Prominent Reduction in Pyramidal Neurons Density in the Orbitofrontal Cortex of Elderly Depressed Patients

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Background: *Elderly depressed patients have more vascular hyperintensities in frontal white matter and basal ganglia than elderly control subjects. Cell pathology that might be related to increased vascular hyperintensities has not been examined.*

Methods: *Postmortem samples from the orbitofrontal cortex (ORB) were collected in 15 elderly subjects with major depressive disorder (MDD) and 11 age-matched control subjects. Cell packing density of neurons and glia, density of pyramidal and nonpyramidal neurons, and cortical and laminar width were measured.*

Results: *The overall (layers I–VI) packing density of ORB neurons with pyramidal morphology was markedly decreased in MDD (by 30%) as compared with control subjects. Further laminar analysis of pyramidal neurons density revealed significant reductions in layers IIIc and V in MDD. In contrast, in MDD the density of nonpyramidal neurons and glia and cortical and laminar width were comparable to control values.*

Conclusions: *In elderly subjects with depression, the density of pyramidal neurons in the ORB was particularly low in cortical layers V and III, the origin of prefronto–striatal and prefronto–cortical and prefronto–amygdalar projections. Degeneration of neurons furnishing these projections might be related to the white matter hyperintensities previously observed. Neuronal pathology seems to be more severe in elderly than in younger subjects with MDD.*

Key Words: Postmortem, morphometry, glial cells, major depression, late-life depression, aging

Growing clinical evidence indicates that depression in the elderly differs from that in younger patients by its etiology, phenomenology, and cerebrovascular pathology. Neuroimaging studies demonstrate that elderly (aged >60 years) patients with depression show reductions in the volume of prefrontal cortex (Kumar et al 1997, 1998) and orbitofrontal cortex (ORB) (Lai et al 2000; Lee et al 2003; Taylor et al 2003). Elderly depressed patients also display more frontal white matter hyperintensities than age-matched nondepressed control subjects, as revealed by structural magnetic resonance imaging studies (reviewed in Taylor and Krishnan 2003). The highest density of these hyperintensities in elderly depressives occurs in the white matter of the ORB and internal capsule of the left cerebral hemisphere (Greenwald et al 1998; MacFall et al 2001; Taylor et al 2001). In addition, hyperintensities are found in periventricular regions and the gray matter of the basal ganglia, although at a lower density (Coffey et al 1989, 1990; Krishnan et al 2004; Kumar et al 1997; MacFall et al 2001; Steffens and Krishnan 1998; Steffens et al 1999). More recently, an association between smaller ORB volume and a greater density of hyperintensities in the basal ganglia has been found in elderly patients with depression (Lee et al 2003). The results summarized above have led to the hypothesis that lesions of the white matter and other subcortical lesions disrupt white matter tracts and subsequently lead to a decrease in the volume of the ORB (Lee et al 2003). This disruption of fronto–striatal circuits caused by the white matter lesions leads to risk for late-life depression (Alexopoulos et al 1997; Taylor et al 2001). Other studies indicate that independent nonvascular factors, such as atrophy of fronto–limbic brain regions, impaired neuronal plasticity, or comorbidity with nonvascular medical conditions related to age, might also predispose for late-life depression (Alexopoulos et al 2004; Kumar et al 2000, 2002; Mattson et al 2004).

Despite these clinical studies suggesting neuronal pathology in the elderly with major depressive disorder (MDD), a quantitative analysis of cells in relevant cortical regions, including the ORB, has not been conducted in older subjects with MDD. A previous cell-counting study of postmortem ORB in a mixed population of younger and older adults with MDD (average age 53 years) revealed only subtle reductions in neuronal cell density and size but prominent reductions in the density of glial cells (Rajkowska et al 1999). In that study, overall neuronal density as measured across all six cortical layers did not significantly differ between subjects with MDD and the age-matched control group. When individual layers and size classes were examined, however, reductions in the density of large neurons were detected in supragranular layers II–IV of the rostral ORB in subjects with MDD. In addition, the mean size of neuronal cell bodies was smaller in layers II and III in MDD. This observation of unchanged overall neuronal density and smaller neuronal sizes in the ORB in MDD has been confirmed by independent studies in other postmortem frontal regions, such as dorsolateral prefrontal cortex, subgenual cortex, and anterior cingulate cortex (Cotter et al 2001, 2002b; Ongur et al 1998; Rajkowska et al 1999).

The above-mentioned reports of neuronal pathology in the frontal cortex were not designed to examine laminar or overall neuronal morphometric parameters specifically in the elderly subjects with MDD as compared with elderly nondepressed control subjects. On the other hand, studies conducted on the normal aging population of nondemented, psychiatrically normal subjects indicate that the frontal cortex is more vulnerable than other brain regions to age-related neuronal and white matter changes (Head et al 2004; Salat et al 2004; Tisserand et al 2002, 2004). Thus, aging-related dysfunction of the ORB might be a risk factor for depression in the elderly.

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The goal of the present study was to assess neuronal pathology of the ORB in neurologically normal elderly patients with a diagnosis of MDD (age range, 63–87 years) and compare this pathology with age-matched nonpsychiatric control subjects (age range, 58–86 years). Moreover, we compared neuronal pathology in elderly depressed subjects from the present study with that described previously (Rajkowska et al 1999) in the same cortical region in younger subjects with MDD (aged <50 years). We hypothesized that neuronal pathology in ORB of elderly subjects with MDD is more severe than in age-matched control subjects or younger subjects with MDD. Furthermore, we hypothesized that ORB pathology will be most prominent in cortical layers III and V, the site of cells bodies of neurons giving rise to prefronto–striatal projections.

