Frontal Cerebral Perfusion After Antidepressant Drug Treatment Versus ECT in Elderly Patients With Major Depression: A 12-Month Follow-Up Control Study

Víctor Navarro, M.D., Ph.D.; Cristóbal Gastó, M.D., Ph.D.; Francisco Lomeña, M.D., Ph.D.; José J. Mateos, M.D.; María J. Portella, Psy.D.; Guillem Massana, M.D., Ph.D.; Miguel Bernardo, M.D., Ph.D.; and Teodoro Marcos, Psy.D., Ph.D.

Background: Little is known about the evolution of brain perfusion alterations in patients with major depression, and still less about the changes in functional neuroimage produced by different antidepressant biological treatments.

Method: Between January 2001 and December 2003, long-term follow-up frontal brain perfusion was compared in 2 subgroups of elderly patients (≥ 60 years) treated for severe unipolar major depression (DSM-IV): one subgroup of 16 patients administered electroconvulsive therapy, and another of 26 patients receiving pharmacologic treatment. All patients were remitters. A medication-free brain single photon emission computed tomography was performed in baseline conditions and after a minimum period of 12 months of euthymia. Twenty-eight age- and sex-matched healthy controls were also assessed.

Results: No significant differences were found between the 2 subgroups in frontal uptake ratios after a 12-month follow-up period of euthymia. During the acute episode, patients presented significant anterior hypofrontality; 12 months later the hypofrontality had disappeared.

Conclusion: The long-term evolution of frontal perfusion in elderly major depressives who respond to antidepressant biological treatment is essentially the same in those who receive electroconvulsive therapy and in those who receive medication.

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Corresponding author and reprints: Víctor Navarro, M.D., Ph.D., Psychiatry Department, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain (e-mail: 30739vno@comb.es).

Many functional neuroimaging reports have shown abnormalities in resting-state major depressed patients.[1] A number of studies have also assessed brain activity changes after acute response to antidepressant treatment in major depression.[1] To our knowledge, however, no comparison of changes in functional activities produced by different antidepressant biological treatments has been performed to date.

The aim of this study was to assess and compare frontal brain perfusion at baseline and after 12 months in remission in 2 subgroups of elderly patients with severe major depression, one administered electroconvulsive therapy (ECT) and the other antidepressant drugs. A sex- and age-matched subject control group was also assessed. Brain perfusion was measured by single photon emission computed tomography (SPECT).

Functional neuroimaging studies,[2,3] structural neuroimaging studies,[4] and neuropsychological studies[5] have all reported the frequent involvement of frontal areas in the physiopathology of major depression in the elderly. For this reason, frontal areas were chosen for examination in the present research.

METHOD

Sample

The study was conducted at the Hospital Clinic in Barcelona, Spain from January 2001 to December 2003. Right-handed inpatients and outpatients with unipolar major depression aged 60 years or over were recruited. To be eligible for inclusion, patients had to fulfill the DSM-IV[6] criteria for a current major depressive episode. Patients with neurologic disorders, those taking medications with potential central nervous system side effects, and those with uncontrolled medical illness at the time of recruitment were not admitted. Psychiatric exclusion criteria included any history of mania, hypomania or non-affective psychosis, and current substance dependence. Similarly, in order to reduce the chance that prior exposure to ECT

might bias the results, patients who had received ECT within 6 months of recruitment were also excluded.

Right-handed control subjects aged 60 or over were recruited from patients' families. They had no personal history of psychiatric illness or substance abuse. The study was approved by the ethical committee of our hospital. All patients (or a close relative when there was doubt about the patient's understanding) and control subjects gave informed written consent.

Clinical Assessment

Depressive symptoms were rated on the Spanish version of the 17-item Hamilton Rating Scale for Depression (HAM-D).[7,8] All patients recruited had a baseline HAM-D score of 21 or greater. We also screened for reduced global cognitive function using the Spanish version of the Mini-Mental State Examination (MMSE).[9,10]

Some researchers have suggested that vascular mechanisms may be the most important factors in the development of elderly major depression.[11,12] Following Baldwin and Tomenson,[13] we quantified vascular risk factors as follows: 0, absent; 1, mild (asymptomatic): for example, controlled hypertension or clinical evidence of arteriosclerosis (e.g., carotid murmur); 2, moderate (symptomatic): for example, poorly controlled hypertension, symptomatic angina, or history of myocardial infarct; 3, severe (active disease): for example, peripheral vascular disease with amputation or transient ischemic attack.

