RESEARCH ARTICLE

Subclinical depressive symptoms during late midlife and structural brain alterations: A longitudinal study of Danish men born in 1953

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Abstract

We explored whether depressive symptoms measured three times during midlife were associated with structural brain alterations quantified using magnetic resonance imaging measurements of volume, cortical thickness, and intensity texture. In 192 men born in 1953 with depressive symptoms measured at age 51, 56, and 59 years, magnetic resonance imaging was performed at age 59. All data processing was performed using the Freesurfer software package except for the texture-scores that were computed using in-house software. Structural brain alterations and associations between depressive symptoms and brain structure outcomes were tested using Pearson's correlation, *t* test, and linear regression. Depressive symptoms at age 51 showed clear inverse correlations with total gray matter, pallidum, and hippocampal volume with the strongest estimate for hippocampal volume ($r = -.22, p < .01$). After exclusion of men ($n = 3$) with scores in the range of clinical depression the inverse correlation between depressive symptoms and hippocampal volume became insignificant ($r = -.13, p = .08$). Depressive symptoms at age 59 correlated positively with hippocampal and amygdala texture-potential early markers of atrophy. Inverse relations with total gray matter and pallidum volumes lost significance when the analysis was adjusted for intracranial volume. In men, depressive symptoms at age 51 were associated with a reduced volume of the hippocampus at age 59 independent of later symptoms. Amygdala and hippocampal textures might be the early markers for brain alterations associated with depression in midlife.

KEYWORDS

depression, gray matter volumes, longitudinal study, structural magnetic resonance imaging

1 | INTRODUCTION

Structural magnetic resonance imaging (MRI) has been widely used to explore different brain areas involved in the pathophysiology of major depressive disorder (MDD). Although results of this research have not been consistent, reductions in total gray matter, prefrontal (dorsolateral, ventromedial), striate (pallidum, putamen), and limbic (amygdala, hippocampus) brain measures seem important neural correlates of MDD (Arnone, McIntosh, Ebmeir, Munafó, & Anderson, 2012; Bora, Fornito, Pantelis, & Yucel, 2012; Du et al., 2012; Wise et al., 2017; Zhang et al., 2016). These structures are also involved in emotion and

fear regulation. A few recent studies have also indicated that structural alterations may occur in subclinical MDD (Brown et al., 2014; Li et al., 2017) or even precede the disease (Whittle et al., 2014). The risk of depression increases during midlife and subclinical symptoms are common in the elderly (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011) and the available evidence indicates significant alterations in volumetric gray matter measures in middle-aged and older individuals with sub-threshold depression (Li et al., 2017; Pink et al., 2017). Further, altered cortical thickness has been observed in "normal" aging (Salat et al., 2004; Singh et al., 2006) and various neurodegenerative disorders are associated with MDD (Grieve, Korgaonkar, Koslow, Gordon, &

Williams, 2013; Salat et al., 2004; Singh et al., 2006). However, relatively few studies have examined cortical thickness in depression itself (Grieve et al., 2013; Pink et al., 2017) and they showed rather inconsistent results.

In this study, we used data on depressive symptoms gathered prospectively at age 51, 56, and 59 to investigate associations with structural brain alterations at age 59 quantified using MRI measurements of volume, cortical thickness, and intensity texture for 192 men born in 1953. Based on the results from previous studies, we hypothesized that high scores on depressive symptom questionnaires would be associated with reductions in total gray matter volume, and in striate (pallidum, putamen) and limbic (amygdala, hippocampus) areas and with lower global and prefrontal (dorsolateral, ventromedial) cortical thickness. We also explored whether any influence of depressive symptoms on brain structure would accumulate over time. Furthermore, based on studies that have indicated that depressive symptoms are associated with biomarkers of Alzheimer's disease among cognitively healthy elderly participants (Donovan et al., 2015) and our previous findings of an association between hippocampal texture and cognitive decline (Sørensen et al., 2016), we also hypothesized that texture, as an early marker of atrophy, might be related to current depressive symptoms. Finally, we performed a supplementary explorative analysis for potential structural changes in other brain regions.

