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Letter to the Editor

Modeling Decline in Alzheimer's Disease

TO THE EDITOR

Brooks and colleagues (1993, 1998) have recently drawn attention to one important aspect of the problems inherent in the assumption of linear decline in Alzheimer's disease (AD). They posited a "trilinear" model, with periods of initial and terminal stability and an interim period of decline. We have also modeled decline in AD (Mitnitski et al., 1999) and agree that the assumption of linear decline across all stages of dementia is generally not valid. Our model is based on the probability of the occurrence of cognitive and/or functional deficits. The deficits are those detected at a clinical examination, and include, for example, individual items of dependence in activities of daily living, the presence of hypertonus, and abnormal gait. The model showed that although such deficits occur across different diagnostic groups, they form characteristic patterns in AD. We assumed, as a first approximation, a simple random mechanism of the emergence of the deficits, and suggested a dynamic model for the decline.

In that model, the rate parameter was related to the average probability of the emergence of a deficit. The estimate of this parameter showed that more severe forms of dementia had greater rates of decline. Our analysis of the distribution of the individual rates of decline showed that the probability distribution for normal aging is exponential, whereas for AD it can best be fitted by a log-normal function.

A logistic function also represents one possibility of describing a process with three stages, in which the (instantaneous) rate of a process is small in the beginning, and then increases, and finally—reflecting a saturation phenomenon—decreases. We were therefore interested to see if such modeling might fit the data described by Brooks and colleagues. Using data from their 1993 publication (Brooks et al., 1993), and examining decline in Mini-Mental State Examination (MMSE) scores over the years following entry into their study, we found that a more parsimonious model (three parameters as compared with their five parameters) showed a high degree of fit to a logistic function, as shown, for example, in Figure 1 on the next page, taken from their Figure 3). We considered a logistic function of decline over time, with three parameters as follows:

$$x = a\left(1 - \frac{1}{1 + b\exp(-ct)}\right)$$

where x is the MMSE score, t = the time in years, and a, b, and c are the following parameters:

a corresponds to the highest MMSE value (usually the initial value, or close to it)

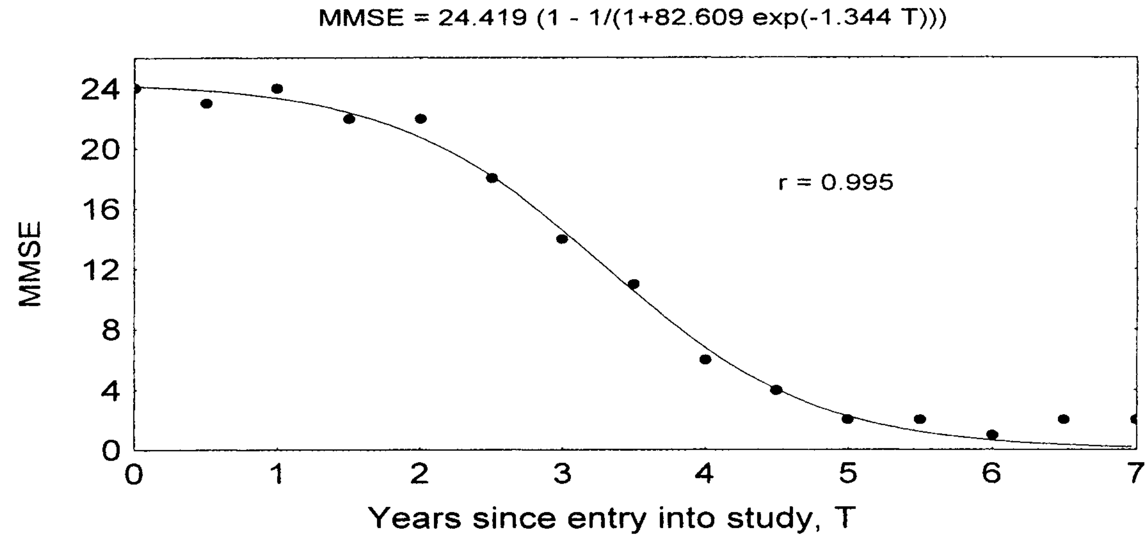

Figure 1. Logistic function fit for Figure 3 (Brooks et al., 1993). MMSE = Mini-Mental State Examination.

b can be expressed as a function of *a* and the initial value of the MMSE x_0, such that if $x_0 = ab/1 + b$, then $b = (x_0a)/(1 - x_0/a)$

c, which has the dimension (1/ years), is proportional to the maximum rate of change in the MMSE $(v = dx/dt)_{max}$. For example, $c = 4v_{max} / a$, when the MMSE score = a / 2. In consequence, the rate of change in the MMSE (dx/dt) can be expressed as: $dx/dt = -cx (1 - x/a)$.