Major depression is often confused with organic cognitive impairment.[14] In order to reduce the chance of error in diagnosis, 2 inclusion criteria were required both for patients and for controls during the 12-month follow-up period: absence of dementia according to the DSM-IV criteria and MMSE score higher than 25.

Study Design

In order to minimize bias due to the administration of psychotropic drugs, patients receiving pharmacologic treatment underwent an antidepressant medication washout period of at least 10 days and a benzodiazepine medication washout period of at least 2 days. Baseline clinical assessments were then conducted, including the baseline brain SPECT, and naturalistic treatment was started. Clinical evaluations (HAM-D) were carried out fortnightly during the first 3 months of follow-up and then on a monthly basis. Patients were considered to be remitters when their 17-item HAM-D score was below 8 for at least 1 month.

Patients considered clinically in remission for 12 months were administered a second brain SPECT. Antidepressant treatment was suspended temporarily for 10 days before performance of the in-remission SPECT. If ECT had been administered to treat the acute depressive episode, the in-remission SPECT was performed at least 12 months after the last ECT session. Control subjects underwent brain SPECT at only 1 timepoint.

Table 1. Antidepressant Treatment During the Follow-Up Period of Euthymia

	Drug Remitters (N = 26)			ECT Remitters (N = 16)		
Antidepressant	N	%	Dose, mg/day Mean (SD)	N	%	Dose, mg/day Mean (SD)
Citalopram	7	26.9	27.1 (9.6)	0	0	0
Nortriptyline	7	26.9	64.3 (19.7)	3	18.8	66.7 (14.4)
Venlafaxine	12	46.2	206.2 (33.9)	13	81.2	207.7 (32.9)

Clinicians were blind to the functional neuroimaging measures.

Treatment Protocol

The naturalistic treatment used complied with standard therapeutic norms, and specifically with our hospital's treatment protocol for elderly major depression patients. The antidepressants normally used were citalopram (20–40 mg/day) as a selective serotonin reuptake inhibitor antidepressant, venlafaxine extended-release (150–225 mg/day) as a norepinephrine and serotonin reuptake inhibitor antidepressant, and nortriptyline (with a blood level between 80 and 120 ng/mL) as a tricyclic antidepressant. In combination with antidepressant treatment, haloperidol (up to 4 mg/day) for management of psychotic symptoms and lorazepam (up to 4 mg/day) for management of anxiety/insomnia were both allowed during the first 4 weeks.

The presence of psychotic symptoms, severe psychomotor retardation, agitation, suicide risk, intolerance of pharmacologic treatment, refusal to eat, and resistance to antidepressant treatment were the items considered when ECT was prescribed. Subjects selected to receive ECT underwent 3 sessions per week with a constant current, brief-pulse device. Under a systematic protocol, all treatment stimuli were delivered with bifrontotemporal electrode placement. EEG and motor seizure manifestations were monitored to ensure adequate duration.[15] Succinylcholine (40–100 mg), atropine (0.5–1 mg), and thiopental (200–300 mg) were used for anesthesia. With the exception of trazodone up to 150 mg/day for management of anxiety or insomnia and/or haloperidol up to 4 mg/day for management of psychotic symptoms during the first 6 ECT sessions, psychoactive drugs were not allowed during ECT.

None of the patients in the final sample received maintenance/continuation ECT. After the acute treatment with ECT, all patients were administered antidepressant drugs (habitually, venlafaxine extended-release 150 mg/day). During euthymia, patients in the pharmacologic treatment subgroup received the same drug and dose as during the acute episode (Table 1).

