Research Paper

Lifetime major depression and grey-matter volume

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Background: There is evidence of structural brain alterations in major depressive disorder (MDD), but little is known about how these alterations might be affected by age at onset or genetic vulnerability. This study examines whether lifetime episodes of MDD are associated with specific alterations in grey-matter volume, and whether those alterations vary according to sex or serotonin transporter-linked promoter region (5-HTTLPR) genotype (LL, SL or SS). **Methods:** We used structural MRI to acquire anatomic scans from 610 community-dwelling participants. We derived quantitative regional estimates of grey-matter volume in 16 subregions using FreeSurfer software. We diagnosed MDD according to DSM-IV criteria. We adjusted analyses for age, sex, total brain volume, education level, head injury and comorbidities. **Results:** Lifetime MDD was associated with a smaller insula, thalamus, ventral diencephalon, pallidum and nucleus accumbens and with a larger pericalcarine region in both men and women. These associations remained after adjustment for false discovery rate. Lifetime MDD was also associated with a smaller caudate nucleus and amygdala in men and with a larger rostral anterior cingulate cortex in women. Late-onset first episodes of MDD (after age 50 years) were associated with a larger rostral anterior cingulate cortex and lingual and pericalcarine regions; early-onset MDD was associated with a smaller ventral diencephalon and nucleus accumbens. Some associations differed according to 5-HTTLPR genotype: the thalamus was smaller in participants with MDD and the LL genotype; pericalcarine and lingual volumes were higher in those with the SL genotype. **Limitations:** This study was limited by its cross-sectional design. **Conclusion:** Major depressive disorder was associated with persistent volume reductions in the deep nuclei and insula and with enlargements in visual cortex subregions; alterations varied according to age of onset and genotype.

Introduction

The identification of sociodemographic, environmental and physiopathological factors associated with onset, recovery and relapse in major depressive disorder (MDD) has become a major public health priority, given the association of MDD with high rates of mortality and comorbidity. While considerable research has been done into the clinical characterization of MDD and its associated risk factors, the neuroanatomical substrates involved in the disorder are still unclear; meta-analyses of structural and functional imaging studies report inconsistent findings.[1] These inconsistencies are likely due to heterogeneity in study design (case–control v. cohort), setting (general population, inpatient or outpatient), population (age, sex), depression characteristics (diagnosis or symptoms, comorbidity, age of onset, recurrent episodes, antidepressant treatment)[1] and methodological issues (not controlling for total brain volume, potential confounding or modifying factors, and different neuroimaging techniques).

The most consistent findings suggest that MDD is associated with dysregulation in neural networks that are implicated in affective and cognitive processing, or in autonomic system activity, resulting in a heterogeneous array of emotive, cognitive and behavioural abnormalities.[2] Grey-matter volume changes constitute network nodes in MDD, of which the hippocampus, amygdala and prefrontal cortex have been extensively examined.[1,3–6] Conversely, structural alterations in deep nuclei (notably the pallidum, thalamus and hypothalamus), as well as in the insula and occipital regions, have rarely been studied despite accumulating evidence for their role in emotion and the neuropathology of stress-related affective disorder.[7–10]

The nature and course of volumetric changes may also vary across the lifespan.[11] Although grey-matter abnormalities in frontal–subcortical and limbic networks are thought to play a key role in the pathophysiology of depression, recent meta-analyses in late-life depression have shown that the most consistent evidence for brain-volume reductions is for the hippocampus, and not for other brain areas.[1,5,12] These meta-analyses made no distinction between current and past (remitted) depression and rarely considered age of onset. Most studies have been limited to clinical cohorts, which may not be representative of the case heterogeneity in the general population. In addition, studies have generally been limited in the brain regions they examine and in sample size, so they lack the power to

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explore modifying factors. More particularly, the influence of sex has rarely been evaluated, despite evidence for sexually dimorphic structural and functional brain differences across the lifespan, and the potential implications of those differences in sex-biased psychiatric conditions.[13] This may be especially important for MDD, because prevalence, age of onset, symptomatology and etiology differ between the sexes, and steroid hormones influence brain development and onset of MDD throughout life.[14] Genetic risk factors may also influence brain volumes and depression,[15,16] but are seldom considered. Serotonergic genes — notably genetic variants in the serotonin transporter-linked promoter region (5-HTTLPR) — have been reported to influence the structure and function of certain brain regions in depressed patients.[17] Whether grey-matter volume alterations are influenced by age-related characteristics (physical and psychiatric comorbidities) also remains to be addressed.

