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Associations between depression, lifestyle and brain structure: A longitudinal MRI study

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ABSTRACT

Background: Depression has been associated with decreased regional grey matter volume, which might partly be explained by an unhealthier lifestyle in depressed individuals which has been ignored by most earlier studies. Also, the longitudinal nature of depression, lifestyle and brain structure associations is largely unknown. This study investigates the relationship of depression and lifestyle with brain structure cross-sectionally and longitudinally over up to 9 years.

Methods: We used longitudinal structural MRI data of persons with depression and/or anxiety disorders and controls ($N_{unique\ participants}$ = 347, $N_{observations}$ = 609). Cortical thickness of medial orbitofrontal cortex (mOFC), rostral anterior cingulate cortex (rACC) and hippocampal volume were derived using FreeSurfer. Using Generalized Estimating Equations, we investigated associations of depression and lifestyle (Body mass index (BMI), smoking, alcohol consumption, physical activity and sleep duration) with brain structure and change in brain structure over 2 (n = 179) and 9 years (n = 82).

Results: Depression status (B = -.053, p = .002) and severity (B = -.002, p = .002) were negatively associated with rACC thickness. mOFC thickness was negatively associated with BMI (B = -.004, p < .001) and positively with moderate alcohol consumption (B = .030, p = .009). All associations were independent of each other. No associations were observed between (change in) depression, disease burden or lifestyle factors with brain change over time.

Conclusions: Depressive symptoms and diagnosis were independently associated with thinner rACC, BMI with thinner mOFC, and moderate alcohol consumption with thicker mOFC. No longitudinal associations were observed, suggesting that regional grey matter alterations are a long-term consequence or vulnerability indicator for depression but not dynamically or progressively related to depression course trajectory.

1. Introduction

Depression has been associated with structural brain disturbances. Smaller hippocampal volume and cortical thinning in regions such as the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) have been most robustly found in persons with depression compared to healthy controls in large meta-analyses (Arnone et al., 2016; Gray et al., 2020; Schmaal et al., 2016, 2017). However, these abnormalities could be either related to a predisposition for depression, develop after disease onset or progress with disease duration or trajectory. Based on cross-sectional studies it is difficult to shed light on potential causality, whereas longitudinal studies are sparse and findings inconsistent (Dohm et al., 2017). Some researchers suggest that depression is related to decreased grey matter (GM) over up to 4 years, with GM changes depending on depression trajectory (Frodl et al., 2008a; Lebedeva et al., 2018; Phillips et al., 2015), while other studies did not find longitudinal changes over time in brain regions often associated with depression (Frodl et al., 2008b; Weber et al., 2012). Inconsistencies in observations could be related to methodological factors, such as small sample sizes, differences in age-ranges, limited time between baseline and follow-up, but also factors such as lifestyle.

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Depression has often been associated with an unhealthy lifestyle (Penninx, 2017). Low physical activity (Vancampfort et al., 2015) and high body mass index (BMI) (Milaneschi et al., 2019) have consistently been associated with depression, as have smoking (Fluharty et al., 2017) and high alcohol consumption (Boden & Fergusson, 2011). Lifestyle aspects, such as shorter (and longer) sleep duration, physical inactivity and increased weight, can be considered correlates of depression, be risk factors for (course of) depression and vice versa (Fluharty et al., 2017; Mendlewicz, 2009; Milaneschi et al., 2019). These associations between depression and an unhealthy lifestyle have also been reported in the sample used in the current study (Boschloo et al., 2011; de Wit et al., 2010; Hiles et al., 2017; Jamal et al., 2012; van Mill et al., 2010). As lifestyle factors have also been related to smaller regional GM volumes (Erickson et al., 2014; García-García et al., 2019; Opel et al., 2020; Scullin, 2017; Topiwala et al., 2017; Vňuková et al., 2017), these could be partly underlying the associations between depression and GM volumes. However, the cross-sectional as well as longitudinal impact of lifestyle on the relation between depression and brain structure is still largely unknown.

The current study therefore investigates the relationship between depression, lifestyle and brain structure across measurement waves as well as longitudinally over up to 9 years. Based on earlier large-scale meta-analyses (Schmaal et al., 2016, 2017), we identified the brain measures with the largest significant effect sizes (adult depressed patients vs controls), and thus focused on cortical thickness of the medial orbitofrontal cortex (mOFC), rostral anterior cingulate cortex (rACC) and hippocampal volume in the current study. These regions were also partly in line with earlier findings in the current sample (van Tol et al., 2010). Presence and severity of depressive symptoms were expected to be associated with lower regional GM thickness/volume, and predictive of regional GM reductions over the course of up to 9 years. Unhealthy lifestyle factors were also expected to be related to decreased regional GM. Associations between depression and brain structure abnormalities and lifestyle and brain structure were not expected to be independent from each other. In order to maximize sample size and based on the high comorbidity of depression and anxiety (Lamers et al., 2011), analyses on severity of depressive symptoms and lifestyle were conducted across persons with current depressive disorder (with potential comorbid anxiety), current anxiety disorder, persons with remitted depression and/or anxiety disorders and healthy controls.

2. Material and methods

2.1. Sample

The Netherlands Study of Depression and Anxiety (NESDA) is a naturalistic longitudinal cohort study, investigating the course of depression and anxiety in a total of 2981 participants aged 18 through 65 years. Persons with depressive and/or anxiety disorders and healthy controls without a lifetime psychiatric diagnosis were included. Participants were recruited from specialized mental health care institutions, general practices and the community (for details see Penninx et al., 2008).

