Lifetime major depression and grey-matter volume

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LIFETIME MAJOR DEPRESSION AND GREY MATTER VOLUME

SHORT-TITLE: Depression and grey matter volume

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ABSTRACT

Background: While there is evidence of structural brain alterations in major depressive disorder (MDD), little is known about how this may 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 volumes and whether this varies according to sex and *5-HTTLPR* genotype.

Methods: Structural magnetic resonance imaging was used to acquire anatomical scans from 610 community-dwelling participants. Quantitative regional estimates of 16 subregional volumes were derived using FreeSurfer software. MDD was diagnosed according to DSM-IV criteria. Analyses were adjusted for age, sex, total brain volume, education, head injury, and comorbidities.

Results: Lifetime MDD was associated with smaller insula, thalamus, ventral diencephalon, pallidum and nucleus accumbens, and larger pericalcarine volumes in men and women. These associations remained after adjusting for the false discovery rate. Lifetime MDD was also associated with smaller caudate nucleus and amygdala in men, and in women, with larger rostral anterior cingulate. Late onset (over age 50) first episodes were associated with larger rostral anterior

cingulate, lingual and pericalcarine volumes whereas early onset cases were associated with smaller ventral diencephalon and nucleus accumbens. Some associations differed by *5-HTTLPR* genotype; thalamus was smaller in the *LL* MDD compared to non-MDD participants, and pericalcarine and lingual were greater in the *SL* heterozygotes.

Limitations: The study is limited by its cross-sectional design.

Conclusions: MDD was associated with persistent volume reductions in deep nuclei and insula and enlargement in visual cortex subregions with variability according to both age of onset and genotype.

KEYWORDS: Depression; grey matter volume; deep nuclei; occipital visual cortex; sex; *5-HTTLPR*.

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 the disorder with high mortality and co-morbidity rates. While there has been considerable research into the clinical characterization of the disorder and its associated risk factors, the neuroanatomical substrates involved in MDD are still unclear, with meta-analyses of structural and functional imaging reporting inconsistent findings.[1] These are likely due to heterogeneity in study design (case-control *vs.* cohort), setting (general population, in- or out- patients), population (age, sex), and depression characteristics (such as diagnosis or symptoms, comorbidity, age of onset, recurrent episodes, antidepressant treatment),[1] as well as methodological issues (not controlling for total brain volumes, potential confounding or modifying factors, and a diversity of neuroimaging techniques).

The most consistent findings suggest that MDD is associated with dysregulation in neural networks implicated in affective and cognitive processing, as well as autonomic system activity resulting in a heterogeneous array of emotive, cognitive and behavioral abnormalities.[2] Grey matter volume (GMV) 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 insula and occipital regions have rarely been studied. This is despite accumulating evidence implicating their role in emotion and neuropathology of stress-related affective disorder.[7-10]

The nature and course of volumetric changes may also vary across the life span.[11] Although GM abnormalities within frontal-subcortical and limbic networks are hypothesized to play a key role in the pathophysiology of depression, recent meta-analyses in late-life depression showed that the most consistent evidence for brain volume reductions were found for the hippocampus but not for other brain areas.[1,5,12] In these meta-analyses, no distinction was made between current and past (remitted) depression and age of onset was rarely considered. Most studies have been limited to clinical cohorts, which may not be representative of case heterogeneity within the general population. Studies have generally been limited in brain regions and sample size, hence lacking the power to examine modifying factors. More particularly, sex has rarely been examined despite evidence for sexually-dimorphic brain structural and functional differences across the lifespan and their potential implication in sex-biased psychiatric conditions.[13] This may be particularly important

for MDD with prevalence, age of onset, symptomatology and etiology differing between the sexes, and given the influence of steroid hormones on brain development and MDD onset throughout the life.[14] Genetic risk factors may also influence brain volumes and/or depression,[15,16] but are seldom considered. Serotoninergic genes, notably the genetic variant in the promoter region of the serotonin transporter (*5-HTTLPR)*, have been reported to influence the structure and function of certain brain regions in depressed patients.[17] Whether GMV alterations could be influenced by age-related characteristics (somatic and psychiatric comorbidity) also remains to be addressed.

To address the limitations of previous studies, we investigated the relationship 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 will be more extensive in the participants with lifetime MDD diagnosis and may persist after recovery. We also hypothesized that these abnormalities will differ according to sex and genetic vulnerability to *5-HTTLPR*. We also considered age of onset and the effect of physical and psychiatric comorbidity. In the absence of availability of prospective lifetime birth cohort data, the study has been conducted retrospectively on elderly people for whom both lifetime MDD episodes and genotype have been recorded.

Methods

Participants

Data were derived from a longitudinal study of neuropsychiatric disorders in community-dwelling French elderly, named "Enquête de Santé Psychologique –Risques, Incidence et Traitemement" (Esprit).[18] Eligible participants, who were at least 65 years of age and non-institutionalized, were recruited by random selection from the electoral rolls between 1999 and 2001. Ethics approval for the study was given by the national ethics committee and written informed consent was obtained from all participants. Of the 1863 participants initially recruited to the Esprit study, only those aged ≤80 years 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 this analysis. Those participants diagnosed with dementia (n=14), who were left-handed (n=16), or with missing data on lifetime MDD or other main covariates (n=28) were excluded from this analysis, leaving 610 participants. Compared to the excluded participants, those included were younger, less frequently women, and living alone and less likely to have cognitive impairment ($p<0.001$ for all these characteristics). They were less likely to have never smoked and to have cardiovascular ischemic pathologies

(p=0.02). They did not differ in the other characteristics including the prevalence of lifetime MDD (p=0.78).

