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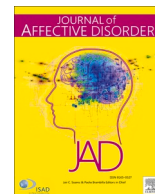
**Citation**

# The association between clinical and biological characteristics of depression and structural brain alterations

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## ARTICLE INFO

## ABSTRACT

*Background:* Structural brain alterations are observed in major depressive disorder (MDD). However, MDD is a highly heterogeneous disorder and specific clinical or biological characteristics of depression might relate to specific structural brain alterations. Clinical symptom subtypes of depression, as well as immuno-metabolic dysregulation associated with subtypes of depression, have been associated with brain alterations. Therefore, we examined if specific clinical and biological characteristics of depression show different brain alterations compared to overall depression.

*Method:* Individuals with and without depressive and/or anxiety disorders from the Netherlands Study of Depression and Anxiety (NESDA) (328 participants from three timepoints leading to 541 observations) and the Mood Treatment with Antidepressants or Running (MOTAR) study (123 baseline participants) were included. Symptom profiles (atypical energy-related profile, melancholic profile and depression severity) and biological indices (inflammatory, metabolic syndrome, and immuno-metabolic indices) were created. The associations of the clinical and biological profiles with depression-related structural brain measures (anterior cingulate cortex [ACC], orbitofrontal cortex, insula, and nucleus accumbens) were examined dimensionally in both studies and meta-analysed.

*Results:* Depression severity was negatively associated with rostral ACC thickness (B = -0.55, $p_{FDR}$ = 0.03), and melancholic symptoms were negatively associated with caudal ACC thickness (B = -0.42, $p_{FDR}$ = 0.03). The atypical energy-related symptom profile and immuno-metabolic indices did not show a consistent association with structural brain measures across studies.

*Conclusion:* Overall depression- and melancholic symptom severity showed a dose-response relationship with reduced ACC thickness. No associations between immuno-metabolic dysregulation and structural brain alterations were found, suggesting that although both are associated with depression, distinct mechanisms may be involved.

## 1. Introduction

Major depressive disorder (MDD) has been associated with subcortical and cortical structural brain alterations (Schmaal et al., 2016; Schmaal et al., 2017). A large meta-analysis has shown that individuals with MDD have lower cortical thickness in the orbitofrontal cortex (OFC), posterior and anterior cingulate cortex (ACC), insula and temporal regions compared to controls (Schmaal et al., 2017). However,

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since MDD is highly heterogeneous, the structural brain alterations found in MDD could be related to specific clinical or biological characteristics of depression. Increased knowledge on the specific associations with structural brain alterations could help the understanding of the biological pathways involved in the symptomatology of depression.

The heterogeneity in symptom expression in depression may result from heterogeneity in etiological pathways and may hamper treatment efficiency (Fried, 2017; Goldberg, 2011). Stratifying MDD patients into more homogeneous subtypes and personalizing treatment to distinct underlying pathophysiology might therefore improve treatment outcome as well as the identification of specific biomarkers. Data-driven clustering studies have repeatedly found a subtype characterised by atypical, energy-related symptoms such as increased appetite, hypersomnia and fatigue, and a subtype with typical, melancholic, symptoms, characterised by decreased appetite and insomnia (Lamers et al., 2010; Lamers et al., 2012; Toenders et al., 2020; Sullivan et al., 2002; Ulbricht et al., 2015).

The subtypes with atypical, energy-related versus typical symptoms do not only differ on a symptom level, but have also been found to show differences on a biological level. The atypical, energy-related subtype has been uniquely associated with higher BMI, higher leptin levels, higher insulin, and higher inflammatory markers such as CRP, IL-6 and TNF-α relative to the melancholic subtype (Lamers et al., 2010; Milaneschi et al., 2017; Simmons et al., 2018a; Caroleo et al., 2019a; Lamers et al., 2013). While changes in appetite and sleep in general have been associated with increased levels of inflammatory markers (Frank et al., 2021; Jokela et al., 2016), a recent study showed that this association is explained by increased appetite and hypersomnia (Milaneschi et al., 2021a). Other biomarkers associated with this depressive subtype are higher levels of triglycerides and low levels of high-density lipoprotein (HDL) cholesterol (Lamers et al., 2013). Melancholic depression has been linked more specifically to higher cortisol levels (Vinkers et al., 2021; Caroleo et al., 2019b).