Part of the NESDA baseline sample (patients and healthy controls) were asked to participate in the NESDA MRI substudy in which structural and functional MRI scans were acquired (van Tol et al., 2010). Follow-up MRI measurements were performed at 2 and 9 years after baseline. At baseline, inclusion criteria for the MRI substudy were fulfilling criteria for a DSM-IV diagnosis of major depressive disorder (MDD) and/or anxiety disorder (social phobia, panic disorder, generalized anxiety disorder) in the six months prior to the interview, but no other axis-I disorder, and for the healthy controls no history of any DSM-IV axis-I disorders and no use of psychotropic medication. Exclusion criteria were age above 57 years, general MRI contraindications, presence or history of a major somatic or neurological disorder, alcohol or drug dependency or abuse disorder according to the DSM-IV in the past year (measured using the diagnostic CIDI interview), use of psychotropic medication except for stable use of selective serotonin reuptake inhibitors (SSRIs) or infrequent benzodiazepine use. At 2- and 9-year follow-up the inclusion criteria were similar, but patients with previous MRI measurements were also allowed to use low doses of other psychopharmaca if the indication was insomnia (<100 mg quetiapine per day, <15 mg mirtazapine per day) or low doses of lithium. All participants provided written informed consent to participate in the study and the study was approved by the Ethical Review Boards of all participating centers and conducted in accordance to the declaration of Helsinki.

At baseline 301 participants were included, of which 12 participants were excluded due to poor image quality (for details see 2.3 Image processing), two because they did not complete the scan due to claustrophobia and one because the interval between baseline interview and scan was too long, leaving a total of 286 participants in the baseline sample. For the 2-year follow-up MRI measurements all participants were asked to participate again, resulting in a sample size of 191 of which two were excluded due to poor image quality, leaving 189 participants. At 9-year follow-up, 86 controls and participants with current depression at one of the earlier measurement waves were again included. In addition, 53 original NESDA participants were newly included in the 9-year imaging wave, also consisting of controls and participants with current depression. Of the 139 conducted scans at 9-year follow-up, 5 were excluded due to poor image quality, resulting in a total sample of 134 (83 recruited at baseline, 51 recruited at 9-year follow-up). The total number of unique participants included in analyses after exclusion of poor image quality data was therefore 347 and the total number of observations was 609. Of the 347 unique participants, 179 participants had data on baseline-to-2-year change, 82 on baseline-to-9-year change, 97 participants on baseline only, 12 participants on 2-year follow-up only, 51 participants on 9-year follow-up only and one participant had data on 2-year and 9-year follow-up only.

The baseline characteristics of the participants with only baseline data (drop-out) compared to participants with at least one follow-up measurement (non drop-out) are presented in Supplementary Table A.1. No differences between these participants were found regarding age, sex, education level, depression severity, anti-depressant use or any of the lifestyle factors ($p > 0.050$). For psychopathology status, the only difference was in the number of healthy controls, with less healthy controls in the drop-out group compared to the non drop-out group ($p = 0.016$), but no differences in drop-out for participants with current depression or anxiety disorder.

2.2. Image acquisition

Imaging data was acquired using 3 Tesla Philips MRI scanners (Philips, The Netherlands) located at the three participating centers (Academic Medical Center Amsterdam (AMC), Leiden University Medical Center (LUMC) and University Medical Centre Groningen (UMCG)). At baseline, a SENSE-6 channel head coil was used at the AMC while at the other sites a SENSE-8 channel head coil was used. At the 2-year follow-up, 8-channel phased array head coils were used at all sites and at the 9-year follow-up 32-channel phased array head coils. At the 9-year follow up, new scanners were used at the AMC and LUMC. At all measurement waves and sites, anatomical images were obtained using 3D gradient-echo T1-weighted sequence (170 sagittal slices, TR: 9ms, TE: 3.5ms, matrix size: 256 × 256, voxel size: 1 mm^3).

2.3. Image processing

FreeSurfer version 6.0 was used for image analysis (Martinos Center for Biomedical Imaging, Harvard-MIT, Boston, MA; http://surfer.nmr.mgh.harvard.edu/), to obtain cortical thickness and (subcortical) volumetric measures. FreeSurfer incorporates averaging and motion correction, Talairach transformation, removal of non-brain tissue, intensity normalization, cortical reconstruction and segmentation of cortical regions and subcortical struc-

tures. For quality assurance, two raters performed visual inspection, using the protocol developed by the ENIGMA consortium (http://enigma.ini.usc.edu/protocols/imaging- protocols/), leading to exclusion of subjects when the data did not meet the criteria posed by ENIGMA. The current study focused on cortical thickness of the mOFC and rACC, and hippocampal volume, all averaged across hemispheres (De Kovel et al., 2019), based on their association with depression (Schmaal et al., 2016, 2017). To check whether potential associations are specific for these brain structure rather than global effects across the whole brain, we also included total GM volume (GMV) in the analyses.

2.4. Clinical assessment

At each assessment wave, severity of depressive symptoms was assessed using the 30-item Inventory of Depressive Symptomatology - Self Report (IDS-SR) (Rush et al., 1996). Participants were also classified as healthy control (no lifetime history of psychiatric disorders), having current depression (with possible comorbid anxiety) or having only current anxiety disorder, all within the last 6 months, or remitted depression and/or anxiety disorder. This classification of diagnostic status was defined at each measurement wave and was based on information on diagnostic status at earlier measurement waves, in between the measurements, as well as at the current measurement wave. For this, the Composite International Diagnostic Interview (CIDI version 2.1) (Wittchen, 1994) was used. Disease burden for depression over 2 and 9 years was determined based on the CIDI and Life Chart Interview (LCI) (Lyketsos et al., 1994). The LCI uses a calendar method to obtain information on presence of depressive and anxiety symptoms and severity of these symptoms per month, as well as life events. The CIDI and LCI were conducted at baseline and 2-, 4-, 6-, and 9-year follow-up. If participants met the criteria for depression in between or at one of the follow-up measurements, time spent with depression was scored as 1 for every month that patients reported depressive symptoms in the time between the last completed measurement and the current measurement. If a patient did not meet the criteria, the time spent with depression in this period was set to 0 for each month. Based on this information, the disease burden was defined as percentage of time within 2 or 9 years that a patient had depressive symptoms. This was calculated for both the baseline-to-2-year and the baseline-to-9-year period, by dividing the number of months with symptoms by the number of months between baseline and the 2-year follow-up measurement, and baseline and the 9-year follow-up measurement.