2 | METHODS

2.1 | Study population

Participants were recruited from the Metropolit 1953 Danish male birth cohort, which includes 11 532 men born in 1953 in Copenhagen (Osler, Lund, Kriegbaum, Christensen, & Andersen, 2006). These men had all been cognitively assessed at age 20, and in 2004, 6292 of the 10351 cohort members (age 51 years) who were still alive responded to a mailed health questionnaire. In 2009, 7799 eligible cohort members (age 56 years) were invited to participate in the Copenhagen Ageing Midlife Biobank (CAMB) study (Lund et al., 2016). Of those invited, 2 486 men filled in a questionnaire and participated in a health examination including cognitive tests. Three years later in 2012, a subsample was selected to participate in a neurophysiological examination based on relative change in cognitive performance estimated by standardized residuals in a linear regression with the cognitive test scores at age 20 and age 57 years. To obtain variance in cognitive change, 2 groups of men with extreme residuals were selected, that is, those with the most negative and positive relative change in cognitive function. The selection procedures are described in detail by (Hansen et al., 2014; Sørensen et al., 2016). In total, 249 men with positive residuals and 303 men with negative residuals were invited. Of these, 192 men now aged 59 participated in the examination including MRI. These men had the same distribution of depression scores, body mass index, alcohol use, and inflammatory biomarkers as the remaining participants in the CAMB study (Osler, Bendix, Rask, & Rod, 2016). The study was approved by the regional ethics committee (Scientific Ethics Committee of the Capital Region, Protocol no. H-3-2010-016) following the

standards of the National Committee of health research ethics. The examinations were conducted in accordance with the Helsinki Declaration and all men gave written consent. The Metropolit study has also been registered by the Danish Data Protection Agency.

2.2 | Measurements

2.2.1 | Assessment of depressive symptoms

Depressive symptoms were assessed 3 times with 2 different depression scores: the *Major Depression Inventory (MDI)* (Bech, Rasmussen, Olsen, Noerholm, & Abildgaard, 2001) and the *Beck depression inventory (BDI)* (Beck, Steer, & Carbin, 1988). At age 51 using MDI by mailed questionnaire, at age 56 in the CAMB examination using the MDI, and again at age 59 using the BDI as a part of the neurophysiological examination. The MDI is a well-validated self-report screening tool of depressive symptoms, which consists of 12 items assessing the frequency of depressive symptoms during the past 2 weeks. Each item was rated on a six point scale ranging from 0 (not at all) to 5 (all the time). Ratings were summed to calculate a total score which can range from 0 to 50 (Bech et al., 2001). The BDI consists of 21 items rated on a four-point scale ranging from 0 to 3. Ratings were summed to a total score ranging from 0 to 63 (Beck et al., 1988). Missing values on 9, 8, and 11 single items within the MDI at age 51, the MDI at age 56 and the BDI scores were imputed with the mean values for the remaining items.

2.2.2 | MRI data acquisition and processing

T1-weighted structural MRI (MP-RAGE; TI, 700 ms, TR, 6.9 ms; flip angle 9°; 137 sagittal slices; $1.1 \times 1.1 \times 1.1 \text{ mm}^3$ voxels) was performed on a 3.0-T Philips Intera Achieva scanner (Philips Medical Systems, Best, the Netherlands). The MRI scans were processed with the cross-sectional pipeline of the freely available FreeSurfer software package version 5.1.0 (Fischl and Dale, 2000; Fischl et al., 2002), and the volumetric and cortical thickness measures of specific regions were computed. In addition, texture scores capturing abnormal intensity patterns were computed in the hippocampus and amygdala using a recently proposed method (Sørensen et al., 2016). In brief, an MRI scan was texture-scored by first filtered the scan using a Gaussian derivative-based, multiscale, rotation-invariant filter bank comprising filters highlighting different aspects of the local image structure. The histograms of filter responses within the amygdala or hippocampus were subsequently fed to a support vector machine (SVM) classifier to produce the texture score for that entire region. The sign of the score indicates whether the SVM classifies an input as abnormal (+) or normal (−), and its amount is proportional to the distance from the decision boundary that separates the two classes. The SVM had already been trained prior to this study using data from the Alzheimer's disease neuroimaging initiative (ADNI) (Petersen et al., 2010) and the decision boundary thus describes the transition between brains of Alzheimer patients and health controls. We examined 10 regions of interests (ROIs) that were predefined as particularly important (total gray matter, putamen, pallidum, hippocampal, and amygdala volume, total cortical and prefrontal (dorsolateral, ventromedial) thickness, hippocampal, and