MRI protocol and image analysis

All the neuroimaging scans were acquired using the same scanner at the examination centre (Gui de Chauliac Neurology Hospital, Montpellier, France). A 1.5-T GE Signa Imaging system (General Electric Medical Systems, Milwaukee,WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-weighed sequence for volumetric estimations (TR=12, TE=2.8, IT=6000, matrix, size=256x256, pixel spacing=0.9375x0.9375mm, NEX=1, slice thickness=1.0mm). Regional reconstruction and segmentation was performed with the FreeSurfer (6.0) image analysis suite (http://surfer.nmr.mgh.harvard.edu/) as described.[19] The FreeSurfer outputs (from 2d and 3d perspectives) of each scan were inspected for error/misclassification. Twenty-eight scans with clear errors were excluded from the analyses. Sixteen regions of interest (ROIs) were defined using Desikan's Atlas.[20] The regions of primary interest were the hippocampus, amygdala, orbitofrontal (OFC) and anterior cingulate cortex (AAC), and several subcortical structures (thalamus, caudate, putamen, pallidum, and accumbens nuclei) which may show neuroimaging abnormalities in depressed patients.[1,3,5,6,21,22] We also examined ROIs which have rarely been evaluated despite accumulating evidence for abnormalities in MDD and their

potential role in emotional processing and symptom characteristics, *e.g.* 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] Total brain volume (grey+white matter) was computed for each participant using the segment m-file of the SPM5 software (Wellcome Department of Cognitive Neurology,UK), SPM showing greater accuracy[28] and consistency[29] and less systematic bias evaluation[30] than FreeSurfer for this measure.

Diagnosis of lifetime psychiatric disorder

The diagnosis of current and past MDD and anxiety disorder (phobia, generalized anxiety disorder, panic disorder, obsessive compulsive disorder as well as post-traumatic stress disorder) was made by psychologists and psychiatric nurses according to DSM-IV criteria and using the Mini-International Neuropsychiatric Interview (MINI, French version 5.00), a standardized psychiatric examination validated within the general population.[31] Positive cases were reviewed by a panel of independent psychiatrists.[32]

Sociodemographic and clinical variables

The standardized interview included information on socio-demographic characteristics, physical health, and medical history. Detailed medical questionnaires (with additional information from general practitioners) were used to obtain

information on history of cardiovascular ischemic pathologies (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, and arteritis). All drugs used in the preceding month, including antidepressants, were recorded from medical prescriptions and drug packaging. Global cognitive function was evaluated using the Mini-Mental State Examination, a score <26 indicating cognitive impairment.[33] Dementia was diagnosed by a neurologist as part of a standardized examination and validated by a panel of independent neurologists.[34]

5-HTTLPR genotyping

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

Statistical analysis

Brain volume measurements were normally distributed. Associations between brain regions and lifetime MDD were evaluated using ANCOVA adjusted for age, sex, and total brain volume (Model M0). Where significant associations were observed, exploratory analyses were used to assess the specificity of these findings. The sex by diagnosis interaction was tested by adding lifetime MDD x sex term to the model and where an interaction effect was observed

(p<0.10), analyses were stratified by sex. Further adjustment was made for other covariates, which has been reported in the literature to modify the association between MDD and brain volumes, *i.e.* education level, head injury, cardiovascular ischemic pathologies, and antidepressant (Model M1), as well as lifetime anxiety disorder (Model M2). For significant bivariate associations, the effect of *5-HTTLPR* was evaluated by stratification into three genotypes (*LL*, *SL*, and *SS*) due to the absence of consensus regarding the choice of a genetic model and frequent report of heterosis for *5-HTTLPR*.[36,37] To account for the multiple brain regions examined, we adjusted the significance levels using the false discovery rate (FDR) method.[38] All tests were 2-sided and SAS (v9.4, SAS Institute, Inc.,NC) was used for the statistical analyses.

Results

Participant characteristics

Baseline characteristics of the 610 participants are summarized in **Table 1**; the median age was 70.7 years and 47.5% were male, 26.6% had lifetime MDD of whom 38.3% had recurrent episodes. Only 2.1% had current MDD and 5.1% were currently taking an antidepressant. Men and women differed in most characteristics; women being younger, more frequently alone, and reporting lifetime psychiatric disorder but less

frequently head injury and cardiovascular risk factors.

Subsegmental brain regions according to lifetime MDD

Adjusted for age, sex, and total brain volume, lifetime MDD was associated with smaller volumes of insula, diencephalic structures and deep nuclei, as well as larger volumes of rostral ACC and two visual cortex subregions (**Table 2**). Alterations in insula, thalamus, ventral diencephalon, nucleus accumbens, pallidum, and pericalcarine survived FDR correction. Similar data were found in the multivariate model further adjusted for education, head injury, cardiovascular ischemic pathologies, and antidepressant (**Supplementary Table S1**). These covariates accounted for a relatively small proportion of the variance in each volume, with the standardized regression coefficients ranging between -0.338 to +0.257 (**Supplementary Table S2**).