2.5. Lifestyle assessment

BMI was obtained by dividing the weight (in kilograms) by the squared height (in meters). Smoking was assessed as self-reported current number of cigarettes per day. Alcohol consumption was measured by average number of drinks per week and categorized as: non-drinker (≤1 drink/year), moderate drinker (men: <21 drinks/week, women: <14 drinks/week), and heavy drinker (men: ≥21 drinks/week, women: ≥14 drinks/week). Physical activity was assessed using the short International Physical Activity Questionnaire (IPAQ) (Booth, 2000) calculating the Metabolic Equivalent Total (MET)-minutes spent per week (see details on www.ipaq.ki.se). Sleep duration was measured as part of a self-report questionnaire in which participants were asked to estimate the average number of hours of sleep during the past 4 weeks in categories: normal or long sleep (“7 or more hours”) or short sleep (“6 or less hours”). Long sleep, often classified as 10 or more hours, was not used as a separate category as there were only few participants in this category.

2.6. Statistical analysis

Analyses were performed in SPSS (version 22; IBM Corp., Armonk, NY). We used Generalized Estimating Equations (GEE) analyses to examine the associations between depression, lifestyle factors and brain structure cross-sectionally across measurement waves and longitudinally. This allowed us to use all available data on brain structure across the measurement waves and all the available data on brain change, while taking within-person correlations into account and allowing for missing data. For all GEE analyses, an independent correlation structure was used as this yielded the best model fit across all outcomes. Multiple testing correction was applied using false discovery rate (FDR) estimation for cross-sectional and longitudinal analyses separately, with $\alpha_{FDR} = 0.05$ as threshold for significance.

In cross-sectional analyses across waves, predictors were severity of depressive symptoms (across all participants), current depression status (comparing healthy controls to persons with current depression), BMI, number of cigarettes per day, alcohol consumption, physical activity and sleep duration. The final sample for all cross-sectional analyses included 154 scans of healthy controls, 263 scans of participants with current depression (with possible comorbid anxiety), 99 scans of participants with only current anxiety and 93 scans of participants with remitted depression and/or anxiety. Outcomes were cortical thickness of mOFC, rACC, and hippocampal volume, with supplementary analyses on total GMV to check whether potential associations are specific for certain brain structures or global effects across the whole brain. For the first cross-sectional analyses, to assess associations between depression and brain measures, we first conducted separate univariate GEE analyses with depression symptom severity and depression diagnosis as predictors and one of the brain measures as outcome variable (mOFC, rACC, hippocampus). Next, to assess which lifestyle variables were associated with our brain measures of interest, we conducted separate univariate GEE analyses with only one of the lifestyle predictors per model (BMI, smoking, alcohol consumption, physical activity or sleep duration), and one of the brain measures as outcome variable (mOFC, rACC, hippocampus). For each analysis, we included the predictor and outcome variable data for all available measurement waves, while controlling for sociodemographic and imaging covariates. Time was coded as 1 (baseline), 2 (2-year follow-up) and 3 (9-year follow-up). To check whether associations were similar across measurement waves, an interaction term of the predictor with time was added to the models. As a second step of the cross-sectional analyses, all lifestyle predictors that were significantly associated with brain outcome variables in the univariate cross-sectional analyses were included in one multivariate GEE model, together with symptom severity of depression or depression diagnosis, to investigate whether the depression predictor variables were related to brain outcome measures independently of lifestyle and vice versa.

For longitudinal analyses, only participants with at least two MRI measurements were included. For the first longitudinal analyses, GEE analyses were performed to associate baseline depression or lifestyle predictors with change in brain structure, running separate univariate GEE analyses with only one of the depression or lifestyle predictors per model. For each analysis, we included predictor data at baseline, and brain outcome data for all available measurement waves, while controlling for sociodemographic and imaging covariates. Time was coded as 1 (baseline), 2 (2-year follow-up) and 3 (9-year follow-up) and a predictor-by-time interaction term was added to test whether baseline predictor was associated with change in brain measures over 2 or 9 years. For the second part of the longitudinal analyses, change in predictor was associated with change in brain measures. Change was calculated for each predictor and outcome measure between baseline and 2-year follow-up (2-year change) and between baseline and 9-year follow-up (9-year change). Longitudinal change analyses were only performed for predictors that were (1) significantly associated with brain structure cross-sectionally and (2) continuous measures, as group sizes were too small to derive change of categorical variables. These analyses were only exploratory. Also, power was reduced and our expectation of finding associations was minimal when a predictor was not associated with brain structure in the (more powerful) cross-sectional analyses. And as an ad-

ditional measure for depression course, disease burden over 2 or 9 years was also investigated as a predictor. Separate linear regressions were conducted per combination of change in predictor and change in outcome over either 2 or 9 years. In these analyses, negative values for change reflect a decrease over time while positive values reflect an increase.

2.7. Covariates

Age and sex at baseline, education level in years, scan location, intracranial volume (ICV) at time of measurement (for volumetric outcomes) and time as categorical variable were included as covariates in the analyses not involving measures of change. For cross-sectional analyses, an interaction term of time*scan location was added, as scanners were replaced at the 9-year follow-up measurement at two of the three sites (AMC and LUMC). Cross-sectional analyses on cortical thickness measures (i.e. mOFC and rACC) were repeated including global mean cortical thickness as a covariate to check whether mean cortical thickness might be driving potential associations with regional cortical thickness. For longitudinal analyses on change, the corresponding baseline measures were added to the model.