TABLE 1 Mean and correlations between depression scores and 10 brain structure measures in 192 Danish men aged 59

Variable	Mean (SD)	Depression score age 51, Pearson (<i>r</i>)	Depression score age 56, Pearson (<i>r</i>)	Depression score age 59, Pearson (<i>r</i>)
Depression score (MDI) age 51	4.87 (5.62)	1		
Depression score (MDI) age 56	6.41 (6.14)	0.63 ^{<i>p</i> < .01}	1	
Depression score (BDI) age 59	3.57 (4.35)	0.45 ^{<i>p</i> < .01}	0.54 ^{<i>p</i> < .01}	1
Volume measures (ml)				
Total gray matter volume	637.6 (43.4)	−0.15 ^{<i>p</i> = .04}		
Putamen volume	11.0 (1.1)			
Pallidum volume	3.5 (0.4)	−0.16 ^{<i>p</i> = .03}		
Hippocampal volume	8.6 (0.8)	−0.22 ^{<i>p</i> < .01}		
Amygdala volume	3.5 (0.4)			
Thickness measures (mm)				
Total cortical thickness	2.40 (0.09)			
Prefrontal ventromedial thickness	2.57 (0.12)			
Prefrontal dorsolateral thickness	2.45(0.12)			−0.15 ^{<i>p</i> = .03}
Texture measures				
Hippocampal texture	−1.29 (0.3)			0.16 ^{<i>p</i> = .03}
Amygdala texture	−1.06 (0.6)			0.14 ^{<i>p</i> = .05}

BDI = beck depression inventor; MDI = major depression inventory.

Numbers in superscript represent *p* values. Only significant results ($p \leq .05$) are presented.

amygdala texture). An additional 19 ROIs were included in a supplementary explorative analysis (total cortical gray matter, total white matter, lateral ventricle, inferior lateral ventricle, cerebellum white matter, cerebellum cortical gray matter, thalamus proper, caudate, accumbens, ventral DC, corpus callosum posterior, corpus callosum mid posterior, corpus callosum central, corpus callosum mid anterior, corpus callosum anterior volumes, and frontal, temporal, parietal, and occipital cortical thickness). Figures were generated using the PMOD v3.9 software (<https://www.pmod.com/web/>).

2.3 | Statistical analysis

We used means (standard deviations) to summarize variables. Significant simple correlations between depression scores and brain structures as continuous variables were tested with bivariate correlations (Pearson's *r*) and linear regression. Linearity was assessed by inspection of graphical plots. We also used post hoc *t* tests to further explore the significant correlations, where we compared outcomes in depressed versus nondepressed as defined using different cutoff values in the clinical depression scores. Cutoffs of 25 and 29 reflect major depression in the MDI (Bech et al., 2001) and BDI (Beck et al., 1988), while a cutoff of 5 was chosen based on visual inspections of the distribution of the MRI data across total score ranges. A multiple linear regression model was used to estimate the independent and any multiplicative cumulative influence (obtained by a multiplication of the estimates for each symptom score from a model where all three scores were

included) of each depression score on the brain structure measures. Standardized scores were added into a cumulative sum score to measure the total symptom load over midlife. Although the study population was relatively homogeneous (men at same age), we performed supplementary analysis with adjustments for intracranial volume to facilitate comparison with previous studies. We used 5% significance levels and *p* values from the explorative analyses were also corrected for multiple testing using the Sidak option in STATA. All statistical analyses were done in STATA version 13.