SPECT Procedure

A drug-free brain ^{99m}Tc-HMPAO SPECT study was performed in each subject. SPECT was performed using a

Table 2. Demographic and Clinical Data of Remitter Subgroups and Controls[a]

Variable	Drug Remitters (N = 26)	ECT Remitters (N = 16)	Controls (N = 28)
Male, N (%)	8 (30.8)	5 (31.3)	8 (28.0)
Age, y	72.19 (7.69)	72.88 (7.54)	71.71 (4.75)
Age at onset, y	70.46 (6.60)	71.69 (7.24)	NA
Psychotic, N (%)	2 (7.7)	5 (31.3)	NA
Inpatient, N (%)	12 (46.2)	14 (87.5)	NA
Vascular risk factor	1.23 (0.59)	1.13 (0.81)	1.29 (0.71)
Baseline HAM-D score	31.00 (6.33)	34.06 (5.82)	NA
12-month HAM-D score	3.00 (1.17)	2.81 (1.68)	2.14 (1.53)
Baseline MMSE score	27.19 (1.02)	26.31 (0.48)	NA
12-month MMSE score	29.15 (0.77)	29.44 (0.73)	29.18 (0.77)

[a]Values are mean (SD) unless otherwise indicated.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MMSE = Mini-Mental State Examination, NA = not applicable.

rotating dual-head gamma camera (Helix, GE Medical Systems), fitted with a high resolution fanbeam collimator. Data acquisition started 20 minutes after intravenous injection of 740 MBq of ^{99m}Tc-HMPAO (Ceretec, Nycomed-Amersham). Sixty 30-second frames were collected in a 360° circular orbit, step and shoot mode, using a 128 × 128 matrix.

Image data were processed on an Elscint SP1 computer (Apex SP-X, software version 3.12). Reconstruction was performed by filtered backprojection, using a Metz Filter (full width at half maximum [FWHM] = 10; power factor = 3). No attenuation correction was performed. The final pixel size was 3.9 mm and the FWHM in the transaxial plane was 10 mm.

Semiquantitative regional cerebral blood flow (rCBF) analysis was performed using irregular regions of interest (ROIs) stored in the computer as a template. The template was obtained from a standard T1 weighted magnetic resonance imaging. The ROIs were placed by the same nuclear medicine physician in ten 7.8-mm thick oblique slices, which were parallel to the frontocerebellum plane. For each hemisphere, anterior frontal-to-cerebellum ratios were obtained as 100 × mean counts per pixel of anterior frontal ROIs divided by the mean counts per pixel of cerebellum ROIs. Using the same formula, posterior frontal ratios were also obtained. The nuclear medicine physician was blind both to the diagnosis and to the timepoint. More exhaustive information about the SPECT procedure has been described elsewhere.[3]

Statistical Procedures

Baseline clinical and demographic data of control subjects, ECT remitters, and antidepressant drug remitters were compared using the Student t test (or the Mann-Whitney U test for nonparametric data) for continuous variables and the chi-square test for discrete variables.

To assess differences between controls and ECT and antidepressant drug remitter subgroups for each ROI, t tests were carried out. Comparisons were made of the pretreatment and posttreatment ratios inside each remitter subgroup and of the posttreatment ratios of the 2 subgroups. The statistical significance level was defined as $p < .05$. Significance values were adjusted by the Bonferroni correction when comparisons were multiple.

RESULTS

Sixty-four patients were initially enrolled. Seven did not complete the study: 3 from the ECT subgroup and 4 from the pharmacologic treatment subgroup. Two died (one of a heart attack and the other in a road accident), 3 did not follow the treatment, and 2 did not attend scheduled visits. Of the 57 patients who completed the study, 42 (73.7%) were considered remitters, 26 from the pharmacologic treatment subgroup and 16 from the ECT subgroup. The study also included 28 age- and sex-matched controls.

Six of the ECT remitters initially received pharmacologic treatment without response or presented intolerance, while the remaining 10 were directly prescribed ECT. The mean number of ECT treatments was 10.0 (SD = 1.15; range = 8–13).

A summary of the baseline and in-remission characteristics of the final sample is shown in Table 2. At baseline, ECT remitters presented higher hospitalization ($\chi^2 = 7.18$, df = 1, $p = .07$) and psychotic rates ($\chi^2 = 3.96$, df = 1, $p = .047$) and lower MMSE score ($U = 98.00$, $z = 3.11$, $p = .002$) than pharmacologic treatment responders. No other baseline clinical difference was found between the subgroups. In remission, no significant differences in clinical or demographic data were found between ECT remitters, pharmacologic treatment remitters, and controls.

Significant differences were found between baseline anterior frontal uptake ratios in controls and in the patient subgroups; both of the patient subgroups presented bilateral hypoperfusion prior to treatment. In contrast, in the posterior frontal areas, no significant differences were found at baseline between controls and either patient subgroup (Table 3).

