

# Modeling the Influence of Extrapyrarnidal Signs on the Progression of Alzheimer Disease

Yaakov Stern, PhD; Xinhua Liu, PhD; Marilyn Albert, PhD; Jason Brandt, PhD; Diane M. Jacobs, PhD; Caridad Del Castillo-Castaneda; Karen Marder, MD, MPH; Karen Bell, MD; Mary Sano, PhD; Fred Bylsma, PhD

**Objective:** To determine how the advent of extrapyramidal signs influences the progression of Alzheimer disease as measured by standard clinical measures.

**Design:** We applied growth curve models to prospective data to characterize patients' cognitive and functional changes over time. To detect changes in disease course related to extrapyramidal signs, their onset was treated as a time-dependent covariate.

**Setting:** Three research medical centers.

**Participants:** Patients (n=217) with probable Alzheimer disease.

**Intervention:** Patients were followed up semiannually for 5 years.

**Main Outcome Measures:** Scores on the modified Mini-Mental State Examination and measures of basic and

instrumental activities of daily living from the Blessed Dementia Rating Scale.

**Results:** For basic and instrumental activities of daily living, disease course was more rapid once extrapyramidal signs developed. Decline in the modified Mini-Mental State Examination score was greater at the time the signs developed, but not at subsequent visits.

**Conclusions:** The point at which extrapyramidal signs emerge is associated with measurable acceleration in the progression of Alzheimer disease. This may in part explain why extrapyramidal signs are associated with a poorer prognosis. The differential influence of extrapyramidal signs on cognitive and functional measures suggests that the pathological changes underlying these disease features may vary.

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From the Departments of Neurology (Drs Stern, Jacobs, Marder, Bell, and Sano) and Psychiatry (Dr Stern) and the Gertrude H. Sergievsky Center (Drs Stern, Liu, Jacobs, Marder, and Sano, and Mr Del Castillo-Castaneda), Columbia University College of Physicians and Surgeons, New York, NY; Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, Md (Drs Brandt and Bylsma); and Departments of Psychiatry and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston (Dr Albert).

SEVERAL STUDIES<sup>1-6</sup> have demonstrated that the presence of extrapyramidal signs (EPS) in a patient with Alzheimer disease (AD) is associated with more rapid progression to disease milestones, including specific scores on tests of cognition and activities of daily living (ADL), nursing home admission, and death. In a recent study,<sup>1</sup> we also evaluated the predictive value of the presence of EPS for the rate of disease progression as assessed by the slope of mental status or functional assessment scores. For both of these measures, we found that the presence of EPS at the initial visit was associated with more rapid decline.

The present study addressed 2 issues associated with these observations. First, most patients develop EPS at some point in the disease.<sup>7</sup> It is of interest then to understand if and how the course of the disease is changed by the onset of EPS. Second, our initial analy-

ses investigated the relationship between linear estimates of rate of disease progression and EPS.<sup>1</sup> It has become clear that change in scores over time in instruments that assess AD severity is not linear.<sup>8-11</sup> It would be valuable to evaluate this relationship using more appropriate models of AD progression.

To address these issues, we used a recently developed method that extends nonlinear growth curve models<sup>12</sup> to characterize the changes in prospectively collected data.<sup>10</sup> This modeling approach is flexible in that it determines the "shape" of the curve that best fits the data. We previously used this approach to compare disease progression.

*See Subjects, Materials, and Methods on next page*

## SUBJECTS, MATERIALS, AND METHODS

### SUBJECTS

All subjects were participants in the Predictors Study,<sup>13</sup> a multisite, longitudinal study of disease course in AD. Two hundred thirty-six patients with probable AD were recruited into the study at 3 sites, Columbia-Presbyterian Medical Center, New York, NY, Johns Hopkins Hospital, Baltimore, Md, and Massachusetts General Hospital, Boston. Details of inclusion and exclusion criteria and recruitment methods have been previously described.<sup>13</sup> Briefly, all patients were required to meet the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria<sup>14</sup> for probable AD. To ensure that severity of dementia was mild at study entry, all patients were required to have a modified Mini-Mental State Examination (MMSE) score of 30 or above (corresponding to approximately 16 on the standard MMSE). Patients with small subcortical lesions that were clinically and historically silent were included. However, patients with cortical lesions of any size or location or with focal cortical atrophy in a specific vascular distribution were excluded.

