Medial Temporal Hypoperfusion and Aggression in Alzheimer Disease

Krista L. Lanctôt, PhD; Nathan Herrmann, MD, FRCPC; Neelesh K. Nadkarni, MD; Farrell S. Leibovitch, MSc; Curtis B. Caldwell, PhD; Sandra E. Black, MD, FRCPC

Background: It is not understood why some patients with Alzheimer disease (AD) display aggression and others do not.

Objective: To examine the relation between regional brain perfusion and aggression in AD.

Design: Single-photon emission computed tomographic scans were coregistered to a standardized template in Talairach space, generating mean ratios of uptake referenced to the cerebellum.

Participants: Forty-nine outpatients (25 men and 24 women; mean±SD age, 74±11 years) with probable AD (Mini-Mental State Examination score, 17.7±5.0; 30 aggressive and 19 nonaggressive), comparable in age, sex, and severity of cognitive impairment.

Main Outcome Measures: Regional perfusion ratios were determined for 5 bilateral regions of interest: orbitofrontal, middle medial temporal, inferior medial temporal, hypothalamus/thalamus, and anterior cingulate.

Results: Compared with nonaggressive patients, aggressive ones displayed hypoperfusion in the right and left middle medial temporal regions of interest (P=.02 for both), but not the others (all t tests, unpaired, 2-tailed). On regression analyses, right middle temporal hypoperfusion (P=.001), younger age (P=.002), greater activity disturbances (P=.004), and higher Mini-Mental State Examination scores (P=.04) independently predicted aggression, accounting for 44% of the total variance (F=8.7; P<.001). Statistical parametric mapping analyses supported right middle medial temporal hypoperfusion in the aggressive group (P=.008).

Conclusion: In this sample of patients with AD, the right middle medial temporal region emerged as an important neural correlate of aggression.

Arch Neurol. 2004;61:1731-1737

Although Alzheimer disease (AD) has predominantly been defined in terms of cognitive impairment, its noncognitive symptoms also play a major role in patient morbidity and ongoing functional decline.1 These symptoms, collectively termed behavioral and psychological symptoms of dementia, include delusions, hallucinations, aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbances, and appetite disturbances.2,3 Among these, aggression has a prevalence of 18% to 65% depending on the series and is associated with considerable patient morbidity and mortality.4-6 Caregiver stress,7 and early institutionalization.8 Despite the importance, the neurobiological characteristics of aggression in AD remain poorly understood.

Many studies have been conducted to analyze the underlying neuroanatomy of aggression. Evidence from animal and human studies suggests that the prefrontal cortex,9 particularly the orbitofrontal cortex,10-12,14 the temporolimbic cortex, particularly the amygdala and hippocampus,15,17,18 and the anterior cingulate cortex form the major components of the human aggression regulatory circuit.19 Although studies in nondemented populations have suggested left laterality in aggression,20 studies in dementia (frontotemporal lobar degeneration) have pointed toward right-sided dominance in socially undesirable behavior.21 Neuroimaging correlates have been investigated for some behavioral disturbances, but there is a paucity of information regarding aggression. Agitation/disinhibition has been correlated with frontal and temporal lobe hypometabolism.22 Aggression in AD has been correlated with temporal lobe atrophy on computed tomographic scans,23 and a single study24 in 20 patients suggested that
hypometabolism in the left anterior temporal cortex correlated with aggression.

We conducted a study to localize the neural areas involved in aggression in AD on the basis of perfusion changes in the brain using single-photon emission computed tomography (SPECT). We hypothesize that the manifestation of aggression in AD is associated with dysfunction in circumscribed areas of the frontal and temporal regions.

METHODS

PARTICIPANTS

The Sunnybrook Dementia Study is a longitudinal study of more than 300 patients with AD and other dementias. Patients who met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association criteria for probable AD and who underwent SPECT within 3 months of their behavioral assessments were included in this substudy. Behaviors were assessed using the Behavior Pathology in Alzheimer Disease scale (BEHAVE-AD). The aggression subscale of the BEHAVE-AD, which ranges from 0 to 9, was used to characterize participants as “aggressive” if they had an aggression score of 1 or more or “nonaggressive” if they had an aggression score of 0. The aggression subscales contain scores ranging from 0 (not present) to 3 (present with additional components) for each of 3 aggressive behaviors: verbal outbursts, physical threats and violence, and agitation. Some participants had 3 or more visits in the database. If any of these visits indicated aggression, the individual was categorized as aggressive, and a BEHAVE-AD score for aggression and the corresponding SPECT scans were used for analysis. The use of psychotropic medications was also documented.