To address the limitations of previous studies, we investigated the association between lifetime MDD and various fronto–subcortical and limbic subregions in a large, community-dwelling, elderly population. We tested the hypothesis that regional brain structure abnormalities would be more extensive in participants with a lifetime MDD diagnosis and may persist after recovery. We further hypothesized that these abnormalities would differ according to sex and genetic vulnerability to 5-HTTLPR. We also considered age of onset and the effect of physical and psychiatric comorbidities. Because prospective lifetime birth cohort data were unavailable, we conducted the study retrospectively in elderly people, for whom both lifetime MDD episodes and genotype had been recorded.

Methods

Participants

We derived data from a longitudinal study of neuropsychiatric disorders in community-dwelling French elderly adults, called "Enquête de Santé Psychologique — Risques, Incidence et Traitemement" (ESPRIT).[18] Eligible participants who were at least 65 years of age and not institutionalized were recruited by random selection from the electoral rolls between 1999 and 2001. Ethics approval for the study was provided by the national ethics committee, and written informed consent was obtained from all participants. Of the 1863 participants initially recruited to the study, only those aged 80 years or younger were invited for an MRI; 760 participants were randomly selected to take part in the imaging study, of whom 668 had complete volumetric data for analysis. Participants with dementia (n = 14), those who were left-handed (n = 16) or were missing data about lifetime MDD or other main covariates (n = 28) were excluded, leaving 610 participants. Compared with those who were excluded, included participants were younger, more frequently men, more likely to live alone and less likely to have cognitive impairment ($p < 0.001$ for all characteristics). They were less likely to have never smoked and to have cardiovascular ischemic pathologies ($p = 0.02$ for both). They did not differ with respect to other characteristics, including the prevalence of lifetime MDD ($p = 0.78$).

MRI protocol and image analysis

We acquired all neuroimaging scans using the same scanner at the examination centre (Gui de Chauliac Neurology Hospital, Montpellier, France). We used a 1.5 T GE Signa Imaging system to acquire a contiguous T_1-weighted sequence for volumetric estimates (axial inversion recovery prepared, spoiled gradient recalled) that was aligned on the anterior–posterior commisure (repetition time 12 ms, echo time 2.8 ms, inversion time 600 ms, matrix size 256 × 256, pixel spacing 0.9375 × 0.9375 mm, number of excitations = 1, slice thickness 1.0 mm). We performed regional reconstruction and segmentation using the FreeSurfer (5.3) image analysis suite (http://surfer.nmr.mgh.harvard.edu/) as described previously.[19] We inspected the FreeSurfer outputs of each scan for errors or misclassifications (from 2D and 3D perspectives), and we excluded 28 scans with clear errors. We defined 16 regions of interest (ROIs) using the Desikan atlas.[20] The regions of primary interest were the hippocampus, amygdala, orbitofrontal cortex and anterior cingulate cortex (ACC), as well as several subcortical structures (thalamus, caudate nucleus, putamen, pallidum and accumbens nuclei) that might show neuroimaging abnormalities in depressed patients.[1,3,5,6,21,22] We also examined ROIs that had rarely been evaluated despite accumulating evidence for abnormalities in MDD and their potential role in emotional processing and symptom characteristics, including the insula,[7,8,23] ventral diencephalon (a region primarily comprising the hypothalamus in FreeSurfer)[9,24,25] and occipital visual cortex.[10,23,26,27] We calculated the total brain volume (grey plus white matter) for each participant using the segment m-file in SPM5 (Wellcome Department of Cognitive Neurology), which showed greater accuracy[28] and consistency[29] and less systematic bias evaluation[30] than FreeSurfer for this measure.

Diagnosis of lifetime psychiatric disorder

Current and previous MDD and anxiety disorders (phobias, generalized anxiety disorder, panic disorder, obsessive compulsive disorder and posttraumatic stress disorder) were diagnosed by psychologists and psychiatric nurses according to DSM-IV criteria and using the Mini-International Neuropsychiatric Interview (MINI, French version 5.00),[31] a standardized psychiatric examination that has been validated in the general population. Positive cases were reviewed by a panel of independent psychiatrists.[32]

Sociodemographic and clinical variables

We used a standardized interview to obtain information on sociodemographic characteristics, physical health and medical history. We used detailed medical questionnaires (with additional information from general practitioners) to obtain participants' history of cardiovascular ischemic pathologies (angina pectoris, myocardial infarction, stroke, cardiovascular surgery and arteritis). We recorded all drugs used by participants in the preceding month (including antidepressants) from medical prescriptions and drug packaging. We evaluated global cognitive function using the Mini-Mental State Examination;[33] a

score below 26 indicated cognitive impairment. Dementia was diagnosed by a neurologist as part of a standardized examination and validated by a panel of independent neurologists.[34]

