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Visual Form of Alzheimer's Disease and its Response to Anticholinesterase Therapy

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The results were compatible with the result of the Wada test[3] and indicated that the repetition task activated bilateral regions in the patient. This strongly suggests that our patient has bilateral representation of the linguistic function, which is in agreement with findings in previous studies involving persons with callosal agenesis.

The repetition-minus-rest CBF subtraction images reflected an input part (consisting of auditory input and word coding) and output part (consisting of articulatory coding, motor programming, and motor output).[18] Bilateral activation maybe partly explained by the bilateral auditory input alone. However, according to the data of Petersen et al.,[18] who measured the input part and the output part of word repetition separately, the contribution of auditory input is limited. Therefore we speculate that bilateral activation observed in our study reflects bilateral representation of the language process.

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ABSTRACT

In a 60-year-old woman with the visual variant of Alzheimer's disease, single photon emission computed tomography abnormalities were most marked in the parieto-occipital regions of the brain. After treatment with donepezil, improvement is noted on neuropsychological testing and on brain SPECT, including increased perfusion (metabolism) in the occipital lobes.

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In typical Alzheimer's disease (AD), the most prominent, earliest symptom is memory loss.[1] As the disease progresses, visuospatial, linguistic, and executive deficits emerge. In this typical form, early neuropathological changes are most marked in the temporoparietal regions of the brain.[2] Similarly, functional neuroimaging studies are most abnormal in the temporoparietal areas.[3,4] In the uncommon visual form of AD, the patient's initial symptoms are visual in nature.[5–7] Patients often seek ophthalmological or optometric consultation with symptoms such as difficulties with vision as well as difficulties in visually based activities such as driving and reading. Neuropsychological evaluation of these patients reveals complex visual disorders including simultaneous agnosia, prosopagnosia, visual agnosia, spatial agnosia, alexia, optic ataxia, ocular apraxia, and topographic disorientation. Patients with the visual form of AD show neuroimaging abnormalities that are greatest in the occipitoparietal and occipitotemporal regions.

Neuropsychological and neuroimaging studies in this patient were consistent with a diagnosis of the visual form of AD. The patient was treated with anti-

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cholinesterase therapy with improvement documented neuropsychologically and by brain single photon emission computed tomography (SPECT).

Patient Report

This 60-year-old high school-educated white woman first noted difficulties in reading, navigating stairs, and estimating distances while driving. She had difficulty going up and down stairs due to misplacement of her foot. She no longer crossed her Ts when writing because she had difficulty finding them on the page. Reading was difficult for her because the lines moved about and she could not stay on the correct line. She stopped correcting her writing because she could not find the place where the correction was needed. She noted difficulties finding objects in drawers. After 9 months of symptoms she sought evaluation. Visual fields, ocular mobility, and visual acuity were normal (20/30 bilaterally). Pupils were equal and reactive to light. Ocular motility was normal without nystagmus. Fundus examination was normal. She was unable to identify any of the Poppelreuter figures (pitcher, cleaver, flatiron, or hammer). Naming of pictures was normal. She was unable to read the "large" version of printed words. Simultaneous agnosia was diagnosed. Neurological examinations of strength, sensation, gait, coordination, and reflexes were normal. Detailed mental status testing revealed finger agnosia and constructional apraxia (spatial agnosia). Her Mini-Mental State Examination score was 28. She was treated with tacrine 20 mg three times daily for 1 month followed by an increase to 30 mg three times daily.[8] She reported improved ability to see, read, and navigate stairs. After 3 months of tacrine therapy she was switched to donepezil 5 mg daily.[9] Neuropsychological testing and brain SPECT was repeated after 1 month of donepezil therapy. Neuropsychological testing is summarized in the Table.

Brain SPECT images (technetium 99m-HMPAO) were obtained. In addition to the three orthogonal displays (coronal, axial, and sagittal), a surface map of relative perfusion values was generated. Image processing was supplemented by using the Statistical Parametric Mapping (SPM) method of Friston et al.[13,14] In essence, SPM is a computer-based technique used widely to compare functional images of positron emission tomography and functional magnetic resonance imaging (MRI). Lately it has been adapted to SPECT[15,16] to evaluate the areas of change between sequential tests on a single subject or between a SPECT image on a single subject compared with a panel of SPECT images from a reference group. To enhance the readability of SPM results, the areas of significant change were also superimposed on a normal MR image, previously normalized to the same Talairach space as the SPECT. The initial brain SPECT showed a pattern of hypometabolism in portions of the occipitoparietal lobes consistent with a visual form of AD (Fig 1). SPM was used to compare both studies with a database of 14 control subjects (Figs 2A, B). This confirmed and delineated the abnormality located in the occipitoparietal regions (more so on the left side). SPM was then used to compare the images obtained before and after treatment (Figs 2C, D). Areas of increased relative perfusion were noted in (1) the right frontal lobe; (2) the right temporal lobe (most notably in the anterior aspect); (3) the right occipitotemporal area; (4) the left temporal lobe (anterior aspect), less pronounced than on right side; and (5) the bilateral postero-occipital lobe. Areas of decreased relative perfusion were found in the left parietal lobe and the cingulate gyrus bilaterally.

