fMRI of triggerable aurae in musicogenic epilepsy

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SPMS are involved in the cascade of events associated with myelin and oligodendrocyte damage and eventually axonal damage. This hypothesis is supported by earlier work showing a predominance of CD8+ T cells in perivascular cuffs and at the leading edge of plaque formation,[1] as well as by more recent work showing CD8+ T cell involvement in acute axonal injury at all stages of demyelination.[3]

SNP frequencies were found to be identical in our RRMS and SPMS groups and did not differ significantly from the published normal frequencies in other control populations[8-10] (see the table). This suggests that the robust lymphotoxin secretion observed with T-cell receptor cross-linking alone in CD8+ T cells from patients with SPMS reflects a state of prior activation and a generalized immune dysregulation acquired as the disease progresses, perhaps in response to repeated rounds of exposure to as yet undefined self antigens or environmental stimuli. These data suggest that the costimulation-independent secretion of lymphotoxin by activated CD8+ T cells is associated with the transition from RR to SPMS, and may be critical to the mechanism of chronic neurodegenerative changes found in later phases of the disease.

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fMRI of triggerable aurae in musicogenic epilepsy

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Abstract—The authors studied a patient with musicogenic epilepsy triggered by one specific musical piece using 3D PRESTO fMRI. During epileptic aurae initiated by the stimulus, signal increases were found in the left anterior temporal lobe, correlating with ictal EEG and SPECT showing a left anterior temporal focus, and the right gyrus rectus. Because fMRI indicated a cascade of recruitment of the ventral frontal lobes by epileptogenic music, left anterior temporal lobe activity could be secondary to a right gyrus rectus focus, possibly triggered by emotional processing of music.

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Musicogenic epilepsy[1,2] is a rare medical condition generally classified as a specific stimulus-triggered (reflex) epilepsy. It is characterized by a long latency between stimulus exposure and seizure induction, frequently in the range of minutes. Musicogenic seizures involve temporal lobe structures[1,2] and are most frequently complex partial.

The uniqueness and specificity of the musical triggers include a wide range: the sound of particular church bells, the melody of the Marseillaise, the metallic character of a singer's voice, or the sound of a street vendor's flute, only at sunset.[1,2] In some cases the trigger for seizures was the actual performance of a specific musical piece on a given instrument. Emotional cofactors may contribute to the development of a brain state close to a threshold from which seizure activity may be initiated.[2]

Few studies have investigated the effects of epi-

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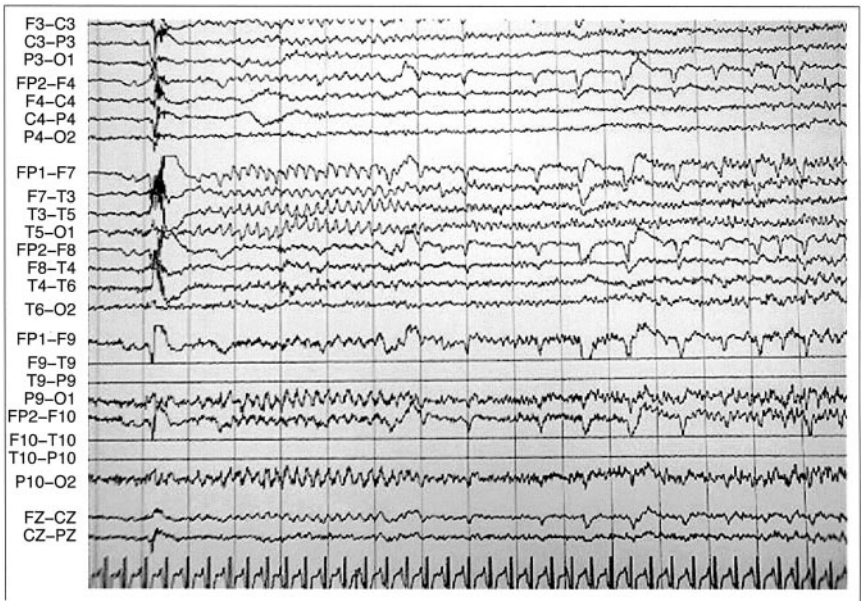

Figure 1. EEG tracing acquired while the patient was exposed to the epileptogenic music. Left temporal seizure activity: a period of θ-rhythmic waves lasting 6 seconds was followed by discharges of lower voltage and higher frequency, which persisted through the end of the record. Electrode positions are indicated. Each gridline represents 1 second.

leptic activity on the fMRI signal in patients with spontaneous epileptic discharges.[3,4] Here we report an fMRI study in an individual with medically well-controlled musicogenic seizures where blood oxygenation level dependent (BOLD) signal changes were induced by epileptic aurae upon exposure to specific epileptogenic music.