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

Subsegmental brain regions according to the age at first major depressive episode

Of the participants with lifetime MDD, 56.5% reported a first onset before 50 years of age. Compared to the participants without lifetime MDD, volumes in rostral ACC, lingual and pericalcarine appeared larger for those with late episode (after 50 years), whereas smaller volumes of ventral diencephalon and nucleus accumbens appeared more related to earlier MDD onset (**Supplementary Table S4**).

Exploratory analyses according to sex

An interacting effect of sex was observed for amygdala (p-interaction=0.094), caudate (p=0.018), and rostral ACC (p=0.055). Examining sex differences, lifetime MDD was associated with smaller volumes of 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=0.567, -0.2%, p=0.886). Conversely, only women with lifetime MDD had a larger volume of rostral ACC (+6.3%, p=0.003 compared with -1.2% in men, p=0.682) (**Fig. 1**).

Exploratory analyses as a function of 5-HTTLPR genotype

Thirty percent of the participants were homozygous carriers of the *L* allele and 23.2% were *SS*. The *5-HTTLPR* genotype frequency did not significantly deviate from Hardy-Weinberg equilibrium (p=0.17). Compared to the participants without

MDD, lifetime MDD was associated with smaller thalamus in the *LL* participants only (-4.9%, p=0.002, compared with -1.2%, p=0.274 and +0.3%, p=0.862 in *SL* and *SS*, respectively) (**Table 3**). Significant differences were found specifically for the *SL* participants with lifetime MDD on insula, ventral diencephalon, lingual, and most significantly pericalcarine volume (+8.2%, p=0.003 compared with +2.5%, p=0.407 and +2%, p=0.551 in *LL* and SS participants, respectively). We observed the same pattern after excluding the participants with current MDD or taking antidepressant, but the association with ventral diencephalon was weakened (p=0.060) and that with lingual was strengthened (p=0.005 in M0 and 0.001 in M2) (data not shown).

Discussion

Lifetime MDD was associated with many GMV differences when compared to non-cases. The most robust finding was the observation of smaller volumes in deep nuclei and insula and larger volumes in the occipital visual cortex. These findings were independent of age, sex, education, head injury, cardiovascular ischemic pathologies, antidepressant, and lifetime anxiety disorder. These differences were also seen in individuals who had been free of MDD for many years [median(IQR)=15(5-24) years]. Lifetime MDD was also associated with smaller caudates and amygdalae in men, and larger rostral ACC in women specifically. Some associations varied according

to the *5-HTTLPR* genotype; most significantly, thalamus was smaller specifically in the *LL* participants with lifetime MDD, whereas pericalcarine and lingual region were larger in the *SL* heterozygotes only, compared to those without lifetime MDD.

Previous reports of morphological brain changes relative to MDD have mostly been based on small case-control studies focusing on the hippocampus, amygdala, OFC and AAC.[1,3,5,6] Inconsistent data have been reported, probably largely attributable to heterogeneity in study design and size, setting, population and depression characteristics.[1] Meta-analyses reported smaller volumes in adults but the effects were small and/or non-significant; they depended on the age of patients and whether it was a first episode, and they were less likely in community-dwelling population and in remitted MDD compared with patients with current or recurrent episodes.[1,3,5,6,21,39,40] In this community-dwelling elderly population, most participants reported only one past episode and the median(IQR) age of first onset was 47(35-57) years, which may explain the lack of significant associations. A highly significant difference was however, found with rostral ACC, which was larger in women with lifetime MDD. Voxel-based morphometry (VBM) studies have reported larger cingulate gyri in remitted geriatric depression,[41] as well as larger ACC in medication wash-out young adult MDD patients.[42] In healthy adults, a negative association was shown between GMV and stress-related brain activity in perigenual ACC.[43]

Basal nuclei

In our study, lifetime MDD was associated with decreased volumes of several basal nuclei. Smaller caudate nuclei have been reported in adult patients[3,40] and in late-life depression, the effect sizes increased with age and with smaller percentage of women.[6] Consistently, we found that lifetime MDD was associated with smaller caudate in men specifically and the association was strengthened after adjusting for several confounders including antidepressants and anxiety disorder (-8.6%, p=0.0025 in M2).

Some meta-analyses on the putamen reported significant volume reduction in lifetime MDD,[3,6] others in early but not late onset,[40] nor current MDD.[5] Other studies found that associations were limited to severe or persistent subtypes.[39] We found a marginal association between lifetime MDD and smaller putamen (p=0.055 after FDR correction) and a greater reduction in those with recurrent episodes (global p-value=0.042).

We also found an association between lifetime MDD and smaller volumes of nucleus accumbens and pallidum. These regions were rarely examined and meta-analyses of studies mainly including adult patients with acute or lifetime MDD failed to report significant associations.[5,21] In an analysis of a high-dimensional set of over 11,000 traits, pallidum volume was reported to be a main endophenotype related to recurrent

depression.[9] We also observed a greater reduction in the participants having reported multiple episodes compared to those with only one or no previous episode (global p-value=0.013).