Table 1. Neuropsychological Testing Results

Test	Score Off Drug	Score On Drug
Verbal Memory Index[a]	68	89
Visual Memory Index[a]	92	110
General Memory Index[a]	68	95
Attention Concentration Index[a]	77	76
Delayed Recall Index[a]	81	94
Boston Naming[10]	51/60	55/60
Benton Facial Recognition[11]	39/54	42/54
Judgement of Line Orientation[11]	16/30	20/30
Verbal IQ[b]	96	100
Performance IQ[b]	81	80
Full-scale IQ[b]	90	91
Verbal Fluency (animals)[12]	13	11
Information[c]	7	10
Digit Span[c]	8	8
Vocabulary[c]	12	9
Comprehension[c]	6	9
Similarities[c]	11	14
Picture Completion[c]	6	4
Picture Arrangement[c]	4	5
Block Design[c]	7	6
Object Assembly[c]	4	5
Digit Symbol[c]	3	3

[a]Wechsler Memory Scale-Revised.
[b]Wechsler Adult Intelligence Scale-Revised.
[c]Wechsler Adult Intelligence Scale-Revised (scaled score).

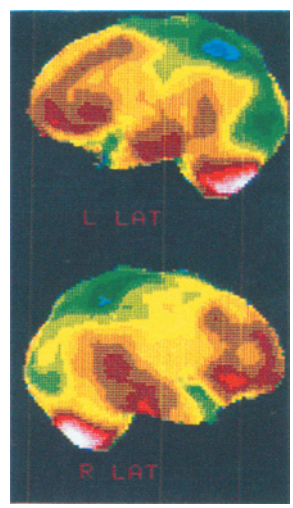

Fig 1. Surface views from initial single photon emission computed tomographic scan prior to therapy. Abnormalities are greatest in the parieto-occipital regions bilaterally. (Top) Left lateral view. (Bottom) Right lateral view.

Discussion

This patient has the typical neuropsychological and neuroimaging findings of the visual form of AD. Although pathological confirmation was not available in this patient, her course and symptoms *closely* match the syndrome of the visual form of AD. Brain SPECT abnormalities were most pronounced in the parieto-occipital regions bilaterally. Clinically she presented with prominent simultaneous ag-