5-HTTLPR genotyping

We collected blood samples after the baseline clinical interview, enabling DNA extraction and 5-HTTLPR genotyping as described previously.[35] We performed replicate independent genotyping using buccal DNA extracts.[32]

Statistical analysis

Brain-volume measurements were normally distributed. We evaluated associations between brain regions and lifetime MDD using analysis of covariance adjusted for age, sex and total brain volume (model M0). Where we observed significant associations, we used exploratory analyses to assess the specificity of these findings. We tested the sex × diagnosis interaction by adding a lifetime MDD × sex term to the model. Where we observed an interaction effect ($p < 0.10$), we stratified analyses by sex. We made further adjustments for other covariates that have been reported to modify the association between MDD and brain volume: education level, head injury, cardiovascular ischemic pathologies and antidepressant use (model M1), as well as lifetime anxiety disorder (model M2). For significant bivariate associations, we evaluated the effect of 5-HTTLPR by stratifying it into 3 genotypes (LL, SL and SS) because of a lack of consensus about the choice of a genetic model and frequent reports of heterosis for 5-HTTLPR.[36,37] To account for the fact that we examined multiple brain regions, we adjusted significance levels using the false discovery rate (FDR) method.[38] All tests were 2-sided, and we used SAS (version 9.4, SAS Institute, Inc.) for the statistical analyses.

Results

Participant characteristics

The baseline characteristics of the 610 participants are summarized in Table 1. The median age of participants was 70.7 years. Of the total population, 47.5% were male, and

Table 1: Participant characteristics (*n* = 610*)

	Group, median (IQR) or %			
Characteristic	Whole sample (*n* = 610)	Men (*n* = 290)	Women (*n* = 320)	*p* value†
Age, yr	70.7 (67.8–74.0)	71.0 (68.4–74.4)	70.1 (67.6–73.5)	0.03
Body mass index, kg/m^2 (*n* = 604)	24.8 (22.8–27.1)	25.8 (24.0–27.7)	24.0 (21.6–26.4)	< 0.001
Cortex volume, cm^3	358 (336–382)	376 (353–402)	344 (324–365)	< 0.001
Total brain volume, cm^3	882 (816–958)	925 (858–998)	850 (788–908)	< 0.001
Education ≤ 5 yr	25.7	23.1	28.1	0.16
Living alone (*n* = 609)	19.7	6.2	32.0	< 0.001
Smoking (*n* = 609)				
Never	53.4	26.9	77.5	< 0.001
Former	38.7	62.1	17.5	
Current	7.9	11.0	5.0	
Head injury	10.2	13.5	7.2	0.01
Lifetime number of major depressive episodes‡				
1	16.4	11.7	20.6	< 0.001
≥ 2	10.2	3.8	16.0	
Current major depressive disorder‡	2.1	0.7	3.4	0.02
Age at first episode (*n* = 609)				
None	73.6	84.5	63.6	< 0.001
< 50 yr	14.9	7.9	21.3	
≥ 50 yr	11.5	7.6	15.1	
Antidepressant use	5.1	2.4	7.5	0.004
Lifetime anxiety disorder‡ (*n* = 576)	26.4	16.4	35.6	< 0.001
Hypertension§	68.5	74.4	63.1	0.003
Cardiovascular ischemic pathologies¶	12.8	17.2	8.8	0.002
Diabetes** (*n* = 606)	8.8	12.9	5.0	< 0.001
Cognitive impairment††	13.4	10.7	15.9	0.06

IQR = interquartile range.
*Unless otherwise specified.
†Kruskal–Wallis tests for continuous variables and χ^2 tests for categorical variables.
‡Diagnosis of past and current major depression or anxiety disorder (phobias, generalized anxiety disorder, posttraumatic stress disorder, panic disorder or obsessive–compulsive disorder) according to DSM-IV criteria and using the Mini-International Neuropsychiatric Interview.[31]
§Hypertension ≥ 140/90 mm Hg or treated.
¶History of cardiovascular ischemic pathologies (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, arteritis).
**Fasting blood glucose ≥ 7.0 mmol/L or treatment.
††Mini-Mental State Examination score < 26.

26.6% had lifetime MDD, of whom 38.3% had recurrent episodes. Only 2.1% had current MDD, and 5.1% were taking an antidepressant. Men and women differed with respect to most characteristics: women were younger, more frequently living alone and more likely to report a lifetime psychiatric disorder, but they had fewer head injuries and fewer cardiovascular risk factors.