Lifetime MDD was also associated with smaller thalamus and ventral diencephalon, a region primarily comprising the hypothalamus. Small meta-analyses of the thalamus reported moderate[6,21] or no significant[3,5,40] volume reduction, and none has included hypothalamus despite its crucial role in emotional behavior and stress response as part of the hypothalamic-pituitary-adrenal axis. Smaller ventral diencephalon volume was however reported to be the first top-ranked neuroimaging endophenotype related to 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 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 VBM studies also showed left insula reductions in young adults with first episode depression.[8] Our study is the first ROI study showing a

significant smaller insula volume in elderly general population with lifetime and remitted MDD.

Visual cortex

Another original finding concerns the association of MDD with larger volumes of pericalcarine and lingual ROI, which appeared especially marked for late-onset MDD. Visual cortex has a central role in the fear conditioning paradigm in humans.[45] The pericalcarine is the initial region of visual processing and lingual gyrus is associated with high level visual processing and visual memory. The associations were highly significant after excluding currently depressed or treated participants (p=0.006 and 0.004, respectively in M2). The link between visual cortex and MDD has only been described in VBM studies and a meta-analysis reported significant GMV increase in the right lingual gyrus in late-life depression.[10] A larger lingual gyrus volume was found to predict early antidepressant response in adults and this was linked to better performance in visual neuropsychological tests.[46] Greater sensory reactivity in visual cortex could also predict resilience against depressive relapse.[47] In healthy young adults, facilitation of processing of aversive stimuli was associated with a disconnection of subcortical limbic connections (insula, putamen, amygdala, hippocampus) together with a compensatory emerging centrality of visual cortex.[45] Whether pericalcarine and lingual region could participate to

neuronal compensatory process to facilitate processing of aversive stimuli and fear or emotional learning in response to abnormal input from other structures, or reflect resilience against relapse, remains to be examined.

5-HTTLPR genotype

Most previous studies have examined the effect of *5-HTTLPR* on GMVs in either depressed or healthy participant groups, but rarely as a modifying factor between MDD risk and GM alterations.[17] There are generally size-limited and focused on the hippocampus and amygdala but rarely on striatum or thalamus where 5-HTT is expressed in high density. The vast majority of the structural imaging genetic studies did not consider *SL* genotype individually despite a lack of consensus regarding genetic model and frequent report of heterosis for *5-HTTLPR*.[37] Heterogeneity in age is another potential source of concern;[48] unlike in younger populations where the *S* allele is a risk factor, the *LL* genotype appears to be a risk factor for mental and physical distress in elderly people highly exposed to chronic disorders and severe stressors.[49]

We found no significant volumetric differences according to *5-HTTLPR* in each group (with or without lifetime MDD) (data not shown) but significant between-group differences. Particularly, the thalamus was smaller in the *LL* homozygotes with lifetime MDD whereas the *SL* heterozygotes only, had larger pericalcarine and lingual volumes compared to 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* genotype are lacking and no studies have examined the pericalcarine or lingual regions despite some indication for serotonergic occipital dysfunction in depression.[51] The same data were found after excluding currently depressed or treated participants, suggesting that these findings 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 the *SL* heterozygotes were more resilient to these factors.[36] We also found that some adverse events during childhood, *e.g.* sexual or physical abuse and having had a mother with mental problems were associated with higher risk of late-life depression[35] but decreased risk of cognitive decline notably in visual memory.[52] This suggests possible cognitive adaptation or resilience effect. Although speculative, this may suggest that the pericalcarine and lingual region could participate in a persistent neuronal compensatory process in the *SL* heterozygotes with a history of MDD.

Sex differences

We found some evidence for sexually dimorphic alterations, with smaller caudates and amygdalae in men with lifetime MDD,

and larger rostral ACC in women specifically. Specific sex differences in depression symptomatology of older adults have been described, with women showing more mood-related symptoms and appetite disturbance, and men more motivation-related symptoms and psychomotor changes[14] and this may involve different biological correlates. However, only a few neuroimaging studies have investigated sex effects, with many including predominantly females and, likely as a consequence, meta-analyses have seldom reported sex differences.[5,10]

In a healthy sample mainly consisting of older women, larger ACC was associated with higher levels of anhedonia.[53] Valence-dependent sex differences in emotional reactivity with divergent activation patterns, notably in the ACC and amygdala, have been reported suggesting difference in recognizing, expressing, or responding to emotions.[54] Rostral ACC and caudate nucleus were shown to be involved in impulse inhibition in young adults in a sex-specific manner suggesting different processing strategies (*e.g.* inhibiting inappropriate response for males *vs.* eliciting appropriate response for females).[55] In ADHD adults, smaller caudate was associated with impulsive/hyperactive symptoms in males but not females.[56] Besides, 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 may influence the nature of changes in some structures or be associated with specific symptoms, processing strategies,

or characteristics of depression (*e.g.* rumination, irritability, impulsivity) remains to be examined.

