Cross-Sectional and Longitudinal Assessment of Structural Brain Alterations in Melancholic Depression

Carles Soriano-Mas, Rosa Hernández-Ribas, Jesús Pujol, Mikel Urretavizcaya, Joan Deus, Ben J. Harrison, Hector Ortiz, Marina López-Solà, Josep M. Menchón, and Narcís Cardoner

Background: Whole-brain imaging approaches may contribute to the characterization of neuroanatomic alterations in major depression, especially in clinically homogenous patient groups such as those with melancholic features. We assessed brain anatomic alterations, both cross-sectionally and longitudinally, in patients with melancholic depression using a whole-brain voxel-wise approach.

Methods: Whole-brain magnetic resonance images were collected from a relatively aged sample of 70 consecutively recruited major depressive disorder inpatients with melancholic features and from a group of 40 healthy control subjects. All patients were clinically followed for at least 2 years, and a subset of 30 depressive patients and 20 control subjects were rescanned after a 7-year period. Imaging data were analyzed with voxel- and tensor-based morphometry techniques.

Results: Melancholic patients showed gray matter reductions in the left insula and white matter increases in the upper brainstem tegmentum. Male patients showed gray matter decreases in the right thalamus, and periventricular white matter reductions were specifically observed in older patients. Volume decreases in the left insula, hippocampus, and lateral parietal cortex predicted a slower recovery after treatment initiation. In longitudinal assessment, white matter of the upper brainstem tegmentum showed a different temporal evolution between groups. Additionally, bilateral gray matter reductions in the insulae were associated with the number of relapses during follow-up.

Conclusions: Structural alterations were identified in regions potentially related to relevant aspects of melancholia pathophysiology. Longitudinal analyses indicated region-specific interactions of baseline alterations with age as well as a significant association of clinical severity with focal changes occurring over time.

Key Words: Major depressive disorder, melancholia, neuroanatomy, neuroimaging, structural magnetic resonance imaging (MRI), voxel-based morphometry

Magnetic resonance imaging (MRI) studies have reported brain anatomic abnormalities in patients with major depressive disorder (MDD), most typically volumetric reductions, although results have been notably heterogeneous in the identification of affected structures. According to recent summaries (1–3), volumetric reductions of the hippocampus, basal ganglia, orbitofrontal cortex, and anterior cingulate cortex, particularly its subgenual division, are the most reliable findings. However, there are also reports of nonsignificant findings for such regions (4–6), whereas other studies have reported volumetric reductions in areas such as the amygdala (7), insula (8), and thalamus (9).

Inconsistency in the identification of brain structural alterations in MDD may be partially explained by the fact that most studies have focused on a certain number of structures selected a priori, as opposed to providing comprehensive whole-brain analyses. Additionally, there has been significant variability in terms of the clinical profile of the assessed patients. Such variability may have prevented the identification of anatomic changes in particular subgroups because different phenotypes of the disorder are likely to be associated with different neuropathologic alterations (10). In this context, the assessment of clinically homogeneous samples using a whole-brain imaging approach may offer a more comprehensive characterization of the anatomic alterations associated with MDD.

Melancholic depression is a relatively homogenous subtype of MDD characterized by anhedonia, psychomotor disturbances, feelings of guilt, early awakening, diurnal variation, and anorexia (11). It has also been related to specific neurobiological correlates such as cortisol dysregulation and alterations in sleep patterns (12). Reports of structural brain alterations in melancholic depression have been few in number, including overlapping results with those of general MDD samples, such as reduced hippocampal volumes (13), and also other findings such as enlargement of cerebrospinal fluid (CSF) spaces surrounding the sylvian fissure (14). Nevertheless, alterations in other gray or white matter regions may be expected because core features of melancholia (e.g., anhedonia, psychomotor retardation, or hyperactivity of the hypothalamic-pituitary-adrenal axis) have been related to abnormalities in distributed brain systems such as "corticostriatal loops" (15,16) or monoaminergic pathways linking the brainstem nuclei and limbic structures (12,17). However, to date, no studies in melancholic patients have employed an exploratory whole-brain voxelwise approach.

