Cerebral Metabolic Response to Passive Audiovisual Stimulation in Patients with Alzheimer's Disease and Healthy Volunteers Assessed by PET

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Alzheimer's disease is associated with reductions in resting-state brain metabolism, as measured by PET, progressing with dementia severity. The purpose of this study was to see to what extent brain regions with reduced resting-state metabolic rates in Alzheimer patients could be activated by a passive audiovisual stimulation test and to compare the result with activation in age-matched healthy volunteers. The extent of activation in Alzheimer's disease is considered to reflect the integrity of synaptic function, or inherent viability, and the potential responsiveness of the Alzheimer brain to drug therapy. **Methods:** Regional cerebral metabolic rates for glucose (rCMR$_{glc}$, in mg/100 g tissue/min) were measured in the resting state (eyes and ears covered) and during passive audiovisual stimulation (watching a movie) in 15 otherwise healthy Alzheimer patients of differing dementia severity (Mattis Dementia Rating Scale score, 23–128) and in 14 age-matched healthy volunteers (score, 141 ± 3) using PET with 2 sequential injections of FDG. **Results:** In the volunteers, audiovisual stimulation caused significant rCMR$_{glc}$ increases in visual and auditory cortical areas but significant decreases in frontal areas. In the mildly demented patients, rCMR$_{glc}$ responses were within 2 SDs of the mean in volunteers. However, the magnitude of the rCMR$_{glc}$ responses during stimulation declined significantly with dementia severity in the right occipitotemporal, right and left occipital association, and left calcarine cortical regions. **Conclusion:** Functional brain responsiveness, evaluated by a passive audiovisual stimulation paradigm with PET, is within normal limits in mildly demented Alzheimer patients but fails with worsening dementia severity. Declining responsiveness may account for the limited success of neurotransmitter replacement therapy in Alzheimer patients with moderate-to-severe dementia.

Key Words: PET; FDG; dementia; brain; activation; cognition

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It is well established that the regional cerebral metabolic rate for glucose (rCMR$_{glc}$) and the regional cerebral blood flow (rCBF), which is coupled to rCMR$_{glc}$, correlate with local brain functional activity at the level of synapses (*1,2*). PET makes possible the quantification of these parameters of functional activity in the living human brain, in health and disease (*3,4*). For example, reductions measured with PET in resting-state rCMR$_{glc}$ and rCBF have been shown to progress with dementia severity in patients with Alzheimer's disease (*5,6*). The reductions in Alzheimer patients are much greater in brain association than in primary cortical areas, consistent with the greater density in association areas of pyramidal neurons containing neurofibrillary tangles with paired helical filaments (*7,8*). The metabolic and flow reductions likely reflect dysfunction and loss of synapses, which are sites of maximum energy consumption during rest and activation (*1,2*). Loss of brain synaptic markers, shown in biopsied and postmortem Alzheimer brains, correlates closely with the severity of dementia before death (*9–11*).

Postmortem neuropathology in Alzheimer's disease represents the sum of neurodegenerative and compensatory processes that took place for many years before death, creating difficulty with distinguishing early from late changes and with identifying initial pathologic processes. In contrast, PET during life allows examination of pathologic processes at the functional level in individuals at risk for Alzheimer's disease and in Alzheimer patients in different stages of dementia. Used as part of a neurophysiologic stress test, PET may permit us to distinguish the extent to which the brain can be functionally activated in response to cognitive or pharmacologic stimulation and, thus, to identify patients who may best respond to therapeutic intervention.

Several attempts have been made to use PET with functional activation to evaluate brain responsiveness in Alzheimer patients during distinct cognitive stimulation paradigms (*12–17*). In activation studies involving a cogni-

tive task requiring subject performance, however, many moderately and certainly all severely demented patients cannot be reliably tested because their attention is limited or they are otherwise unable to perform the task. This restriction limits the usefulness of such paradigms for evaluating brain responsiveness at all levels of dementia severity. We therefore sought to develop a compliance-free stimulation paradigm in which brain activation can be evaluated with PET throughout the brain and at all levels of dementia severity. Such a paradigm would show to what extent functional responsiveness is maintained in Alzheimer's disease and how the functional response of the brain is affected by the progression of dementia.

We used a passive audiovisual task that is easily administered, does not demand subject compliance, and has been shown to activate wide areas of the brain in healthy volunteers (*18*). In older adults with Down syndrome, who are known to have some degree of Alzheimer neuropathology, this paradigm has been shown to identify reduced functional responsiveness before the onset of dementia (*19*). We hypothesized that in patients with cerebral glucose hypometabolism at rest, this audiovisual stress test will elicit a metabolic response in the same brain regions as in healthy volunteers but that the magnitude of the response in the patients will progressively decrease as a function of dementia severity.