Context of the findings

Retrospectively determined incidence of lifetime MDD was found to be associated in our study with smaller striatum, pallidum, thalamus, hypothalamus, and insula but 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, as well as sensorimotor and interoceptive processing[23,58,59] with some evidence for sex difference regarding emotion production and regulation. We did not observe reduced volumes of hippocampus or frontal subregions reported in currently depressed adults. In a meta-analysis of fMRI studies, Graham and colleagues suggested frontal areas as state markers of MDD whereas striatal regions are trait vulnerability markers which may be less affected by treatment.[23] They also stressed the potential key roles of regions not included within the prevailing models of MDD, such as insula and occipital subregions, the latter showing over-activity in MDD.[23] Sustained remission from MDD has been associated with a combination of the normalization of 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 visual corticostriatal loop in remitted elderly with volume enlargement of visual occipital regions and reduction in subcortical structures.[60] They also suggest a link between certain sensory/visual function (thalamus for sensory relay as well as pericalcarine and lingual region for visual processing and visual memory) and *5-HTTLPR* vulnerability (to stress-induced relapse) or resilience to MDD. The question however, remains as to whether these abnormalities represent a biological long-term vulnerability (endophenotype as intermediate expression of genetic vulnerability factors).

Limitations and strengths

Limitations include the cross-sectional design of the study and thus we cannot determine whether volume alterations precede or are subsequent to MDD. Data related to lifetime MDD were retrospective. This may introduce recall bias and lead to an underestimation of the associations, even if we have excluded participants diagnosed with probable/possible dementia to minimize inaccuracies. The volume variations associated with lifetime MDD ranged between 2-5% for deep nuclei and insula and 5-8% for visual cortex ROIs suggesting a relatively small effect size. State-like characteristics were not examined due to the low prevalence of current MDD in this

relatively healthy community sample and it is possible that the lack of associations with some ROIs could be related to normalization after sustained remission/treatment. Finally, multiple analyses have been performed potentially increasing the risk of type 1 error, but most remained significant even after correction for multiple comparisons.

This study constitutes the largest structural MRI study targeting lifetime MDD, in terms of the number of participants and ROIs examined. Brain volumes were measured by 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 examination, according to DSM-IV criteria. Further clinical validation of the cases minimized false positives. Extensive information available on clinical status and medications helped minimizing exposure misclassification. In contrast with previous studies, we controlled for numerous potential confounding factors, particularly education, head injury, physical and mental comorbidity.

Conclusion

GMV differences were observed between persons retrospectively reporting lifetime MDD and those who did not. These structural correlates of MDD may constitute useful imaging phenotypes of

depression, treatment responsiveness, or resilience. The question remains as to whether volume enlargement may be linked to neuronal adaptive compensatory process in response to dysfunction of other structures or instead represent trait-like, developmental differences that underlie a neurobiological vulnerability to the illness 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/dimensions of depression, also remains to be examined. Further work is required to understand the significance of these volumetric differences including prospective multimodal and complimentary imaging studies. This will help in deciphering between a causal role and neural correlate of MDD, the result of shared underlying causes (*e.g.* genetic predisposition) or bidirectional/mutual reinforcement, thus 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 lead 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 and all authors were involved in its revision and gave final approval to the submitted manuscript.

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Table 1: Characteristics of the 610* participants

	Whole sample n=610	Men n=290	Women n=320	*p*-value†
	Median (IQR)			
Age, years	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)	<0.0001
Cortex, cm^3	358 (336-382)	376 (353-402)	344 (324-365)	<0.0001
Total brain volume, cm^3	882 (816-958)	925 (858-998)	850 (788-908)	<0.0001
Education level (≤ 5years)	25.7%	23.1%	28.1%	0.16
Living alone (n=609)	19.7%	6.2%	32.0%	<0.0001
Smoking (n=609)				
Never	53.4%	26.9%	77.5%	<0.0001
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%	<0.0001
≥ 2	10.2%	3.8%	16.0%	
Current major depressive disorder‡	2.1%	0.7%	3.4%	0.02

Table 1 cont.

	Whole sample	Men	Women	*p*-value†
Age of first episode (n=609)				
None	73.6%	84.5%	63.6%	<0.0001
< 50 years	14.9%	7.9%	21.3%	
≥ 50 years	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%	<0.0001
Hypertension (≥140/90 mm Hg or treated)	68.5%	74.4%	63.1%	0.003
Cardiovascular ischemic pathologies§	12.8%	17.2%	8.75%	0.002
Diabetes¶ (n=606)	8.8%	12.9%	5.0%	0.0006
Cognitive impairment (MMSE score <26)	13.4%	10.7%	15.9%	0.06

IQR = Interquartile range; MMSE = Mini-Mental State Examination.

*Unless specified otherwise.

†Kruskal-Wallis tests for continuous variables and Chi-square tests for categorical variables.

‡Diagnosis of past and current major depression or anxiety disorder (phobia, generalized anxiety disorder, post-traumatic stress disorder, panic disorder or obsessive compulsive disorder) according to DSM-IV criteria and using the MINI.[31]

§History of cardiovascular ischemic pathologies (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, arteritis).

¶Fasting glucose ≥ 7.0 mmol/L or treatment.