Methods and Materials

Postmortem samples from the left ORB were collected at autopsies performed at the Cuyahoga County Coroner's Office in Cleveland, Ohio. Brain tissue was collected from 15 elderly (average age, 75 ± 9 years [mean ± SD]; 8 male, 7 female) subjects with MDD and 11 age-matched control subjects (average age, 72 ± 8 years; 7 male, 4 female) (Table 1). In accordance with the policies of the institutional review board of the University of Mississippi Medical Center, written consent was obtained from the next-of-kin for all subjects included in the study. Retrospective, informant-based psychiatric assessments were performed for all depressed and control subjects. A trained interviewer administered the Structured Clinical Interview for DSM-IV Psychiatric Disorders (First et al 1996) to knowledgeable next-of-kin as previously described (Stockmeier et al 2004). Both lifetime and recent (last 2 weeks of life) Axis I psychopathology was assessed, and a consensus diagnosis was reached in conference according to DSM-IV criteria (American Psychiatric Association 1995) with information from the interview and medical records. In addition, information was also collected about prior psychoactive substance use, medication history, and postmortem toxicology (see Table 1 for information on subjects). Subjects were excluded from the study if they ever showed evidence of head trauma or neurologic disease (including Alzheimer's disease), established by postmortem neuropathological examination that included immunostaining for β-amyloid (neuritic plaques) or Tau protein (neurofibrillary tangles). Psychoactive substance use disorder within the last year of life was also an exclusion criterion. According to the clinical records, all control and nearly all depressed subjects exhibited signs of vascular disease, defined as the presence of one or more of the following conditions: a history of myocardial infarction, a diagnosis of coronary artery disease, myocardial infarction listed as the reason of death, atherosclerotic vascular disease by autopsy or other medical documentation, a history of hypertension, hypertensive cardiomyopathy, diabetes mellitus, amyloidosis, or renal stenosis. Thus, there were no differences in vascular risk between control and depressed subjects. There were no significant differences between the depressed and control groups in postmortem interval or time the tissue was kept in formalin (Table 1). The average postmortem interval (hours, mean ± SD) of the two groups was 21 ± 6 (MDD) and 22 ± 4 (control subjects). The average time in formalin was 23 ± 16 months (MDD) and 24 ± 9 months (control subjects). There was a small (2%) but significant [$t(24) = 2.139$, $p = .043$] difference in tissue pH between the groups. The average pH was 6.59 ± 0.18 (MDD) and 6.73 ± 0.14 (control subjects) (Table 1).

The MDD group included 8 subjects with early onset of MDD (before age 60 years), and 7 subjects with late onset (after age 60 years). Of the 15 depressed subjects, 12 had a recent (within the last month of life) prescription for an antidepressant medication (Table 1). Only 3 of these 12 subjects were responders; 5 were nonresponders, 1 was noncompliant, and for 3 others there was no information available regarding whether they were a responder or nonresponder. An antidepressant medication was present in the blood of only 4 of the 12 with a recent prescription (Table 1). Of the 12 depressed subjects with a prescription for an antidepressant medication, 3 had also been treated with electroconvulsive therapy.

Celloidin-embedded sections were cut at 40 μm, stained with cresyl violet (final thickness after processing was 35–38 μm), and sampled in the rostral ORB region from Brodmann's area 47, located on the medial wall of the medial orbital sulcus (Figure 1A). This same area was targeted in our previous study of younger subjects (Rajkowska et al 1999), and it was identified according to the same cytoarchitectonic criteria. In each brain, three sections spaced evenly (800–1200 μm) were selected for cell counting. Neurons and glia were distinguished according to morphological criteria described previously (Selemon et al 1995). Pyramidal were distinguished from nonpyramidal neurons by the presence of a triangular cell body, a thick apical dendrite, and thinner basal dendrites.

The overall and laminar density of neurons and glial cells, the density of pyramidal and nonpyramidal neurons, as well as the thickness of the cortex and relative width of each of its layers, were measured in three-dimensional counting boxes (120 μm × 100 μm × 25 μm; 5μm guard zone from the top) with the "Linear Optical Dissector" probe of Stereo Investigator software (5.05.4 MicroBrightField, Williston, Vermont). Mean overall cell density was compared between the groups by analysis of covariance (ANCOVA) ($p < .05$), with postmortem delay, time in formalin, pH, and age as covariates. Cell packing density in individual cortical layers was compared between the groups by multivariate repeated-measures ANCOVA (five cortical layers: I, II, IV, V, VI; and three sublayers: IIIa, IIIb, IIIc of layer III) followed by post hoc univariate contrast analyses. A Bonferroni-adjusted p value of .006 (.05/8) was considered statistically significant for laminar analyses. Correlations between age, age at onset, and duration of depression and neuronal densities were analyzed with Pearson correlation matrices, and the heterogeneity of covariance was also evaluated.

Results

Neuronal Packing Density

Analysis of variance without adjusting for covariates revealed that the overall density of the general population of ORB neurons (pyramidal plus nonpyramidal) in all cortical layers combined was significantly reduced [by 14%; $F(1,24) = 7.547$, $p = .01$] in the group of elderly depressed subjects as compared with the age-matched control group (Figure 1B); however, according to ANCOVA with postmortem delay, time in formalin, tissue pH, and age as covariates, the difference was not statistically significant [$F(1,20) = 3.090$, $p = .089$] (Figure 1B). The pH of the brain tissue was the only confounding variable, which was significantly correlated with the overall neuronal density in the control subjects ($r = .791$, $p = .004$) and at slightly less magnitude in the depressed group ($r = .532$, $p = .041$); however, pH was not correlated with either postmortem delay or age at the time of death.

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