Regarding structural brain alterations, it was found that lower surface area of the anterior insula and lower thickness of the lateral OFC were associated with depressive symptoms of increased appetite in young people (Toenders et al., 2020; Mehler et al., 2021). It has also been found that individuals with melancholic depression have lower insula volume compared to healthy controls (Soriano-Mas et al., 2011). Prior research has also shown that thickness of the rostral ACC is associated with immuno-metabolic dysregulation (van Velzen et al., 2016). Inflammation has also been found to lead to neurotoxicity, which could induce cortical thinning (Han and Ham, 2021). Metabolic syndrome, characterised by increased blood pressure and excess body fat around the waist, has also been associated with grey matter alterations, including the insula and OFC (Kotkowski et al., 2019). Lastly, in a study where depressed patients were selected solely on a change in appetite (increased versus decreased appetite), higher insulin resistance was associated with higher posterior and dorsal-mid insula activity in the increased appetite subtype while looking at pleasant food stimuli (Simmons et al., 2018b).

To summarise, structural brain alterations of depression could be associated to specific clinical or biological characteristics of depression. Clinical subtypes of depression, including the atypical, energy-related subtype, have been linked to specific structural and functional brain alterations. In addition, heightened inflammation and metabolic dysregulation, often seen in this subtype, have also been associated with structural and functional brain changes.

The findings from prior literature suggest that the functional and structural neurobiological alterations associated with clinical and biological characteristics of depression are interwoven, as both the clinical subtypes and the (immuno-metabolic) biological characteristics show associations with structural brain alterations and with each other. However, previous studies have not directly examined whether clinical subtypes of depression and the biological characteristics related to immuno-metabolic dysregulation associated with depression, show

overlap in their association with brain structure. Detailing the mechanisms behind these biological changes, could increase our understanding of the biological aspects of clinical profiles of depression. In addition, small effect sizes of biological mechanisms in psychiatry have hampered findings in the past, but decreasing the heterogeneity of the clinical measure of interest by studying clinical profiles could reveal novel associations.

Therefore, we aimed to investigate if specific clinical (atypical, energy-related symptoms, melancholic symptoms) and biological (inflammatory, metabolic syndrome and immuno-metabolic indices) characteristics of depression are associated with unique and shared brain abnormalities compared to depression in general. We studied the surface area and thickness of earlier identified depression-related brain regions including the OFC, ACC, insula and nucleus accumbens. From research findings so far (Toenders et al., 2020; Mehler et al., 2021; Costi et al., 2021), it can be hypothesised that atypical, energy-related symptoms are associated specifically with alterations in the insula and OFC, and that immuno-metabolic dysregulations might show the same associations as well as specific associations with the nucleus accumbens.

## 2. Methods

### 2.1. Participants

Data from two studies were combined in a meta-analysis. Three waves (timepoints) from the longitudinal Netherlands Study of Depression and Anxiety (NESDA) study were used, as well as the baseline assessment of the MOod Treatment with Antidepressants or Running (MOTAR) study.

#### 2.1.1. NESDA

Three waves from the longitudinal NESDA study were part of this study: baseline, 2-year and 9-year follow-up (Penninx et al., 2008; van Tol et al., 2021). NESDA aimed to study the naturalistic course of depression. Participants were aged between 18 and 67 years old at baseline and were recruited from the general population, primary care and specialized mental health care. They were diagnosed with depressive and/or anxiety disorders or included as healthy controls. Participants had to be classified as having a depressive and/or anxiety disorder within the previous six months using the Composite International Diagnostic Interview (CIDI version 2.1) (Wittchen, 1994). The NESDA imaging substudy included 328 unique participants who had data available at least at one timepoint. In total, 541 observations were included (Supplemental Fig. S1). Specific exclusion criteria for the neuroimaging substudy included having a substance abuse or dependency diagnosis in the last year, age above 57 years at baseline, antidepressant use other than selective serotonin reuptake inhibitors, MRI contraindications or a present or past internal or neurological disorder. The subsample included in the imaging study was representative for the NESDA study in terms of sex, depression severity and inflammatory markers. All participants provided written consent and the study was approved by the Ethical Review Boards of the three participating centers. Since depressive symptoms are studied dimensionally, both healthy controls and people with MDD and anxiety disorders are included in all analyses.

#### 2.1.2. MOTAR

A total of 123 healthy controls and participants with MDD and/or anxiety disorder (aged 18–70 years old) from the baseline assessment of the MOTAR study were included (Van Milligen et al., 2019). The MOTAR study aimed to examine the effectivity of running therapy compared to treatment with antidepressant medication in patients with MDD over a period of 16 weeks. Follow-up measurements were not included since in this study we were not interested in the effect of the intervention. Participants were recruited from the general population and specialized mental health care. Depressive and/or anxiety disorder

diagnosis was assessed using the CIDI (Wittchen, 1994). Exclusion criteria included antidepressant use in the past two weeks, use of psychotropic medication, regular exercising or medical contra-indications to running therapy or antidepressants, psychiatric diagnosis other than MDD or anxiety disorders, acute suicidal risk, MRI contraindications and a present or past internal or neurological disorder. All participants provided written consent and the study was approved by the Medical Ethical Committee VU University Medical Centre.