Table 2: Association of subsegmental brain region volumes with lifetime major depressive disorder among 610 participants

	No lifetime MDD (n=448)		Lifetime MDD (n=162)			
	Mean*	SD	Mean*	SD	*p*†	*p*‡
Medial orbitofrontal	8962.94	43.20	8939.55	73.61	0.786	0.786
Lateral orbitofrontal	11652.40	46.37	11718.13	79.01	0.477	0.545
Rostral anterior cingulate	3347.51	28.37	3458.73	48.34	0.050	0.089
Caudal anterior cingulate	2993.71	25.67	3065.27	43.73	0.163	0.217
Hippocampus	7061.54	33.88	7033.17	57.73	0.675	0.720
Amygdala	2634.05	14.88	2580.65	25.34	0.072	0.115
Insula	11954.83	48.80	11722.33	83.14	0.017	0.045
Thalamus	11806.32	43.44	11575.64	74.01	0.008	0.038
Ventral diencephalon	6794.71	28.62	6624.44	48.76	0.003	0.038
Caudate nucleus	6852.97	52.58	6669.85	89.58	0.081	0.118
Putamen	9453.97	52.75	9215.18	89.87	0.024	0.055
Nucleus accumbens	997.39	7.14	960.92	12.17	0.011	0.038
Pallidum	2983.73	16.17	2893.75	27.55	0.005	0.038
Cuneus	4765.02	30.27	4839.00	51.58	0.221	0.272
Pericalcarine	3404.66	28.46	3547.02	48.48	0.012	0.038
Lingual	10714.10	67.51	10984.78	115.01	0.045	0.089

FDR = false discovery rate; MDD = major depressive disorder; SD = standard deviation.

*Mean (SD) values expressed as mm^3 and adjusted for age, sex, and total brain volume.

†Raw p-values not adjusted for multiple comparisons.

‡p-values after FDR correction.

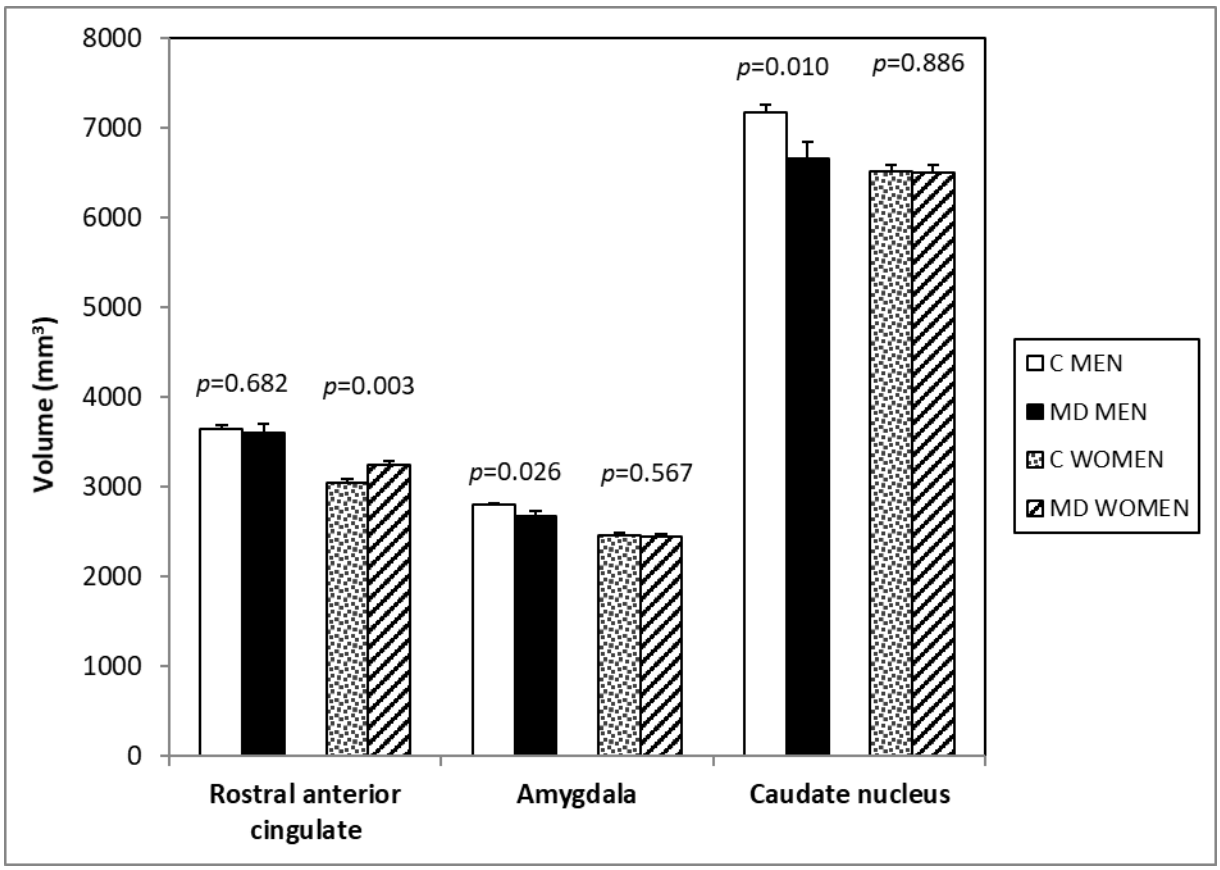

Fig. 1: Association between lifetime major depressive disorder and volumes* of rostral anterior cingulate, amygdala, and caudate nucleus in elderly men and women

*Mean (SD) values expressed as mm^3 and adjusted for age and total brain volume.