MATERIALS AND METHODS

Subjects

We studied 15 patients who met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke Alzheimer Disease and Related Disorders Association for probable Alzheimer's disease (*20*) and 14 healthy volunteers who did not differ significantly from the patient group in age, education, or sex distribution. No healthy volunteer had a family history of Alzheimer's disease. Clinical and demographic data are listed in Table 1. Two patients who later died showed neuropathologic changes at autopsy meeting the criteria for definite Alzheimer's disease (*20*). The healthy volunteers and the patients (or their holders of durable power of attorney) gave written informed consent to participate in the study after explanation of the procedures and risks involved (institutional review board–approved National Institutes of Health [NIH] protocol 93-AG-139).

Clinical Screening and Examination

We reviewed the medical history of each subject and the findings of physical, neurologic, and psychiatric examinations; blood and urine tests, including routine blood counts, clotting studies, and serum chemistry; liver, kidney, and thyroid function tests; cholesterol and triglyceride tests; HIV and venereal disease research laboratory tests; antinuclear antibody and rheumatoid factor tests; vitamin B_{12} and folate tests; chest radiography, electrocardiography, and electroencephalography brain MRI; and audiologic and visual assessments, including visual acuity, pupillary function, eye fundus, extraocular movements, and peripheral visual fields. Exclusion criteria were radiologic evidence of intracranial disease or a history or the presence of significant medical, neurologic, or psychiatric illness, including hypertension, diabetes mellitus, malig-

TABLE 1
Clinical and Demographic Characteristics of Subjects

| | Healthy volunteers (n = 14) | Alzheimer patients | | |
		All (n = 15)	Mild disease (n = 6)	Moderate-to-severe disease (n = 9)
Age (y)	71 ± 8	70 ± 10	66 ± 8	73 ± 10
Sex (M/F)	6/8	9/6	3/3	6/3
MMSE*	29.8 ± 0.4	16.6 ± 7.0	21.7 ± 4.2	12.3 ± 5.9
Mattis DRS				
total†	141 ± 3	91 ± 33	120 ± 9	72 ± 28
Education (y)	16.5 ± 1.5	15.0 ± 3.6	14.7 ± 3.9	15.2 ± 3.6
Handedness (R/L)	13/1	14/1	5/1	9/0

*Healthy volunteers (V) vs. all patients: t = 7.4, $P < 0.0001$; V vs. patient subgroups: overall F (df = 2; F = 59.3; $P < 0.0001$); V vs. mild disease (t = 7.5; $P < 0.0001$); V vs. moderate-to-severe disease (t = 11.2; $P < 0.0001$); mild disease vs. moderate-to-severe disease (t = 3.3; $P < 0.005$).

†V vs. all patients: t = 5.5, $P < 0.0001$; V vs. disease subgroups: overall F (df = 2; F = 47.9; $P < 0.0001$); V vs. mild disease (t = 7.9; $P = 0.0001$); V vs. moderate-to-severe disease (t = 9.0; $P < 0.0001$); mild disease vs. moderate-to-severe disease (t = 4.0; $P < 0.001$).

MMSE = Mini-Mental State Examination (maximum normal score, 30 (*37*)); Mattis DRS = Mattis Dementia Rating Scale (maximum total score, 144 (*22*)).

nancy, renal or hepatic disease, cardiac disease, epilepsy, stroke, transient ischemic attack, head trauma with prolonged loss of consciousness, exposure to toxic substances, psychoses, or substance abuse. Substantial ocular disease (e.g., cataract, glaucoma), decreased visual fields, corrected visual acuity less than 20/30, or decreased hearing ability (other than reduced high-frequency discrimination) also were exclusionary criteria (*19*). All subjects discontinued medication, including over-the-counter preparations, at least 2 wk before entering the study (4 wk for psychotropic drugs).

PET Procedure

Technique. A high-resolution PET scanner (PC2048-15B; Scanditronix, Uppsala, Sweden) with an axial resolution of 6 mm, full width at half maximum, and FDG were used to measure $rCMR_{glc}$. Radioactivity in the brain was simultaneously measured from 15 contiguous transaxial planes with a slice-to-slice separation of 6.5 mm, for a total axial field of 97.5 mm. Subjects were placed in the scanner in a quiet, dimly lit room. A thermoplastic mask was used to maintain head positioning during scanning. To correct for attenuation of radiation, multislice transmission scans were obtained at the same levels as the emission scans.

Each subject underwent 2 sequential FDG studies, 1 in the resting state and the other during audiovisual stimulation. Thirty-five minutes after intravenous injection of 155 MBq FDG, a 15-min emission scan was obtained parallel to and from 10 to 100 mm above the inferior orbitomeatal line. Arterial blood samples were collected for plasma radioactivity and glucose concentration measurements. $rCMR_{glc}$ was calculated in milligrams of glucose per 100 g brain tissue per minute, using a modification of the operational equation of Sokoloff et al. (*21*). After completion of the first scan (total time, 50 min), a second bolus of 155 MBq FDG was

injected intravenously and a second scan was obtained. Data from the second scan were corrected for residual radioactivity from the first injection (FDG half-life, 118 min) using a published mathematic model (22).