Subsegmental brain regions according to lifetime MDD

After adjustment for age, sex and total brain volume, lifetime MDD was associated with smaller grey-matter volumes in the insula, diencephalic structures and deep nuclei, and with larger volumes in the rostral ACC and 2 visual cortex subregions (Table 2). Alterations in the insula, thalamus, ventral diencephalon, nucleus accumbens, pallidum and pericalcarine region survived FDR correction. We observed similar alterations in the multivariate model that was further adjusted for education level, head injury, cardiovascular ischemic pathologies and antidepressant use (Appendix 1, Table S1, available at jpn.ca/180026-a1). These covariates accounted for a relatively small proportion of the variance in each volume: the standardized regression coefficients ranged between −0.338 and 0.257 (Appendix 1, Table S2).

In our sample, 576 participants were also evaluated for lifetime anxiety disorder, and we observed a similar pattern after controlling for anxiety disorder (data not shown). We conducted a sensitivity analysis excluding 41 participants who were currently depressed or taking antidepressants, and observed similar patterns, except for a slightly weaker association for the nucleus accumbens but a stronger association for the lingual region (Appendix 1, Table S3).

Subsegmental brain regions according to age at first major depressive episode

Of the participants with lifetime MDD, 56.5% reported first onset before 50 years of age. Compared with participants who did not have lifetime MDD, grey-matter volumes in the rostral ACC and lingual and pericalcarine regions were larger for those with late onset (after age 50 years). Smaller volumes in the ventral diencephalon and nucleus accumbens appeared to be more related to earlier onset (Appendix 1, Table S4).

Exploratory analyses according to sex

We observed an interacting effect of sex on the amygdala ($p = 0.09$), caudate nucleus ($p = 0.018$) and rostral ACC ($p = 0.06$). Lifetime MDD was associated with smaller grey-matter volumes in the amygdala and caudate nucleus in men (−4.3%, $p = 0.026$, and −7.2%, $p = 0.010$, respectively) but not in women (−0.8%, $p = 0.57$, and −0.2%, $p = 0.89$, respectively). Conversely, only women with lifetime MDD had larger volumes in the rostral ACC (+6.3%, $p = 0.003$ v. −1.2% in men, $p = 0.68$; Fig. 1).

Exploratory analyses as a function of 5-HTTLPR genotype

Of all participants, 30% were homozygous carriers of the L allele, and 23.2% were SS homozygotes. The frequency of the 5-HTTLPR genotypes did not deviate significantly from Hardy–Weinberg equilibrium ($p = 0.17$). Lifetime MDD was associated with a smaller thalamus in LL participants only (−4.9%, $p = 0.002$, v. −1.2%, $p = 0.27$ in SL participants and +0.3%, $p = 0.86$, in SS participants; Table 3). We found

Table 2: Association of subsegmental brain region volumes with lifetime major depressive disorder (n = 610)

Brain region	No lifetime MDD (n = 448), mean ± SD*	Lifetime MDD (n = 162), mean ± SD*	p value†	p_{FDR} value‡
Medial orbitofrontal cortex	8 962.94 ± 43.20	8 939.55 ± 73.61	0.79	0.79
Lateral orbitofrontal cortex	11 652.40 ± 46.37	11 718.13 ± 79.01	0.48	0.55
Rostral anterior cingulate cortex	3 347.51 ± 28.37	3 458.73 ± 48.34	0.05	0.09
Caudal anterior cingulate cortex	2 993.71 ± 25.67	3 065.27 ± 43.73	0.16	0.22
Hippocampus	7 061.54 ± 33.88	7 033.17 ± 57.73	0.68	0.72
Amygdala	2 634.05 ± 14.88	2 580.65 ± 25.34	0.07	0.12
Insula	11 954.83 ± 48.80	11 722.33 ± 83.14	0.017	0.045
Thalamus	11 806.32 ± 43.44	11 575.64 ± 74.01	0.008	0.038
Ventral diencephalon	6 794.71 ± 28.62	6 624.44 ± 48.76	0.003	0.038
Caudate nucleus	6 852.97 ± 52.58	6 669.85 ± 89.58	0.08	0.12
Putamen	9 453.97 ± 52.75	9 215.18 ± 89.87	0.024	0.06
Nucleus accumbens	997.39 ± 7.14	960.92 ± 12.17	0.011	0.038
Pallidum	2 983.73 ± 16.17	2 893.75 ± 27.55	0.005	0.038
Cuneus	4 765.02 ± 30.27	4 839.00 ± 51.58	0.22	0.27
Pericalcarine region	3 404.66 ± 28.46	3 547.02 ± 48.48	0.012	0.038
Lingual region	10 714.10 ± 67.51	10 984.78 ± 115.01	0.045	0.09

FDR = false discovery rate; MDD = major depressive disorder; SD = standard deviation.
*Values expressed in mm^3 and adjusted for age, sex and total brain volume.
†Raw p values not adjusted for multiple comparisons.
‡False-discovery rate–corrected.

significant differences in insula, ventral diencephalon, lingual and (most significantly) pericalcarine volume for SL participants with lifetime MDD (+8.2%, $p = 0.003$ v. +2.5%, $p = 0.41$ for LL participants and +2%, $p = 0.55$ for SS participants). We observed the same pattern after excluding participants who had current MDD or were taking antidepressants, although association with the ventral diencephalon was weakened ($p = 0.060$) and that with the lingual region was strengthened ($p = 0.005$ in M0 and $p = 0.001$ in M2; data not shown).