### PROCEDURES

All patients were evaluated at 6-month intervals. Cognitive function was examined using the modified MMSE.<sup>15</sup> This instrument includes all items from the standard MMSE<sup>16</sup> and also includes the Wechsler Adult Intelligence Scale Digit Span subtest<sup>17</sup> and additional attention and calculation, general knowledge, language, and construction items. The maximum score on this test is 57. This is a valid and reliable instrument<sup>18</sup> that is brief yet informative.

Functional capacity was rated using the Blessed Dementia Rating Scale (part 1)<sup>19</sup> using a structured interview to guide and standardize administration. A previous factor analysis of this instrument yielded 4 factors with a distinct pattern of progression.<sup>20</sup> In the current analyses, we concentrated on 2 factors that reflect 2 specific types of ADL. Instrumental ADL (IADL) were assessed by items 1 through 7, which address functions such as orientation, performing chores, and remembering lists. These items are traditionally scored on a 3-point scale as absent (0), partially impaired (0.5), or fully impaired (1). To simplify analysis, this 3-point scale was recoded and ranged from 0 to 2. Thus, the maximum score for IADL was 14. Basic ADL (BADL) were measured by 3 items: eating, dressing, and toileting. These are rated on a 4-point scale ranging from 0 to 3. Thus, the maximum BADL score was 9. For both ADL domains, a higher score denotes more impairment.

Selected items from the Unified Parkinson's Disease Rating Scale<sup>21</sup> were used to rate EPS. The reliability of the scale for use in probable AD has been established.<sup>22</sup> Hypophonia, masked faces, resting tremor, rigidity (neck and each limb), bradykinesia or hypokinesia, and posture and gait abnormalities were rated as absent, slight, mild-moderate, marked, or severe (see Richards et al<sup>22</sup> for complete form). For all analyses, patients who had at least 1 sign rated as mild-moderate were considered to have EPS.

We used this criterion since ratings of EPS of this severity are more reliable and are likely to be noted by a clinician.<sup>22</sup> The EPS were coded as idiopathic, probably induced by current neuroleptic medication, or possibly induced by previous neuroleptic medication. Our analyses focused on non-drug induced EPS. If a patient's EPS were possibly or probably drug induced when they were first noted, then that patient's observations were not included in the statistical analyses.

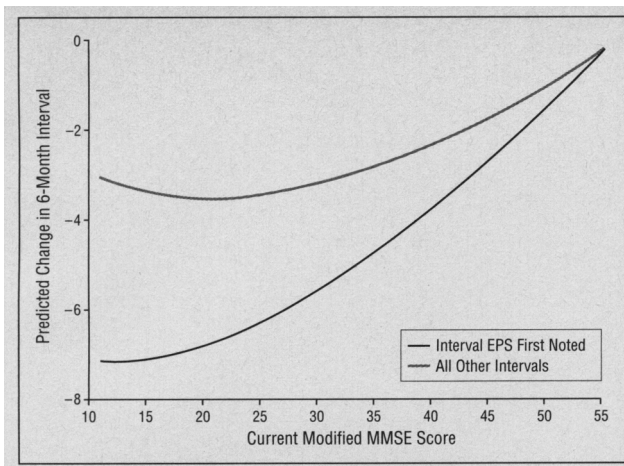
### STATISTICAL ANALYSIS

The mathematical properties of the modeling approach have been described.<sup>10</sup> It applies the principles of growth models, which can be specified by an equation that assumes that the growth rate, or change in a test score, is a function of the present score. The modeling procedure begins by calculating changes in test scores between all adjacent 6-month visits for each subject. Thus, only patients with at least 2 consecutive scores on a measure can be included in the calculations. The goal is to characterize the conditional average change in a score based on the current score,  $E(Y_{k+1} - Y_k / Y_k)$ , where  $Y_k$  represents a test score at time  $k$ ,  $Y_{k+1} - Y_k$  is the change in the next interval, and  $E$  denotes the expectation operation. We model the conditional average change with a function in a form similar to the von Bertalanffy growth curve model,<sup>12</sup> which unifies various types of models including monomolecular, logistic, and Gompertz. The values of the model parameters determine the shape of the model and the point of maximal change in scores (if one exists). A quasi-likelihood approach is used to estimate model parameters to best fit the data. The procedure minimizes the mean square error of prediction of changes in test scores. The 95% confidence intervals can be calculated for the various model parameters as well.