Materials and methods. *Patient.* A 48-year-old right-handed woman had a history of music-induced "strange feelings" since age 41. Beginning at age 42, she had music-induced complex partial seizures. The musical triggers were one song performed by Whitney Houston and one by Boyz II Men. She underwent continuous EEG monitoring during which four episodes of musicogenic complex partial seizures (triggered by music by Boyz II Men) with a left anterior temporal focus were captured (figure 1). An ictal SPECT scan showed left temporal hyperperfusion; the interictal SPECT revealed mild hypoperfusion in the same area. Results on MRI studies and neurologic examination were normal. Medication included phenobarbital and Tegretol (Novartis, East Hanover, NJ).

Music tasks. The tune "I believe in you and me" by Whitney Houston was selected as the trigger condition causing strong aurae feelings: pressure in the abdominal and then pectoral area, a "rushing" sensation, palpitations, and heart racing. A similar sounding song ("Somebody bigger than you and I," from the same album) served as control condition. Both tunes were played each time from the beginning of the track. The patient was instructed to press a response button at aura onset. Each of the 10 imaging sessions included 39 seconds of control music (8 scans) followed by 39 seconds (8 scans) of the epileptogenic music in a block design fashion. The patient was allowed to rest for a few minutes between sessions while her baseline pulse rate recovered, and she was examined for alertness and well being.

Imaging. T1-weighted spin-echo images using a 1.5 Tesla Philips (Eindhoven, the Netherlands) Gyroscan MRI scanner were acquired as anatomic reference; a version of the three-dimensional gradient-recalled shifted-echo PRESTO pulse sequence was used for functional studies.[5] PRESTO has the advantages of a soft, monotonous, noise level, good image quality with low image distortion rates (especially of the ventral brain surface), slice timing consistency, and inherently low susceptibility to blood inflow effects. In-plane resolution was 3.75 × 3.75 mm, slice thickness 3.5 mm, effective echo time 35 msec, repetition time (TR) 24 msec, flip angle 30°, and 5 echoes/TR. The acquisition time for 16 slices (one scan) was approximately 5 seconds. In each fMRI session, two dummy scans were discarded.

fMRI analysis. A total of 160 functional scans were spatially realigned, smoothed with a Gaussian filter of 10 mm, and coregistered with the anatomic scan using SPM99 (http://www.fil.ion.ucl.ac.uk/spm). A boxcar model was used to contrast epileptogenic vs control music conditions and aura vs nonaura sessions. All contrasts were examined with a voxelwise significance level of 0.05 (*t*-test) corrected for multiple comparisons across the brain volume. A separate small volume correction, taking into consideration the area of the left temporal lobe, was applied to the significance threshold for the assessment of the aura effect in the left anterior temporal lobe (laTL) (contrasting the epileptogenic music conditions during the aura vs nonaura sessions). Cluster size threshold was kept at zero voxels. The mean over all significant voxels in a given region of interest was determined using the time series of the realigned and smoothed data set as source.

A second, fundamentally different, model- and assumption-free method of analysis based on independent component analysis (ICA) was applied to decompose the time series into spatial and temporal components[6] using the software program MELODIC (http://www.fmrib.ox.ac.uk/fsl/). Resulting activity maps were defined by the selected spatial component superimposed on anatomic slices whereas the corresponding temporal component was the source for the variance-normalized time course and representative for all voxels displayed.

Results. The patient reported an aura onset in 5 of 10 fMRI sessions (twice in the fifth session). Average response time for the first button press after initiation of the epileptogenic music was 23.6 seconds (SD_{n-1} = 5.6 seconds, n = 5). No abnormal movements or adverse reactions were observed. Pulse rate increased from about 92 beats per minute (bpm) to 105 to 110 bpm toward the end of the control music conditions with maximum of 110 to 116 bpm reached by the end of the seizure triggering music conditions. Figure 2 shows the SPM99 comparison of the two music conditions (epileptogenic vs control music): signal increases were found in both aura sessions and nonaura sessions in the bilateral frontal poles, right anterior cingulate, and the right gyrus rectus (rGR), whereas signal decreases occurred bilaterally in the caudal GR and adjacent structures in the orbital and subcallosal cingular gyri (not shown). Differential activation for the aura sessions (during epileptogenic music) was evident in rGR and laTL. The raw fMRI signal time course (figure 2, lower panels) shows signal increases for the epileptogenic music in rGR during the first four aura sessions.