Discussion

Lifetime MDD was associated with many grey-matter volume differences. The most robust finding was smaller volumes in the deep nuclei and insula and larger volumes in the occipital visual cortex. These findings were independent of age, sex, education level, head injury, cardiovascular ischemic pathologies, antidepressant use and lifetime anxiety disorder. They were also seen in individuals who had been free of MDD for many years (median [interquartile range] = 15 [5–24] years). Lifetime MDD was also associated with smaller caudate nuclei and amygdalae in men, and a larger rostral ACC in women. Some associations varied by 5-HTTLPR genotype: most importantly, the thalamus was smaller in LL participants with lifetime MDD, whereas the pericalcarine and lingual regions were larger in SL participants only.

Previous reports of morphological brain changes relative to MDD have mostly been based on small case–control studies that focused on the hippocampus, amygdala, orbitofrontal cortex and ACC.[1,3,5,6] Inconsistent findings have been reported, probably attributable to heterogeneity in study design, size, setting, population and depression characteristics.[1] Meta-analyses reported smaller volumes in adults, but the effects were small and/or nonsignificant; effects depended on patients' age and whether they were experiencing a first episode, and were less likely in the community-dwelling population or in patients with remitted MDD compared with those who had current or recurrent episodes.[1,3,5,6,21,39,40] In the community-dwelling elderly population in our study, most participants reported only 1 previous depressive episode, and the median (interquartile range) age of first onset was 47 (35–57) years, which may explain the lack of significant associations. However, we did find a highly significant difference for the rostral ACC, which was larger in women with lifetime MDD. Voxel-based morphometry studies have reported larger cingulate gyri in geriatric patients with remitted depression,[41] and a larger ACC in medication-washout young adults with MDD.[42] In healthy adults, a negative association has been shown between grey-matter volume and stress-related brain activity in the perigenual ACC.[43]

Basal nuclei

In our study, lifetime MDD was associated with decreased grey-matter volumes in several basal nuclei. Smaller caudate nuclei have been reported in adult patients[3,40] and, in late-life depression, effect sizes increased with age and with a smaller percentage of women.[6] Consistent with these results, we found that lifetime MDD was associated with a smaller caudate nucleus in men, and the association was strengthened after adjusting for several confounders, including antidepressant use and the presence of an anxiety disorder (–8.6%, $p = 0.003$, in M2).

Some meta-analyses on the putamen have reported significant grey-matter volume reduction with lifetime MDD,[3,6] and others in early- but not late-onset[40] or current MDD.[5] Other studies have found that associations were limited to severe or persistent subtypes.[39] We found a marginal association between lifetime MDD and a smaller putamen ($p_{FDR} = 0.055$) and a greater grey-matter volume reduction in those with recurrent episodes (global p value = 0.042).

We also found an association between lifetime MDD and smaller volumes in the nucleus accumbens and pallidum. These regions have been examined rarely, and meta-analyses of studies including mainly adult patients with acute or lifetime MDD have failed to report significant associations.[5,21] In an analysis of a high-dimensional set of more than 11 000 traits, the pallidum volume was reported to be a main endophenotype associated with recurrent depression.[9] We also observed a greater grey-matter volume reduction in participants who reported multiple MDD episodes compared with those who reported 1 or no previous episodes (global $p = 0.013$).

Lifetime MDD was also associated with a smaller thalamus and ventral diencephalon — a region primarily comprising the hypothalamus. Small meta-analyses of the thalamus have reported moderate[6,21] or no significant[3,5,40] volume reduction, but none has included the hypothalamus, despite its crucial role in emotional behaviour and stress response as part of the

