, K., Zee, P.C., Herrmann, N., Lyketsos, C.G., 2013. Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. Alzheimers Dement. 9, 602–608. https://doi.org/10.1016/j.jalz.2012.12.001. J. Alzheimers Assoc.

Guo, J.Y., Isohanni, M., Miettunen, J., Jääskeläinen, E., Kiviniemi, V., Nikkinen, J., Remes, J., Huhtaniska, S., Veijola, J., Jones, P.B., Murray, G.K., 2016. Brain structural changes in women and men during midlife. Neurosci. Lett. 615, 107–112. https://doi.org/10.1016/j.neulet.2016.01.007.

Hanseeuw, B.J., Jonas, V., Jackson, J., Betensky, R.A., Rentz, D.M., Johnson, K.A., Sperling, R.A., Donovan, N.J., 2018. Association of anxiety with subcortical amyloidosis in cognitively normal older adults. Mol. Psychiatry 1–9. https://doi.org/10.1038/s41380-018-0214-2.

Harrington, K.D., Lim, Y.Y., Gould, E., Maruff, P., 2015. Amyloid-beta and depression in healthy older adults: a systematic review. Aust. N. Z. J. Psychiatry 49, 36–46. https://doi.org/10.1177/0004867414557161.

Hayakawa, Y.K., Sasaki, H., Takao, H., Mori, H., Hayashi, N., Kunimatsu, A., Aoki, S., Ohtomo, K., 2013. Structural brain abnormalities in women with subclinical depression, as revealed by voxel-based morphometry and diffusion tensor imaging. J. Affect. Disord. 144, 263–268. https://doi.org/10.1016/j.jad.2012.10.023.

Holmes, S.E., Esterlis, I., Mazure, C.M., Lim, Y.Y., Ames, D., Rainey-Smith, S., Fowler, C., Ellis, K., Martins, R.N., Salvado, O., Doré, V., Villemagne, V.L., Rowe, C.C., Laws, S. M., Masters, C.L., Pietrzak, R.H., Maruff, P., 2018. Trajectories of depressive and anxiety symptoms in older adults: a 6-year prospective cohort study. Int. J. Geriatr. Psychiatry 33, 405–413. https://doi.org/10.1002/gps.4761.

Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., 2018. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 14, 535–562. https://doi.org/10.1016/j.jalz.2018.02.018. J. Alzheimers Assoc.

Karsten, J., Hartman, C.A., Smit, J.H., Zitman, F.G., Beekman, A.T.F., Cuijpers, P., van der Does, A.J.W., Ormel, J., Nolen, W.A., Penninx, B.W.J.H., 2011. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. Br. J. Psychiatry J. Ment. Sci. 198, 206–212. https://doi.org/10.1192/bjp.bp.110.080572.

Krell-Roesch, J., Lowe, V.J., Neureiter, J., Pink, A., Roberts, R.O., Mielke, M.M., Vemuri, P., Stokin, G.B., Christianson, T.J., Jack, C.R., Knopman, D.S., Boeve, B.F., Kremers, W.K., Petersen, R.C., Geda, Y.E., 2018. Depressive and anxiety symptoms and cortical amyloid deposition among cognitively normal elderly persons: the mayo clinic study of aging. Int. Psychogeriatr. 30, 245–251. https://doi.org/10.1017/S1041610217002368.

Krell-Roesch, J., Ruider, H., Lowe, V.J., Stokin, G.B., Pink, A., Roberts, R.O., Mielke, M. M., Knopman, D.S., Christianson, T.J., Machulda, M.M., Jack, C.R., Petersen, R.C., Geda, Y.E., 2016. FDG-PET and neuropsychiatric symptoms among cognitively normal elderly persons: the mayo clinic study of aging. J. Alzheimers Dis. JAD 53, 1609–1616. https://doi.org/10.3233/JAD-160326.

Kühn, S., Schubert, F., Gallinat, J., 2011. Structural correlates of trait anxiety: reduced thickness in medial orbitofrontal cortex accompanied by volume increase in nucleus accumbens. J. Affect. Disord. 134, 315–319. https://doi.org/10.1016/j.jad.2011.06.003.

La Joie, R., Perrotin, A., Barré, L., Hommet, C., Mézenge, F., Ibazizene, M., Camus, V., Abbas, A., Landeau, B., Guilloteau, D., de La Sayette, V., Eustache, F., Desgranges, B., Chételat, G., 2012. Region-specific hierarchy between atrophy, hypometabolism, and β-amyloid (Aβ) load in Alzheimer's disease dementia. J. Neurosci. 32, 16265–16273. https://doi.org/10.1523/JNEUROSCI.2170-12.2012. Off. J. Soc. Neurosci.

Laborde-Lahoz, P., El-Gabalawy, R., Kinley, J., Kirwin, P.D., Sareen, J., Pietrzak, R.H., 2015. Subsyndromal depression among older adults in the USA: prevalence, comorbidity, and risk for new-onset psychiatric disorders in late life. Int. J. Geriatr. Psychiatry 30, 677–685. https://doi.org/10.1002/gps.4204.