3 | RESULTS

Table 1 provides the means of the depression scores measured at age 51, 56, and 59 years and the different brain structure measures at age 59. Mean volumes of the total gray matter and the hippocampus and the mean total cortical thickness all seemed to be within the range reported in the literature (Brown et al., 2014; Grieve et al., 2013; Krogh et al., 2014). Of the 10 brain outcomes a priori hypothesized to be associated with depressive symptoms, total gray matter, pallidum, and hippocampal volume showed a clear inverse correlation with the MDI score at age 51 years with strongest estimate for hippocampal volume ($r = -.22, p < .01$). Figure 1 shows the volume for two men randomly selected from the 10 men with highest (left) and lowest (right) MDI score. Post hoc analysis using different cut-off points for the MDI score at age 51 showed that men scoring more than 5 (34%) had significantly

FIGURE 1 Hippocampal volume for two men randomly selected from the 10 men with highest (left) and lowest (right) MDI score from PMOD v3.9 output [Color figure can be viewed at wileyonlinelibrary.com]

lower hippocampal volume when compared to those with lower scores (8.4 versus 8.7 ml, $p = .03$). The difference was even larger when the cutoff point for clinical defined depression (score ≥ 25) was used (7.5 versus 8.6 ml, $p < .01$). After exclusion of those defined with depression ($n = 3$), the inverse correlation between MDI and hippocampal volume became insignificant ($r = -.13$, $p = .08$). Total gray matter and pallidum volume showed no significant mean differences at any specific value when the depression score were dichotomized at different cutoff points. The depression score measured at the same point in time as the MRI scans (age 59) correlated negatively with dorsolateral prefrontal thickness and positively with the texture of hippocampus and amygdala. The score based on the sum of the three depression scores was associated with total hippocampal volume ($r = -.019$, $p = .01$).

Table 2 shows that the negative association between MDI at age 51 and hippocampal volume became stronger when depressive symptoms at age 56 and 59 or intracranial volume were adjusted for. The

estimates for the scores at later ages were close to 0 and thus did not support any multiplicative cumulative effects of depressive symptoms during middle age on hippocampal volume. The associations between MDI at age 51 and total gray matter and pallidum volumes attenuated to insignificance when intracranial volume was adjusted for. Depression scores at age 59 showed a negative association with dorsolateral prefrontal cortical thickness and borderline significant positive association with amygdala texture after adjustments.

The more explorative analyses (Supporting Information, Table 1) showed significant correlations between the MDI at age 51 and reduced total white matter and nucleus accumbens volumes. The BDI at age 59 was correlated with the volume of the central part of corpus callosum, while the MDI score measured at age 56 was not correlated with any of the brain structures examined. However, when multiple testing was taken into account, none of the explorative ROIs retained significance.

TABLE 2 Simple and multiple linear regression results, with selected^a brain structure measures at age 59 as dependent variables and depressive symptom scores at age 51 and 59 as independent variables in 192 Danish men

MRI	Change in volume (ml) for every SD increase in depressive symptom score at age 51		
	Unadjusted, β^p value	Adjusted for depressive symptoms age 56 and 59, β^p value	Adjusted for intracranial volume, β^p value
Total gray matter volume	$-0.16^p = .03$	$-0.27^p = .02$	$-0.11^p = .11$
Pallidum volume	$-0.16^p = .02$	$-0.22^p = .06$	$-0.10^p = .31$
Hippocampal volume	$-0.29^p < .01$	$-0.42^p < .01$	$-0.44^p < .01$
	Unit change for every SD increase in depressive symptom score at age 59		
	Unadjusted, β^p value	Adjusted for depressive symptoms age 56 and 51, β^p value	Adjusted for intracranial volume, β^p value
Prefrontal dorsolateral thickness	$-0.15^p = .03$	$-0.06^p = .16$	$-0.16^p = .04$
Hippocampal texture	$0.16^p = .03$	$0.10^p = .33$	$0.10^p = .30$
Amygdala texture	$0.14^p = .05$	$0.19^p = .06$	$0.19^p = .06$

^aThe outcomes variables significant in simple correlation analysis (Table 1).

4 | DISCUSSION

In this cohort of 192 men born in 1953 with measurements of depressive symptoms at age 51, 56, and 59 years, symptoms at age 51 were clearly associated with a reduced volume of the hippocampus with no indication of cumulative influence of later symptoms. However, after exclusion of 3 men with depression score values of 25 or above assumed to have clinical depression (Bech et al., 2001) the inverse correlation between MDI and hippocampal volume became insignificant. The associations of depressive symptoms at age 51, 56, or 59 years with other MRI measurements of volume, cortical thickness, and intensity texture were less clear. Thus, the association with total gray matter volume was explained by differences in intracranial volume, while the associations with current depressive symptoms and texture were borderline significant. None of the explorative ROIs were significant when multiple testing was taken into account.