### 2.2. Measures

#### 2.2.1. Depression severity

Depression severity in both studies was assessed by the 30-item Inventory of Depressive Symptomatology self-report (IDS-SR30) (Rush et al., 2003). Three depression symptom profiles were created that have been used in previous studies; 1) depression severity (total score on the IDS ranging between 0 and 84), 2) atypical, energy-related depressive symptoms (defined as the sum score of the following items: hypersomnia, increased appetite, weight gain, leaden paralysis and fatigue and ranging between 0 and 15), 3) melancholic symptoms (defined as the sum score of the following items: diurnal variation (mood worse in the morning), early morning awakening, distinct quality of mood, excessive guilt, decreased appetite, decreased weight, psychomotor agitation and psychomotor retardation and ranging between 0 and 24) (Lamers et al., 2020; Khan et al., 2006; Milaneschi et al., 2021b). All symptom profiles were standardised. The IDS was assessed within 8 weeks prior to scanning.

#### 2.2.2. Imaging

The MRI in the NESDA study took place at three different scanning sites. The T1-weighted scans were acquired on a 3 T Philips MR scanner (Philips, Best, The Netherlands). At baseline, two of the sites used a SENSE-8 channel head coil, while one site used a SENSE-6 channel head coil (TR: 9 ms; TE: 3.5 ms; matrix: 256 * 256; voxel size: 1 mm3; 170 slices). At wave 3, all sites used 8-channel phased array head coils and at wave 6 all sites made use of 32-channel phased array head coils. At the 9-year follow up, new scanners were used at the AMC and LUMC. The T1-weighted scans in the MOTAR study were acquired on a 3 T Philips MR scanner (Philips, Best, The Netherlands) with the same following acquisition parameters. The same protocol was followed as in NESDA to calculate the mean cortical thickness, surface area and volume per ROI.

Cortical segmentation was performed using FreeSurfer version 6.0 (Dale et al., 1999). The segmentation was visually inspected, using an ENIGMA quality assessment protocol (http://enigma.ini.usc.edu/protocols/imaging-protocols). Based on prior research (Schmaal et al., 2017; Toenders et al., 2020; Mehler et al., 2021; Soriano-Mas et al., 2011; van Velzen et al., 2016; Kotkowski et al., 2019; Simmons et al., 2018b; Costi et al., 2021; Binnewies et al., 2021), cortical thickness and surface area of subregions (anterior and posterior) of the insula, ACC and OFC, and volume of the nucleus accumbens were included as regions of interest. The anterior and posterior insula were anatomically defined by the Destrieux atlas (Destrieux et al., 2009), all other regions were based on the Desikan-Killiany atlas (Desikan et al., 2006). We calculated the mean cortical thickness, surface area and volume across both hemispheres.

#### 2.2.3. Immuno-metabolic dysregulation

IL-6 and high sensitivity CRP were assessed in fasting blood samples and kept frozen at −80 °C. At baseline, CRP plasma levels were assayed by an in-house high-sensitivity enzyme-linked immunosorbent assay (ELISA) based on purified protein and poly- clonal anti-CRP antibodies (Dako, Glostrup, Denmark). The lower detection limit of plasma CRP was 0.1 mg/l and intra-and inter-assay coefficients of variation were respectively 5 % and 10 %. At both follow-ups CRP was measured in duplicate by a high-sensitivity particle enhanced immunoturbidimetric assay (CRPHS, Roche Diagnostics, Indianapolis, IN, USA). The lower

detection limit was 0.15 mg/l and intra and inter-assay coefficients of variation were 5 % and 4 % (at wave 3) and 7 % and 9 % (wave 6) respectively. In addition, plasma IL-6 levels were also measured in duplicate by a high sensitivity ELISA (PeliKine Compact ELISA, Sanquin, Amsterdam, The Netherlands), the lower detection limit was 0.35 pg/ml and the intra- and inter-assay coefficients of variation 8 % and 12 %. At follow-up IL-6 was assessed in duplicate by a high sensitivity ELISA (Human IL-6 Quantikine HS kit, R&D Systems, Minneapolis, MN, USA) with a lower detection limit of 0.08 pg/ml and intra- and inter-assay variability of 7.8 % and 7.2 %.