Lavretsky, H., Kumar, A., 2002. Clinically significant non-major depression: old concepts, new insights. Am. J. Geriatr. Psychiatry 10, 239–255. Off. J. Am. Assoc. Geriatr. Psychiatry.

Lenze, E.J., 2003. Comorbidity of depression and anxiety in the elderly. Curr. Psychiatry Rep. 5, 62–67. https://doi.org/10.1007/s11920-003-0011-7.

Lyness, J.M., Chapman, B.P., McGriff, J., Drayer, R., Duberstein, P.R., 2009. One-year outcomes of minor and subsyndromal depression in older primary care patients. Int. Psychogeriatr. 21, 60–68. https://doi.org/10.1017/S1041610208007746.

Mattis, S., 1976. Mental status examination for organic mental syndrome in the elderly patients. Geriatric Psychiatry: A Handbook For Psychiatrists and Primary Care Physicians. Geriatr. Psychiatry Handb. Psychiatr. Prim. Care Physicians, pp. 77–121.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry J. Ment. Sci. 134, 382–389. https://doi.org/10.1192/bjp.134.4.382.

Perna, G., Iannone, G., Alciati, A., Caldirola, D., 2016. Are anxiety disorders associated with accelerated aging? A focus on neuroprogression. Neural Plast, 8457612. https://doi.org/10.1155/2016/8457612.

Petkus, A.J., Reynolds, C.A., Wetherell, J.L., Kremen, W.S., Pedersen, N.L., Gatz, M., 2016. Anxiety is associated with increased risk of dementia in older Swedish twins. Alzheimers Dement. 12, 399–406. https://doi.org/10.1016/j.jalz.2015.09.008. J. Alzheimers Assoc.

Pietrzak, R.H., Lim, Y.Y., Neumeister, A., Ames, D., Ellis, K.A., Harrington, K., Lautenschlager, N.T., Restrepo, C., Martins, R.N., Masters, C.L., Villemagne, V.L., Rowe, C.C., Maruff, P., Australian Imaging, Biomarkers, and Lifestyle Research Group, 2015. Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. JAMA Psychiatry 72, 284–291. https://doi.org/10.1001/jamapsychiatry.2014.2476.

Pink, A., Przybelski, S.A., Krell-Roesch, J., Stokin, G.B., Roberts, R.O., Mielke, M.M., Knopman, D.S., Jack, C.R., Petersen, R.C., Geda, Y.E., 2017a. Cortical thickness and depressive symptoms in cognitively normal individuals: the Mayo clinic study of aging. J. Alzheimers Dis. JAD 58, 1273–1281. https://doi.org/10.3233/JAD-170041.

Pink, A., Przybelski, S.A., Krell-Roesch, J., Stokin, G.B., Roberts, R.O., Mielke, M.M., Spangehl, K.A., Knopman, D.S., Jack, C.R., Petersen, R.C., Geda, Y.E., 2017b. Cortical thickness and anxiety symptoms among cognitively normal elderly persons: the mayo clinic study of aging. J. Neuropsychiatry Clin. Neurosci. 29, 60–66. https://doi.org/10.1176/appi.neuropsych.15100378.

Potvin, O., Bergua, V., Meillon, C., Le Goff, M., Bouisson, J., Dartigues, J.-.F., Amieva, H., 2013. State anxiety and cognitive functioning in older adults. Am. J. Geriatr. Psychiatry 21, 915–924. https://doi.org/10.1016/j.jagp.2013.01.029. Off. J. Am. Assoc. Geriatr. Psychiatry.

Potvin, O., Forget, H., Grenier, S., Préville, M., Hudon, C., 2011. Anxiety, depression, and 1-year incident cognitive impairment in community-dwelling older adults. J. Am. Geriatr. Soc. 59, 1421–1428. https://doi.org/10.1111/j.1532-5415.2011.03521.x.

Ritchie, S.J., Cox, S.R., Shen, X., Lombardo, M.V., Reus, L.M., Alloza, C., Harris, M.A., Alderson, H.L., Hunter, S., Neilson, E., Liewald, D.C.M., Auyeung, B., Whalley, H.C., Lawrie, S.M., Gale, C.R., Bastin, M.E., McIntosh, A.M., Deary, I.J., 2018. Sex differences in the adult human brain: evidence from 5216 UK biobank participants. Cereb. Cortex 28, 2959–2975. https://doi.org/10.1093/cercor/bhy109. N. Y. N 1991.

Serfaty, M.A., Haworth, D., Blanchard, M., Buszewicz, M., Murad, S., King, M., 2009. Clinical effectiveness of individual cognitive behavioral therapy for depressed older people in primary care: a randomized controlled trial. Arch. Gen. Psychiatry 66, 1332–1340. https://doi.org/10.1001/archgenpsychiatry.2009.165.