Experimental Conditions. During resting-state scanning, subjects lay quietly on the scanner bed with their eyes patched and their ears plugged. During audiovisual-stimulation scanning, subjects watched and listened to a colorful movie, *The Wizard of Oz,* as described previously (19). The same 50-min segment was presented to each subject by retroprojecting it onto a semiopaque screen 55–60 cm from the subject's eyes. The screen was tilted to be perpendicular to the viewer's line of sight and centered in the field of view. Sound was delivered by 2 stereo speakerphones, 1 on the right and 1 on the left of the subject, about 2 m from the ears. The volume was adjusted to a comfortable level for each individual, essentially the level that person normally used when watching a movie on television. During the movie, the room was dimly lit. The presentation order of the 2 conditions (movie and resting) was counterbalanced across subjects. Subjects were allowed to adjust to each condition for 2 min before isotope injection.

Data were analyzed for subjects who completed the entire study and who were monitored throughout to ensure that they remained awake, alert, and attentive to the PET scanning condition. Subjects who had never been scanned underwent a training PET session to maximize compliance and minimize anxiety (19).

Data Analysis. Regional brain radioactivity was determined using a template of 475 circular regions of interest (ROIs), each 8 mm in diameter (48-mm² area), derived from a PET scan of a healthy volunteer (adapted from Kumar et al. (6)). Each of 15 PET slices from this individual was compared with an atlas of a human brain sectioned in the same inferior orbitomeatal plane as the PET scan. The ROIs were spaced evenly throughout the cortical ribbon and centered in subcortical regions. The template was placed over the corresponding PET slices for each subject and was adjusted to fit each individual brain. Adjustments could easily be made for differences in head size and shape or for the presence of atrophy. The same ROI template was used for scans obtained under both experimental conditions (19).

Values of rCMR$_{glc}$ in the individual circular ROIs were grouped into larger anatomic areas within the frontal, limbic, temporal, sensorimotor, parietal, and occipital cortices, for a total of 29 larger regions, according to a standard neuroanatomic atlas (19).

Statistical Analysis. Student *t* tests and χ^2 tests were used to compare the demographic variables of the groups. Group differences in neuropsychologic measures were determined using *t* tests with a Bonferroni adjustment. To reduce the number of comparisons, differences in resting-state absolute values of rCMR$_{glc}$ between the patients and the healthy volunteers were calculated using a 2-factor repeated-measure ANOVA, with the hemisphere for homologous brain regions as the repeated measure. A 2-factor repeated-measure ANOVA with the task condition and hemisphere as the repeated measures was used to identify the regions that showed significant differences in rCMR$_{glc}$ between the stimulation and resting conditions within the healthy volunteer and patient groups. The magnitude of the rCMR$_{glc}$ differences between the stimulation and resting conditions in the ROIs with significant task-related differences, in both the healthy volunteer group and the patient group, was calculated by subtracting rCMR$_{glc}$ at rest from rCMR$_{glc}$ during stimulation. The significance of correlation between significant rCMR$_{glc}$ differences and dementia severity in the patient group was assessed using regression analysis. To test

rCMR$_{glc}$ differences between dementia severity subgroups in cerebral regions affected by the stimulation paradigm, a 3-way ANOVA (subgroup by task condition by hemisphere for homologous brain regions) followed by protected *t* tests was performed. For posterior cingulate rCMR$_{glc}$ and global gray matter CMR$_{glc}$, ANOVA and *t* tests were used as appropriate. Data were analyzed for absolute values of rCMR$_{glc}$ (mg/100 g brain/min) in resting and stimulation conditions and for ratios of activated rCMR$_{glc}$ to resting-state rCMR$_{glc}$, to reduce intersubject variability. $P < 0.05$ was considered statistically significant.