In the present analyses we applied an extension of the modeling technique that allows for the incorporation of the onset of EPS as a time-dependent covariate. Thus, we could model how progression changes when the patient develops EPS. The modeling procedure was applied separately to the modified MMSE total score and the 2 ADL factors.

To visually display the consequences of developing EPS for the progression of each measure, we used 2 approaches. First, we used the model to generate the predicted change in a score over the next 6 months as a function of each value of the current test score in patients with and without EPS. These were graphed and compared with the empirically observed changes in scores. Second, we modeled the progression in a test score over time, given a specific starting score. In this case, the starting score generates a prediction of the score at the next time interval, and this process is repeated until the score reaches its upper or lower bound. The generated curve is therefore a generalized representation of the progression of the test score over time. The procedure uses all patient data to derive a model progression of a test score from its highest to its lowest point even though no individual patient's data may span this entire range. Therefore, the period represented in the graphed model of progression is often longer than the time any individual patient is followed up.

To demonstrate the modeled impact of the onset of EPS, we graphed progression in a hypothetical patient who never develops EPS. We then graphed progression when EPS developed at 2 different points in time.



**Figure 1.** Based on the growth curve model, predicted average change of modified Mini-Mental State Examination (MMSE) scores over a 6-month interval as a function of the current score. Two predictions are presented for each score, one for the interval in which extrapyramidal signs (EPS) are first noted and another for all other intervals.

as assessed by the modified Mini-Mental State Examination and by measures of instrumental and basic ADL.<sup>11</sup> The modeling technique also allows the incorporation of subgroups or time-dependent covariates. In the present analyses, we used our modeling approach to investigate how the onset of EPS may influence the course of AD by treating the onset of EPS as a time-dependent covariate.

## RESULTS

### MODIFIED MMSE PROGRESSION

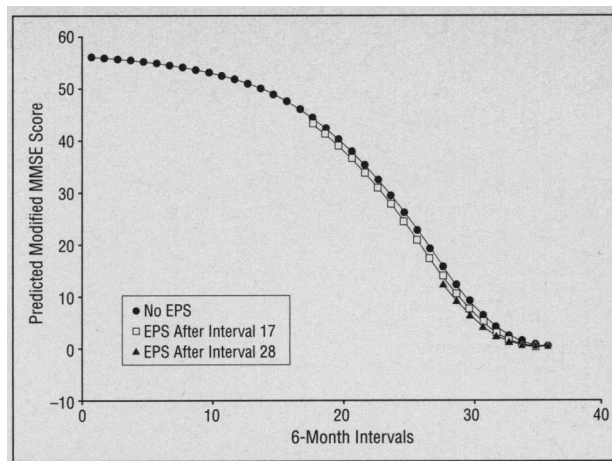
Of 217 patients with data amenable to the analysis, 56 patients developed EPS at some point during their follow-up. The modified MMSE score at the time EPS occurred ranged from 14 to 48 with a mean of 31.9 (SD=7.98).

We calculated the mean of the empirically observed changes over a 6-month interval for each modified MMSE score. Overall, there was no difference in these changes in scores in patients with and without EPS. Observation of the data suggested that the change in modified MMSE score was increased at the interval in which EPS developed.

In the modeling procedure, the introduction of the status of EPS as a time-dependent covariate produced a statistically significant increase in the accuracy of the model. However, the contribution of EPS to the model occurred only at the point that EPS develop; the predicted change in the modified MMSE score at any other interval remained the same whether EPS were present. The derived growth curve function was as follows:

$$E(Y_{k+1} - Y_k / Y_k, X_k) = -0.1687Y_k \log(57/Y_k) - 0.0882X_k(57 - Y_k)$$

In this equation,  $Y_k$  is the modified MMSE score at time  $k$ .  $X_k$  equals 1 if EPS developed during the  $k$  time interval;  $X_k$  equals 0 if there was no change in status of the EPS between times  $k$  and  $k+1$ . Thus, for any patient  $X_k$  can equal 1 only once during the progres-



**Figure 2.** A time series of modified Mini-Mental State Examination (MMSE) scores generated by the growth curve model, beginning with an initial score of 56. EPS indicates extrapyramidal signs.