SPECT SCANS AND REGIONAL PERFUSION RATIOS

The SPECT scans were obtained on all patients with the use of a triple detector gamma camera (Prism 3000XP; Philips Medical Systems Inc, Cleveland, Ohio) 30 minutes after injection of 0.02 Ci (740 MBq) of the radiopharmaceutical technetium Tc 99m ethyl cysteinate dimer. Scans were reconstructed by ramp-filtered back projection, followed by a 3-dimensional postfilter (Wiener filter, multiplier 1.0). Reconstructed images were coregistered to a standardized SPECT template in Talairach space, generating mean ratios of uptake in 79 regions of interest (ROIs) referenced to the cerebellum, thereby providing semiquantitative regional perfusion ratios for each patient. Details of this procedure have been published elsewhere. Although brain SPECT does not provide a quantitative measure of regional cerebral blood flow (rCBF), technetium Tc 99m ethyl cysteinate dimer uptake is known to be approximately proportional to rCBF. Uptake in an individual region, scaled to a standard region in the cerebellum, was used to approximate rCBF.

REGIONS OF INTEREST

From the 1 unilateral and 39 bilateral regions defined by Lobaugh et al, 5 ROIs were chosen a priori on the basis of previous literature implicating these regions in aggressive behaviors: the orbitofrontal,18-22 2 temporolimbic cortex ROIs (the middle and inferior regions of the medial temporal gyrus),17,19,22-25 the anterior cingulate cortex,18 and the hypothalamus region.6-38 The volumes of the orbitofrontal ROIs were 24.9 cm³ (right) and 25.69 cm³ (left) and included the frontal poles (Brodmann area [BA] 10) and orbitofrontal gyri (BA 11).33 The volumes of the middle medial temporal ROIs were 13.38 cm³ (right) and 13.46 cm³ (left) and included the hippocampus, parahippocampus, and posterior amygdala (BAs 28/35/36). The volumes of the inferior medial temporal ROIs were 11.87 cm³ (right) and 8.80 cm³ (left) and included the posterior hippocampus, parahippocampal gyrus, and fusiform gyrus (BAs 28/35/36/37). The volumes of the anterior cingulate ROIs were 12.29 cm³ (right) and 11.65 cm³ (left) and included the combined dorsal (BA 25), middle (BAs 24/32/33), and lateral (BAs 24/32/33) regions of the anterior cingulate. The volumes of the hypothalamus/thalamus ROIs were 10.73 cm³ (right) and 10.75 cm³ (left). Mean rCBF in patients with vs without aggression were compared using unpaired, 2-tailed t tests, and rCBF was correlated with aggression scores using Pearson product moment correlations. Because data analysis was hypothesis driven rather than exploratory, correction for multiple comparisons was not performed. Subsequently, to confirm independent predictors of aggression, backward linear regression using forced entry followed by stepwise removal of the least significant predictor was performed until the best model was reached (SPSS version 10.0; SPSS Inc, Chicago, Ill). Variables entered were ROIs with significant correlations, standard covariates (age, sex, and Mini-Mental State Examination [MMSE] score), and behaviors that differed between aggressive and nonaggressive participants.

IMAGE ANALYSES BY STATISTICAL PARAMETRIC MAPPING

Data analysis was also conducted using statistical parametric mapping (SPM) software (SPM 99; Wellcome Department of Cognitive Neurology, London, England) running under the MATLAB environment (MATLAB version 6.0; The MathWorks Inc, Natick, Mass) on Windows XP (Microsoft Corp, Redmond, Wash). The program does not analyze data using predefined regions but instead on a voxel-by-voxel basis, producing a map of significance wherein each voxel has a statistical value used to characterize and define regionally specific effects in imaging data. These regionally specific effects are expressed as differences and similarities in intergroup and intragroup comparison of individuals, respectively, over a sequence of observations. The SPM analyses provide uncorrected and corrected P values, where adjustment involves a Bonferroni correction conservatively based on number of voxels in a cluster. Because the voxelwise comparison correction is known to be stringent and prone to false negatives, uncorrected and corrected P values are reported. The SPM approach is generally used to identify functionally specialized brain regions and is the most prevalent approach for characterizing functional anatomy and disease-related changes in SPECT, positron emission tomographic, and functional magnetic resonance imaging studies. The SPM analyses did not directly test the ROI hypotheses of the study but instead were exploratory. Images in each group were normalized (transformed) into a standardized stereotactic space using a template image supplied by SPM 99. This template image conforms to the Montreal Neurological Institute template and closely approximates the space described in the atlas by Talairach and Tournois. These normalized images were then smoothed to accommodate intragroup subject differences in anatomy using an isotropic gaussian kernel of 12 mm. Analysis of variance was used to compare the smoothed images in the aggressive and nonaggressive groups. Statistically significant differences in regional perfusion were analyzed by setting opposite contrasts for each group.
RESULTS