Another relevant feature of melancholia is its interaction with age. As a group, patients with melancholic depression have a later onset of illness compared with nonmelancholic samples (18). Furthermore, certain clinical (i.e., psychomotor disturbances) (19) and neuropathologic (i.e., subgenual cortex dysfunction) (6) alterations of melancholic depression are more prominent in older patients. This interaction suggests that some of the pathologic features of melancholia may be "degenerative" in nature, because of an accu-

From the Institut d'Alta Tecnologia— Parc de Recerca Biomèdica de Barcelona (CS-M, RH-R, JP, JD, HO, ML-S, NC), Centre Radiològic Computeritzat Hospital del Mar; Human Pharmacology and Neurosciences (CS-M), Fundació Institut Municipal d'Investigació Mèdica; Department of Psychiatry (RH-R, MU, JMM, NC), Hospital Universitari Bellvitge; Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (JP); Department of Clinical and Health Psychology (JD), Autonomous University of Barcelona; and Clinical Sciences Department (ML-S), University of Barcelona; Networking Research Center on Mental Health (MU, JMM, NC), Barcelona, Spain; and Melbourne Neuropsychiatry Centre (BJH), Department of Psychiatry, the University of Melbourne, Australia.

Address correspondence to Carles Soriano-Mas, Ph.D., Institut d'Alta Tecnologia—PRBB, CRC Hospital del Mar, Passeig Marítim 25-29, Barcelona 08003, Spain; E-mail: csoriano@crccorp.es.

Received Jan 14, 2010; revised Jul 28, 2010; accepted Jul 29, 2010.

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.07.029

mulation of pathogenic insults throughout a patient's life (20). Longitudinal imaging approaches may be optimal for testing this hypothesis because they allow for the assessment of relationships between measures of clinical severity (e.g., number of relapses) and anatomic changes observed over time. Such studies also allow examining interactions between illness and age-related brain structural alterations, especially when long follow-up periods are employed.

The initial aim of this study was to assess brain anatomic alterations in a large sample of melancholic patients compared with a group of control subjects of similar age and gender in the context of a whole-brain voxelwise approach. Gender-specific and age-related alterations in brain anatomy were specifically evaluated, as well as correlations with clinical data. A subset of participants was followed up 7 years after the initial imaging examination. This analysis allowed us to make a further assessment of the potential interaction between anatomic changes and age and to study the relationship between anatomic alterations and illness severity (i.e., number of relapses between scans).

Methods and Materials

Subjects

We assessed 70 MDD patients (41 female) consecutively recruited from the Mood Disorders Unit of the Bellvitge University Hospital. All but three patients were right-handed according to the Edinburgh Inventory (21). The group comprised patients with a current depression episode fulfilling DMS-IV criteria for MDD with melancholic features and who required hospital admission for treatment. Patient diagnosis was independently confirmed by two senior psychiatrists (MU and NC) using the Structured Clinical Interview for DSM-IV Axis I Disorders—Clinician Version (22). MDD severity was assessed with the Hamilton Rating Scale for Depression (HAM-D) (23). Upon inclusion, all patients had a HAM-D score higher than 18. This was a sample of relatively old patients (mean ± SD age = 61.56 ± 9.68 years, Table 1), although only 16 subjects (22.9% of the sample) had late-onset MDD (> 60 years), and the mean age at disorder's onset was 51.11 ± 12.57 years (Table 2). Exclusion criteria included the presence or past history of other Axis I diagnoses, presence or past history of neurologic or other serious medical conditions (including dementia), abnormal MRI upon visual inspection, or any contraindication to MRI scanning. The presence of hypertension or diabetes mellitus Type 2 (DM-II) was not considered as an exclusion criterion. Specifically, 17 patients had hypertension (24.3% of the sample), and four patients had DM-II (5.7% of the sample). In any case, we excluded subjects with evidence of ischemic tissue damage in the MRI to avoid including cases of cardiovascular etiology.