Similar effects of music conditions in the frontal cortex were also found in the ICA analysis. Figure 3 depicts the spatial extent and time course of the ICA component best corresponding to the stimulus paradigm (frequency spectrum) in all 10 sessions. A comparison of the signal amplitudes in the two music conditions—control and epileptogenic—during the aura vs the nonaura sessions was significant (interaction between music × aura, gen-

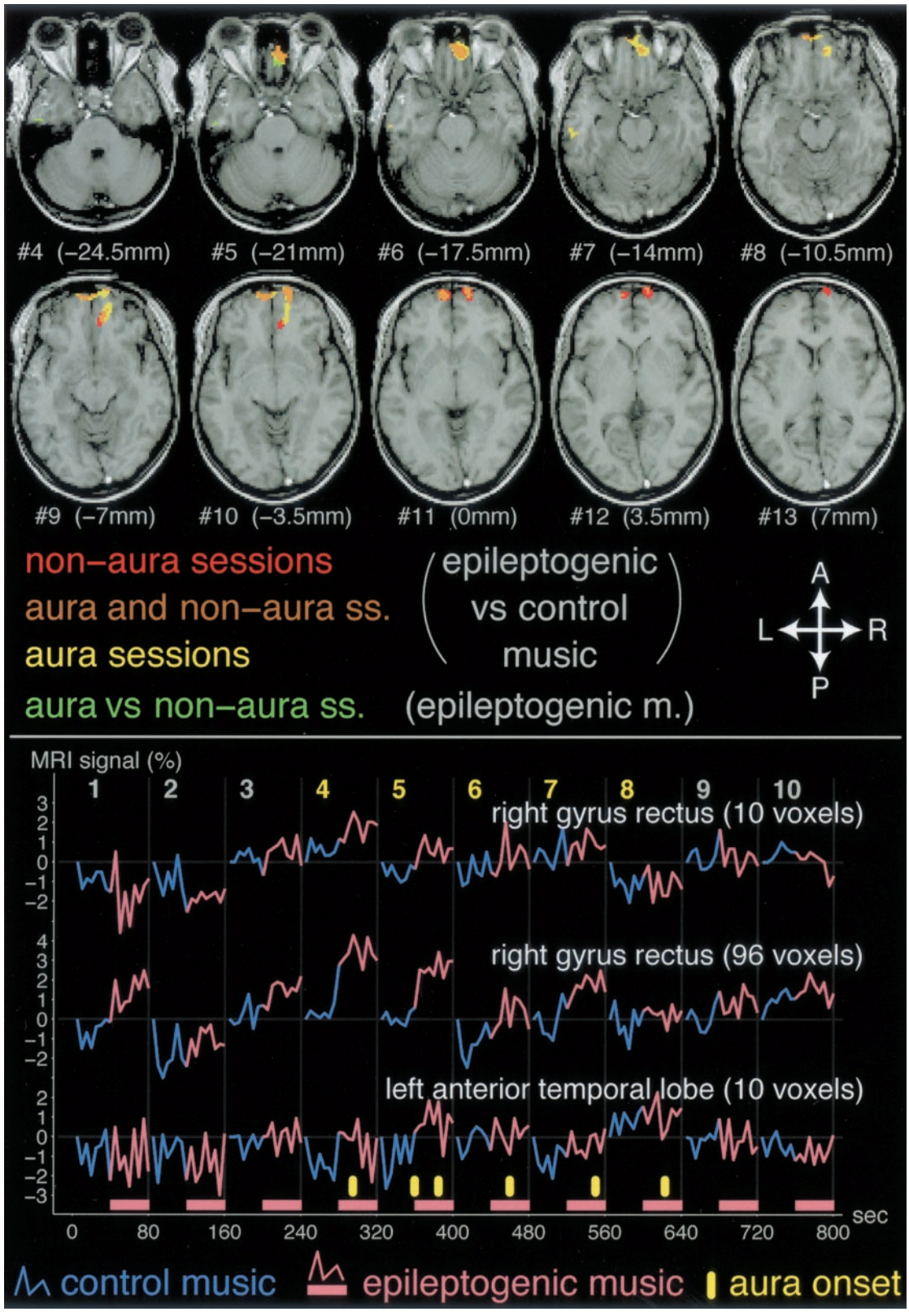

Figure 2. fMRI activity maps for the epileptogenic music effect and for the aura effect superimposed on anatomic MRI slices (slice numbers and positions relative to anterior commissure/posterior commissure plane indicated). Red and yellow represent voxels with significant fMRI signal increase for the seizure music conditions: red in the nonaura sessions, yellow in the aura sessions. Orange voxels represent overlapping signal increases in both session types. Voxels in green in the rGR and the left anterior temporal lobe (laTL) demonstrate significantly higher fMRI signals during the epileptogenic music in the aura as compared to the nonaura sessions. Lower panels show the averaged fMRI signal time course: top, the 10 green voxels in the rGR; middle, the orange, yellow, and green voxels in the rGR; bottom, green and yellow laTL voxels. Blue curve = control music conditions; pink curve = seizure music conditions. Vertical yellow marks indicate aura onset report times.