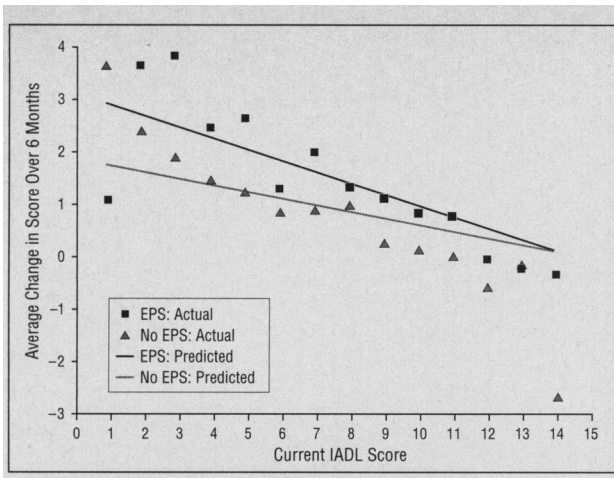
sion of the disease. Substituting a current modified MMSE score for  $Y_k$  and the appropriate value for  $X_k$  in the equation generates a prediction of the amount of decline in the modified MMSE score over the subsequent 6-month interval. This model indicates that the initial occurrence of EPS result in accelerated decline in modified MMSE in that interval. In addition, the amount of additional decline associated with the advent of EPS is larger when the modified MMSE score is lower. This is illustrated in **Figure 1**, which plots the model's predictions of the change in modified MMSE score over the next 6-month interval based on the current modified MMSE score. Two predicted changes are plotted, one that applies only to the interval in which EPS are first noted, and another that applies to all other study intervals. Note that the additional decline associated with the onset of EPS is greater when the modified MMSE score is lower.

**Figure 2** illustrates 3 hypothetical patients, each beginning with a modified MMSE score of 56. The first patient never develops EPS and exhibits the pattern of progression for the modified MMSE score in AD that we have described previously. The other 2 patients develop EPS at intervals 17 and 28, respectively. There is a larger change in the modified MMSE score at the interval that EPS develop. However, subsequent rate of decline in modified MMSE score is not affected.

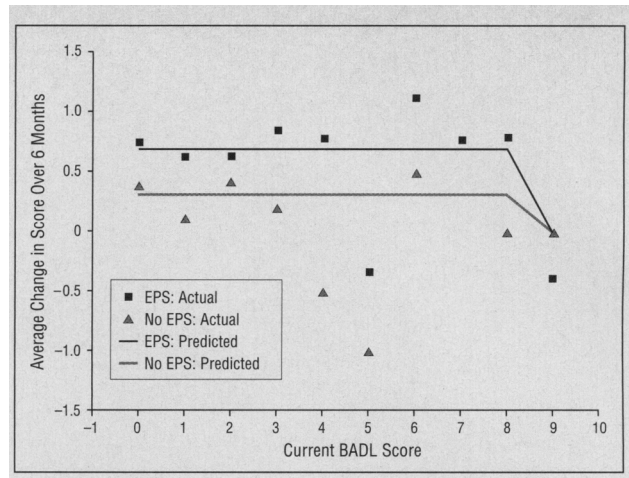
### IADL PROGRESSION

The observed average change in IADL score over the next 6-month interval was calculated separately for each initial IADL score. These changes differed significantly in patients with and without EPS, as illustrated in **Figure 3**. In almost every case, observed change was greater in patients with EPS.

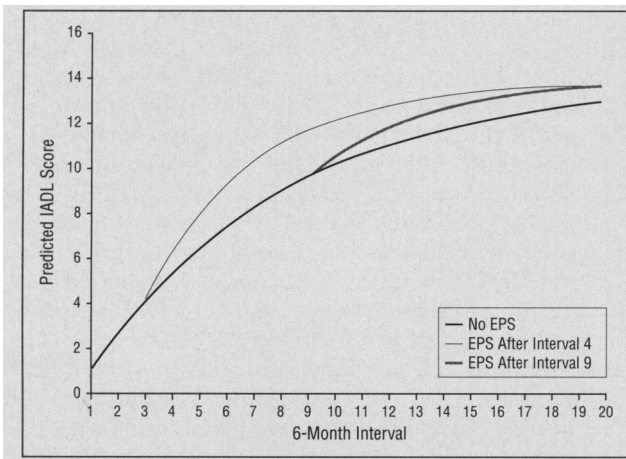
At the time EPS were first noted, IADL scores ranged from 0 to 14, with a mean score of 8.4 (SD=2.87). In the modeling procedure, the introduction of the onset of EPS as a time-dependent covariate yielded a significant in-