PATIENTS AND BEHAVIORS

Forty-nine patients with AD were included in the study (25 men and 24 women; mean±SD age, 74.0±10.7 years). The mean±SD MMSE score in all participants was 17.7±5.0, showing moderate impairment. Thirty patients had evidence of verbal or physical aggression with or without agitation (mean±SD BEHAVE-AD aggression score: 3.0±1.8; 13 patients scored 1-2, 10 scored 3-4, and 7 scored 5-7), and 19 showed no evidence of aggression or agitation. There were no significant differences between the aggressive and nonaggressive groups with respect to age, cognitive status, or sex (P>0.05 for all). When the 2 groups were compared for other psychiatric symptoms on the BEHAVE-AD, the aggressive group had higher mean±SD scores on activity disturbances (eg, wandering) (1.7±2.0 vs 0.6±1.1; P=.03) and sleep disturbances (0.7±1.0 vs 0.2±0.4, P=.02), whereas mean±SD scores on anxiety (2.2±1.7 vs 1.6±2.4), delusions (2.0±2.1 vs 1.3±2.3), emotions (1.2±1.7 vs 0.7±1.2), and hallucinations (1.2±2.2 vs 0.7±1.2) did not differ between the 2 groups (aggressive vs nonaggressive, P>.05 for all).

ROI ANALYSES

Total Sample

Aggressive patients had statistically significantly lower mean rCBF in the right and left middle medial temporal cortices (Figure 1 and Figure 2) but not in the other ROIs (Table 1). Although a statistically significant correlation was seen between aggression and hypoperfusion in the middle section of the right medial temporal gyrus, only a trend was seen in the left middle medial temporal gyrus (Table 2).

Regression analysis confirmed that right middle medial temporal hypoperfusion (P=.001), younger age (P=.002), greater activity disturbances (P=.004), and higher MMSE scores (P=.04) independently predicted aggression. The overall model was significant (F=8.7;
P<.001), accounting for 44% of the total variance on BEHAVE-AD aggression. Sleep disturbance (P=.77) and sex (P=.63), were removed from the final model. Sleep disturbance and activity disturbance were included as possible covariates in addition to age, MMSE score, and sex because average ratings on these 2 BEHAVE-AD subscales differed at baseline between the aggressive and nonaggressive groups.

Aggressive Patients Only

To study the relationship between regional perfusion and aggression severity, correlations for the ROIs were repeated in the aggressive group only (n=30) (Table 2). In this subset, a significant correlation between aggression and hypoperfusion in the right orbitofrontal gyrus was seen (Table 2). Regression analysis confirmed that right middle medial temporal hypoperfusion (P=.02), higher MMSE scores (P=.03), and younger age (P=.004) independently predicted level of aggression. The overall model was significant (F=5.7; P=.004), accounting for 40% of the variance in severity of aggression. Right orbitofrontal perfusion (P=.41), sex (P=.90), sleep disturbance (P=.45), and activity disturbance (P=.06) were removed from the final model.

SPM RESULTS

Comparison of SPECT images in aggressive and nonaggressive patients on SPM analyses is shown in Figure 3. The Talairach coordinates of areas with significant differences in perfusion are listed in Table 3. The right temporolimbic region, comprising the middle and inferior temporal and parahippocampal regions, constituted the major region of perfusion change on SPM analyses (P<.01, uncorrected). A difference in perfusion was also seen in the neighboring right parahippocampal and right inferior temporal gyri (P=.01, uncorrected, for both). Other areas of difference in perfusion appeared in more posterior regions of the right occipital lobe and right cerebellum (P<.01, uncorrected, for both). Although none of the corrected P values were significant, this analysis supported the ROI findings.
CONCOMITANT MEDICATIONS

The proportions of aggressive vs nonaggressive participants using cholinesterase inhibitors (14/30 vs 8/19), antipsychotics (1/30 vs 1/19), antidepressants (9/30 vs 1/19), anxiolytics (3/30 vs 1/19), mood stabilizers (0/30 vs 1/19), and antiepileptics (2/30 vs 4/19) were not significantly different based on Fisher exact tests ($P > .05$ for all). Furthermore, perfusion in the right middle medial temporal gyrus was not significantly different for individuals taking cholinesterase inhibitors compared with those who were not ($t = 1.0; P = .30$) or for those taking antidepressants compared with those who were not ($t = .92; P = .36$).