RESULTS

rCMR$_{glc}$ Differences at Rest

Compared with the healthy volunteers, in the resting state the patient group showed significantly lower absolute values for rCMR$_{glc}$ in frontal, temporal, parietal, and occipital association cortical areas, with relative sparing of the sensorimotor and calcarine cortex and the subcortical regions (Fig. 1). When the patients were grouped on the basis of dementia severity (Table 1), rCMR$_{glc}$ in the mildly demented patients (n = 6) differed from rCMR$_{glc}$ in healthy volunteers in bilateral inferior parietal regions (F = 4.6; degrees of freedom [df] = 1, 18; $P = 0.047$), whereas rCMR$_{glc}$ in the moderately to severely demented patients (n = 9) differed from control values in all cortical areas (ranging from calcarine cortex [F = 5.0; df = 1, 21; $P = 0.04$] to inferior parietal cortex [F = 58.9; df = 1, 21; $P = 0.0001$]).
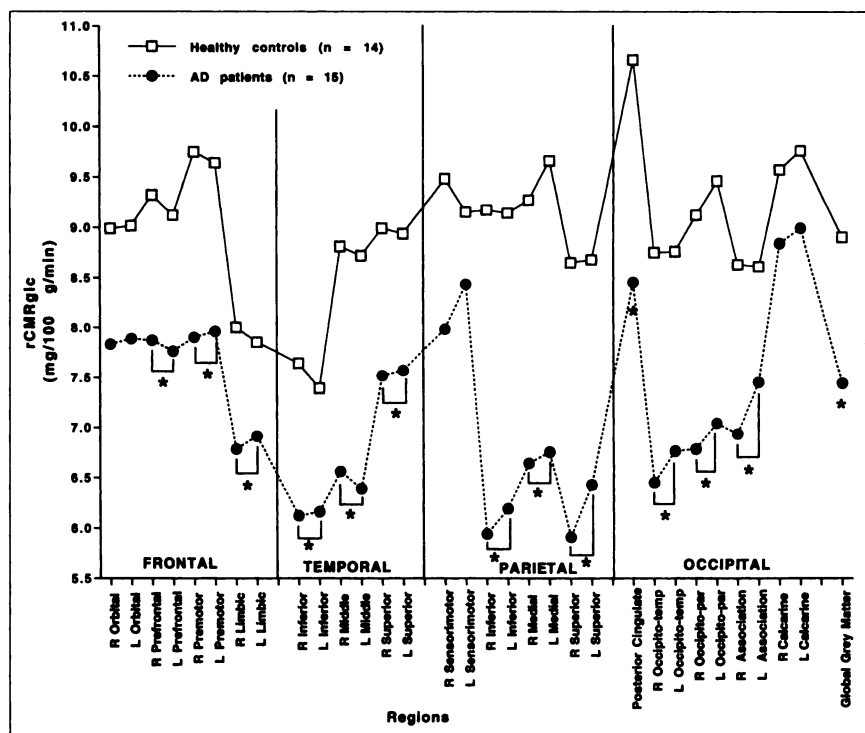
rCMR$_{glc}$ Response to Audiovisual Stimulation

Magnitudes of absolute rCMR$_{glc}$ at rest and in response to audiovisual stimulation are illustrated in Figure 2A for healthy volunteers and in Figure 2B for patients. In the volunteers, statistically significant increases in rCMR$_{glc}$ during audiovisual stimulation relative to rest were observed in auditory and visual cortical areas (F = 11.1; df = 1, 13; $P < 0.005$ for the superior temporal area; F = 30.3, df = 1, 13, $P < 0.0001$ for the occipital association area; F = 12.6; df = 1, 13; $P < 0.004$ for the occipitoparietal area; F = 19.4; df = 1, 13; $P < 0.0007$ for the occipitotemporal area; F = 50.5; df = 1, 13; $P < 0.0001$ for the calcarine area), whereas significant reductions from rest were detected in the orbitofrontal cortex (F = 5.5; df = 1, 13; $P < 0.04$) and bilaterally in the limbic regions (F = 6.0; df = 1, 13; $P < 0.03$).

Like the healthy volunteers, the patients had significant rCMR$_{glc}$ increases during audiovisual stimulation in the superior temporal (F = 4.6; $P < 0.05$), occipital association (F = 22.2; df = 1, 14; $P < 0.0003$), occipitoparietal (F = 18.8; df = 1, 14; $P < 0.0007$), and calcarine (F = 23.6; df = 1, 14; $P < 0.0003$) regions. rCMR$_{glc}$ increases relative to rest also were significant in the inferior (F = 7.5; df = 1, 14; $P < 0.02$) and medial (F = 7.3; df = 1, 14; $P < 0.02$) parietal cortex. No significant rCMR$_{glc}$ reduction during audiovisual stimulation was found in the patient group.

Relation of Audiovisual Responsiveness to Dementia Severity

Figure 3 shows the relationship between rCMR$_{glc}$ changes in response to audiovisual stimulation and the severity of

FIGURE 1. Cerebral glucose metabolism during resting state in healthy volunteers and demented Alzheimer patients. Mean absolute rCMR$_{glc}$ is expressed in mg/100 g brain tissue/min for all cerebral regions examined in volunteers and patients. AD = Alzheimer's disease; L = left hemisphere; R = right hemisphere. *Mean rCMR$_{glc}$ significantly different from control mean ($P <$ 0.05).

dementia, as measured by the Mattis Dementia Rating Scale score (23). The magnitude of the metabolic response to audiovisual stimulation declined significantly in relation to dementia severity in the right occipitotemporal cortex ($r = 0.60$; $P = 0.02$), right ($r = 0.53$; $P = 0.04$) and left ($r = 0.74$, $P = 0.002$) occipital association cortex, and left calcarine region ($r = 0.79$, $P = 0.0005$). No significant correlation was found between inferior and medial parietal rCMR$_{glc}$ differences and dementia severity. In the mildly demented patients, the magnitudes of brain metabolic activation in the primary and association visual cortical areas fell within 2 SDs of the mean activation in the healthy volunteers (Fig. 3; Table 2).