Forty control subjects (23 female) from the same sociodemographic environment were selected. These subjects (one left-handed) were of similar age and gender as the patients (Table 1). Control subjects were selected according to guidelines established by Shtasel *et al.* (24). A detailed medical history was recorded for each subject, and a structured interview was administered to detect subjects who fulfilled exclusion criteria (presence or past history of any Axis I or Axis II diagnosis, presence or past history of neurologic or other relevant medical conditions, abnormal MRI upon visual inspection, or any contraindication to MRI scanning). The percentage of control subjects with hypertension was 27.5% (11 subjects) and with DM-II was 7.5% (3 subjects).

All patients were clinically followed for at least 2 years through contact with the Mood Disorders Unit. During this period, no prodromal signs of dementia were detected, and a positive response to antidepressant treatment was observed. A subset of participants (30 patients and 20 control subjects) was rescanned approximately 7 years (mean 84.72 months, range 78–90 months) after the first MRI. Table S1 (see Supplement 1) details the reasons for follow-up discontinuation over this 7-year period. One-sample *t* tests and chi-square tests confirmed that original and follow-up samples did not differ on any sociodemographic variable (Table 1). For patients, the original and follow-up samples differed only in the "time to remission" of the clinical episode upon inclusion (Table 2).

Informed consent was obtained from all subjects after detailed description of the study, and the study was approved by the local ethics committee and performed according to ethical standards of the Declaration of Helsinki.

MRI Acquisition and Preprocessing

Subjects were scanned with a 1.5-T scanner (Signa, GE Medical Systems, Milwaukee, Wisconsin) at baseline and follow-up to obtain a 60-slice three-dimensional spoiled gradient recoil sequence in the axial plane (repetition time 40 msec, echo time 4 msec, pulse angle 30°, field of view 26 cm, matrix size 256 × 192 pixels, in-plane resolution 1.02 mm^2, and section thickness 2.5 mm). Imaging data were processed on a Microsoft Windows platform using technical computing software (MATLAB ver. 7; Mathworks, Natick, Massachusetts) and Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, United Kingdom).

Data Preprocessing for Cross-Sectional Analyses. Image preprocessing was performed with the VBM2 toolbox (25). First, we obtained study-specific template and prior images following procedures described elsewhere (26). Given the unequal number of subjects in our samples, 40 randomly selected patients and the 40 control subjects were used in this first step. Second, native-space MRIs were segmented into gray matter, white matter and CSF and optimally normalized to their tissue specific template. During this process, images were resliced to a final voxel size of 1 mm^3. The Jacobian determinants derived from the spatial normalization were used to modulate image voxel values to restore volumetric information (27). Finally, images were smoothed with a 12-mm full width at half maximum isotropic Gaussian kernel, which allows for parametric statistical testing in unbalanced designs (28).

Table 1. Sociodemographic Characteristics of the Study Samples

	Original Sample		Follow-Up Sample	
	Patients (n = 70) Mean ± SD (Range)	Controls (n = 40) Mean ± SD (Range)	Patients (n = 30) Mean ± SD (Range)	Controls (n = 20) Mean ± SD (Range)
Age at Inclusion	61.56 ± 9.68 (37–82)	59.23 ± 7.09 (49–76)	59.13 ± 8.01 (44–73)	58.80 ± 6.30 (49–71)
Age at Second MRI	—	—	66.57 ± 8.20 (51–81)	65.30 ± 6.34 (55–78)
Gender, F, *n* (%)	41 (58.6)	23 (57.5)	16 (53.3)	11 (55.0)
Left-Handed, *n* (%)	2 (2.9)	1 (2.5)	1 (3.3)	0 (0.0)

No significant differences were observed between groups in any of the variables.
F, female; MRI, magnetic resonance imaging scan.