Enlargement of Brain Cerebrospinal Fluid Spaces as a Predictor of Poor Clinical Outcome in Melancholia

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Background: A number of recent neuroimaging findings in depression have provided new insight into the biological substratum of depressive illness. The question now is what particular relevance the structural brain alteration described may have within the clinical context of depressive patients. We investigated a possible relationship between brain cerebrospinal fluid (CSF) space changes and patient prognosis in melancholic depression.

Method: Fifty-five patients who met DSM-IV criteria for major depressive disorder with melancholic features were examined with 3-dimensional magnetic resonance imaging, and CSF volumes were measured for global brain CSF and for lateral ventricles and left and right sylvian fissure regions. Clinical outcome was prospectively assessed during a 6-month standardized antidepressive treatment period (Phase I) and in a 2-year follow-up (Phase II) of recovered patients. The outcome measurements were total days to symptom remission (Phase I) and to eventual symptom relapse or recurrence (Phase II). The study took place from July 1998 to Dec. 2001.

Results: Phase I: Enlargement of CSF spaces in the left sylvian fissure region predicted poor treatment response. Volume measurements from this region accounted for 35% of remission time variance. Median time to full clinical remission was 82 days in patients with severe changes, 51 days in the case of mild-to-moderate CSF enlargement, and 35 days in patients with no left sylvian fissure region alterations. Phase II: Severe enlargement of global cortical CSF spaces was associated with increased risk of depression relapse or recurrence. Patients with severe cortical CSF changes showed a 7.8-fold excess risk of depression relapse/recurrence compared with patients with no cortical CSF space alteration.

Conclusion: Our data suggest that MRI-detected CSF space enlargement may be an important neuroimaging marker for poor prognosis in melancholic depression.

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While major depressive disorder is generally contemplated as a reversible psychiatric illness, there is substantial heterogeneity in the clinical outcome of depressive patients. While some patients achieve rapid remission and remain free of symptoms for extended periods, there are others who achieve remission but suffer relapses or recurrences and those who show a refractory illness.[1] Different studies have detected a variety of clinical, psychosocial, and biological factors associated with delayed, partial, or nonsustained treatment response.[1–6]

Alterations in brain structure may be present in depressed patients with refractory forms of depressive illness. Magnetic resonance imaging (MRI) studies have shown an association of widespread white matter lesions with poor response to initial treatment[7] and unfavorable long-term outcome.[8–10] Regional and global atrophy have also been reported in neuroimaging studies of mood disorders, particularly in late-onset[11–12] or severe depression.[13–15] The cumulated data indeed suggest some association between structural alterations and poor clinical outcome. Further prospective assessment may help to define the usefulness of the neuroimaging findings as markers of patient prognosis and a possible role in the management of refractory depression.[9]

Melancholic depression is a severe depressive disorder subtype showing a clinical course little influenced by psychological[16] and social factors,[17] in which biological determinants seem to be relevant.[18–20] Paradoxically, in melancholia, for which an organic origin of symptoms has been repeatedly suggested, few studies have specifically

investigated possible MRI alterations and their clinical significance.[18]

Recently, we found a general enlargement of brain cerebrospinal fluid (CSF) spaces in patients with severe melancholia, which was prominent in the sylvian fissure region and more evident in the left hemisphere.[21] In the current study, we carried out a follow-up of these melancholic patients to investigate a possible relationship between CSF space changes and the patient's clinical outcome, using both time to clinical remission and time to eventual symptom relapse or recurrence as outcome measurements.

METHOD

Subjects

A total of 55 patients (33 women and 22 men) made up our study series, which corresponds to the patient sample previously reported in Pujol et al.[21] with the exception of 2 subjects (1 man and 1 woman) who refused to be included in our standardized antidepressive treatment. This was a series of relatively elderly patients with severe melancholic-subtype depression requiring hospital admission for treatment. Patient recruitment was carried out by 2 experienced psychiatrists (M.U., L.B.) who independently examined consecutive subjects referred to the Affective Disorder Unit of Bellvitge University Hospital, Barcelona. Patients with DSM-IV criteria for major depressive disorder with melancholic features and a Hamilton Rating Scale for Depression (HAM-D) score[22] higher than 18 points were eligible when both research examiners agreed on all criteria. All subjects were interviewed using the Schedule for Affective Disorders and Schizophrenia.[23]