Table 3. Uptake Ratios of Pre- and Posttreatment Remitter Subgroups and Controls

Subgroup/Region	Pretreatment[a]	Posttreatment[a]	Controls[a]	t	df	Significance
ECT remitters (N = 16)						
Left anterior frontal	94.06 (2.09)		100.42 (3.02)	7.45	42	< .0001
Right anterior frontal	97.51 (3.18)		101.62 (3.49)	3.89	42	< .0001
Left posterior frontal	91.47 (4.90)		92.08 (4.94)	0.39	42	NS
Right posterior frontal	92.11 (4.34)		92.70 (4.91)	0.40	42	NS
Left anterior frontal		99.54 (5.51)	100.42 (3.02)	0.68	20.26	NS
Right anterior frontal		101.43 (4.44)	101.62 (3.49)	0.16	42	NS
Left anterior frontal	94.06 (2.09)	99.54 (5.51)		3.72	19.22	.001
Right anterior frontal	97.51 (3.18)	101.43 (4.44)		2.88	30	.007
Drug remitters (N = 26)						
Left anterior frontal	94.93 (3.69)		100.42 (3.02)	6.00	52	< .0001
Right anterior frontal	98.29 (2.85)		101.62 (3.49)	3.82	52	< .0001
Left posterior frontal	90.27 (3.84)		92.08 (4.94)	1.50	52	NS
Right posterior frontal	93.03 (4.85)		92.70 (4.91)	0.25	52	NS
Left anterior frontal		99.09 (6.31)	100.42 (3.02)	1.00	35.31	NS
Right anterior frontal		101.18 (4.62)	101.62 (3.49)	0.40	52	NS
Left anterior frontal	94.93 (3.69)	99.09 (6.31)		2.90	40.35	.006
Right anterior frontal	98.29 (2.85)	101.18 (4.62)		2.71	41.63	.01

[a]All values are mean (SD).
Abbreviation: NS = not significant.

Table 4. Posttreatment Uptake Ratios of Both Remitter Subgroups[a]

Region	ECT Remitters (N = 16)	Drug Remitters (N = 26)	t	df	Significance
Left anterior frontal	99.54 (5.51)	99.09 (6.31)	0.24	40	NS
Right anterior frontal	101.43 (4.44)	101.18 (4.62)	0.17	40	NS

[a]All values are mean (SD).
Abbreviation: NS = not significant.

Both subgroups of remitter patients presented a significant increase in perfusion in the anterior frontal region after treatment (Table 3). Similarly, in remission, no significant differences were found in frontal brain perfusion ratios either between the patient subgroups and controls (Table 3) or between ECT remitters and antidepressant drug remitters (Table 4).

DISCUSSION

The main finding of our study is that no significant differences were found in frontal uptake ratios after a 12-month follow-up period of euthymia between 2 subgroups of elderly major depressed patients in remission, one of which had received ECT and the other antidepressant drugs. To our knowledge, this is the first study to compare the long-term effect of 2 different biological antidepressant treatments on brain perfusion in major depressed patients. Two other important findings should be stressed. First, we observed anterior frontal hypoperfusion during the acute episode in both the ECT and the pharmacologic treatment remitter groups. Second, anterior frontal perfusion normalized after clinical remission with both antidepressant biological treatments.

ECT and Brain Perfusion

The functional brain effects of ECT are still a matter of controversy. To date, few studies of the short-term (≤ 1 week) effects of ECT have been published, and the results are contradictory: some show short-term increases,[16–18] some show decreases,[19–21] and some report no net effect on brain perfusion/metabolism.[22,23] Only one study, by Awata et al.,[24] has reported functional brain effects of ECT in major depression in the mid-term; those authors found the brain perfusion pattern to be similar before and after ECT, a result that was not reproduced in our research. The 3-month study by Awata et al. is also the only previous report of brain activity after ECT in the elderly.

