Left Frontotemporal Hypoperfusion Is Associated With Aggression in Patients With Dementia

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Background: Aggressive behavior is common in patients with dementia. Temporolimbic and prefrontal cortical lesions can produce pathological aggression; however, involvement of these structures has not been established in aggressive patients with dementia.

Objective: To study the relation between regional brain perfusion and aggressive behavior in patients with dementia.

Methods: We compared the pattern of regional cerebral perfusion determined with technetium Tc 99m-labeled hexamethylpropelene amineoxime single photon emission computed tomography in 2 groups of 10 patients with dementia with and without aggression, that were comparable for demographic factors, severity of cognitive impairments, and other behavioral symptoms as measured by the Neuropsychiatric Inventory.

Results: Patients with aggression revealed significant (P<.001) hypoperfusion in the left anterior temporal cortex; additional bilateral dorsofrontal and right parietal cortex were also found to be significantly hypoperfused.

Conclusion: These results indicated an association between aggression and decreased perfusion in the left anterior temporal cortex.

Arch Neurol. 2000;57:861-866

Behavioral symptoms manifest in patients with dementia and have a major influence on quality of life and social affiliations for patients and caregivers. Among these behavioral problems, aggressive outbursts are frequent and may pose the greatest caregiver distress.1,2 Agitation or aggression are reported in 12% to 65% of patients with Alzheimer disease (AD) or other dementias.3,4,5,6,7,8 Aggressive behavior causes serious burden and depression in caregivers,1,2,9,10 and increases the likelihood of hospitalization, early institutionalization, and abuse of patients.1,3,9,10,11 In the nursing home, aggressive behavior is associated with a need for increased staff supervision,12 and the use of physical restraints. Moreover, aggressive behaviors may have severe adverse consequences, including injury, which may lead to the death of patients or others.13 Therefore, evaluation and management of aggressive behaviors are of considerable importance in the care of patients with dementia.

Although functional factors, such as pathological rearing, psychological trauma, and social stress, are important in the occurrence of aggression, regional brain lesions can produce pathological aggression in animals and humans. Among these regions, the temporolimbic and prefrontal cortices have been most frequently implicated.9,10 Aggressive verbalization and rage occur with stimulation of the amygdala and hippocampus in animals.11 Although destruction of the amygdala in monkeys and humans usually results in placidity, Rosvold et al12 reported that amygdalec- tomy in submissive monkeys increased aggression, suggesting that amygdalar dysfunction modifies aggressive behavior in a variety of ways. Recently, Zagrodzka et al13 reported that unilateral damage to the central nucleus of the amygdala alone increased the expression of aggressive behavior in the cat. Patients with temporal lobe epilepsy may have increased aggression during interictal periods in addition to ictal and postictal aggressive outbursts.14,15 Furthermore, violent patients with focal lesions are most likely to have focal temporal abnormalities on electroencephalography16,17 and structural abnormalities in temporal lobes.18 Functional neuroimaging studies using positron emission tomography...
or single photon emission computed tomography (SPECT) in aggressive individuals show hypometabolism or hypoperfusion in temporal lobes, particularly on the left side.28,30-33 Dysfunction of the prefrontal cortex also has been implicated in aggressive behavior. Increased aggressive feelings are reported by patients with focal orbitofrontal lesions.34 Neuropsychological53-57 and electrophysiological studies support a relationship between frontal lobe dysfunction and aggression, and functional neuroimaging studies indicate an association between aggression and hypometabolism in the prefrontal cortices, especially the orbitofrontal cortex.28,30-32,36-40

The underlying mechanism for aggression in patients with dementia is unclear and involvement of the orbitofrontal and temporolimbic cortex has not been established. Studies evaluating focal brain lesions related to aggression in dementia are lacking. Sultzer et al41 reported, in a study of 21 patients with AD, that the agitation/disinhibition factor score of the Neurobehavioral Rating Scale correlated with glucose metabolism in the frontal and temporal lobes, but they did not evaluate aggression separately.

In this study, we compared the pattern of regional cerebral perfusion between 2 groups of 10 patients with dementia with and without agitation/aggression as measured by the Neuropsychiatry Inventory (NPI). The NPI emphasizes noncompliance, refusal to cooperate with the caregiver, obstinence, resistance, cursing, kicking, and being “hard to handle” within the agitation/aggression section. Groups were comparable on all demographic factors, severity of cognitive impairments, and all other be-
injection of the radiolabeled substance. Approximately 1 hour after injection, during which time washout of the tracer from the brain had occurred, SPECT images of the brain were obtained using the a SPECT scanner (Picker Prism 3000XP SPECT scanner; Picker International Inc, Cleveland, Ohio) with low-energy, ultrahigh-resolution fan beam collimators. Images were reconstructed by filtered back-projection using lowpass filter, order 8, with a spatial fre-
quency cutoff of 0.23 to 0.25 cycles per pixel. Transverse, sagittal, and coronal planes as 128 × 128-pixel slices were generated. Pixel sizes were nominally 3.56 × 3.56 mm. Resolu-
tion of the system was approximately 6-mm full-width half maximum.