The hippocampus is an important part of the brain network that regulates emotional behavior and is one of the brain alterations most studied in relation to MDD. A number of reviews and meta-analyses (Campbell, Marriott, Nahmias, & MacQueen, 2004; Geerlings and Gerritsen, 2017; Videbech and Ravnkilde, 2004) have suggested that patients with MDD have significantly lower hippocampal volumes than healthy controls. Among the studies which have examined the influence of depressive symptoms, the findings have been inconsistent. Thus, some studies including both young (Whittle et al., 2014), adult (Brown et al., 2014), and older (Zhou et al., 2016) populations have suggested smaller hippocampal volumes among those with depressive symptoms, while others showed no such relation (Hayakawa et al., 2013; Pink et al., 2017). In our study, only depressive symptoms measured 8 years before the MRI scans were associated with reduced hippocampal volume. It has been suggested that susceptible individuals may have a pre-existing smaller hippocampus (Chan et al., 2016; Rao et al., 2010). A recent small cross-sectional study (Chan et al., 2016) has suggested that individuals vulnerable to depression have lower hippocampal volumes. Unfortunately, we did not have longitudinal MRI data, and we do not know whether the lower hippocampal volumes were present at age 51 or if the hippocampi had in fact decreased during midlife due to long-term effect of depressive symptoms.

We are the first to study measures of brain texture in relation to depression. It has been suggested that textural changes in the intensity patterns in the hippocampus can detect plaque accumulation prior to atrophy in patients at risk for Alzheimer's disease (Sørensen et al., 2016), and depressive symptoms have also been associated with biomarkers of Alzheimer's disease (Donovan et al., 2015; Sun et al., 2008). Our study indicates an association between current depressive symptoms and hippocampal texture, suggesting that this might be an early marker for the brain alterations associated with depression. However, the finding was borderline significant and needs to be replicated in future studies.

The strength of this study is that it was based on prospectively collected repeated measures of depressive symptoms in a sample of men with no clinical signs of mental disorder. This allowed us to study any cumulative influence of depressive symptoms during midlife on brain

structure. The assessment of depressive symptoms was conducted with two different tests, the MDI was used at age 51 and 56 and the BDI at age 59. On the other hand, with a correlation above 0.50 between the two tests, we assume that errors of measurement and differences between the tests contribute relatively little to the variance. Participants did not represent a random sample of cohort members, but analysis of any selective nonparticipation has shown that participants had the same distribution on mental health variables compared to the other participants in the CAMB study (Osler et al., 2016; Rask et al., 2016). Our sample was relatively small and the study was not sufficiently powered to detect weak associations or adjust for a large number of covariables, but the study population was relative homogeneous as it only included men of the same age and this will limit potential confounding. We did consider adjusting for variables associated with depression and brain measures such as smoking and alcohol use. However, we found it most likely that they represent factors mediating any association and should therefore not be adjusted for. We did consider performing the analysis on a per-voxel basis such as voxel-based morphometry (VBM) in addition to the volume/texture of complete ROIs such as the hippocampus. Both VBM and ROI have been applied to study gray matter pathology in MDD (Arnone et al., 2012; Zhang et al., 2016). There is, however, significant heterogeneity in these results, and it seems generally unknown whether both methodologies are consistent in their sensitivity to detect neuropathological alterations. Moreover, we did not have a prior hypothesis of a selected part of the hippocampus being special relevant and a voxel-wise analysis would increase the number of comparisons considerably.

In conclusion, our study suggests that depressive symptoms in early midlife are associated with lower hippocampal volume 8 years later. We also suggest that amygdala and hippocampal texture might be an early marker for brain alterations associated with subclinical depression.

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CONFLICT OF INTEREST AND DISCLOSURE

The authors have no conflicts of interest to declare with regard to this work.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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