C: Controls without lifetime major depressive disorder; MD: lifetime major depression.

Table 3: Association of subsegmental brain region volumes with lifetime major depressive disorder according to *5-HTTLPR* genotype

5-HTTLPR	*LL* (n=160)					*SL* (n=250)					*SS* (n=124)				
	No lifetime MDD (n=112)		Lifetime MDD (n=48)			No lifetime MDD (n=184)		Lifetime MDD (n=66)			No lifetime MDD (n=93)		Lifetime MDD (n=31)		
	Mean*	SD	Mean*	SD	*p*†	Mean*	SD	Mean*	SD	*p*†	Mean*	SD	Mean*	SD	*p*†
Rostral anterior cingulate	3394.88	60.80	3537.88	94.35	0.220	3345.48	43.42	3400.87	74.31	0.521	3346.62	63.48	3498.30	112.93	0.243
Insula	11847.14	99.97	11963.30	155.14	0.544	11996.04	78.88	11628.15	134.99	0.020	11833.83	103.71	11520.94	184.48	0.141
Thalamus	11966.39	98.90	11376.42	153.47	0.002	11843.10	65.47	11700.58	112.05	0.274	11685.44	89.60	11717.36	159.39	0.862
Ventral diencephalon	6726.12	57.73	6524.76	89.59	0.070	6869.44	46.83	6659.23	80.15	0.025	6765.45	59.92	6731.95	106.59	0.784
Putamen	9530.94	131.13	9093.75	203.49	0.083	9591.21	75.65	9323.70	129.47	0.076	9257.61	108.03	8955.26	192.18	0.172
Nucleus accumbens	996.60	14.19	966.80	22.02	0.273	1003.50	11.03	984.31	18.88	0.382	980.00	16.80	921.09	29.89	0.088

Table 3 cont.

5-HTTLPR	*LL* (n=160)					*SL* (n=250)					*SS* (n=124)				
	No lifetime MDD (n=112)		Lifetime MDD (n=48)			No lifetime MDD (n=184)		Lifetime MDD (n=66)			No lifetime MDD (n=93)		Lifetime MDD (n=31)		
	Mean*	SD	Mean*	SD	*p*†	Mean*	SD	Mean*	SD	*p*†	Mean*	SD	Mean*	SD	*p*†
Pallidum	2957.48	32.98	2852.01	51.18	0.096	3033.56	24.32	2952.72	41.62	0.095	2994.12	37.38	2869.91	66.50	0.106
Pericalcarine	3422.87	54.66	3509.63	84.83	0.407	3362.83	47.23	3639.30	80.83	0.003	3444.39	56.29	3512.98	100.13	0.551
Lingual	10870.88	135.40	10875.23	210.12	0.987	10620.67	110.25	11142.98	188.68	0.018	10943.15	133.37	10991.36	237.26	0.859

MDD = major depressive disorder; SD = standard deviation.

*Mean (SD) values expressed as mm^3 and adjusted for age, sex, and total brain volume.

†Raw p-values.

Table S1: Association of subsegmental brain region volumes with lifetime major depressive disorder among 610 participants in multivariable model adjusted for age, sex, total brain volume, education level, head injury, cardiovascular ischemic pathologies, and antidepressant use

	No lifetime MDD (n=448)		Lifetime MDD (n=162)		
	Mean*	SD	Mean*	SD	*p*†
Rostral anterior cingulate	3364.37	72.64	3471.48	78.44	0.059
Insula	12053.26	125.78	11813.70	135.83	0.015
Thalamus	11597.33	111.61	11381.19	120.52	0.013
Ventral diencephalon	6704.75	73.67	6540.86	79.55	0.004
Putamen	9409.72	135.46	9173.56	146.28	0.025
Nucleus accumbens	970.78	18.34	935.73	19.80	0.014
Pallidum	3003.19	41.68	2911.07	45.01	0.005
Pericalcarine	3462.15	73.24	3601.43	79.09	0.015
Lingual	10628.71	173.68	10901.94	187.55	0.044

MDD = major depressive disorder; SD = standard deviation.
*Mean (SD) values expressed as mm^3.
†Raw p-values

Table S2: Strength of the associations with covariates evaluated using standardized regression coefficient