Exclusion criteria for participation included other Axis I diagnosis, history of neurologic illness, serious medical disease, and history of alcohol or substance abuse. We screened for cognitive status using the Mini-Mental State Examination.[24] No study subject scored below 28 points on this scale. All but 2 patients were right-handed. Mean ± SD age was 60.6 ± 9.4 years (range, 37–79 years), and illness duration was 10.5 ± 9.9 years (disorder onset age, 50.5 ± 11.8 years). Severity of depression assessed with the HAM-D showed a mean ± SD score of 28.9 ± 7.8 points (range, 19–51 points). Thirteen patients (24%) had 3 or more previous depressive recurrences. Twenty-two patients (40%) showed psychotic symptoms in the index episode. A total of 14 patients had received electroconvulsive therapy in a prior episode. Cerebrovascular risk factors were hypertension in 14 cases, diabetes in 3, hyperlipidemia in 9 (3 with additional hypertension), and atrial fibrillation in 1.

Thirty-seven comparative control subjects proceeding from the same sociodemographic environment were also evaluated to obtain reference imaging measurements.[21] These subjects were volunteers who had been referred to our center to undergo an MRI musculoskeletal examination. A detailed medical history was recorded and a psychiatric interview was administered before inclusion by a research psychiatrist. This interview was specifically structured to detect subjects who fulfilled exclusion criteria defined according to guidelines by Shtasel et al.[25] Selected volunteers, 1 of whom was left-handed, were of similar age (mean ± SD = 58.6 ± 7.3 years; range, 42–76 years; $t = 1.23$, $df = 90$, $p = .22$) and gender distribution (22 women and 15 men). Cerebrovascular risk factors were also comparable to the patient group, given that 8 subjects reported hypertension, 2 diabetes, 5 hyperlipidemia, and none showed atrial fibrillation.

After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the Institutional Ethical Committee.

Clinical Outcome Assessment

The clinical course of our patients was prospectively evaluated in 2 phases by 2 experienced psychiatrists, blind to the MRI findings. Phase I consisted of a 6-month standardized antidepressive treatment period, during which total days to full symptom remission defined treatment response. Phase II began after clinical remission was achieved and comprised a 2-year follow-up, in which the outcome measurement was total days to eventual symptom relapse or recurrence.

Standardized antidepressive treatment: phase I. A 15-day washout period preceded the active treatment. The first stage in our strategy was a 9-week trial of a tricyclic antidepressant (imipramine, 150–300 mg/day). Patients showing less than 50% reduction in their initial HAM-D score were considered unresponsive and were included in the second treatment stage, which involved a course of electroconvulsive therapy (bilateral, 3 times weekly up to a minimum of 6 and a maximum of 12 treatment sessions). Patients who showed no response to electroconvulsive therapy were given treatment strategies for resistant depression.[26]

Treatment response was evaluated for a maximum period of 6 months. In each particular case, this phase finished when the patient achieved full clinical remission according to Frank et al.[27] criteria (HAM-D score ≤ 7 for more than 15 days). Patients who never fully recovered were deemed to have a remission time of 180 days (equivalent to the entire treatment period).

Two-year follow-up: phase II. Once the treatment had been specifically adjusted for each case, the patients who showed full remission (52 of 55 cases) were followed up for 2 years on a monthly basis. Clinical data were prospectively collected and the HAM-D was administered to rate depression severity. According to Frank et al. criteria,[27] relapse was defined as a return of the depressive syndrome within the 6 months following remission and

recurrence when occurring after the initial 6 months of the follow-up period. To define depression relapse/recurrence, DSM-IV criteria for melancholia and HAM-D score higher than 18 points were required. When patients remained symptom-free by the end of the follow-up, a relapse/recurrence time of 730 days (2 years) was assigned.

MRI Examination

Imaging studies were obtained within the 2 weeks following inclusion using a 1.5-T magnet (Signa; General Electric Medical Systems, Milwaukee, Wis.). Sixty-slice 3-D spoiled gradient recalled acquisition in the steady-state sequences (TR 40 ms, TE 4 ms, pulse angle 30°, section thickness 2.3 mm, field of view 26 cm, and matrix size 256 × 192 pixels) were acquired in the sagittal and axial planes. The image in the axial plane was used to obtain measurements with no reorientation to a reference plane.