IMAGE ALIGNMENT PROCESSING

Spatial alignment of all 20 SPECT data sets was accomplished via 12-parameter affine registration. All data sets were first aligned to one randomly selected target to ob-
tain an “average SPECT” which in turn was registered to the International Consortium of Human Brain Mapping probabilistic atlas. To minimize resampling of data, the 2 above warping fields were concatenated and applied to each SPECT data set. The relative perfusion scans of each patient then underwent linear intensity normalization, on a voxel-by-voxel basis, to the global mean intensity value of all 10 patients within each group, thus equalizing the mean intensities across intragroup data sets. This normal-
ization step did not alter the variance of data.

Once all normalized data sets were in the common International Consortium of Human Brain Mapping probabilistic atlas space, a voxel-by-voxel subtraction was conducted between the aggressive and nonaggressive groups. Subvolume thresholding (SVT) was used to cre-
ate a statistical map of these subtraction results as previ-
ously described. Briefly, SVT uses the probabilistic ana-
tomical partitioning of the International Consortium of Human Brain Mapping atlas (partitions include the frontal, parietal, temporal, insular, and occipital cortex, along with the putamen, caudate, thalamus, and cerebellum) to model the different regions as separate stationary random fields thereby accommodating nonuniform global brain ac-
tivity. In addition, the probability clouds of the Interna-
tional Consortium of Human Brain Mapping atlas allow us to control for spatial errors, imposed by registration and anatomical variability, by weighting the contribution of voxel intensities based on their location within an anatomical cloud. Thus, voxels within the center of a region have the highest probability of belonging to that region while vox-
els at the edge of a region have a lower chance of being ac-
curately identified owing to registration error and normal anatomical variability.

The SVT approach departs from other functional im-
aging techniques. In the first step of significance evalua-
tion, an estimate of the pooled variance for the average voxel intensity, which is dependent on the topology of the ana-
tomical subvolume of interest, is used to assess the glob-
ally significant variability of data within each region sepa-
ately, permitting a functional-anatomical test of the sub-
traction paradigm. This novel approach is particularly suited for the assessment of functional imaging studies in dementia since parietal and temporal regions may have sig-
nificantly different means and variances, across subjects, than frontal or subcortical regions given the local path-
ological distribution of dementing disease. Ignoring these potential differences by modeling the entire data set as a stationary random field, done by many other functional as-
sessments, will oblitrate disease-specific variability. Af-
ter the first SVT step identifies globally significant re-
gions, the second step maps the location of voxels, with a difference z score above 2.5, in those regions. This is a stan-
dard procedure in most functional statistical mapping tech-
niques with 2 exceptions: (1) voxel location tests are run only over those regions identified by the global search in step 1 and (2) variance estimates are pooled over subjects and across voxels. Once the locations of voxels within a region of interest have been assigned a z-score value, a sig-
nificance level must be determined for voxels above a z-
score threshold. The SVT local search within globally sig-
nificant regions derived from the between-group subtraction is corrected for multiple voxelwise testing to control for type I errors in assessing significance. For each of the se-
lected voxels outside of our a priori hypothesized regions, a Bonferroni correction is conducted by dividing the sig-
nificance level associated with the z score by the number of voxels constituting a single search (this voxel number is equal to the size of the full-width half maximum of the scanner—6 mm). For voxels within our a priori hypothe-
sized regions, we employed a bootstrap analysis to de-
termine the significance of the selected voxels.

Behavioral symptoms captured by the NPI, including delusions, hallucinations, disinhibition, irritability, apathy, anxiety, and depression. We hypothesized that patients with dementia with significant agitation/aggression would have significantly lower anterior temporal and lateral orbitofrontal perfusion on SPECT analysis compared with patients without agitation/aggression.

Table 1 and Table 2 show the demographic features, psychotropic medications, Mini-Mental State Examina-
tion (all other cognitive indices assessed by our battery were comparable between groups), and behavioral pro-
files of the 2 groups. Of the 10 aggressive patients with dementia 8 were diagnosed as having AD, and 2 were di-
agnosed as having vascular dementia. Of the 10 nonag-
gressive patients with dementia 8 were diagnosed as hav-
ing AD, 1 was diagnosed as having dementia with Lewy bodies, and 1 was diagnosed as having normal pressure hydrocephalus. Agitation/aggression was the only behavior assessed by the NPI that was statistically sig-
nificant (P < .001) different between the 2 groups. The Figure and Table 3 show the Talairach and Tournoux atlas location of the peak significance for regions with significantly lower perfusion in the 10 patients with de-
mentia who had high aggression scores compared with the 10 nonaggressive patients. Patients with aggression revealed statistically significant (P < .001) hypoperfu-
sion in the left anterior temporal cortex (Brodmann ar-
eas 20, 21, and 38); the difference in the orbitofrontal cortices was not significant. Besides the regions we hy-
pothesized would be affected in aggressive patients with dementia, patients with aggression also revealed significant (P<.001) hypoperfusion in the right and left superior frontal cortices (Brodmann area 9) and the right superior parietal area (Brodmann area 7) with between-group differences after Bonferroni correction. Possible confounding effects of medication on cerebral perfusion were controlled for by composing the groups to have an equal percentage of patients with neuroleptic and antidepressant use in both groups.