Triglyceride and HDL-cholesterol levels were measured with standardised laboratory methods. The intra- and inter-assay coefficients of variation of triglycerides were 1.5 % and 1.8 % respectively, and 1.0 % and 1.3 % for HDL-cholesterol. Leptin levels were measured in ethylenediaminetetraacetic acid plasma using an ELISA (Human Leptin ELISA Kit; Linco Research, Inc., St. Charles, Missouri). The lower detection limit was 0.5 μg/l, and intra-assay and inter-assay variations were respectively 3 % to 8 % and 6 %. Glucose levels were determined using a Vitros 250 glucose assay (Johnson & Johnson, Rochester, USA). Waist circumference, a measure of abdominal obesity, was measured between the lowest front rib and highest point of the pelvis (in centimetres). Systolic blood pressure was measured on the right arm using the Omron M4-I, HEM 752A. Triglyceride levels, HDL-cholesterol level, glucose levels and systolic blood pressure were adjusted for medication use (Lamers et al., 2020; Licht et al., 2010; Grundy et al., 2005). When a participant used fibrates (ATC code: C10AB) 0.10 mmol/l was subtracted of HDL-cholesterol and 0.67 mmol/l of triglycerides. For nicotinic acid use (C10AD, C10BA01) 0.15 mmol/l was subtracted of HDL-cholesterol and 0.19 mmol/l of triglycerides. In participants that had glucose levels above 7.0 mmol/l and used anti-diabetic medication, 7.0 mmol/l was added to glucose. For participants using antihypertensive medication 10 mmHg was added to systolic blood pressure.

In the MOTAR study blood serum samples were taken at baseline, and analysed for inflammation markers. Serum levels of IL-6 were measured using a multiplex sandwich immunoassay (V-PLEX Human Proinflammatory Panel I, Meso Scale Diagnostics, Rockville, MD, USA) with a lower detection limit of 0.05–0.09 pg/ml. The average intra-assay and inter-assay coefficients of variation were 5.4 % and 4.0 %, respectively. Serum levels of CRP were measured in duplicate by an in-house high-sensitivity enzyme linked immunosorbent assay (ELISA, CRPHS, Roche Diagnostics, Indianapolis, IN, USA) based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark) with a lower detection limit of 0.15 mg/l and a functional sensitivity of 0.3 mg/l. The intra- and inter-assay coefficients of variation were 1 % and 5.25 % respectively.

Based on earlier research (Lamers et al., 2020), the inflammatory index was defined as the mean of standardised, log transformed CRP and IL-6 measures. As having high levels on multiple inflammatory markers is indicative of systemic inflammation, this inflammatory index, rather than individual inflammatory marker levels, was used. The metabolic syndrome index was defined as the mean of standardised triglycerides, reversed HDL scores, systolic blood pressure, fasting glucose and waist circumference. A combined, immuno-metabolic index was created by summing the inflammatory index and metabolic syndrome index.

### 2.3. Statistical analyses

As a descriptive analysis, the overall Pearson's correlation coefficients between symptom profiles and (immuno-metabolic) biological indices, over studies and waves, were calculated using the meta-analytic approach described below. Then, the association between the symptom profiles of depression and biological indexes of depression was also examined using the meta-analytic approach.

Generalized estimating equations (GEE) were used to examine associations between ROIs and clinical and biological characteristics of depression in NESDA. Analyses were done in R using the 'geepack'

package (Halekoh et al., 2006; Rstudio, 2015). An exchangeable correlation structure was used for all analyses. Age, sex, wave and scan site were included as covariates. The interaction between scan site and wave was also included to account for scanner and coil updates between waves. In addition, intracranial volume (ICV) was added as a covariate for cortical surface area and subcortical volume, but not for cortical thickness as it is not associated with head size (Barnes et al., 2010).

On MOTAR data general linear models were used, as only one timepoint was included, to examine associations between brain structure and depression and immuno-metabolic dysregulation. Age, sex, and ICV (for subcortical volume and cortical surface area) were used as covariates.

The estimate (B) and standard error of the GEE and linear model were used for the meta-analysis. In a sensitivity analysis BMI, use of anti-inflammatory medication (yes/no, ATC codes: M01A, M01B, A07EB, A07EC) and statins (yes/no, ATC codes: C10AA, C10B) were also added as covariates.

A random effect meta-analysis was performed using the estimates and standard errors from the NESDA and MOTAR studies using the 'rmeta' package (Lumley, 2018). False discovery rate (FDR) correction was applied (3 symptom profiles and 3 biological indices * 13 ROIs = 78 tests). Tau^2 was calculated as an estimate of the between study variance. When tau^2 approaches 0 the heterogeneity between the studies is low.