The results of this study indicate that hypoperfusion in the middle region of the right medial temporal gyrus may be associated with aggressive behaviors in AD. This region of the temporal lobe includes the hippocampus, parahippocampus, and posterior amygdala and corresponds to BAs 28/35/36. The temporolimbic lobes have been implicated in episodes of rage and aggression. In particular, the medial temporal lobe has been associated with aggression in experimental paradigms in healthy volunteers, in neurosurgical manipulation in animals, and in nondemented aggressive populations using SPECT and positron emission tomography. A previous study of AD reported an association between the presence of aggression ($n = 22/136$), defined as behavior that results in actual or potential harm to another person, and a higher proportion of subjects with temporal lobe atrophy on computed tomographic scans ($22/22$ vs $103/114$). Our findings are an extension of those findings and specifically implicate the middle section of the right medial temporal region. A second study, by Hirono et al, correlated aggression with hypoperfusion in the anterior temporal cortex of a group with mixed dementia. Our study differs from that study in 4 important ways. First, we used a novel quantitative analysis method in addition to SPM analyses to delineate areas of altered perfusion in the aggressive and nonaggressive groups in AD. Second, our results are based on a considerably larger sample of aggressive individuals, and the previous study was limited to 10 aggressive patients. There are also differences in coexisting behavioral disturbance. The aggressive subjects in the study by Hirono et al also had high levels of apathy and depression. In fact, the mean scores on the apathy and depression scales were higher than that on the aggression/agitation subscale. In our aggressive patients, the mean score on the aggressive subscale was the highest of all the subscales. Last, 20% of that population had diagnoses other than probable AD.

The difference in mean right medial temporal perfusion between the aggressive and nonaggressive groups was approximately 0.05 (difference in ratio of rCBF values referenced to the cerebellum: 0.58 vs 0.63). Although this difference is small compared with some of the differences between regions, it is of the same magnitude as significant regional differences in other SPECT studies. The expected magnitude of differences leading to neuropsychiatric symptoms is unknown. In the studies by Burns et al and Hirono et al, regional differences are not quantified. Our findings imply that a certain threshold may be crossed in this region relative to others.

The temporolimbic lobe structures—the entorhinal cortex, amygdala, hippocampus, and parahippocampus—also play an important role in cognition and are implicated in the pathologic processes of AD early in its course. Our results suggest that this region is a correlate of aggression even when cognitive status is taken into account. In addition to greater right medial temporal hypoperfusion, level of aggression was correlated with a higher MMSE score and a younger age, indicating that there may be a subgroup of patients experiencing earlier and more extensive right-sided medial temporal atrophy.

The results of this study also support the relationship of right-hemisphere dominance in regulation of behaviors. Right medial temporal hypoperfusion discriminated aggressive and nonaggressive participants. These findings are in contrast to those of Hirono et al, who found left-sided dominance. As mentioned previously herein, the Hirono et al population had high levels of depression and apathy, higher in fact than the aggression scores. Apathy has been associated with a right anterior cingulate deficit, and depression has been associated with decreased left medial temporal activity, which may

### Table 3. Results of Statistical Parametric Mapping Analyses

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Talairach Coordinates</th>
<th>$P$ Value</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Uncorrected</th>
<th>Corrected</th>
<th>z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right middle temporal gyrus (BA 21)</td>
<td></td>
<td></td>
<td>34</td>
<td>-32</td>
<td>-12</td>
<td>.008</td>
<td>.9</td>
<td>2.41</td>
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<tr>
<td>Right parahippocampal gyrus (BA 37)</td>
<td></td>
<td></td>
<td>34</td>
<td>-32</td>
<td>-12</td>
<td>.008</td>
<td>.9</td>
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</tr>
<tr>
<td>Right inferior temporal gyrus (BA 20)</td>
<td></td>
<td></td>
<td>52</td>
<td>-66</td>
<td>0</td>
<td>.006</td>
<td>.9</td>
<td>2.53</td>
</tr>
<tr>
<td>Right lingual gyrus</td>
<td></td>
<td></td>
<td>18</td>
<td>-48</td>
<td>-50</td>
<td>.007</td>
<td>.9</td>
<td>2.45</td>
</tr>
</tbody>
</table>

Abbreviation: BA, Brodmann area.