Table 2 illustrates absolute and relative (as percentage of resting-state rCMR$_{glc}$) rCMR$_{glc}$ changes in the healthy volunteers and in the patients with mild and moderate-to-severe dementia during audiovisual stimulation. Significant subgroup-by-condition interaction effects were found in primary and association visual cortical areas for both absolute and percentage rCMR$_{glc}$ changes. Follow-up t tests showed that the patients with moderate-to-severe dementia differed significantly from the healthy volunteers in absolute rCMR$_{glc}$ changes in the right and left occipitotemporal, occipital association, and calcarine regions and in percentage rCMR$_{glc}$ changes in the right and left occipitotemporal and left calcarine regions. Additionally, moderately to severely demented patients differed from mildly demented patients in the right occipitotemporal region. In moderately to severely demented patients, absolute and percentage rCMR$_{glc}$ increases in the right and left occipitoparietal cortex, and percentage rCMR$_{glc}$ increases in the right and left occipital association and right calcarine regions, did not

differ significantly from control values. Changes in mildly demented patients did not differ from changes in healthy volunteers.

DISCUSSION

These results indicate that regions of brain metabolic responsiveness to audiovisual stimulation are similar in patients and in age- and sex-matched healthy volunteers. These response effects were observed despite reduced rCMR$_{glc}$ at rest. The magnitude of the response in patients declined with dementia severity.

Brain glucose metabolism was activated relative to rest by a passive audiovisual stress paradigm to the same extent in mildly demented patients as in healthy age-matched volunteers, suggesting that the brain retains a significant capacity for functional responsiveness, or significant "viability" (14), in the early stages of Alzheimer's disease. This capacity was present even though resting-state rCMR$_{glc}$ was significantly and bilaterally reduced in mildly demented patients in the inferior parietal cortical regions, which are particularly vulnerable to the early effects of Alzheimer's disease (19,24–26). In contrast, values for the difference in rCMR$_{glc}$ between stimulation and rest were less in moderately demented patients than in healthy volunteers, and severely demented patients showed no significant activation over the resting-state condition.

As a group, the patients with moderate-to-severe dementia had significantly smaller absolute rCMR$_{glc}$ increments in most visual cortical areas during audiovisual stimulation than did healthy volunteers. Given that we compared rCMR$_{glc}$ responses during audiovisual stimulation in relation to resting-state metabolism, subgroup differences in atrophy
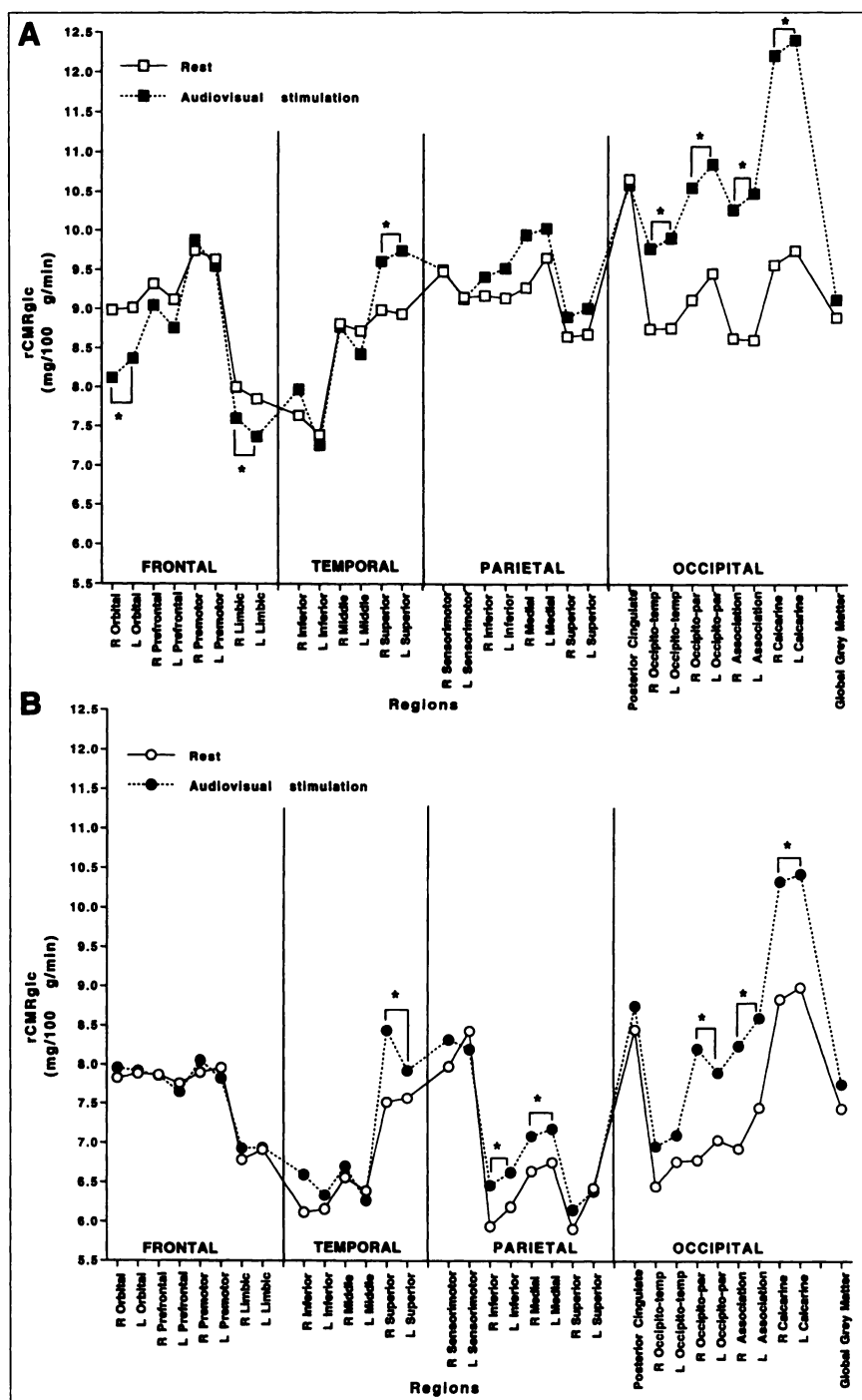
FIGURE 2. Brain glucose metabolism in healthy volunteers and Alzheimer patients during resting state and audiovisual stimulation. Mean absolute rCMR$_{glc}$ values are expressed in mg/100 g brain tissue/min for all cerebral regions examined in volunteers (A) and patients (B). L = left hemisphere; R = right hemisphere. *Mean rCMR$_{glc}$ during audiovisual stimulation significantly different from resting mean ($P < 0.05$).