Covariate	Low education level (≤ 5 years)				Antidepressant use				Head injury				Cardiovascular ischemic pathologies			
	β	SE	STβ	Pr > |t|*	β	SE	STβ	Pr > |t|*	β	SE	STβ	Pr > |t|*	β	SE	STβ	Pr > |t|*
Medial orbitofrontal	19.73	85.13	0.017	0.817	305.26	168.87	0.257	0.071	204.26	122.46	0.172	0.096	22.73	112.31	0.019	0.834
Lateral orbitofrontal	-39.07	91.39	-0.029	0.669	40.36	181.80	0.030	0.824	156.89	131.63	0.116	0.234	152.22	120.44	0.112	0.207
Rostral anterior cingulate	-132.64	55.82	-0.183	0.018	164.69	111.34	0.227	0.140	69.20	80.80	0.095	0.392	-94.05	73.89	-0.129	0.203
Caudal anterior cingulate	-29.68	50.64	-0.051	0.558	31.88	100.74	0.054	0.752	68.74	72.98	0.117	0.347	-87.00	66.74	-0.148	0.193
Hippocampus	-1.58	66.77	-0.002	0.981	-302.22	132.23	-0.338	0.023	-65.49	96.23	-0.073	0.496	-207.66	87.68	-0.232	0.018
Amygdala	-2.66	29.39	-0.007	0.928	-15.22	58.45	-0.037	0.795	-6.87	42.37	-0.017	0.871	8.13	38.77	0.020	0.834
Insula	-47.49	96.58	-0.032	0.623	145.11	192.04	0.099	0.450	-8.18	139.27	-0.006	0.953	55.59	127.42	0.038	0.663
Thalamus	-27.14	86.09	-0.022	0.753	-190.57	171.06	-0.151	0.266	-198.76	123.86	-0.158	0.109	-178.21	113.35	-0.142	0.116
Ventral diencephalon	-14.26	56.81	-0.016	0.802	-61.05	112.96	-0.068	0.589	-126.73	81.74	-0.142	0.122	-82.67	74.87	-0.093	0.270
Caudate nucleus	-174.43	103.62	-0.149	0.093	112.70	206.53	0.096	0.585	90.99	149.70	0.078	0.543	480.79	135.62	0.410	0.0004
Putamen	-208.49	104.03	-0.167	0.045	-161.68	207.49	-0.129	0.436	116.48	150.40	0.093	0.439	45.04	137.68	0.036	0.744
Nucleus accumbens	1.12	14.15	0.006	0.937	-18.85	28.13	-0.105	0.503	-13.67	20.39	-0.076	0.503	-43.86	18.58	-0.245	0.019
Pallidum	-12.08	32.07	-0.029	0.706	50.09	63.75	0.121	0.432	2.95	46.24	0.007	0.949	-27.76	42.29	-0.067	0.512
Cuneus	-111.61	59.55	-0.142	0.061	81.48	118.74	0.103	0.493	-16.40	86.11	-0.021	0.849	79.74	78.73	0.101	0.311
Pericalcarine	-43.89	56.33	-0.064	0.436	50.10	112.08	0.074	0.655	47.00	81.23	0.069	0.563	112.09	74.21	0.165	0.131
Lingual	-203.10	133.20	-0.116	0.128	13.63	265.44	0.008	0.959	127.75	192.34	0.073	0.507	-140.00	175.97	-0.080	0.427

β = regression coefficient estimated by multivariate linear regression; SE = standard error; STβ = standardized regression coefficient (computed by dividing the original estimates by the sample standard deviation of the ROI volume).

*Adjusted for age, sex, and total brain volume.

Table S3: Association of subsegmental brain region volumes with past major depressive disorder among 569 participants*

	No lifetime MDD (n=431)		Lifetime MDD (n=138)		
	Mean†	SD	Mean†	SD	*p*‡
Rostral anterior cingulate	3350.62	29.35	3431.81	52.75	0.184
Insula	11968.72	50.46	11738.44	90.70	0.028
Thalamus	11831.79	44.75	11600.21	80.44	0.013
Ventral diencephalon	6808.89	29.58	6639.74	53.16	0.006
Putamen	9470.14	54.52	9250.33	97.99	0.053
Nucleus accumbens	999.18	7.35	970.77	13.21	0.063
Pallidum	2985.99	16.54	2885.81	29.74	0.004
Pericalcarine	3416.70	29.39	3555.78	52.82	0.023
Lingual	10731.67	69.51	11098.32	124.93	0.011

MDD = major depressive disorder; SD = standard deviation.

*Excluding 41 participants with current MDD or taking antidepressants.

†Mean (SD) values expressed as mm^3 adjusted for age, sex, and total brain volume.

‡Raw p-values.

Table S4: Association between ROIs and lifetime major depressive episode as a function of age at first episode

	No Lifetime MDE (n=448)		First MDE < 50 yrs (n=91)		First MDE ≥ 50 yrs (n=70)		
	Mean†	SD	Mean†	SD	Mean†	SD	*p*‡
Rostral anterior cingulate	3349.00	28.35	3401.15	64.07	3541.18	72.00	0.045*
Insula	11957.35	48.83	11772.02	110.38	11657.00	124.05	0.042
Thalamus	11808.36	43.51	11564.14	98.34	11597.12	110.51	0.030
Ventral diencephalon	6796.51	28.66	6608.33	64.79	6649.31	72.81	0.011**
Putamen	9455.09	52.81	9200.91	119.37	9226.88	134.15	0.071
Nucleus accumbens	997.67	7.15	954.48	16.16	968.25	18.16	0.030**
Pallidum	2984.24	16.20	2900.17	36.61	2886.44	41.14	0.020
Pericalcarine	3405.81	28.42	3517.80	64.24	3598.43	72.20	0.024*
Lingual	10717.52	67.45	10864.28	152.47	11162.62	171.35	0.050*

MDE = major depressive episode; SD = standard deviation.

†Mean (SD) values expressed as mm^3 and adjusted for age, sex, and total brain volume.

‡Global raw p-values when comparing early (1), late (2) onset and no lifetime MDE (0); significant 2 by 2 comparisons (Bonferroni-adjusted p-value, <0.05): *2 *vs.* 0, **1 *vs.* 0.