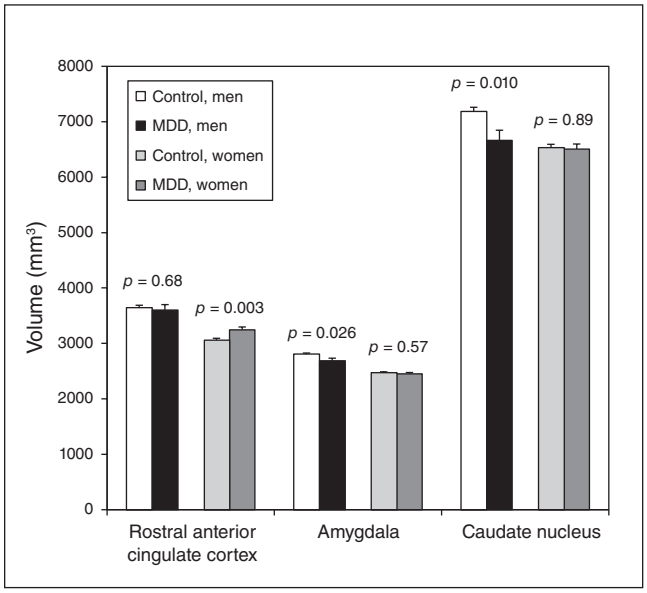

Fig. 1: Association between lifetime major depressive disorder (MDD) and volumes of rostral anterior cingulate cortex, amygdala and caudate nucleus in elderly men and women. Mean ± standard deviation (SD); values expressed in cubic millimetres and adjusted for age and total brain volume. Members of the control group did not have lifetime MDD; members of the MDD group had lifetime MDD.

Table 3: Association of subsegmental brain region volumes with lifetime MDD according to 5-HTTLPR genotype

	LL (n = 160)			SL (n = 250)			SS (n = 124)		
5-HTTLPR	No lifetime MDD (n = 112), mean ± SD*	Lifetime MDD (n = 48), mean ± SD*	p value†	No lifetime MDD (n = 184), mean ± SD*	Lifetime MDD (n = 66), mean ± SD*	p value†	No lifetime MDD (n = 93), mean ± SD*	Lifetime MDD (n = 31), mean ± SD*	p value†
Rostral anterior cingulate cortex	3394.88 ± 60.80	3537.88 ± 94.35	0.22	3345.48 ± 43.42	3400.87 ± 74.31	0.52	3346.62 ± 63.48	3498.30 ± 112.93	0.24
Insula	11847.14 ± 99.97	11963.30 ± 155.14	0.54	11996.04 ± 78.88	11628.15 ± 134.99	0.020	11833.83 ± 103.71	11520.94 ± 184.48	0.14
Thalamus	11966.39 ± 98.90	11376.42 ± 153.47	0.002	11843.10 ± 65.47	11700.58 ± 112.05	0.27	11685.44 ± 89.60	11717.36 ± 159.39	0.86
Ventral diencephalon	6726.12 ± 57.73	6524.76 ± 89.59	0.07	6869.44 ± 46.83	6659.23 ± 80.15	0.025	6765.45 ± 59.92	6731.95 ± 106.59	0.78
Putamen	9530.94 ± 131.13	9093.75 ± 203.49	0.08	9591.21 ± 75.65	9323.70 ± 129.47	0.08	9257.61 ± 108.03	8955.26 ± 192.18	0.17
Nucleus accumbens	996.60 ± 14.19	966.80 ± 22.02	0.27	1003.50 ± 11.03	984.31 ± 18.88	0.38	980.00 ± 16.80	921.09 ± 29.89	0.09
Pallidum	2957.48 ± 32.98	2852.01 ± 51.18	0.10	3033.56 ± 24.32	2952.72 ± 41.62	0.10	2994.12 ± 37.38	2869.91 ± 66.50	0.11
Pericalcarine region	3422.87 ± 54.66	3509.63 ± 84.83	0.41	3362.83 ± 47.23	3639.30 ± 80.83	0.003	3444.39 ± 56.29	3512.98 ± 100.13	0.55
Lingual region	10870.88 ± 135.40	10875.23 ± 210.12	0.99	10620.67 ± 110.25	11142.98 ± 188.68	0.018	10943.15 ± 133.37	10991.36 ± 237.26	0.86

MDD = major depressive disorder; SD = standard deviation.
*Values expressed in mm^3 and adjusted for age, sex and total brain volume.
†Raw p values.

hypothalamic–pituitary–adrenal axis. However, smaller ventral diencephalon volume has been reported to be the top-ranked neuroimaging endophenotype associated with recurrent MDD in adults[9] and to correlate with the number of depressive episodes in late-life depression.[25]

Insula

The insula plays a role in emotional, sensorimotor and interoceptive processing, but it has rarely been examined, despite some evidence for abnormalities in MDD and related phenotypes (sadness, irritability, sleep disorders).[7,8] A small case–control study reported reduced anterior insular cortex in current and remitted young adult patients compared with healthy controls.[44] A meta-analysis of voxel-based morphometry studies also showed left insula volume reductions in young adults with first-episode depression.[8] Our study is, to our knowledge, the first ROI study to show a significant smaller insula volume in an elderly general population with lifetime and remitted MDD.