are not likely to explain our results. Furthermore, in a report that included many of the patients and controls from this study, our laboratory showed significant cerebral hypometabolism at rest in the patient group with and without an MRI-based atrophy correction (27). Whether measured as absolute values or as percentages, rCMR$_{glc}$ in the severely demented patients showed minimal or no response to audiovisual stimulation. The inability of the brain at this late stage of disease to respond to audiovisual stimulation implies a loss or otherwise severe dysfunction of its synaptic elements and neurotransmitter integrity. Synaptic and neuro-

transmitter changes in relation to disease progression have been reported (9–11,13,28).

The results of this study, together with those of Grady et al. (12) and Duara et al. (14), show that the functional responsiveness of the brain is maintained in mild and, to a lesser extent, moderate stages of dementia in Alzheimer's disease. Biopsy and postmortem studies of the density and size of synaptic elements in the Alzheimer brain suggest stages of loss that may correspond to 2 stages of responsiveness in life (10,13). In the first stage, some presynaptic terminals are lost, but the remaining presynaptic terminals
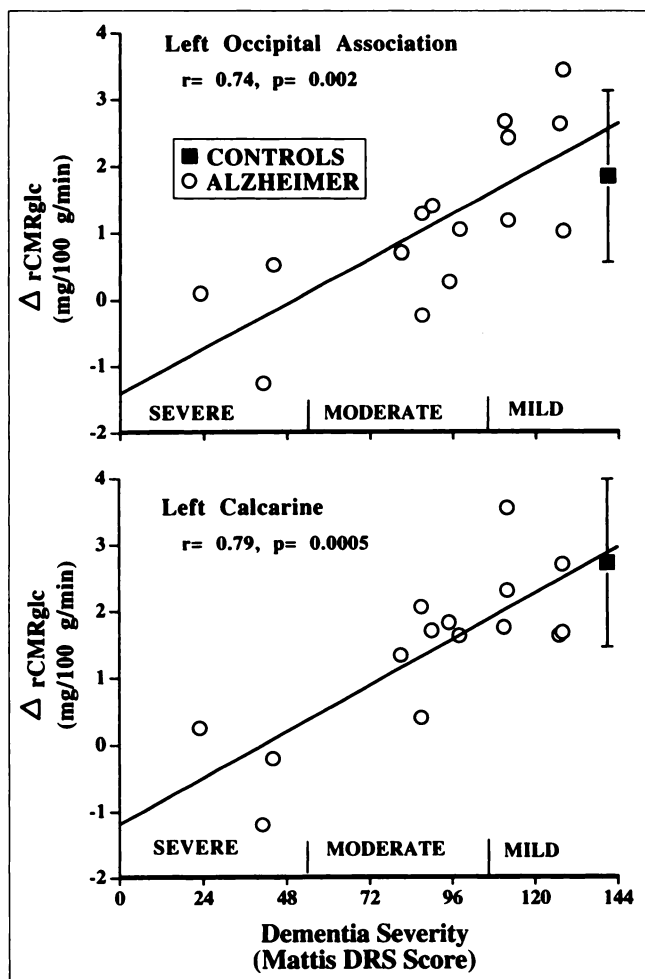
FIGURE 3. Relationship between dementia severity and brain metabolic response to audiovisual stimulation. Abscissa represents dementia severity measured by Mattis Dementia Rating Scale score (maximum score, 144) (23). Ordinate represents regional differences in absolute rCMR$_{glc}$ in mg/100 g brain tissue/min between audiovisual stimulation and resting state for Alzheimer patients. Mean ± SD bar for healthy volunteers is shown at right of figure. Mildly demented patients had rCMR$_{glc}$ increases in visual cortical areas within 2 SDs from control mean.

have enlarged sufficiently to maintain a normal net contact area between pre- and postsynaptic elements. In the second stage, evident in postmortem Alzheimer brain, additional presynaptic dropout occurs without such compensation, and net contact area is reduced. These results agree with other postmortem evidence that early neurofibrillary changes in pyramidal cortical neurons in the Alzheimer brain are associated with selective downregulation of mitochondrial gene expression (mRNA levels) for enzymes involved with mitochondrial oxidative phosphorylation, whereas higher degrees of neurofibrillary tangle accumulation are accompanied by a general reduction in gene transcription (11,28,29).