As the focus of this paper is on the impact of current depression, additional dummies were included in analyses on diagnostic status, one coded for only current anxiety, to explore whether results were specific for depression or also present in anxiety. Another dummy coded for remitted depression (which was only present at follow-up, not at baseline), so that the contrast truly describes the effect of current depression versus healthy controls. All analyses indicating associations with depression were repeated including use of antidepressants as additional covariate.

3. Results

3.1. Sample description

Descriptive statistics of the study sample across time points are presented in Table 1. We included 347 participants, of which 119 participants had data on two and 71 on three time points, yielding a total number of 609 observations. At baseline, the sample included 68.2% females, the mean age was 37.6 (SD = 10.2, range 18–57) and 54.9% had a diagnosis of current depression.

3.2. Cross-sectional associations of depression, depressive symptoms and lifestyle with brain structure across waves

As shown in Table 2 and illustrated in Fig. 1, more severe depressive symptoms across the whole sample were associated with lower cortical thickness of the mOFC (B = -0.001, p = 0.018) and rACC (B = -0.002, p = 0.002). Also, when comparing persons with current depression to healthy controls, depression was associated with lower cortical thickness of mOFC (B = -0.036, p = 0.013) and rACC (B = -0.053, p = 0.002). However, associations of depression status or severity of depressive symptoms with the mOFC did not remain significant when correcting for multiple comparisons. Including use of antidepressants in the models on depression status did not affect the associations with depression status, with B's remaining similar (mOFC: B = -0.031, rACC B = -0.051). Severity of depressive symptoms or depression status were not associated with hippocampal volume. A diagnosis of only current anxiety showed similar associations as current depression with the mOFC (B = -0.036, p = 0.044) and the rACC (B = -0.055, p = 0.005).

Higher BMI was associated with lower cortical thickness of mOFC (B = -0.004, p < 0.001) and rACC (B = -0.003, p = 0.017) but not with hippocampal volume, with the association of the rACC not remaining significant when adjusting for multiple comparisons. Persons with moderate alcohol consumption displayed larger cortical thickness of mOFC (B = 0.030, p = 0.009) and rACC (B = 0.029 p = 0.044) compared to non-drinkers (illustrated in Fig. 1), with the association with rACC not remaining significant when correcting for multiple comparisons. No differences were found between heavy drinkers and non-drinkers. Shorter sleep duration (6 or less hours) relative to 7 h or more, was associated with higher cortical thickness of the mOFC (B = 0.019, p = 0.021), but not significantly associated after correction for multiple comparisons. There were no associations between any of the brain regions of interest and number of cigarettes per day or physical activity. Exploratory analyses showed that presence of current depression was associated with total GMV (B = -0.069, p = 0.027) but not when correcting for multiple comparisons. Severity of depressive symptoms was not associated with total GMV and neither were any of the lifestyle measures (see Supplementary Table A.2). When adding global mean cortical thickness as additional covariate to analyses including regional cortical thickness (i.e. mOFC and rACC) associations remained similar in direction and magnitude (see Supplementary Table A.3).

Adding the interaction term between depression or lifestyle factors with time showed no significant interactions when correcting for multiple testing, showing that associations were consistent across measurement waves. Associations of severity of depressive symptoms with rACC, BMI with mOFC and alcohol consumption with mOFC remained significant when all three variables were included in one multivariate model (Supplementary Table A.4). This was true as well when depression status was added to the model instead of severity of depressive symptoms (see Supplementary Table A.4).

3.3. Change in brain structure over 2 and 9 years

Fig. 2 illustrates change in brain structures over 2 ($N_{2\text{-year change}}$ = 179) and 9 years ($N_{9\text{-year change}}$ = 82). Change over time was more pronounced over 9 years than over 2 years. Over 2 years increases as well as decreases of cortical thickness or volume were observed for all brain structures, while over 9 years decreases were more pronounced, especially for total GMV and hippocampal volume.

3.4. Longitudinal associations of depression and lifestyle with change in brain structure

Longitudinal associations of baseline severity of depressive symptoms and lifestyle factors with change in brain structures over up to 9 years are presented in Table 3. Baseline moderate alcohol consumption (B = -0.028, p = 0.034) and heavy alcohol consumption (B = -0.034, p = 0.009) were associated with more decrease in cortical thickness over 2 years of the mOFC, compared to no alcohol consumption. However, none of these associations remained significant when correcting for multiple testing. No associations with brain changes were found for baseline severity of depressive symptoms (illustrated in Supplementary Figure A.1), baseline depression status or other lifestyle factors. Change in severity of depressive symptoms over 2 or 9 years was also not associated with changes in brain structure, and neither was disease burden over 2 or 9 years, measuring time spent with depressive symptoms see (Supplementary Table A.5). Change in BMI over 2 or 9 years was also not associated with parallel change in brain structure.

4. Discussion

The current study investigated the relation between depression, lifestyle and brain structure cross-sectionally and longitudinally over up to 9 years. Cross-sectionally, measured across three time-points, higher severity of depressive symptoms as well as current depression diagnosis were associated with a thinner rACC. Higher BMI was associated with thinner mOFC, and moderate alcohol consumption compared to no alcohol consumption with thicker mOFC. All of these associations were independent of each other. Longitudinally, no convincing associations between (change in) depression or lifestyle and brain change over up to 9 years were found.