Image analysis was performed on an auxiliary workstation (SPARCstation 20; Sun Microsystems, Mountain View, Calif.), using commercially available software (GE Advantage Windows, version 2.0; GE Medical Systems). This system enabled us to construct 3-D brain models, to identify and isolate specific brain regions, and to perform volume measurements of the isolated structures. All these procedures are used routinely in our MRI center to assist neurosurgery.[28] We obtained different brain measurements with a specific image analysis protocol.[21]

The first step in this protocol was to build a 3-D surface rendering of each patient's brain. Volume segmentation was used to isolate brain from the surrounding CSF. The operator visually guided this procedure and attempted to operatively establish the segmentation limit at the half-height maximum intensity value between the hypointense CSF spaces and hyperintense brain parenchyma. Additionally, in each case, "open bridges" (factor 2) and "erosion" (factor 1) functions were applied to facilitate brain isolation from the rest of the head. After brain selection, a restoring "dilatation" was applied.

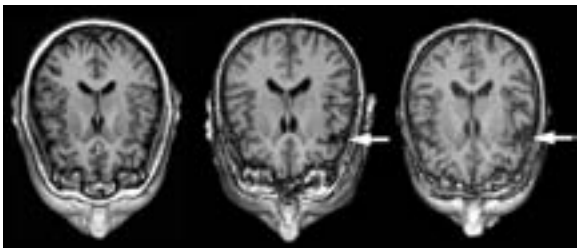
The second step involved defining the sylvian fissure region. As no agreement exists as to the point of sylvian fissure posterior termination,[29] we used a lateral projection of the insular contour to delimit our region of interest, which included insular CSF, sylvian fissure proper, and the most proximal portion of its rami. In contrast, the most posterior part of the sylvian fissure was excluded.

A third step involved restoration of CSF spaces on brain surface rendering (by applying the "close gaps" function with factor 20 and "dilatation"). Further segmentation allowed us to accurately isolate CSF spaces, as this latter model did not include cranial structures beyond dura mater.

Cerebral CSF volume, lateral ventricles volume, and left and right sylvian fissure CSF volumes were directly obtained after isolation and were the main study measurements. Two computations were performed: cortical CSF (cerebral CSF minus lateral ventricles) and intracranial volume (brain volume plus cerebral CSF). Normalization to intracranial volume (ratio) was calculated for all neuroimaging measurements.

The imaging process was performed by a single researcher (N.C.), blind to all subjects' data. Reliability of measurements was also confirmed in blinded conditions by repeating the image analysis in 30 randomly selected MRI examinations 4 weeks later. We found intraclass correlation coefficients ranging from 0.95 (sylvian CSF) to 0.98 (lateral ventricles).

Figure 1. Illustrative Magnetic Resonance Imaging Pictures From 3 Patients Showing Different Degrees of Left Sylvian Fissure Cerebrospinal Fluid (CSF) Space Enlargement[a]



[a]Arrows on the left side of the brain indicate where CSF space enlargement was more apparent.

Statistical Analysis

An exploratory correlation analysis was initially performed to establish the relationship between clinical and imaging variables. Significant imaging variables (at $p < .05$) were further evaluated in a survival analysis, using Cox regression to identify imaging alterations affecting remission and relapse/recurrence times and to obtain relative risks.

In a first approach, all significant imaging variables (normalized indexes) were included in the Cox stepwise regression to establish the best prediction of remission and relapse/recurrence times. Thereafter, in order to provide data with direct clinical applicability, the analysis was repeated using variables entering the equation and classifying patients into 3 subgroups according to the severity of CSF space enlargement: no CSF space enlargement (i.e., values below 75th percentile of control group), mild-to-moderate CSF enlargement (i.e., values at and above 75th percentile and below 90th percentile of control group), and severe CSF enlargement (i.e., values at and above 90th percentile of control group.). Figure 1 shows MRI pictures of a representative patient from each subgroup defined according to the severity of left sylvian fissure CSF space enlargement.

Table 1. Volume Measurements for Control Group and Patient Group With Melancholic Depression[a]