Despite a normal metabolic response to audiovisual stimulation in mildly demented patients, evidence of reduced resting-state rCMR$_{glc}$ nevertheless indicates functional defects, which likely underlie the early cognitive

changes involving memory and attention. Such defects have been identified using passive stimulus paradigms that involve exposing the subject to alternating flashing lights at various frequencies while measuring rCBF with H$_2$^{15}O and PET (16,17). The mildly demented patients in that study showed reduced rCBF responses in striate and extrastriate visual areas, particularly at stimulation frequencies of 8 Hz and higher, suggesting vulnerability of the high-frequency responding magnicellular visual system. In another study, older (>40 y) nondemented Down syndrome subjects, in whom Alzheimer's disease pathology routinely occurs, had lower increments in rCMR$_{glc}$ in parietal and temporal cortical areas than did younger Down syndrome adults in response to the audiovisual stimulus used in this study (19). This finding suggests that the passive audiovisual paradigm, by increasing the functional demand on the brain, can identify early brain metabolic abnormalities in nondemented at-risk patients.

Although responding to audiovisual stimulation with significant rCMR$_{glc}$ increments in visual and auditory cortical areas, the healthy volunteers had significant rCMR$_{glc}$ reductions in frontal and limbic regions during stimulation. Reductions in brain activity relative to baseline in areas not directly involved in a task has been reported in other sensory and cognitive activation studies (30–32). This deactivation has been ascribed to regional depression of synaptic activity (30) in relation to cross-modal inhibition during selective attentional processing (32). The absence of such regional metabolic depression in the patient group may reflect disruption of corticocortical connectivity (33,34).

The patients had significant rCMR$_{glc}$ increments in the inferior and medial parietal cortex during audiovisual stimulation, whereas the healthy volunteers did not. In the patients, more cortical networks may have been recruited to compensate for failure of other cortical networks (12). Indeed, such differential activation of the parietal cortex during the same audiovisual paradigm was found in older nondemented adults with Down syndrome (19). Activation of the parietal cortex, which usually is the first area to show resting-state rCMR$_{glc}$ abnormalities (19,24–26), highlights the capability of the Alzheimer brain to respond to stimulation during early stages of disease.

This study confirms the prediction by Rapoport and Grady (13) that stimulation or stress paradigms can be used with PET to evaluate synaptic responsiveness and neurotransmission in relation to dementia severity in Alzheimer's disease. Because all subjects were continuously monitored during PET (19) and the paradigm did not require active performance, differences in compliance or attention could not have accounted for observed group differences in resting and activation rCMR$_{glc}$. Exclusion of subjects with significant ocular or auditory deficits minimized the potential contribution of peripheral sensory impairment to diminished rCMR$_{glc}$.

Altered internal processing alone (i.e., a reduced cognitive elaboration in response to the complex audiovisual

TABLE 2
Absolute (mg/100 g tissue/min) and Percentage rCMR$_{glc}$ Changes During Audiovisual Stimulation