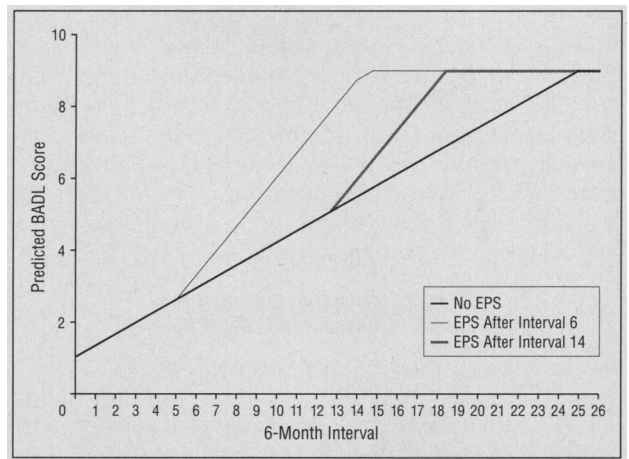
**Figure 3.** For each instrumental activities of daily living (IADL) score, the predicted and the observed average change in score over the next 6-month interval in patients with and without extrapyramidal signs (EPS).



**Figure 5.** For each basic activities of daily living (BADL) score, the predicted and the observed average change in score over the next 6-month interval in patients with and without extrapyramidal signs (EPS).



**Figure 4.** A time series of instrumental activities of daily living (IADL) scores generated by the growth curve model, beginning with an initial score of 1. EPS indicate extrapyramidal signs.



**Figure 6.** A time series of basic activities of daily living (BADL) scores generated by the growth curve model, beginning with an initial score of 1. EPS indicate extrapyramidal signs.

crease in the accuracy of the model. In contrast to the modified MMSE, the rate of progression of IADL scores differed for all intervals in which EPS were present. The derived growth curve function was as follows:

$$E(Y_{k+1} - Y_k / Y_k, X_k) = (14 - Y_k)(0.1266 + 0.0874X_k)$$

Again,  $Y_k$  is in the IADL score at time  $k$ .  $X_k$  equals 1 if EPS are present at time  $k$ ;  $X_k$  equals 0 if EPS are not present. Substituting the current IADL value for  $Y_k$  and the appropriate value for  $X_k$  into the equation yields a prediction of the change in IADL scores over the next 6-month interval. This model indicates that once EPS develop, the rate of change in IADL scores is increased at all subsequent visits. The accelerated rate of change associated with EPS becomes more marked as IADL scores increase. The model-based predicted change in IADL score associated with each current IADL score for patients with and without EPS is plotted in Figure 3.

**Figure 4** illustrates 3 hypothetical patients, each beginning with an IADL score of 1. The first patient

never develops EPS and exhibits the typical pattern of progression for IADL scores in AD that we have described previously.<sup>10</sup> The other 2 patients develop EPS at intervals 4 and 9, respectively. Note that the progression of IADL scores is altered in the presence of EPS.

### BADL PROGRESSION

At the time of onset of EPS, BADL scores ranged from 0 to 9, but the mean score was 1.6 (SD=1.97) and the model score was 0. We separately calculated the mean of the empirically observed changes over a 6-month interval for each initial BADL score. These changes differed significantly in patients with and without EPS, as illustrated in **Figure 5**. Again, patients with EPS had greater changes in scores than those without EPS.

In the modeling procedure, the introduction of the onset of EPS as a time-dependent covariate yielded a significant increase in the accuracy of the model. As with IADL scores, the rate of progression of BADL

scores differed for all intervals in which EPS were present. The derived growth curve function was as follows:

$$E(Y_{k+1} - Y_k / Y_k < 9, X_k) = 0.3086 + 0.3745X_k$$
$$E(Y_{k+1} - Y_k / Y_k = 9, X_k) = 0$$

Again  $Y_k$  indicates the BADL score at time  $k$ .  $X_k$  equals 1 if EPS are present at time  $k$  and 0 if they are not. Once the BADL score reaches its maximum of 9, it does not change over time. The model-based predicted change in BADL score associated with each current BADL score for patients with and without EPS is shown in Figure 5.