	Control Group (N = 37)		Patient Group (N = 55)	
Area	Median Volume	25th–75th Percentile Volume	Median Volume	25th–75th Percentile Volume
Cerebral CSF				
Raw	149	(116–167)	181	(148–200)
Normalized	11.4	(10.2–13.5)	13.7	(11.2–15.2)
Lateral ventricles				
Raw	13.8	(9.75–17.7)	20.1	(12.7–31.7)
Normalized	1.11	(0.76–1.31)	1.49	(0.93–2.48)
Cortical CSF				
Raw	132	(110–150)	156	(131–180)
Normalized	10.2	(9.0–12.1)	11.8	(10.2–12.9)
Left SF CSF				
Raw	5.00	(4.35–7.70)	8.20	(6.25–10.45)
Normalized	0.45	(0.32–0.60)	0.62	(0.47–0.78)
Right SF CSF				
Raw	5.90	(4.90–7.85)	8.00	(6.05–9.60)
Normalized	0.46	(0.39–0.63)	0.59	(0.47–0.72)
Brain				
Raw	1090	(1024–1190)	1149	(1084–1256)
Normalized	88.6	(86.5–89.8)	86.3	(84.8–88.8)

[a]Volumes are in milliliters, and normalized indexes are percentages of the intracranial volume.
Abbreviations: CSF = cerebrospinal fluid, SF = sylvian fissure.

Table 2. Correlation Between Clinical Variables and Magnetic Resonance Imaging Measurements for the Patient Group[a]

	Remission Time (N = 55)		Relapse/Recurrence Time (N = 52)[b]	
Volume	r Value	p Value	r Value	p Value
Cerebral CSF				
Raw	0.28	.038	–0.26	.059
Normalized	0.41	.002	–0.27	.057
Lateral ventricles				
Raw	0.28	.039	–0.02	.892
Normalized	0.33	.015	–0.02	.909
Cortical CSF				
Raw	0.23	.087	–0.32	.023
Normalized	0.36	.007	–0.33	.016
Left SF CSF				
Raw	0.49	< .001	–0.17	.221
Normalized	0.59	< .001	–0.16	.265
Right SF CSF				
Raw	0.28	.042	–0.17	.228
Normalized	0.37	.006	–0.16	.258
Brain				
Raw	–0.17	.207	–0.06	.652
Normalized	–0.41	.002	0.27	.057

[a]r Values express Pearson correlation coefficients; p values are 2-tailed.
[b]Of the 55 patients in the study, 52 showed full remission and were followed up for relapse/recurrence time.
Abbreviations: CSF = cerebrospinal fluid, SF = sylvian fissure.

The Kaplan-Meier method was performed to estimate survival curves between the different patient groups, and the log-rank test was used to test statistical significance.

RESULTS

Neuroimaging measurements are summarized in Table 1. Global and regional volume measurements of CSF spaces are provided in raw and normalized values. Data from the statistical comparison between groups were previously reported.[21]

Phase I: Treatment Response

Median remission time for the 55 subjects was 51 days (95% confidence interval [CI] = 41 to 61 days). All but 3 patients showed clinical remission during the treatment period.

Correlation analysis. Enlargement of brain CSF spaces, both in raw and normalized measurements correlated positively with remission time (Table 2). Correlations were stronger for sylvian fissure CSF spaces, particularly for the left side (r = 0.59), accounting for 35% of remission time variance. Correlation was negative for brain volume and significant only for the normalized values.

Survival analysis. In Cox stepwise regression, left sylvian fissure CSF volume entered the equation in the first and last step, showing a risk ratio of 0.05 with a 95% CI ranging from 0.01 to 0.21 (B = –2.9, Wald = 17.9, p < .0001). No other imaging variables showed further contribution. Potential clinical moderators such as age, age at illness onset, gender, depression severity, number of prior episodes, presence of delusion, and presence of cardiovascular risk factors were also assessed in this model. None of these variables significantly modified the results. The survival analysis was also conducted including the potential clinical moderators first. No clinical variable entered the equation in this case.

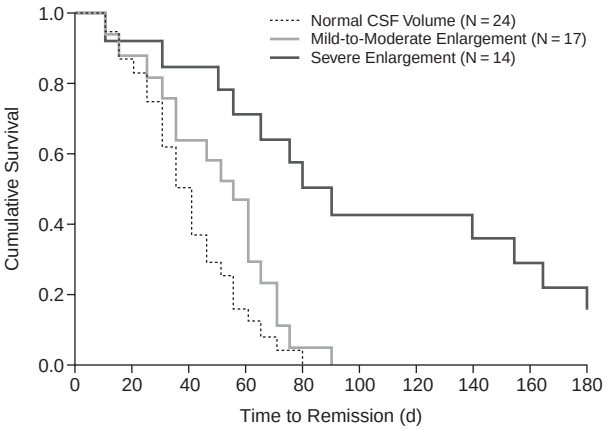
We estimated the relative risk of showing a delayed treatment response for the 3 defined patient subgroups (no, mild-to-moderate, and severe left sylvian fissure CSF enlargement). Patients with severe CSF enlargement (N = 14) showed a 6.5-fold likelihood (95% CI = 2.7 to 15.8) of presenting a delayed response to treatment compared with patients with no left sylvian fissure alterations (N = 24). Risk differences between the mild-to-moderate subgroup (N = 17) and patients with no alterations were not significant. The excess risk for poor treatment response of patients with severe changes relative to the mild-to-moderate subgroup was 3.9-fold (95% CI = 1.6 to 9.5).