Visual cortex

Another original finding concerns the association of MDD with larger grey-matter volume in the pericalcarine and lingual ROIs, a finding that was especially marked for late-onset MDD. The visual cortex plays a central role in the fear-conditioning paradigm in humans.[45] The pericalcarine region is the initial region of visual processing, and the lingual gyrus is associated with high-level visual processing and visual memory. The associations were highly significant after excluding participants who were currently depressed or treated for depression (p = 0.006 and 0.004, respectively, in M2). The link between the visual cortex and MDD has been described only in voxel-based morphometry studies; a meta-analysis reported a significant grey-matter volume increase in the right lingual gyrus in late-life depression.[10] A larger lingual gyrus volume was also found to predict early antidepressant response in adults and was linked to better performance on visual neuropsychological tests.[46] Greater sensory reactivity in the visual cortex could predict resilience against depressive relapse.[47] In healthy young adults, facilitation of processing of aversive stimuli was associated with the breaking of subcortical limbic connections (insula, putamen, amygdala, hippocampus), together with a compensatory emerging centrality of the visual cortex.[45] Whether the pericalcarine and lingual regions could participate in a neuronal compensatory process to facilitate the processing of aversive stimuli and fear or emotional learning in response to abnormal input from other structures, or whether they reflect resilience against relapse, remains to be examined.

5-HTTLPR genotype

Most previous studies have examined the effect of 5-HTTLPR on grey-matter volumes in either depressed or healthy participant groups, but rarely as a modifying factor between MDD risk and grey-matter alterations.[17] These studies were generally size-limited and focused on the hippocampus and amygdala,

rarely on the striatum or thalamus, where 5-HTT is highly expressed. The vast majority of the structural imaging genetic studies did not consider the SL genotype individually, despite a lack of consensus regarding the genetic model and frequent report of heterosis for 5-HTTLPR.[37] Heterogeneity in age is another potential source of concern:[48] in younger populations, the S allele is a risk factor for mental and physical distress, but the LL genotype appears to be a risk factor in elderly people, who are highly exposed to chronic disorders and severe stressors.[49]

We found no significant volumetric differences according to 5-HTTLPR within groups (with or without lifetime MDD; data not shown) but we did find significant between-group differences. In particular, the thalamus was smaller in LL homozygotes with lifetime MDD, but only SL heterozygotes with lifetime MDD had larger pericalcarine and lingual volumes compared with their non-MDD counterparts. The thalamus is rich in serotonergic neurons, and reduced 5-HTT availability has been described in the thalamus of depressed patients,[50] but data on the effect of 5-HTTLPR genotypes are lacking, and no studies have examined the pericalcarine or lingual regions, despite some indication for serotonergic occipital dysfunction in depression.[51] Our findings were unchanged after excluding patients who were currently depressed or treated for depression, suggesting that they were related to serotonergic vulnerability to the disorder.

In a subsample of the ESPRIT study, we reported that past MDD and stressful events were risk factors for current depression in LL homozygotes specifically, whereas SL heterozygotes were more resilient to these factors.[36] We also found that some adverse events during childhood (for example, sexual or physical abuse, or having a mother with mental illness) were associated with higher risk of late-life depression[35] but lower risk of cognitive decline, notably in visual memory,[52] suggesting a possible cognitive adaptation or resilience effect. Although these findings are speculative, they may suggest that the pericalcarine and lingual regions could participate in a persistent neuronal compensatory process in SL heterozygotes with a history of MDD.

Sex differences

We found some evidence for sexually dimorphic alterations: smaller caudate nuclei and amygdalae in men with lifetime MDD, and larger rostral ACC in women. Specific sex differences in the depression symptomatology of older adults have been described, with women showing more mood-related symptoms and appetite disturbance and men showing more motivation-related symptoms and psychomotor changes;[14] these differences may involve distinct biological correlates. However, only a few neuroimaging studies have investigated sex effects, many including predominantly women and, likely as a consequence, meta-analyses have seldom reported sex differences.[5,10]

In a healthy sample consisting mainly of older women, a larger ACC was associated with higher levels of anhedonia.[53] Valence-dependent sex differences in emotional reactivity have been reported, with divergent activation patterns, notably in the ACC and amygdala, suggesting a difference in recognizing, expressing or responding to emotions.[54] The rostral ACC and caudate nucleus are involved in impulse inhibition in young adults in a sex-specific manner, suggesting different processing strategies (e.g., inhibiting inappropriate response in males v. eliciting appropriate response in females).[55] In adults with attention-deficit/hyperactivity disorder, a smaller caudate nucleus was associated with impulsive/hyperactive symptoms in men, but not in women.[56] In addition, increased resting rostral ACC activity has been linked to adaptive cognitive aspects of rumination and could predict better antidepressant response and recovery.[57] Whether sex influences the nature of changes in some structures or is associated with specific symptoms, processing strategies or characteristics of depression (e.g., rumination, irritability, impulsivity) remains to be examined.