## 3. Results

Sample characteristics for the NESDA (per measurement wave) and MOTAR studies are displayed in Table 1. Correlations between the symptom profiles and biological indices, the inflammatory and metabolic indices, can be found in Supplemental Fig. S2.

The meta-analytic results showed that metabolic syndrome and immuno-metabolic indices were positively associated with the atypical, energy-related symptom profile (B = 0.06 (0.01), $p < 0.01$ and B = 0.08 (0.04), $p = 0.02$), while the inflammatory index was not significantly associated (B = 0.03 (0.02), $p = 0.28$). The melancholic symptom profile and overall depression severity were not associated with any of the biological indices.

In Table 2 the results of the meta-analysis on the association between clinical and biological characteristics of depression and structural brain changes are shown. Supplemental Tables S1 and S2 show the associations for the NESDA and MOTAR study separately and, tau^2 can be found in Supplemental Table S3.

Depression severity showed a negative association with rostral ACC (rACC) thickness (B = -0.55 (0.17), $p_{FDR} = 0.03$) (Fig. 1). This did not seem to be differential for atypical or melancholic symptoms as they both did not show a significant association with rACC thickness (B = −0.41 and −0.38 respectively). The melancholic symptom profile showed a negative association with caudal ACC (cACC) thickness (B = −0.42 (0.12), $p_{FDR} = 0.03$). In Supplemental Fig. S3 forest plots can be found that show these two associations in both studies. The immuno-metabolic indices did not show an association with structural brain measures. The results did not change when additional covariates were added.

## 4. Discussion

This study examined the unique and common association of clinical and biological characteristics of depression with structural brain differences in two studies including participants with MDD, anxiety disorders, and healthy controls. Higher overall depression severity was associated with thinner rostral ACC in a linear manner, as has been shown in previous studies (Schmaal et al., 2017; Binnewies et al., 2021). This was not driven by specific symptom profiles, i.e., atypical, energy-related symptoms or melancholic symptoms. The melancholic symptom profile was however associated with thinner caudal ACC, while overall depression severity was not. No association was found between the atypical, energy-related symptom profile and structural brain measures, nor between indices of metabolic and inflammatory dysregulation and structural brain measures.

Earlier studies showed that the thinner rostral ACC in depression was not dependent on lifestyle or BMI, and thinning has especially been observed in first-episode patients (Schmaal et al., 2017; Binnewies et al., 2021). The ACC is involved in emotional and cognitive processing. It can be divided into the rostral and caudal (also called dorsal) ACC, based on cytoarchitectural, lesion and connectivity studies (Vogt et al., 1992; Vogt et al., 1995; Devinsky et al., 1995; Drevets and Raichle, 1998). Meta-analyses have shown that the caudal ACC is mainly involved in cognitive processes, while the rostral ACC is an important link between regions involved in emotion processing and cognitive control (Drevets and Raichle, 1998; Bush et al., 1998; Bush et al., 1999; Bush et al., 2000). The association between thinner rostral ACC and higher severity of depression was not driven by one of the symptom profiles studied, which could mean that it is mostly driven by affect symptoms. This would be in line with the role of the rostral ACC in emotion regulation (Bush et al., 2000). It could also be driven by all symptoms combined, given that the overall depression severity score showed the strongest association with rostral ACC thickness suggesting no specific effects for symptom dimensions.

Since the regions that have previously been associated with depression also have been found to play a role in inflammatory and metabolic disturbances, we hypothesised to find associations between the inflammatory and metabolic biological measures and structural brain measures, especially because the atypical, energy-related symptom profile showed associations with immuno-metabolic dysregulation. Prior research indicated that connectivity between the ACC and ventral