Table 1
Descriptives of study sample

	Baseline N = 286	2-year follow-up N = 189	9-year follow-up N = 134
Sociodemographics			
Age, mean years (SD)	37.6 (10.2)	40.2 (10.1)	48.6 (10.1)
Female gender, n (%)	195 (68.2)	125 (65.8)	85 (63.4)
Education level, mean years (SD)	12.8 (3.2)	13.0 (3.2)	13.4 (3.0)
Scan location, n (%)			
Amsterdam	93 (32.5)	56 (29.5)	37 (27.6)
Leiden	104 (36.4)	80 (42.1)	62 (46.3)
Groningen	89 (31.1)	54 (28.4)	35 (26.1)
Clinical characteristics			
Severity of depressive symptoms, mean IDS score (SD)	23.5 (14.2)	16.3 (11.6)	16.2 (12.7)
Psychopathology status			
Healthy controls, n (%)	65 (22.7)	48 (25.4)	41 (30.6)
Current depression (possible comorbid anxiety disorder), n (%)	157 (54.9)	58 (30.7)	48 (35.8)
Current anxiety disorder (without comorbid depression), n (%)	64 (22.4)	23 (12.2)	12 (9.0)
Remitted depression and/or anxiety disorder, n (%)	0 (0)	60 (31.7)	33 (24.6)
Anti-depressant use, n (%)	77 (26.7)	40 (20.9)	26 (19.4)
Lifestyle factors			
BMI, mean score (SD)	24.9 (4.5)	25.1 (4.5)	25.8 (4.8)
Current smoker, n (%)	96 (33.6)	59 (39.9)	25 (18.7)
Cigarettes per day, mean number (SD)	7.7 (10.1)	5.1 (7.6)	3.2 (5.9)
Alcohol consumption			
Non-drinker, n (%)	52 (18.2)	35 (19.0)	24 (18.6)
Moderate drinker, n (%)	215 (75.4)	135 (72.8)	96 (74.4)
Heavy drinker, n (%)	18 (6.3)	15 (8.2)	9 (6.7)
Physical activity, mean in 1000 MET minutes/week (SD)	3.6 (3.4)	4.0 (3.6)	3.5 (3.1)
Sleep duration			
7 or more hours, n (%)	197 (76.4)	139 (76.8)	94 (70.1)
6 or less hours, n (%)	61 (23.6)	42 (32.2)	40 (29.9)
Brain structure			
mOFC thickness, mean (SD)	2.24 (0.11)	2.22 (0.11)	2.19 (0.11)
rACC thickness, mean (SD)	2.63 (0.14)	2.63 (0.16)	2.62 (0.16)
Hippocampal volume, mean cm^3 (SD)	3.98 (0.39)	3.93 (0.41)	3.89 (0.41)
Total GMV, mean in 100 cm^3 (SD)	6.43 (0.60)	6.34 (0.62)	6.21 (0.57)
ICV, mean in liter (SD)	1.52 (0.17)	1.51 (0.18)	1.52 (0.18)

Note: Abbreviations: BMI=body mass index, MET=metabolic equivalent total, mOFC=medial orbitofrontal cortex, rACC=rostral anterior cingulate cortex, GMV=grey matter volume, ICV=intracranial volume

Table 2
Cross-sectional associations across measurement waves of brain structure with depression and lifestyle factors ($N_{unique\ participants}$ = 347, $N_{observations}$ = 609)

	mOFC thickness		rACC thickness		Hippocampal volume	
	B	p	B	p	B	p
Depression						
Severity of depressive symptoms	-0.001	0.018#	-0.002	0.002*	-0.001	0.360
Depression status						
Healthy control	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Current depression	-0.036	0.013#	-0.053	0.002*	-0.026	0.478
Lifestyle factors						
BMI	-0.004	<0.001*	-0.003	0.017#	0.001	0.729
# Cigarettes per day	0.001	0.238	-0.0004	0.636	0.0002	0.920
Alcohol consumption						
Non-drinker	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Moderate drinker	0.030	0.009*	0.029	0.044#	0.033	0.131
Heavy drinker	0.037	0.064	-0.007	0.789	0.048	0.200
Physical activity	-0.001	0.204	-0.003	0.086	0.001	0.677
Sleep duration						
7 or more hours	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
6 or less hours	0.019	0.021#	0.010	0.471	0.017	0.319

Note: Separate Generalized Estimating Equation models per predictor, adjusted for sociodemographic and imaging variables (age, sex, education, scan location, ICV, time and interaction of time*scan location); abbreviations: mOFC=medial orbitofrontal cortex, rACC=rostral anterior cingulate cortex, BMI=body mass index

* significant at $p_{FDR} < 0.05$

\# $p < 0.05$ & $p_{FDR} > 0.05$ (i.e. not significant after FDR correction)