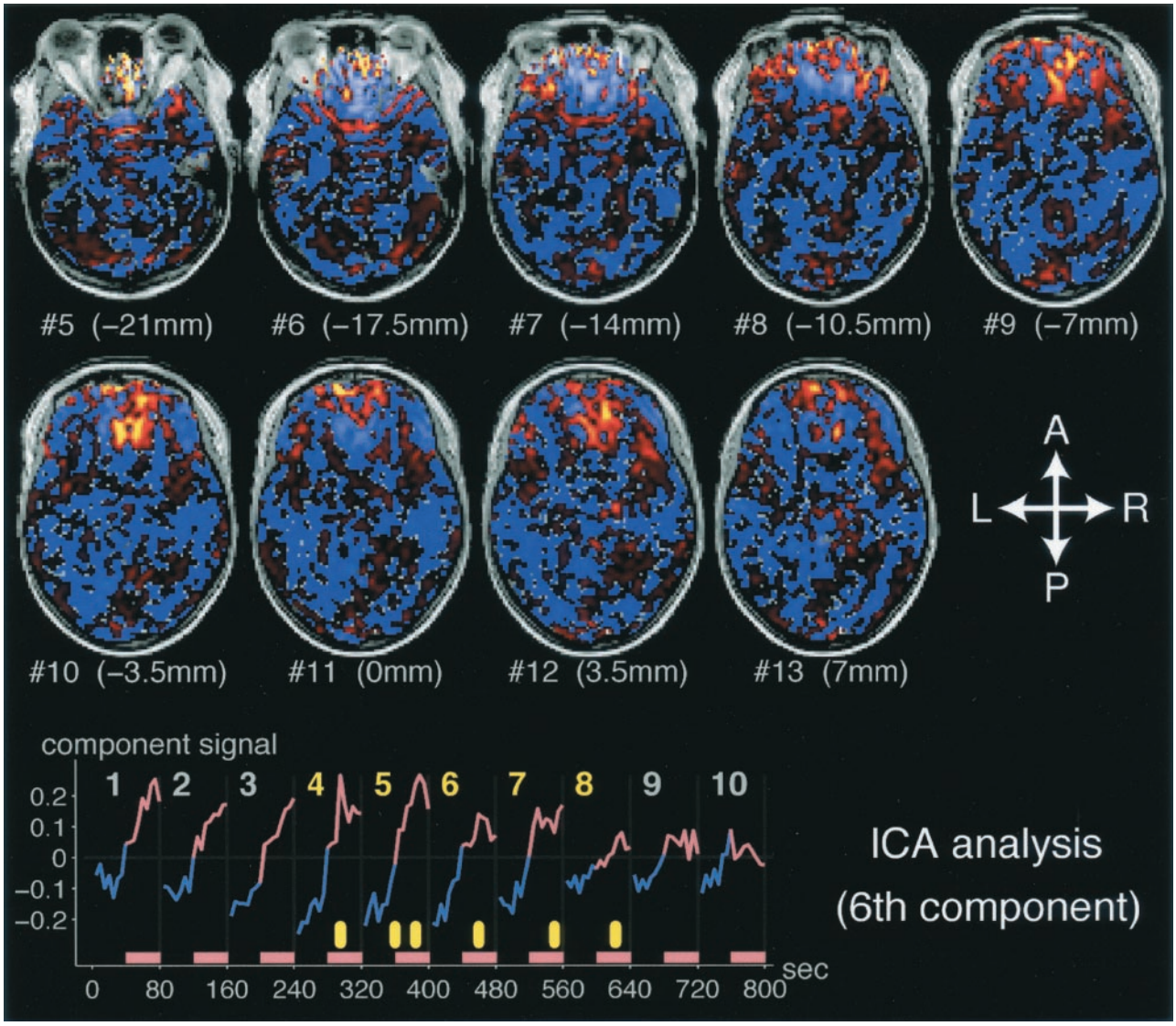

Figure 3. fMRI activity maps show the spatial extent of the sixth component (selected for its frequency spectrum, best corresponding with stimulus paradigm) of the 10-dimensional independent component analysis. Voxels are rescaled with unit variance. Red to yellow represent voxels with increased component intensity whereas blue to light blue represent signal decreases. Lower panel = the time course for the corresponding temporal (variance-normalized) component; symbols and color coding as in figure 2.

eral linear model–analysis of variance for repeated measures, $F[1,7] = 20.97$, $p < 0.0025$).

Two mathematical control experiments tested for movement-related artifacts in areas prone to susceptibility by movement artifacts. The inclusion of movement parameter estimates as covariates in the SPM99 design matrix and the application of the Unwarp technique[7] (http://www.fil.ion.ucl.ac.uk/spm/toolbox/unwarp.html) made no substantial difference in the analysis results.

Discussion. Repeated exposure to the unique seizure-triggering music resulted in two distinct patterns of consistent BOLD signal changes: one related to the actual triggering of musicogenic aurae, the other related to exposure to the specific epileptogenic music. The fMRI data and the ictal EEG and SPECT measurements indicated the laTL as a locus for seizure-related activity. However, the PRESTO fMRI measurements not only revealed additional foci in the ventral frontal lobes but also indicated that the rGR activation, occurring at an earlier phase of exposure to epileptogenic music, may have initiated the seizure cascade. This is supported by the finding that the laTL (not known to play any role in music processing) was not activated by seizure-music exposure per se, as the fronto-orbital lobes were. The fronto-orbital structures are believed to be key structures in processing emotional aspects of music.[2,8]

Fronto-orbital activation was found in a PET study[8] in which the effect of increasingly pleasant music was investigated. Lesion studies also support that emotional processing of music depends on the fronto-orbital brain.[9] The patient reported here expressed no interest in music in general, has never played a musical instrument, and had no particular memories or feelings related to the triggering pieces

of music. However, her pulse measurements indicated that she was having an autonomic response even before being exposed to the epileptogenic music.