**Table 1**
Characteristics of NESDA and MOTAR samples.

| | | NESDA | | | MOTAR |
| --- | --- | --- | --- | --- | --- |
| | | Baseline | 2-year FU | 9-year FU | Baseline |
| **Sociodemographics** | | | | | |
| n | | 255 | 163 | 123 | 123 |
| Age | | 38.0 (10.1) | 40.5 (10.2) | 50.0 (27.0) | 39.3 (13.5) |
| Sex (n Female (%)) | | 175 (68 %) | 108 (66 %) | 79 (64 %) | 64 (52 %) |
| MDD cases (with or without comorbid anxiety) (n (%)) | | 135 (53 %) | 48 (29 %) | 43 (34 %) | 40 (33 %) |
| Anxiety disorder cases (n (%)) | | 60 (23 %) | 23 (14 %) | 10 (8 %) | 15 (12 %) |
| Healthy controls (n (%)) | | 61 (24 %) | 95 (58 %) | 72 (58 %) | 73 (59 %) |
| Antidepressant use (n (%)) | | 69 (27 %) | 35 (22 %) | 23 (19 %) | 0 (0 %) |
| BMI | | 24.8 (4.5) | 25.0 (4.4) | 25.9 (4.9) | 24.8 (4.2) |
| **Clinical measures** | | | | | |
| Depression severity | | 23.1 (14.5) | 16.1 (11.6) | 16.3 (12.8) | 21.2 (21.3) |
| Atypical, energy-related symptom profile | | 3.7 (3.0) | 2.6 (2.5) | 2.6 (2.6) | 3.2 (3.2) |
| Melancholic symptom profile | | 5.1 (4.1) | 3.4 (3.2) | 3.1 (3.4) | 4.6 (5.3) |
| **Biological measures** | | | | | |
| Inflammatory index | | 0.45 (0.1) | 0.47 (0.2) | 0.43 (0.1) | 0.39 (0.1) |
| Metabolic syndrome index | | 0.15 (0.1) | 0.21 (0.1) | 0.18 (0.1) | 0.12 (0.1) |
| Immuno-metabolic index | | 0.60 (0.2) | 0.68 (0.2) | 0.61 (0.2) | 0.48 (0.2) |

Mean (SD) are displayed unless otherwise specified. BMI: Body mass index, FU: follow-up, MDD: Major Depressive disorder, n: sample size, SD: standard deviation. Depression severity is measured by the Inventory of Depressive Symptomatology.

**Table 2**
Results of the meta-analysis on the association between structural brain measures and depressive symptoms and biological measures of inflammatory and metabolic dysregulation. Displayed are the estimates and p-values per brain region.

| | | Surface area | | | | | | | | | | | | Thickness | | | | | | | | | | | | Volume | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | lOFC | | mOFC | | rACC | | cACC | | aIns | | pIns | | lOFC | | mOFC | | rACC | | cACC | | aIns | | pIns | | Nac | |
| | | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR | B (se) | P_FDR |
| Clinical profiles | Depression severity | −0.11 (0.29) | 0.82 | −0.14 (0.13) | 0.71 | −0.06 (0.13) | 0.82 | −0.21 (0.11) | 0.34 | −0.27 (0.15) | 0.40 | −0.26 (0.28) | 0.75 | −0.20 (0.13) | 0.50 | −0.39 (0.16) | 0.20 | −0.55 (0.17) | 0.03* | −0.37 (0.14) | 0.14 | −0.16 (0.33) | 0.82 | −0.05 (0.15) | 0.82 | −0.32 (0.21) | 0.50 |
| | Atypical symptom profile | 0.02 (0.12) | 0.91 | −0.10 (0.13) | 0.81 | 0.05 (0.12) | 0.82 | −0.20 (0.11) | 0.39 | −0.17 (0.14) | 0.66 | 0.03 (0.20) | 0.92 | −0.10 (0.12) | 0.77 | −0.30 (0.14) | 0.29 | −0.41 (0.14) | 0.11 | −0.21 (0.13) | 0.46 | −0.11 (0.19) | 0.82 | −0.07 (0.15) | 0.82 | −0.26 (0.11) | 0.21 |
| | Melancholic symptom profile | −0.19 (0.38) | 0.82 | −0.20 (0.12) | 0.46 | −0.10 (0.11) | 0.75 | −0.16 (0.10) | 0.47 | −0.19 (0.15) | 0.66 | −0.19 (0.29) | 0.82 | −0.20 (0.13) | 0.50 | −0.29 (0.14) | 0.30 | −0.38 (0.15) | 0.17 | −0.42 (0.12) | 0.03* | −0.22 (0.38) | 0.82 | −0.17 (0.14) | 0.82 | −0.36 (0.25) | 0.57 |
| Biological indices | Inflammatory index | −0.85 (0.92) | 0.75 | −0.77 (0.84) | 0.75 | 0.09 (0.18) | 0.82 | 0.09 (0.15) | 0.82 | 0.23 (0.66) | 0.82 | 0.28 (0.88) | 0.82 | 0.66 (1.39) | 0.82 | 0.05 (0.64) | 0.97 | 0.05 (0.81) | 0.97 | −0.08 (0.21) | 0.82 | −0.36 (0.62) | 0.82 | 0.34 (0.25) | 0.61 | −0.07 (0.21) | 0.82 |
| | Metabolic syndrome index | −0.51 (0.30) | 0.46 | −0.34 (0.52) | 0.82 | 0.27 (0.29) | 0.75 | 0.32 (0.27) | 0.66 | −0.25 (0.62) | 0.82 | −0.46 (0.89) | 0.82 | 0.31 (0.89) | 0.82 | −0.90 (0.43) | 0.30 | 0.59 (1.31) | 0.82 | −0.44 (0.35) | 0.66 | −0.44 (0.36) | 0.66 | 0.28 (0.52) | 0.82 | −0.41 (0.36) | 0.68 |
| | Immuno-metabolic index | −0.51 (0.48) | 0.71 | −0.52 (0.56) | 0.75 | 0.09 (0.13) | 0.82 | 0.09 (0.13) | 0.82 | −0.06 (0.33) | 0.91 | 0.10 (0.67) | 0.92 | 0.26 (0.77) | 0.82 | −0.14 (0.42) | 0.82 | 0.01 (0.16) | 0.98 | −0.14 (0.16) | 0.75 | −0.08 (0.18) | 0.82 | 0.21 (0.23) | 0.75 | −0.14 (0.16) | 0.75 |