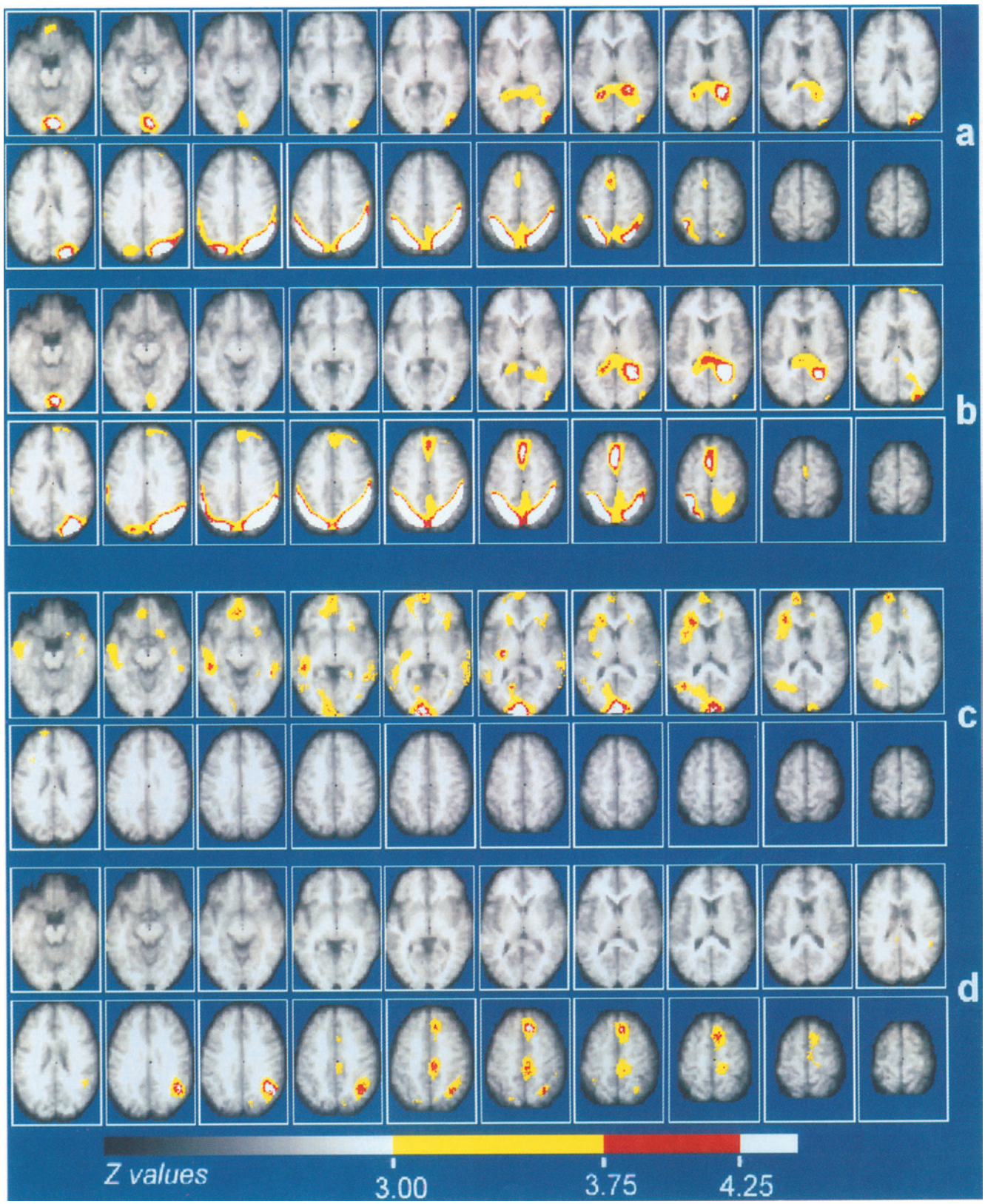

Fig 2. SPM results superimposed on a normal magnetic resonance image previously normalized to the Talairach space. The higher the *z*-value the more significant the change. (A) Axial images showing areas of decreased activity on the first single photon emission computed tomography (SPECT) scan compared with normal control subjects. (B) Axial images showing areas of decreased activity on the second SPECT scan compared with normal control subjects. (C) Axial images showing areas of increased activity (perfusion) on the second SPECT scan compared with the first SPECT scan. (D) Axial images showing areas of decreased activity (perfusions) on the second SPECT scan compared with the first SPECT scan.

nosia. Subsequently, the patient was treated with two different anticholinesterase drugs: tacrine and donepezil. Neuropsychological testing and brain SPECT were repeated 4 months after initiation of therapy. Subjectively the patient reported improved visual functioning. She was able to drive her car again around the block. She was able to read better. She felt less dizzy and noted less visual instability when walking or climbing stairs. These subjective improvements in visual functioning corresponded to improvements on the Benton Line Orientation Test and on the Visual Memory Index of the Wechsler Memory Scale-Revised. She did not improve on facial recognition, the Boston Naming Test, or the verbal or performance subtests of the Wechsler Adult Intelligence Scale. Her subjective improvement in visual functioning correlated with increased metabolism in the occipital lobes as demonstrated by SPM comparison of her pretreatment and posttreatment SPECT scans.

Statistical Parametric Mapping was useful in mapping precisely the areas of greatest abnormalities in the bilateral parieto-occipital regions. After treatment with anticholinesterases, the greatest neuropsychological improvements occurred in those functions related to memory (see the Table), consistent with the hypothesis that cholinergic systems are critical to memory functions. We used SPM to identify areas of greatest improvement on brain SPECT after treatment with anticholinesterases. Areas of improvement included both temporal lobes and both occipital lobes. The SPM documented improvement in relative brain perfusion in the occipital lobes correlated with the patient's observation that she was "seeing better." However, it did not correlate with a definite improvement in tests related to visual functioning. The SPM documented improvement in relative temporal lobe perfusion correlated with improvement in test scores for both verbal and visual memory (see the Table). This case report suggests that SPM may be useful in assessing the response to anticholinesterase therapy in AD. Furthermore, it suggests that patients with the visual form of AD may be responsive to anticholinesterase therapy.

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