The experimental data shown in Brooks and colleagues (1993) can be well fitted using these equations. For example, using the data shown in the fourth panel of Figure 2 of that publication, we find that a = 28.316, b = 33.554, and c = 0.754, as shown in Figure 2 on the next page. In addition to this example, we obtained results from Figures 2.1, 2.2, and 2.4 with correlation coefficients all higher than 0.979, indicating more than 95% of the variance is explained by this approach.

In summary, although the trilinear model addresses the important issue of the representation of individual longitudinal data in a nonlinear fashion, we suggest that a logistic function, which can model a process that is small in the beginning, increases after some time, and then decreases, better describes the decline on MMSE scores seen in AD. Brooks and colleagues have raised the possibility that treatment effects can be modeled by comparing the rates of decline by treatment groups, a proposition that is exciting and which merits further investigation.

Arnold Mitnitski, PhD
University of Montreal
Montreal, Canada
Janice Graham, PhD
University of British Columbia
Vancouver, Canada
Kenneth Rockwood, MD
Dalhousie University
Halifax, Canada

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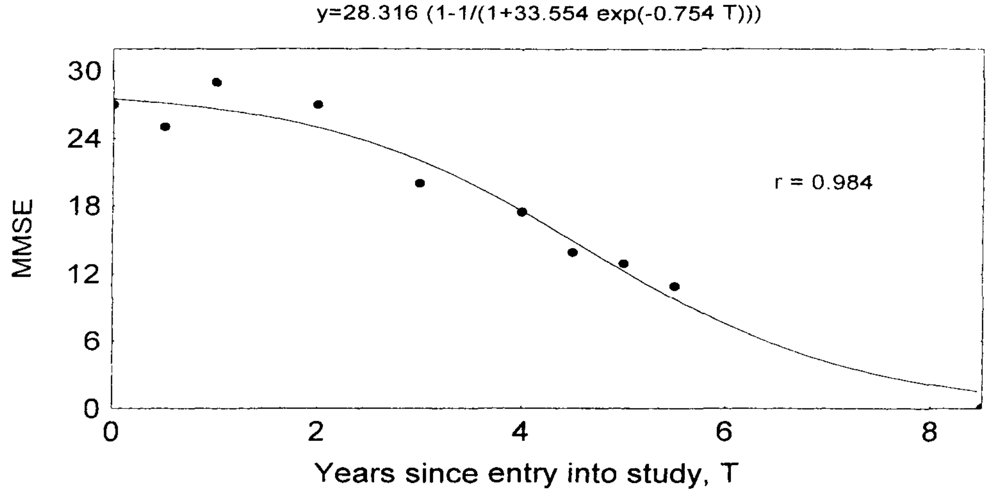

Figure 2. Logistic function fit for Figure 2.4 (Brooks et al., 1993). MMSE = Mini-Mental State Examination.

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THE REPLY

The measurement of decline of Alzheimer's disease is at last receiving its due. For many years, decline was measured as a difference score or as the linear rate of change over the period of time measured. In 1993, we posited the trilinear model (Brooks et al., 1993) to allow for an initial period of stability, a period of change, and a final period of stability, as shown in Figure 1, on the next page. This model is at least as comprehensive as a linear model because the linear model is a special case of the trilinear model—a case in which there are neither initial nor final periods of stability. The differences between estimates of decline obtained with the linear model and those with the trilinear model can be notable (Brooks et al., 1998).

As we stated in our original report, "it is undoubtedly true that Alzheimer's disease does not exactly follow a trilinear pattern" (Brooks et al., 1993, p. 627). There are likely more than two periods of stability, and the transition from a period of stability to one of change is not as abrupt as a linear junction. Mitnitski and colleagues (1999a, 1999b) have recently questioned whether a logistic function would account for data better than a trilinear one. The function suggested by Mitnitski and coworkers was

$$x = a\left(1 - \frac{1}{1 + b\exp(-ct)}\right)$$