lOFC: lateral orbitofrontal cortex, mOFC: medial orbitofrontal cortex, rACC: rostral anterior cingulate cortex, cACC: caudal anterior cingulate cortex, aIns: anterior insula, pIns: posterior insula, Nac: nucleus accumbens. * = pFDR < 0.05. Models adjusted for age, sex, scan location, and ICV (for surface area and volume only).
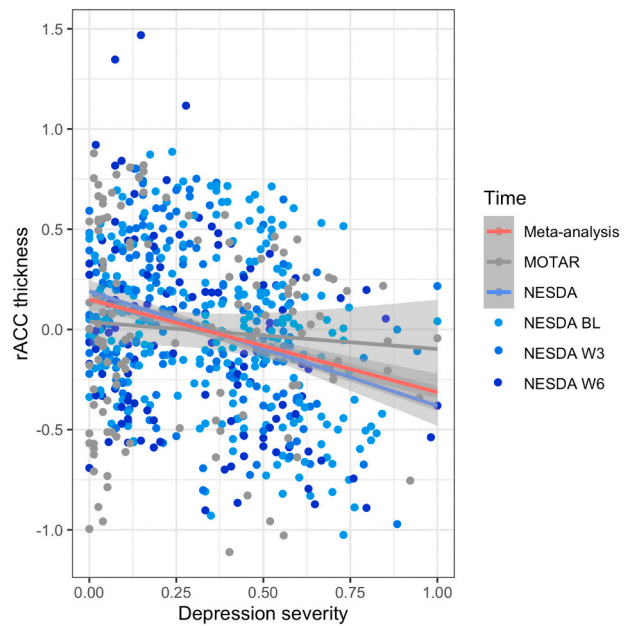


**Fig. 1.** Association between depression severity and rACC thickness in NESDA and MOTAR.

striatum mediated the association between insulin resistance and depressive symptoms (Ryan et al., 2012). In addition, the association between subgenual ACC (which is part of the rostral ACC in the Desikan atlas) connectivity to prefrontal and striatal regions with decreased mood was modulated by IL-6 after typhoid injection (Harrison et al., 2009). Therefore, the rostral ACC is thought to play a role in the association between mood and immuno-metabolic dysregulation. However, no associations were found with immuno-metabolic dysregulation in the current study, even though there are direct feedback loops from these biological pathways to the ACC (Critchley and Harrison, 2013). There are several potential explanations for this negative finding. One is that the association between the biological measures might be difficult to study due to temporal complexities. While inflammatory and metabolic markers are known to fluctuate (Sothern et al., 1995), brain structure does not show large temporal differences (Rubinov et al., 2009; Bethlehem et al., 2021). Functional brain measures are temporally more dynamic, which might explain why associations with endocrine and inflammatory markers have previously been found mostly for fMRI measures (Simmons et al., 2016a). Furthermore, while no association was present between immuno-metabolic dysregulation and structural brain measures when measured cross-sectionally, they might still affect each other over time. Immuno-metabolic dysregulation may induce cortical thinning, that might last long after the immuno-metabolic dysregulation itself has ceased. Finally, it could be that the inflammatory and metabolic syndrome markers and brain structures studied in this meta-analysis are biological characteristics that are independently associated with depression but do not affect each other.