Siegel, A.M., Mathews, S.B., 2015. Diagnosis and treatment of anxiety in the aging woman. Curr. Psychiatry Rep. 17, 93. https://doi.org/10.1007/s11920-015-0636-3.

Singh-Manoux, A., Dugravot, A., Fournier, A., Abell, J., Ebmeier, K., Kivimäki, M., Sabia, S., 2017. Trajectories of depressive symptoms before diagnosis of dementia: a

28-year follow-up study. JAMA Psychiatry 74, 712–718. https://doi.org/10.1001/jamapsychiatry.2017.0660.

Spalletta, G., Piras, F., Caltagirone, C., Fagioli, S., 2014. Hippocampal multimodal structural changes and subclinical depression in healthy individuals. J. Affect. Disord 152–154, 105–112. https://doi.org/10.1016/j.jad.2013.05.068.

Spampinato, M.V., Wood, J.N., De Simone, V., Grafman, J., 2009. Neural correlates of anxiety in healthy volunteers: a voxel-based morphometry study. J. Neuropsychiatry Clin. Neurosci. 21, 199–205. https://doi.org/10.1176/jnp.2009.21.2.199.

Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M.V., Phelps, C.H., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 280–292. https://doi.org/10.1016/j.jalz.2011.03.003. J. Alzheimers Assoc.

Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., 1970. Manual for the state-trait anxiety inventory. Consulting Psychologist Press, California.

Taki, Y., Kinomura, S., Awata, S., Inoue, K., Sato, K., Ito, H., Goto, R., Uchida, S., Tsuji, I., Arai, H., Kawashima, R., Fukuda, H., 2005. Male elderly subthreshold depression patients have smaller volume of medial part of prefrontal cortex and precentral gyrus compared with age-matched normal subjects: a voxel-based morphometry. J. Affect. Disord. 88, 313–320. https://doi.org/10.1016/j.jad.2005.08.003.

Teachman, B.A., 2006. Aging and negative affect: the rise and fall and rise of anxiety and depression symptoms. Psychol. Aging 21, 201–207. https://doi.org/10.1037/0882-7974.21.1.201.

Tomadesso, C., Gonneaud, J., Egret, S., Perrotin, A., Pélerin, A., de Flores, R., de la Sayette, V., Desgranges, B., Chételat, G., La, J.R., 2019. Is there a specific memory signature associated with Aβ-PET positivity in patients with amnestic mild cognitive impairment? Neurobiol. Aging 77, 94–103. https://doi.org/10.1016/j.neurobiolaging.2019.01.017.

van Zoonen, K., Buntrock, C., Ebert, D.D., Smit, F., Reynolds, C.F., Beekman, A.T.F., Cuijpers, P., 2014. Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. Int. J. Epidemiol. 43, 318–329. https://doi.org/10.1093/ije/dyt175.

van't Veer-Tazelaar, P.J., van Marwijk, H.W.J., van Oppen, P., van Hout, H.P.J., van der Horst, H.E., Cuijpers, P., Smit, F., Beekman, A.T.F., 2009. Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. Arch. Gen. Psychiatry 66, 297–304. https://doi.org/10.1001/archgenpsychiatry.2008.555.

Villain, N., Desgranges, B., Viader, F., de la Sayette, V., Mézenge, F., Landeau, B., Baron, J.-C., Eustache, F., Chételat, G., 2008. Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. J. Neurosci. 28, 6174–6181. https://doi.org/10.1523/JNEUROSCI.1392-08.2008. Off. J. Soc. Neurosci.

Vito, A.de, Calamia, M., Greening, S., Roye, S., 2017. The association of anxiety, depression, and worry symptoms on cognitive performance in older adults. Aging Neuropsychol. Cogn.

Wilson, R.S., Begeny, C.T., Boyle, P.A., Schneider, J.A., Bennett, D.A., 2011. Vulnerability to stress, anxiety, and development of dementia in old age. Am. J. Geriatr. Psychiatry 19, 327–334. https://doi.org/10.1097/JGP.0b013e31820119da.

Yamasue, H., Abe, O., Suga, M., Yamada, H., Inoue, H., Tochigi, M., Rogers, M., Aoki, S., Kato, N., Kasai, K., 2008. Gender-common and -specific neuroanatomical basis of human anxiety-related personality traits. Cereb. Cortex 18, 46–52. https://doi.org/10.1093/cercor/bhm030.

Yankner, B.A., Lu, T., Loerch, P., 2008. The aging brain. Annu. Rev. Pathol. 3, 41–66. https://doi.org/10.1146/annurev.pathmechdis.2.010506.092044.

Yochim, B.P., Mueller, A.E., Segal, D.L., 2013. Late life anxiety is associated with decreased memory and executive functioning in community dwelling older adults. J. Anxiety Disord. 27, 567–575. https://doi.org/10.1016/j.janxdis.2012.10.010.