**Figure 6** illustrates 3 hypothetical patients, each beginning with a BADL score of 1. The first patient never develops EPS and exhibits the typical linear progression for BADL score in AD that we have described previously. The other 2 patients develop EPS at intervals 6 and 14, respectively. Note that the progression of BADL scores is altered in the presence of EPS.

#### COMMENT

While it has been established that the presence of EPS has prognostic implications for the rapidity of the course of AD, it has not been clear whether or how disease progression actually changes when EPS develop. The present analyses suggest that there is a change in disease progression that coincides with the onset of EPS.

It is notable that the clinical detection of EPS was associated with changes in the rapidity of disease progression. Typically, EPS are viewed as the culmination of an insidious degenerative process. For example, in Parkinson disease it has been estimated that EPS do not emerge until dopaminergic input to the basal ganglia is about 80% depleted.<sup>23</sup> While the neuropathological cause of EPS in AD has not been established, it is equally likely that the causal pathological changes are slowly progressive and could influence the course of AD even before EPS emerge. However, the present analyses indicate that the onset of clinically appreciable EPS has direct consequences for progression. This suggests that the pathological changes underlying EPS must reach a certain level of severity before they markedly influence disease course.

For measures of IADL and BADL, the clinical detection of EPS was associated with a persistent change in the course of the disease: a greater change in scores over each subsequent 6-month interval. This was not the case for the modified MMSE, where there was an accentuated decline in the modified MMSE score only in the interval in which EPS emerged. It is not clear why the effect of EPS should differ between the ADL measures and the modified MMSE. We have already reported that the shape of the progression curve differs in each of the 3 measures.<sup>11</sup> We hypothesized that while these differences may to some degree be a function of psychometric properties of the tests, they probably also represent real differences in how various facets of the disease progress over time. The differential effect of the onset of

EPS on ADL and modified MMSE progression lends some support to the latter concept.

Extrapyramidal signs are an important feature of AD. Two studies<sup>24,25</sup> have demonstrated that the presence of subtle EPS in nondemented elderly people is actually a risk factor for incident AD. One actuarial study<sup>7</sup> suggested that, with careful observation, EPS are eventually noted in all patients with AD. Our group and others have demonstrated that the presence of EPS is associated with a poorer prognosis and more rapid disease progression. Patterns of performance on neuropsychological tests differ in patients with AD with and without EPS<sup>26,27</sup>; those with EPS appear to have the typical pattern of cognitive change, along with an overlay of additional cognitive deficit.<sup>27</sup>

While pathological determinants of EPS in AD are unclear, most likely several processes are implicated. One postmortem study<sup>28</sup> of patients with probable AD and EPS indicated that neuropathological changes of AD and Parkinson disease, including degeneration in the substantia nigra and Lewy bodies, may coexist. Several investigators<sup>26,29,30</sup> have suggested a Lewy body variant of AD, characterized by some unique cognitive and behavioral changes and the presence of EPS. However, we have noted clinically that not all patients with AD and EPS meet other clinical criteria for the Lewy body variant. In addition, the majority of the patients in the present study who developed EPS at some point before death and underwent autopsy did not have cortical or subcortical Lewy bodies. We therefore propose that for the majority of patients the occurrence of EPS may represent a developmental stage of AD and not a subgroup or disease variant. Data from a previous study<sup>7</sup> support the idea that EPS, myoclonus, and psychosis are typical clinical features that can emerge at different stages of disease. We compared cumulative risk functions for putative predictors and found that in the early stages of AD, EPS and psychosis were more likely to develop than myoclonus. As AD progressed, the risk of developing myoclonus became as great as that of developing the other 2 signs. More than 1 sign often coexisted in the same patient. Thus, the various clinical signs have different probabilities of emerging at different points in the disease. Clinical heterogeneity might then be viewed as reflecting variation in this probability distribution. Whenever EPS emerge, they are associated with a poorer prognosis.

In summary, the onset of EPS is associated with more rapid functional decline and with an abrupt decline in intellectual function. These changes may elucidate the poor prognosis associated with EPS in AD.

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*Reprints: Yaakov Stern, PhD, Sergievsky Center, 630 W 168th St, New York, NY 10032 (e-mail: ys11@columbia.edu.).*

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