	Absolute changes			Percentage changes		
		Alzheimer patients			Alzheimer patients	
Region	Healthy volunteers (n = 14)	Mild disease (n = 6)	Moderate-to-severe disease (n = 9)	Healthy volunteers (n = 14)	Mild disease (n = 6)	Moderate-to-severe disease (n = 9)
Orbitofrontal						
Right	−0.87 ± 1.44	0.16 ± 1.08	0.14 ± 1.20	−8.1 ± 16.0	2.5 ± 13.1	3.1 ± 14.8
Left	−0.65 ± 1.15	−0.15 ± 1.11	−0.06 ± 1.65	−5.9 ± 13.4	−0.9 ± 13.4	1.3 ± 18.6
Limbic						
Right	−0.40 ± 0.90	0.43 ± 1.08	−0.04 ± 1.14	−4.8 ± 11.2	6.3 ± 13.6	2.1 ± 15.4
Left	−0.48 ± 0.79	0.43 ± 0.78*	−0.24 ± 1.49	−4.7 ± 10.2	6.1 ± 10.4	0.9 ± 24.0
Superior temporal						
Right	0.62 ± 0.83	1.67 ± 0.58	0.42 ± 1.71	7.9 ± 12.3	19.3 ± 6.1	9.9 ± 20.0
Left	0.82 ± 0.92	0.99 ± 0.83	−0.07 ± 0.76*†	10.2 ± 11.9	11.5 ± 9.1	0.3 ± 9.4*
Inferior parietal						
Right	0.24 ± 0.68	0.63 ± 0.77	0.45 ± 0.63	3.7 ± 8.9	8.6 ± 10.5	9.7 ± 12.5
Left	0.38 ± 1.01	0.47 ± 0.61	0.41 ± 0.88	5.5 ± 12.3	5.8 ± 7.7	10.4 ± 20.0
Medial parietal						
Right	0.67 ± 1.03	0.24 ± 0.71	0.58 ± 0.78	8.1 ± 12.4	3.3 ± 8.8	10.5 ± 12.3
Left	0.37 ± 0.99	0.62 ± 0.72	0.31 ± 0.77	4.6 ± 10.7	7.0 ± 8.5	6.0 ± 11.3
Occipitotemporal						
Right	1.03 ± 1.10	1.53 ± 1.24	−0.17 ± 0.60*	12.5 ± 12.3	17.9 ± 15.0	−2.1 ± 12.8*†
Left	1.16 ± 0.92	0.99 ± 1.17	−0.08 ± 1.13*	13.4 ± 10.1	10.5 ± 14.7	0.3 ± 15.6*
Occipitoparietal						
Right	1.44 ± 1.66	1.71 ± 0.77	1.24 ± 0.85	17.5 ± 20.3	20.3 ± 9.9	24.5 ± 16.3
Left	1.40 ± 1.48	1.51 ± 1.38	0.43 ± 1.43	16.1 ± 16.9	17.6 ± 17.4	11.0 ± 19.4
Occipital association						
Right	1.64 ± 1.12	2.09 ± 0.79	0.80 ± 0.60*	19.3 ± 12.6	24.4 ± 9.1	15.5 ± 12.4
Left	1.88 ± 1.33	2.23 ± 0.94	0.43 ± 0.84*	22.1 ± 15.3	25.2 ± 11.0	9.3 ± 13.3
Calcarine						
Right	2.65 ± 1.64	2.46 ± 1.02	0.85 ± 1.06*	29.4 ± 20.2	24.8 ± 12.8	12.8 ± 15.5
Left	2.65 ± 1.27	2.28 ± 0.75	0.87 ± 1.11*	27.7 ± 12.5	21.8 ± 8.2	13.8 ± 14.9*
Global gray matter	0.22 ± 0.68	0.73 ± 0.44	0.04 ± 0.97	3.2 ± 8.6	8.7 ± 5.3	2.2 ± 12.2

*Significant difference from control mean.
†Significant difference from mean in mildly demented patients.
Data are reported for all regions that showed a significant change during audiovisual stimulation in healthy volunteers, Alzheimer patients, or both.

stimulation of the movie) in the severely demented patients is unlikely to account for the reduced brain activation. Dementia-related metabolic impairment was observed also in the visual cortical areas, including the calcarine cortex. These are regions that respond directly to the immediate visual input. Further, the parietal cortex in the patients was activated by audiovisual stimulation. These 2 observations suggest that neuronal dysfunction and reorganization is part of the disease process.

rCMR$_{glc}$ may be a more reliable index of brain functional integrity than rCBF, which has been measured in most other activation studies (12,16,17). Although repeated FDG PET studies in the same individuals are limited because of the long ^{18}F-fluorine half-life, CMR$_{glc}$ measures are integrated over a longer time (20–30 min) than are rCBF measures (1–4 min) and thus may provide a better signal-to-noise ratio and have less inter- and intrasubject variability.

The loss of multiple neurotransmitter markers in Alzhei-

mer's disease has led to therapy to enhance the function of neurotransmitter systems (35). However, the efficacy of single-transmitter intervention remains controversial (36,37). Limited effectiveness observed with single-neurotransmitter intervention has suggested the need to improve the function of more than 1 neurotransmitter system (10) and may be related to loss of receptors or defective signal transduction mechanisms (36). Another possible reason is the inclusion of patients with moderate-to-severe dementia in whom disease, including synaptic loss, is so advanced that they cannot respond to drugs (9–11). The results of our study provide in vivo evidence that a significant disruption of synaptic integrity indeed occurs in moderate-to-severe Alzheimer's disease; this synaptic dysfunction may prevent neurotransmitter-enhancing drugs from achieving a successful response in patients with advanced disease.

PET with stimulation paradigms provides a way to study the in vivo functional consequences of graded synaptic loss

or dysfunction. This information, in turn, may reveal regional differences in synaptic functional integrity in different dementia stages of Alzheimer's disease and help physicians decide whether patients will respond to drug intervention.

CONCLUSION

Brain functional responsiveness, evaluated by a PET paradigm involving passive audiovisual stimulation that enhances the metabolic demand on the brain, is within normal limits in mildly demented patients with Alzheimer's disease but fails with worsening dementia severity. Declining responsiveness indicates a progressive loss of synaptic integrity that may account for the limited success of neurotransmitter replacement therapy in Alzheimer patients in advanced phases of dementia.

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