Kaplan-Meier survival curves (Figure 2) graphically illustrate the observed group differences in remission time. This analysis was significant, showing a log rank test statistic of 20.3, df = 2, p < .0001. Median remission time for patients with no left sylvian fissure CSF enlargement was 35 days (95% CI = 27 to 43), for patients with mild-to-moderate CSF enlargement 51 days (95% CI = 46 to 56), and for patients with severe CSF enlargement 82 days (95% CI = 53 to 111).

Phase II: Follow-Up Period

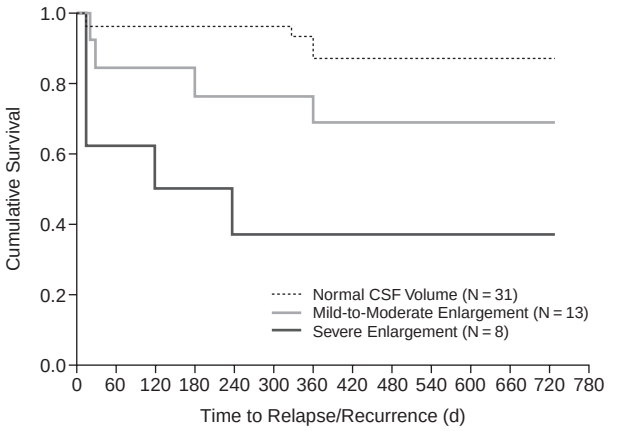
Median time to depression relapse/recurrence for the 52 patients included in this study phase was 587 days (95%

Figure 2. Remission Time Curves for the 3 Melancholic Patient Subgroups Defined According to Left Sylvian Region Cerebrospinal Fluid (CSF) Volumes[a]



[a]Note major response delay in the patient subgroup with severe CSF space enlargement in this region.

Figure 3. Relapse/Recurrence Time Observed for the 3 Melancholic Patient Subgroups Defined According to Cortical Cerebrospinal Fluid (CSF) Volumes[a]



[a]Patients with severe cortical CSF enlargement showed a reduced survival time with earlier relapse or recurrence in the 2-year follow-up.

CI = 517 to 657 days). Seven patients (13.5%) showed clinical relapse (symptom reappearance within the first follow-up semester) and 6 additional patients (11.5%) suffered from depression recurrence in the second semester. No patient experienced recurrence of depression during the second year. In total, 13 patients (25%) suffered depression relapse/recurrence in this study.

Correlation analysis. Table 2 indicates that only the CSF measurement involving all cortical CSF spaces (cortical CSF) showed a linear negative association with days to relapse/recurrence at the exploratory significance level of $p < .05$ (2-tailed).

Survival analysis. The risk of showing symptom relapse/recurrence associated with this sole significant imaging variable was estimated by using Cox regression. We found that patients with severe cortical CSF space enlargement showed a 7.8-fold likelihood (95% CI = 2.1 to 29.6) of suffering depression relapse/recurrence compared with patients with no cortical CSF space enlargement. Risk differences between the mild-to-moderate subgroup and the other 2 subgroups (no alterations and severe CSF space enlargement) were not significant. The inclusion of the potential clinical moderators described above, in addition to remission time, did not significantly modify the results. Again in this analysis, we found that no variable entered the equation when including clinical moderators first.

Kaplan-Meier survival curves are shown in Figure 3. Group differences in relapse/recurrence time were significant, showing log rank of 12.4, df = 2, p = .0021. Relapse or recurrence of depression occurred in 4 (13%) of 31 patients showing no cortical CSF enlargement (median relapse/recurrence time for these cases was 346 days), in 4 (31%) of 13 patients with mild-to-moderate CSF enlargement (median relapse/recurrence time 106 days), and in 5 (63%) of 8 patients with severe CSF enlargement (median relapse/recurrence time 121 days).