Seemingly, several studies have suggested that aggressive behavior is associated with demographic factors including male gender,6,58,59 and increasing cognitive loss,3,17,59 in patients with dementia. Therefore, we minimized the confounding effects of these variables: age, sex, education level, psychotropic medications, Mini-Mental State Examination scores, and cognitive performance, all of which were similar between the patients groups with and without aggressive behavior. Moreover, because aggression has been associated with other neuropsychiatric manifestations including delusions, hallucinations, irritability, and depression,3,11,38,60.61 we also ensured that the neuropsychiatric symptoms in the 2 groups were comparable. This approach aids identification of the brain regions that, when dysfunctional, may be specific to aggressive behavior.

Generalizability of this study is limited by the small sample size. The study demonstrated a clear association between aggressive behavior and hypoperfusion in the left anterior temporal cortex but failed to demonstrate the expected involvement of the orbitofrontal cortices in patients with dementia. This failure might be caused by the lack of statistical power due to the small sample size.

The anterior temporal cortex has reciprocal connections with the amygdaloid complex. The amygdala has abundant connections with association cortices of multiple cortical sensory systems; visceral brain areas including brainstem and hypothalamus; basal ganglia; and other limbic structures such as parahippocampal gyrus, insula, and cingulate cortices.62,63 Anterior temporal structures have been posited to play an important role in associating sensory experiences with emotion. Dysfunction of these areas has been implicated in causing abnormal emotional associations to external sensory stimuli, and in provoking inappropriate aggressive acts to trivial or misinterpreted stimuli.10,20,60

In addition to involvement of the left anterior temporal cortex, we found significant regional hypoperfusion in the right and left dorsolateral frontal and right superior parietal regions. Within the prefrontal regions, the disturbances of orbitofrontal cortices have been linked most often to aggression; however, several studies have shown the involvement of the dorsolateral frontal region in aggression.3,30,32,38,40 Dorsolateral frontal regions are considered important to critical thinking and planning,7 and reduced metabolic activity in these regions may lead to misinterpretation of environmental and social situations, which might be related to aggressive behavior. Raine et al32 described significantly decreased glucose metabolism in both superior parietal regions in murderers as compared with normal controls. These findings also are compatible with the fact that aggressive behaviors are more frequent in patients with frontotemporal dementia, who usually have dysfunction of dorsolateral frontal regions as well as of anterior temporal structures, as compared with patients with AD.64 The superior parietal lobes are critical for sensorimotor integration providing subjective knowledge of both the world and one’s own body.65 Dysfunction of the superior parietal lobes may cause the sensory information processing deficits and abnormal assessments of both the world and one’s own body resulting in abnormal emotional responses.

This study bears importantly on the understanding of agitation in dementias. Agitation encompasses many behaviors including aggressive behavior assessed by the NPI. The pathogenesis of agitation in dementia is controversial with some investigators considering it a primary symptom of brain dysfunction and others viewing it as a symptom of psychopathology. In this study,
patients had comparable levels of nonaggressive behaviors, differing only on the aggression/agitation scores of the NPI. Regional brain dysfunction was identified as the correlate of these behavioral differences. These observations support the hypothesis that this type of agitation can occur as a primary behavioral disturbance with unique anatomical underpinnings.

**CONCLUSIONS**

We prospectively studied aggressive behaviors in patients with dementia and the relevant regional cerebral hypoperfusion by using SPECT and an established method of neuropsychiatric assessment in dementia. We demonstrated an association between aggression and decreased perfusion in the left anterior temporal cortex. Our results support previous reports of anterior temporal involvement in aggressive behaviors, irrespective of disease origin. This finding might predict the development of aggression and the effectiveness of therapeutic interventions used for the patients with dysfunction in this region.

Accepted for publication December 22, 1999.

This investigation was supported by Career Development Award K08AG100784 from the National Institute on Aging, National Institutes of Health, Bethesda, Md (Dr Mega); Alzheimer's Disease Research Center grant P50 AG16570 from the National Institute on Aging (Dr Cummings); an Alzheimer's Disease Research Center of California grant, Los Angeles (Dr Cummings); and the Sidell-Kagan Foundation, Los Angeles (Drs Mega and Cummings).

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