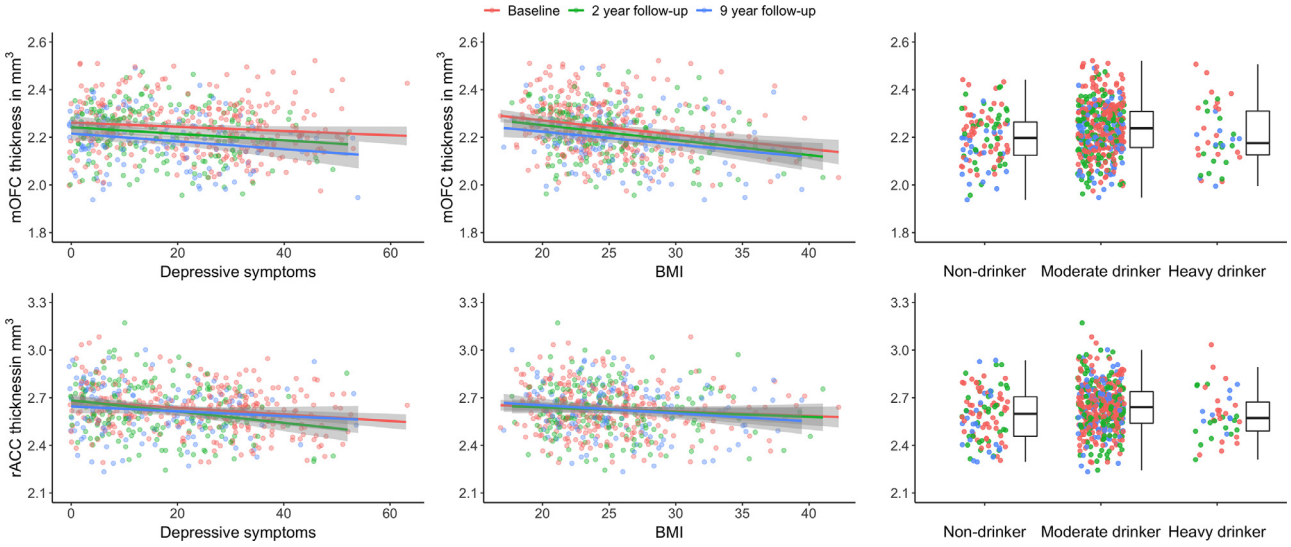

Fig. 1. Associations of severity of depressive symptoms, BMI and alcohol consumption with thickness of mOFC and rACC. Plots illustrating the associations of severity of depressive symptoms, BMI and alcohol consumption with thickness of medial orbitofrontal cortex (mOFC) and rostral anterior cingulate cortex (rACC), without adjustment for sociodemographic and imaging variables. Similarity of slopes of the regression lines per measurement wave illustrate that there is no interaction with time with depression severity or BMI.

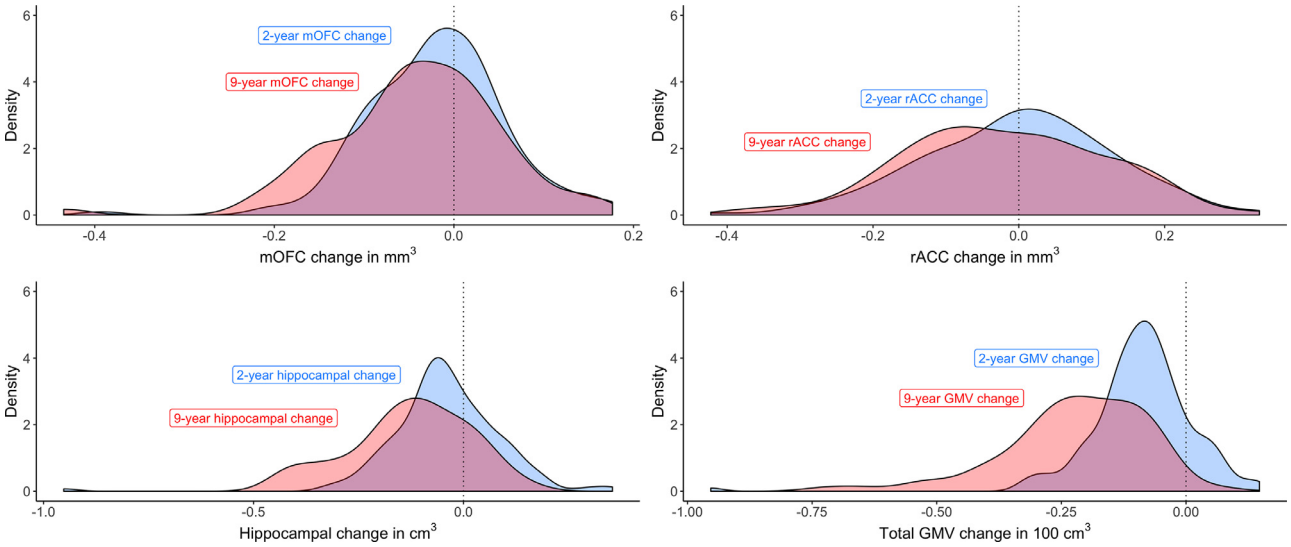

Fig. 2. Illustration of change of brain structures over 2 and 9 years. Density plots representing the distributions of change of thickness of the medial orbitofrontal cortex (mOFC), rostral anterior cingulate cortex (rACC), hippocampal volume and total grey matter volume (GMV) over 2 years and 9 years. Negative values for change reflect a decrease over time while positive values reflect an increase.

Severity of depressive symptoms as well as depression diagnosis were associated with lower rACC thickness. This is in line with earlier large meta-analyses linking presence of depression to the (rostral) ACC (Arnone et al., 2016; Gray et al., 2020; Schmaal et al., 2016) and in line with findings from voxel-based morphometry analyses in a subset of the current sample (van Tol et al., 2010). These associations confirm that depressive symptoms are related to regional brain structure in a dose-response fashion (Webb et al., 2014), also across persons with a (remitted) depression, anxiety and controls. These associations were not driven by the use of antidepressants: the associations between depression and rACC thickness remained stable when correcting for antidepressant use. This is also in line with that only a small part of the sample was using antidepressants (24%), suggesting the associations are not likely to be driven by antidepressant use. The associations between depression and mOFC or hippocampus found in earlier meta-analyses were not convincingly confirmed in the current study, though a trend association of mOFC thickness with severity of depressive symptoms as well as diagnosis was observed. No associations with total GMV were found and the association of rACC and depression remained when correcting for global mean cortical thickness, indicating regional rather than global effects. Associations of only current anxiety were similar to current depression, indicating there might be common mechanisms or disturbances in the brain related to depression and anxiety, which has also been suggested based on strong comorbidity of these disorders (Kessler et al., 2015).