*Only anatomical regions with $P<.001$, uncorrected, are shown.
The SPM analyses were used to identify additional areas potentially involved in aggression that were not evaluated in the hypothesis-driven ROI analysis. Findings from the SPM analyses suggest that 2 other regions, 1 in the occipital lobe and 1 in the cerebellum, might also be related to aggressive behavior. The bilateral cerebellar activation found on the SPM analyses is in keeping with the disinhibited or inappropriate behavior often seen in cerebellar lesions, described as the cerebellar cognitive affective syndrome. Although the occipital cortices are not typically involved in aggression, it is possible that visual disturbances may lead to misinterpretation of stimuli, which in turn stimulates aggression. The occipital cortices are typically involved later in the course of AD, a stage of AD characterized by prominent behavioral symptoms. However, the possibility of hypoperfusion in the occipital, lingual, fusiform, and precentral gyri in the SPM analyses being associated with stage of disease rather than aggression per se cannot be ruled out. The SPM analyses did not include covariates such as cognitive status and age, which were correlated with aggression. Studies that use larger sample sizes should be undertaken to fully understand the potential role of these individual regions in the manifestation of aggression. We offer these results to stimulate further testing of traditional and newly identified areas in new and larger samples.

The presence of activity disturbances was also found to be a predictor of aggression. The activity disturbances subscale of the BEHAVE-AD includes items for wandering, purposeless repetitive activity, inappropriate sexual behavior, and disinhibition. Agitation is a descriptive term also used to collectively describe wandering, pacing, restlessness, inappropriate disrobing, and verbal outbursts. Agitation is one of the items of the aggression subscale of the BEHAVE-AD. Therefore, patients with agitation could be expected to elicit scores on the aggression and activity disturbances subscales. Thus, the fact that activity disturbances were a predictor of aggression may be because of the presence of agitated behaviors in many of the aggressive participants.

These results must be interpreted with caution, because many participants were taking concomitant medications that could affect cerebral perfusion. An excessive use of medications in the aggressive group, however, would not be expected to lead to the hypoperfusion that was demonstrated. Nevertheless, although our analysis showed that the proportion of participants taking each major class of psychotropic medications was not different for aggressive and nonaggressive patients, the possibility of confounding by concomitant medications cannot be ruled out. Furthermore, because data analysis was hypothesis driven rather than exploratory, correction for multiple comparisons was not performed. As a result, the possibility of a type I error is greater than .05.

In summary, we sought to elucidate the neurobiological characteristics of aggression in AD using SPECT. We found that hypoperfusion in the middle part of the right medial temporal gyrus was associated with the presence of aggression and correlated with the severity of aggression in AD. These findings further support the hypothesis that pathologic processes in this region are responsible for specific behavioral manifestations that accompany cognitive deficits.

Accepted for Publication: March 19, 2004.
Correspondence: Krista L. Lanctôt, PhD, Neuropsychology Research, Department of Psychiatry, Sunnybrook and Women’s College Health Sciences Centre, 2075 Bayview Ave, Room FG 05, Toronto, Ontario, Canada M4N 3M5 (Krista.Lanctot@sw.ca).

Author Contributions: Study concept and design: Lanctôt, Herrmann, and Black. Acquisition of data: Lanctôt, Caldwell, and Black. Analysis and interpretation of data: Lanctôt, Herrmann, Nadkarni, Leibovitch, Caldwell, and Black. Drafting of the manuscript: Lanctôt, Herrmann, and Nadkarni. Critical revision of the manuscript for important intellectual content: Lanctôt, Herrmann, Nadkarni, Leibovitch, Caldwell, and Black. Statistical analysis: Lanctôt, Nadkarni, and Leibovitch. Obtained funding: Black. Administrative, technical, and material support: Herrmann, Leibovitch, Caldwell, and Black. Study supervision: Black.

Funding/Support: This study was supported by grant MT13129 from the Canadian Institutes of Health Research, Ottawa, Ontario (Dr Black) and by the Kunin-Lunenfeld Applied Research Unit of the Baycrest Centre for Geriatric Care, Toronto, Ontario (Dr Lanctôt).

Acknowledgment: We thank Stephanie J. Hevenor, Shehnaz Moosa, and Lyla R. Khan for their invaluable assistance in technical and administrative matters involved in completing this project.

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