DISCUSSION

We have prospectively observed a significant association between enlargement of brain CSF spaces and the short- and long-term clinical outcome of patients with melancholic depression. Enlargement of CSF spaces in the left sylvian fissure region predicted poor treatment response, and severe global cortical CSF space changes were associated with increased risk of depression relapse or recurrence during the 2-year follow-up.

Although this study was based on 3-dimensional MRI, using a specific research measurement protocol, the described global cortical and sylvian fissure CSF alterations may easily be detected by conventional neuroimaging. Therefore, possible implications of this study may be found in the clinical context. All in all, our findings suggest putative neuroimaging markers for patient prognosis.

Early computed tomography scan studies reported increased mortality risk in depressed elderly patients showing ventricular enlargement.[30] More recent work was based on MRI and focused on the presence of white matter hyperintensities. In these studies, white matter alterations were associated with poor initial response to treatment[7,31] and poor long-term outcome.[8–10] Therefore, both the white matter alterations previously described and the abnormal appearance of CSF spaces assessed in this study seem to be more prevalent in the subgroup of patients with an unfavorable clinical course.

Our findings should not be extrapolated to the whole depression spectrum as they specifically concern rela-

tively elderly patients with severe melancholia requiring hospital admission for treatment. Melancholic depression is considered a symptomatically severe subtype of major depressive disorder, with an autonomous course, unlikely to remit spontaneously, and with good response to biological treatments.[19,32] Factors such as selection of this depression subtype without other Axis I comorbidity, exclusion of severe physical illness or neurologic disorder, the use of a standardized antidepressive treatment, and the hospitalized status of all patients (a guarantee of higher treatment compliance), could well improve treatment response and account in part for the high remission rate observed in our patients.

We found no significant association between clinical outcome measurements and other well-established factors of poor prognosis in major depressive disorder, such as symptom severity,[33] patients' age,[4] or the number of previous episodes.[5,34] We studied a homogeneous group of melancholic patients, with similar severity, relatively late-onset illness debut, and low rate of recurrence. The idiosyncrasy of our sample may perhaps be responsible for this lack of association between prognosis and specific clinical variables. Nevertheless, our patient selection possibly favored the detection of the effect of brain structural abnormalities on treatment response and rate of symptom relapse/recurrence.

We would specifically mention that the association between CSF space enlargement in the left sylvian fissure region and poor treatment response is consistent with a growing body of data suggesting involvement of left perisylvian structures in response to antidepressive strategies.[35–38] The specific participation of left perisylvian cortices in the complex process of regulating mood is not clear. Nevertheless, current knowledge suggests that this region may indeed be one of the brain resources required for sustaining mood and for mood restitution with probable linking of the left (verbal) neocortex with the limbic system.[20,21,39–41]

The origin of structural brain changes detected in depression is not completely understood. According to Kumar et al.,[12] parenchyma volume alterations and white matter lesions are relatively independent and complementary contributors to depressive illness. High intensity white matter lesions seem to be related to neuropathologic changes associated with older age and other medical disorders. Nevertheless, the mechanisms leading to volume alterations of some intracranial structures in specific patient groups remain less clear.[42] Both neurodevelopmental and neurodegenerative processes have been considered. We focused our study on measuring brain CSF spaces, where eventual alterations are maximally evident upon neuroradiological inspection. CSF space enlargement, however, may be either an indicator of neural loss (atrophy) or a "hypertrophy of arachnoidal spaces," related to some increased somatic development (involving meningeal structures). Novel voxel-based MRI morphometry will better detect parenchyma volume reduction in specific brain locations, as the recent study of Kaufmann et al.[43] suggests. These authors found a reduction specifically of gray matter volume in depressed patients, which was, as in our study, also particularly evident in the left perisylvian region.

We would stress that, despite uncertainties as to the origin of structural brain alterations in depression, their detection may be of clinical interest in the extent to which they may represent neuroimaging markers of poor prognosis. It is evident that, according to the data provided, MRI-detected brain alterations cannot identify a patient with a specific type of depression and may not significantly assist a therapeutic decision. At the moment, however, relevant enlargement of the left sylvian fissure CSF spaces may suggest an excess risk for delayed treatment response, a situation in which more intensive treatment is often required. Likewise, global CSF enlargement at the cortical level in melancholic patients suggests some increased risk for symptom relapse or recurrence, a clinical situation in which both maintenance treatment and closer patient monitoring are often recommended.

Drug name: imipramine (Tofranil, Surmontil, and others).

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