No convincing longitudinal associations were observed between depression and change in brain structure: baseline severity of depressive symptoms or diagnosis did not predict change in rACC or mOFC thickness or hippocampal volume, nor did change in depressive symptoms or disease burden over 2 or 9 years co-vary with changes in brain structure. This is partly in line with inconsistent findings of earlier longitudinal studies (Dohm et al., 2017). Most of the earlier studies relating depression to longitudinal brain change focused on trajectories of depression

Table 3
Longitudinal associations of change in brain structure over a 9-year period with baseline depression and lifestyle ($N_{Time\ 2}$ = 179, $N_{Time\ 3}$ = 82)

	Δ mOFC thickness		Δ rACC thickness		Δ Hippocampal volume	
	B	p	B	p	B	p
Depression						
Severity of depressive symptoms						
Severity of depressive symptoms * time 2	0.0002	0.613	0.0001	0.347	-0.001	0.052
Severity of depressive symptoms * time 3	-0.00002	0.972	-0.001	0.853	-0.0001	0.897
Depression status						
Healthy control	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Current depression						
Current depression * time 2	0.006	0.626	0.019	0.415	-0.011	0.635
Current depression * time 3	0.008	0.796	0.057	0.068	0.024	0.482
Lifestyle factors						
BMI						
BMI * time 2	-0.001	0.441	0.00006	0.977	-0.00008	0.964
BMI * time 3	-0.003	0.263	-0.005	0.142	-0.003	0.283
# Cigarettes per day						
# Cigarettes per day * time 2	0.0003	0.699	0.002	0.122	-0.0002	0.755
# Cigarettes per day * time 3	0.001	0.502	0.002	0.069	-0.001	0.558
Alcohol consumption						
Non-drinker	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Moderate drinker						
Moderate drinker * time 2	-0.028	0.034[#]	-0.009	0.732	-0.001	0.954
Moderate drinker * time 3	-0.034	0.082	0.001	0.981	0.036	0.281
Heavy drinker						
Heavy drinker * time 2	-0.063	0.009[#]	-0.032	0.475	-0.020	0.638
Heavy drinker * time 3	-0.023	0.266	0.104	0.089	0.057	0.292
Physical activity						
Physical activity * time 2	-0.001	0.716	0.006	0.067	0.001	0.575
Physical activity * time 3	-0.002	0.621	0.004	0.320	0.003	0.527
Sleep duration						
7 or more hours	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
6 or less hours						
6 or less hours * time 2	-0.006	0.648	-0.036	0.105	-0.001	0.956
6 or less hours * time 3	-0.035	0.053	-0.002	0.927	-0.052	0.112

Note. Separate Generalized Estimating Equation models per predictor, adjusted for sociodemographic and imaging variables (age, sex, education, scan location, ICV, time and corresponding brain measure at baseline); abbreviations: Δ = change, mOFC=medial orbitofrontal cortex, rACC=rostral anterior cingulate cortex, BMI=body mass index
[#] $p < 0.05$ & $p_{FDR} > 0.05$ (i.e. not significant after FDR correction)

diagnosis, comparing remitters to non-remitters, rather than change in symptom severity (Frodl et al., 2008b; Isikli et al., 2013; Taylor et al., 2014). One of the few studies examining depressive symptoms in relation to brain change found depressive symptoms to be predictive of subsequent 4-year decline in some regions, such as the superior temporal cortex, and change in symptoms to be related to brain changes in other regions, such as the left superior frontal gyrus (Lebedeva et al., 2018). However, none of these regions were examined in the current study as they were not consistently associated with depression in large cross-sectional meta-analyses (Arnone et al., 2016; Schmaal et al., 2017). Also, the sample of the Lebedeva et al. study was older than the current sample and it might be that in the current sample there was not enough change over time in the included brain regions to find the accelerated biological ageing related to depression that Lebedeva et al. reported. For example, hippocampal volume generally shows almost no decline between age 20 and 60 but substantial decline after 60 (Fjell et al., 2019; Pomponio et al., 2020). It has also been suggested that late-onset depression might be more strongly related to decline of brain structure than early-onset depression (Dohm et al., 2017; Hickie et al., 2005; Schmaal et al., 2016), which might also explain inconclusive findings.

In the current study depression was cross-sectionally but not longitudinally associated with rACC thinning. The rACC has been implicated in depression as it is an important region for integration of cognitive and affective input, social cognition and emotion regulation (Bush et al., 2000; Stevens et al., 2011). In depressed patients, a thicker rACC was shown to predict positive treatment response to repetitive transcranial magnetic stimulation (rTMS) (Boes et al., 2018) and rACC volume also predicted treatment response to Internet-Based Cognitive Behavioral Therapy (Webb et al., 2018). Also, increase in rACC thickness over time during treatment with rTMS was linked to a positive treatment outcome and decrease to a less favorable outcome (Boes et al., 2018). Though we did not investigate change in brain structure as predictor of treatment response, we did not observe associations between with naturalistic course of change in depressive symptoms over time and change of rACC thickness.

The association between depression and rACC thickness was independent of lifestyle factors: when lifestyle and depression were included in one multivariate model, associations remained. This indicates that the negative association between depression and rACC thickness was not driven by an unhealthy lifestyle, such as higher BMI. But there are also other factors that might contribute to the lower cortical thickness observed in depression, such as (early life) stress potentially leading to increased inflammation and neuronal atrophy (Price & Duman, 2019) or a vulnerability for depression affecting brain structure (Boes et al., 2008). Taken together, this could suggest that lower rACC thickness is not related to disease progression or the trajectory of depressive symptoms but might either already be present before onset and relate to vulnerability for developing depression or be a long-term consequence of depression. However, larger longitudinal studies are needed to confirm these findings. Studies in subclinical populations and with larger age-ranges may shed more light on onset of cortical thinning and the potential interactions with age.