Antidepressant Drug Treatment and Brain Perfusion

Preclinical studies have shown that pharmacologic treatment, particularly fluoxetine and tricyclic antidepressants, has pronounced effects on capillary permeability, cerebral blood flow, and cerebral metabolic rate.[25–27] In contrast, studies of changes in functional brain activity following effective pharmacologic treatment of major depression have yielded inconsistent results. Some authors have argued that functional activity is decreased, particularly in the ventrolateral and orbital cortex.[28] However, several studies have shown no change in at least some baseline cortical abnormalities,[29–32] though others have found at least partial reversal of baseline cortical deficits, particularly in the dorsolateral prefrontal cortex,[33,34] or complex patterns of increases and decreases.[35]

Antidepressant Drug Treatment and Brain Perfusion in the Elderly

None of the pharmacologic studies cited have concentrated on long-term functional neuroimaging changes in elderly major depression. To our knowledge, only 2 functional neuroimaging studies have assessed rCBF in elderly major depression after treatment response.[36,37] Nobler et al.[37] found that the baseline depressed sample presented lower rCBF in frontal, temporal, and anterior parietal cortical regions than the control group; after 6 to 9 weeks of pharmacologic treatment, rCBF fell still further in pharmacotherapy responders in selective frontal and anterior temporal regions. In contrast, with a smaller sample (N = 35) than in the present study, we reported[36] that acute major depressed patients presented significantly lower uptake in the left anterior frontal region (not bilaterally, as in the present study) than a control group, and that 12 months after remission the left anterior frontal cerebral perfusion abnormalities had disappeared. In the present research, carried out in a different sample, the results of the intragroup comparisons (pre- and posttreatment), in both subgroups (ECT or antidepressant medication) corroborate our previous results regarding the normalization of frontal perfusion after obtaining clinical remission.

Previous functional neuroimaging reports of elderly major depressed patients during acute episodes (not during remission) have shown globally decreased uptake of the radiotracer compared with controls[38]; decreased uptake in the thalamus, right posterior cingulate, right parietal cortex, and right caudate[39]; significant reductions in perfusion in the right and left parietal, left temporal, and left occipital regions[40]; and, as in the present report, reduced uptake in both the left and the right anterior frontal regions.[3,36]

Clinical Implications of the Reversibility of Brain Perfusion Abnormalities

Though it was not our intention to assess the etiopathogeny of elderly major depression, we should mention that the frontal functioning neuroimaging results of our study do not support Alexopoulos and colleagues' proposal of a degenerative ischemia-type process as the cause of elderly major depression (vascular depression).[11] Alexopoulos' hypothesis is not borne out by our observation that alterations in frontal brain perfusion are reversible regardless of the biological treatment used.

To explain this unexpected result, we suggest that most studies of vascular depression are associative[41,42] rather than causative and that the frequently observed association between elderly major depression and vascular disease may in fact be due to unknown confounding factors. A vascular etiology has been proposed for late-onset depression on the strength of the presence of hyperintensities, though in fact the physiopathologic bases of these lesions have not been definitively determined in patients with major depression.[43] We should add that ours is not the first study to obtain results that raise doubts about the degenerative vascular hypothesis for elderly major depression.[3,42,44,45] Our results suggest that the pattern of anterior frontal perfusion reflects a primary alteration of neuronal activity, probably reversible, and that there may not necessarily be a primary vascular substrate.

Limitations

The lack of homogeneity in the results obtained in functional neuroimaging studies of major depression (both during acute episode and after remission) is probably due to the wide range of methodological approaches, statistical analyses, and demographic characteristics of the samples in each study. Our results should be considered in the light of 2 main limitations: a relatively small sample size and a naturalistic treatment. In addition, only severely depressed elderly patients were included in our sample, meaning that the results cannot be extrapolated to the general population. Another conceivable limitation of the study is the fact that we used family members as controls, since altered uptake ratio may be a genetic risk factor for depression that would obviously be overrepresented in families of individuals who develop major depressive episodes. However, over 50% of the controls were spouses or in-laws, not first-degree relatives.

Finally, because of the lack of conclusive studies of the minimum washout period needed to avoid interferences between drug treatment or ECT and brain uptake ratios, we cannot be entirely sure that this factor did not influence our results. However, given the similarities between the SPECT data for both remitter subgroups, and, above all, the similarities in the perfusion rates in controls and remitters, our findings support the idea that antidepressant biological treatment does not produce alterations in frontal brain activity that are able to outweigh the changes produced directly by clinical remission.

Drug names: atropine (Atropen and others), citalopram (Celexa), fluoxetine (Prozac and others), haloperidol (Haldol and others), lorazepam (Ativan and others), nortriptyline (Aventyl, Pamelor, and others), succinylcholine (Quelicin, Anectine, and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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