The melancholic symptom profile showed an association with thickness of the caudal ACC, a region that plays an important role in cognitive processes such as attention, salience, interference and response competition (Davis et al., 2005). Depression in general, and melancholic depression specifically, has been associated with cognitive deficits, including attentional and inhibitory deficits, in previous studies (Withall et al., 2010; Roca et al., 2015). However, some studies examining cognition in melancholic versus non-melancholic depression defined melancholic depression categorically using the DSM specifier or CORE index (Roca et al., 2015), in contrast to the dimensional melancholic symptoms score as used in the current study, which does not require an arbitrary cut-off but instead studies the trait of interest across

the whole spectrum. The negative association between caudal ACC thickness and melancholic depression could underlie the cognitive deficits found in melancholic depression. In a meta-analysis it was shown that cognitive training can reduce depressive symptoms, however the results were heterogeneous (Motter et al., 2016). Future studies could therefore examine if cognitive training is more effective in a subset of patients with melancholic depression, and thinner caudal ACC.

Based on previous research we expected insula and OFC structural measures to be specifically associated with the atypical symptom profile, especially because in young people it was shown that a subtype expressing atypical, energy-related symptoms showed decreased surface area in these regions (Toenders et al., 2020). In addition, functional MRI studies implicated a role of these regions in this subtype (Simmons et al., 2018b; Simmons et al., 2016b). The lack of an association between insula and OFC structural brain measures and severity of atypical symptoms in the current study may be explained by methodological differences with those previous studies, namely that in the current study the atypical, energy-related symptom were studied dimensionally instead of categorically. Another possible explanation is that in the current study the associations between symptom profiles and brain structure were studied in a sample of individuals with and without depressive and/or anxiety disorders, which enables studying the trait across the whole dimension, but could also add more noise.

Notably, while an association was found between atypical, energy-related symptoms and metabolic and immuno-metabolic indices, no association was found with the inflammatory index. However, the latter might be because of limited power. In a larger sample from the NESDA study (2875 participants, 7078 observations), where those without neuroimaging data were also included, an association in the same direction of a similar strength was found, and in this larger sample it did reach statistical significance (Lamers et al., 2020). The effect size of the association between clinical profiles and inflammatory measures was rather small, which limits the ability to detect this effect with modest sample sizes. In addition, the direction of the association is in line with previous research showing that atypical, energy-related symptoms of depression are associated with immuno-metabolic dysregulations (Lamers et al., 2013; Simmons et al., 2018b), even though not reaching significance. As mentioned, the effect size of biological characteristics associated with depression is small, which is consistent in line with other meta-analysis for structural brain alterations and psychiatric disorders, as shown in several ENIGMA meta-analyses (Schmaal et al., 2017; Boedhoe et al., 2017; van Erp et al., 2018). However, small effect sizes can still contribute to the understanding of the unique and shared brain abnormalities associated with biological and clinical characteristics of depression.

The findings of the current study add to the knowledge about the underlying (neuro)biological alterations in more homogeneous clinical profiles of depression. These profiles may have unique biological mechanisms, although the atypical, energy-related symptom profile did not show any unique associations. Therefore, the structural brain alterations specific to symptom profiles of depression might not contribute towards a model of stratified treatment in depression. However, the association between the thinner caudal ACC and melancholic depression requires future research, especially its link with cognition and perhaps its role in stratifying into treatment options.

A number of methodological limitations regarding the present study need to be considered. In the NESDA study, multiple scanners were used, and they were subject to a software update between the waves, a potential source of variation we tried to overcome by adding scan site as covariate in analyses. In addition, different kits for the inflammatory markers were used across studies. Lastly, while the depressive symptoms and immuno-metabolic markers were assessed on the same day, the MRI scan took place on a different day. The main strength of this study was the use of two datasets, with two different study designs, which boosts the reliability of the current findings. However, despite the use of two datasets, the power to detect small effect sizes was still limited.

To conclude, using a meta-analytic approach, this study found that overall depression severity was associated with a thinner rostral ACC, and severity of melancholic symptoms of depression was specifically associated with a thinner caudal ACC. The atypical, energy-related symptom profile was not associated with any brain structure measures. This symptom profile was associated with immuno-metabolic dysregulation, however, the inflammatory and metabolic dysregulation, unlike clinical characteristics of depression, did not show a relationship with depression-related structural brain measures. This suggests that structural brain changes and peripheral inflammatory and metabolic dysregulation might be distinct biological processes underlying depression.

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## CRediT authorship contribution statement

Yara Toenders: conceptualization, statistical analysis, writing – original draft. Lianne Schmaal, Laura Nawijn, Yuri Milaneschi, Femke Lamers: conceptualization, writing – review & editing. Julia Binnewies, Laura K.M. Han, Marie-José van Tol, Nic J.A. van der Wee, Dick J. Veltman: writing – review & editing. Brenda W.J.H. Penninx: conceptualization, writing – review & editing, funding acquisition.

## Conflict of interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.06.056.

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