Higher BMI was associated with thinner mOFC cross-sectionally. This is in line with earlier studies linking lower volume of this region to BMI (García-García et al., 2019), also in persons with depression (Opel et al., 2015). The mOFC has often been linked to obesity through

its involvement in reward processing (Gehring & Willoughby, 2002), with a thinner mOFC potentially being related to disturbances in these processes. No associations were found between BMI and rACC or hippocampal volume. The association of BMI with mOFC was found to be independent of depression, which is also in line with earlier research (Opel et al., 2015, 2020), and also independent of other lifestyle factors. It was also independent of global mean cortical thickness, indicating the effect of BMI is regional rather than global. Factors potentially underlying this association might be immuno-metabolic dysregulation or cardio-vascular problems, which have been associated with high BMI (Van Gaal et al., 2006) and may explain decreased prefrontal cortical thickness (van Velzen et al., 2017), for example through neurodegeneration or neuroplasticity.

No convincing longitudinal associations between BMI and regional brain structure were observed: BMI at baseline was not predictive of decline in cortical thickness of the mOFC, rACC or hippocampal volume, nor was change in BMI over up to 9 years associated with simultaneous change in regional brain structure. This is also in line with inconsistent findings of earlier longitudinal studies, some associating higher BMI with more cortical thinning over time (Bobb et al., 2014; Walhovd et al., 2014) while other studies do not observe longitudinal associations (Croll et al., 2019).

Interestingly, moderate alcohol consumption compared to no alcohol consumption was associated with thicker mOFC. This might indicate a positive effect of moderate alcohol consumption, which has also been suggested for other neurological health outcomes, such as dementia (Ruitenberg et al., 2002), stroke (Cleophas, 1999), and somatic diseases (Nyberg et al., 2020). However, this is not in line with other studies finding negative associations between moderate alcohol consumption and brain structure (Topiwala et al., 2017). An alternative explanation for this association might be that the non-drinkers represent a relatively unhealthy population ('sick-quitter' hypothesis, Wannamethee & Shaper, 1988). Abstinence might be an indicator of somatic diseases or previous heavy drinking which could (partly) underlie the smaller GM observed in non-drinkers. This might also be in line with the trend association of baseline moderate as well as heavy alcohol consumption with subsequent thinner mOFC found in the current study. However, these adverse effects of heavy alcohol consumption were not observed cross-sectionally in the current study, so these findings could also be due to chance and need further investigation in larger studies. Here, it is important to keep in mind that persons with alcohol abuse or dependence disorders were excluded in the current study, indicating that in the current sample heavy drinking does not measure disorders related to alcohol consumption but rather heavy drinking as a lifestyle behavior in the absence of alcohol abuse and dependency disorders. No associations were found between alcohol consumption and rACC or hippocampal volume, nor between any of the brain regions and sleep duration, smoking or physical activity.

4.1. Strengths and limitations

Some limitations need to be kept in mind. Firstly, longitudinal sample size was limited, especially over 9 years, which may have reduced the power to observe any convincing longitudinal associations. The longitudinal power might also have been affected by changes in the scanners that were used, as well as hardware updates of the scanners. We observed trend associations of baseline moderate and heavy alcohol consumption with change decrease in mOFC thickness over time, which did not remain significant when correcting for multiple testing. Future studies with a larger longitudinal sample, preferably with a large follow-up interval and broader age range, might indicate if convincing longitudinal associations are present, and allow further exploration of the interaction with age on these associations. For these studies, it would also be relevant to include depression longitudinally to assess illness duration and changes in depressive symptoms over time. Also, examining subclinical symptoms of depression might shed more light on potential brain correlates present before onset of depression. For future studies, it might also be interesting to examine the role of inflammation or (early life) stress in the associations of depression, BMI and brain structure to disentangle potential underlying mechanisms. Strengths of the current study include the design, combining all of the available cross-sectional data across measurement waves and all longitudinal change data, resulting in relatively large sample sizes for an MRI study in a clinical sample. Also, the current study had a relatively long follow-up interval for study in a clinical population and the sample was well-phenotyped, with diagnoses based on clinical interviews.

5. Conclusion

Overall, our study confirmed that higher severity of depressive symptoms and depression diagnosis are associated with thinner rACC, independent of lifestyle factors. No convincing longitudinal associations were observed: baseline depression did not predict change in brain structure over a 9-year follow-up period, and change in depressive symptoms was not associated with change in brain structure. Higher BMI was associated with thinner mOFC, whereas moderate alcohol consumption was associated with thicker mOFC, all independent of other lifestyle factors and depression (-severity). Other lifestyle factors were not associated with brain structure and no convincing longitudinal associations of lifestyle with change in brain structure were observed. The consistent cross-sectional, but absent longitudinal association of depression with brain structure might suggest that it is a long-term consequence or vulnerability indicator for depression but not dynamically or progressively related to depression course or symptom trajectory. However, careful interpretation of the absent longitudinal relationships is warranted as absence of evidence is not the same as evidence of absence (Dienes et al., 2014). This study provides insight into the cortical abnormalities related to depression and the role of lifestyle in this association. Future studies should aim to investigate the longitudinal associations in larger samples with a wider age-range, to gain further insight in the association between depression and brain structure across the lifespan.

Declaration of Competing Interest

BP has received (non-related) research grants from Boehringer Ingelheim and Jansen Research. None of the other authors declare conflicts of interest.

Credit authorship contribution statement

Julia Binnewies: Conceptualization, Writing - original draft, Methodology, Formal analysis, Visualization. **Laura Nawijn:** Conceptualization, Writing - review & editing, Methodology, Supervision. **Marie-José van Tol:** Writing - review & editing, Investigation. **Nic J.A. van der Wee:** Writing - review & editing, Investigation. **Dick J. Veltman:** Writing - review & editing, Investigation. **Brenda W.J.H. Penninx:** Conceptualization, Writing - review & editing, Methodology, Funding acquisition, Supervision.

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Data availability statement

The data used for this study can be requested through submitting a research proposal to the NESDA board (nesda@ggzingeest.nl). This research proposal includes a short description of the background of the research, specific research questions, methodology, and the proposed statistical analyses. Forms can be downloaded from www.nesda.nl.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.117834.

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