Because our experimental fMRI design was inherently sensitive to the effect of prolonged listening to music (control followed by epileptogenic music), the observed activity changes in the fronto-orbital lobes may have reflected emotional arousal and memory related to the music[1,2] rather than seizure activity per se. Our findings suggest that during the patient's aura, the main differential evoked activity was localized in the rGR. Nevertheless, the control music may have contributed to the enhancement of the patient's susceptibility to the ensuing seizure-inducing music, possibly in the form of progressive cortical recruitment.[2] Indeed, the large negative activations that surrounded the rGR in the epileptogenic music conditions may indicate uncompensated hypermetabolism or vascular dysregulation.[10]

Even within the relatively short time frame of the fMRI study, the ability of the same stimulus to evoke an epileptic aura varied. The imminent exposure to the feared stimulus and the foreign atmosphere of an fMRI experiment may have contributed to the failure to induce epileptic aurae in the first three exposures, whereas the results for the final two sessions are suggestive of habituation to the repeated stimulus presentation.[1,2] A similar habituation was found for the signal in the rGR during the aura sessions although a clear-cut correlation with the button press latencies was not evident.

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Trends in dementia mortality from two National Mortality Followback Surveys

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Abstract—The National Center for Health Statistics conducted National Mortality Followback Surveys (NMFS) in 1986 and 1993. The next-of-kin's report of a physician's diagnosis of AD before death and a listing of AD or other dementia as the underlying cause increased significantly among women but remained stable among men. Currently, AD is among the top 10 leading causes of death in elderly white men and women in the United States.

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As the US population ages, mortality from dementia is likely to increase concomitantly due to the well-known association between incidence of dementia-related diseases and aging.[1,2] Planning for future health care services, especially long-term care, is served by knowledge of trends in dementia mortality. The National Center for Health Statistics (NCHS) provided data for an initial examination of national estimates of dementia mortality in the 1986 National Mortality Followback Survey (NMFS).[2] Although death certificate data are known to seriously underestimate the presence of dementia,[2,3] the NMFS also provided rates based on next-of-kin interviews addressing the decedent's history of physician diagnoses and disabilities before death.

In 1993, the NCHS conducted a second NMFS.[4]

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