Context of the findings

We found that retrospectively determined incidence of lifetime MDD was associated with a smaller striatum, pallidum, thalamus, hypothalamus and insula, but with larger pericalcarine and lingual regions, even many years after recovery. These findings are partly consistent with a neurobiological model of current depression that posits dysfunction of the cortico–striatal–pallidal–thalamic network involved in emotion, cognition and motor control; reward and stress systems; and sensorimotor and interoceptive processing.[23,58,59] There is also some evidence for sex differences with respect to emotion production and regulation. We did not observe the reduced volumes in the hippocampus or frontal subregions previously reported in currently depressed adults. In a meta-analysis of functional MRI studies, Graham and colleagues[23] suggested that frontal areas could be state markers of MDD, but that striatal regions were trait vulnerability markers that might be less affected by treatment. They also stressed the potential key roles of regions that are not included in prevailing models of MDD, such as the insula and occipital subregions, the latter showing overactivity in MDD.[23] Sustained remission from MDD has been associated with normalized reactivity of certain prefrontal and limbic regions and greater sensory reactivity in visual cortices,[47] as well as hyperactivity and/or reduced deactivation in the rostral ACC.[57] Our data further suggest a key role of the visual corticostriatal loop in elderly patients with remitted MDD, with volume enlargement in visual occipital regions and reduction in subcortical structures.[60] They also suggest a link between certain sensory/visual functions (thalamus for sensory relay, and pericalcarine and lingual regions for visual processing and visual memory) and 5-HTTLPR vulnerability (to stress-induced relapse) or resilience to MDD. However, it remains to be determined whether these abnormalities represent biological long-term vulnerability (endophenotype as intermediate expression of genetic vulnerability factors).

Limitations

Limitations of our study include the cross-sectional design; we could not determine whether volume alterations preceded or followed MDD. Data related to lifetime MDD were

retrospective, which may have introduced recall bias and led to an underestimation of associations, even if we had excluded participants diagnosed with probable/possible dementia to minimize inaccuracies. The volume variations associated with lifetime MDD were 2% to 5% for deep nuclei and insula and 5% to 8% for visual cortex ROIs, suggesting a relatively small effect size. We did not examine state-like characteristics because of the low prevalence of current MDD in this relatively healthy community sample, and the lack of associations with some ROIs could have been related to normalization after sustained remission/treatment. Finally, we performed multiple analyses, potentially increasing the risk of type 1 errors, but most findings remained significant even after correction for multiple comparisons.

This study constitutes the largest structural MRI investigation targeting lifetime MDD, in terms of the number of participants and ROIs examined. We measured brain volumes using FreeSurfer automated segmentation, enabling accurate evaluation of volumetric changes of smaller deep brain structures. Lifetime MDD was assessed by trained staff using a standardized psychiatric evaluation, according to DSM-IV criteria. Further clinical validation of the cases minimized false positives. Extensive information available on participants' clinical status and medications helped minimize exposure misclassification. In contrast to previous studies, we controlled for numerous potential confounding factors, particularly education level, head injury, and physical and mental comorbidities.

Conclusion

We observed grey-matter volume differences between those who retrospectively reported lifetime MDD and those who did not. These structural correlates may constitute useful imaging phenotypes of depression: treatment responsiveness or resilience. It remains to be determined whether grey-matter volume increases are linked to a neuronal adaptive compensatory process in response to dysfunction in other structures, or whether they represents trait-like, developmental differences that underlie a neurobiological vulnerability associated with etiological pathways. Whether sex influences the nature of changes in some brain structures (which could help account for the sex differences observed in epidemiological and clinical studies of depression) or is associated with sex-specific traits or dimensions of depression also remains to be examined. Further work is required to understand the significance of these volumetric differences, including prospective multimodal and complementary imaging studies. This will help distinguish between causal roles and neural correlates of MDD, the result of shared underlying causes (for example, genetic predisposition) or bidirectional/mutual reinforcement, opening up the potential for effective therapeutic strategies.

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Contributors: M-L. Ancelin designed the study. M-L. Ancelin and K. Ritchie led the ESPRIT study and the collection of data. J. Maller and C. Meslin processed all neuroimaging data. I. Carrière performed all statistical analyses. M-L. Ancelin, S. Artero, J. Ryan and I. Chaudieu were involved in the interpretation of the data. M-L. Ancelin drafted the manuscript, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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