



Hierarchical Bayesian cognitive processing models to analyze clinical trial data

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Abstract

Identifying disease-modifying treatment effects in earlier stages of Alzheimer's disease (AD)—when changes are subtle—will require improved trial design and more sensitive analytical methods. We applied hierarchical Bayesian analysis with cognitive processing (HBCP) models to the Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog) and MCI (mild cognitive impairment) Screen word list memory task data from 14 Alzheimer's disease AD patients of the Myriad Pharmaceuticals' phase III clinical trial of Flurizan (a γ -secretase modulator) versus placebo. The original analysis of 1649 patients found no treatment group differences. HBCP analysis and the original ADAS-Cog analysis were performed on the small sample. HBCP analysis detected impaired memory storage during delayed recall, whereas the original ADAS-Cog analytical method did not. The HBCP model identified a harmful treatment effect in a small sample, which has been independently confirmed from the results of other γ -secretase inhibitor. The original analytical method applied to the ADAS-Cog data did not detect this harmful treatment effect on either the full or the small sample. These findings suggest that HBCP models can detect treatment effects more sensitively than currently used analytical methods required by the Food and Drug Administration, and they do so using small patient samples.

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Small samples; Episodic memory; Short-term memory; Delayed recall; γ -Secretase inhibitors

1. Introduction

In Alzheimer's disease (AD), no Food and Drug Administration (FDA) clinical trial has successfully identified a disease-modifying treatment effect [1–4]. As AD trials expand to earlier stages where functional and cognitive abilities progress more slowly over many years, better trial designs and more sensitive analytical methods are becoming increasingly important.

One analytical method that may be more powerful involves combining hierarchical Bayesian analysis with

models of how cognitive processes generate cognitive test scores. We refer to this method as hierarchical Bayesian cognitive process (HBCP) modeling. HBCP models belong to the class of generative models, which specify how the observed data are generated by jointly modeling the model's parameters and the data. The parameters of the HBCP model represent key components of the underlying cognitive processes involved in generating the word list memory (WLM) test scores. Once estimated, these cognitive processing parameters can be used to predict the observed item response data. These parameters can be influenced by other factors, including treatment, cognitive test used, biomarker levels, and potentially confounding covariates. To our

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knowledge, HBCP methodology has not been previously applied in AD research.

In this study, we compared an HBCP model of WLM task performance with the analytical method used in the randomized double-blind FDA clinical trial of 1649 AD patients treated with either placebo or the γ -secretase modulator Flurizan (Myriad Pharmaceuticals, Salt Lake City, UT). These two analytical methods were compared in their ability to detect treatment effects in a subsample of 14 AD subjects from the clinical trial. This small sample was chosen because these subjects had received both the Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog) and the MCI (mild cognitive impairment) Screen (MCIS) [5,6] WLM tasks, had ADAS-Cog total score data, and had item response data for the two WLM tests. This study had three objectives: (1) to determine whether the analytical method used for total score data versus that used for item response data differed in their ability to detect treatment effects, (2) to apply HBCP modeling to the ADAS-Cog and MCIS WLM item response data to determine whether either test was more sensitive in detecting treatment effects, and (3) to apply HBCP modeling to the MCIS WLM item response data to examine changes in memory performance before, during, and after the Flurizan trial.

2. Methods

2.1. Flurizan trial synopsis

The Myriad Pharmaceuticals' Flurizan phase III FDA clinical trial was a multicenter, randomized, double-blind, placebo-controlled trial enrolling 1684 mild AD patients at 133 trial sites in the United States between February 21, 2005, and April 30, 2008 [2]. Flurizan, 800 mg, or placebo was administered twice daily. Concomitant treatment with cholinesterase inhibitors and memantine was permitted. Patients were assessed for primary and secondary outcome measures at baseline and then 3, 6, 9, 12, 15, and 18 months later. The primary cognitive outcome was the change in the total score on the subscale of the ADAS-Cog (80-point version) from baseline to 18 months. The primary functional outcome was the Alzheimer Disease Cooperative Studies—Activities of Daily Living (ADCS-ADL) scale scores. Additional prespecified slope analyses explored the possibility of disease modification. The analysis included 1649 patients, of whom 1046 completed the trial. Using an intent-to-treat analysis, Flurizan had no beneficial effect on the coprimary outcomes based on least squares means (ADAS-Cog, 0.1 points change [95% confidence interval, 95% CI = -0.9 to 1.1]; $P = .86$; ADCS-ADL, -0.5 points change [95% CI = -1.9 to 0.9]; $P = .48$). The Clinical Dementia Rating scale (CDR) Sum of Boxes score was the only significant secondary outcome ($P = .046$) and indicated that the Flurizan group experienced a more severe decline in memory storage than the placebo group over the 18 months of the study (mean \pm standard deviation of change in the

CDR Sum of Boxes score: placebo, 2.43 ± 3.12 ; Flurizan, 2.91 ± 3.21).

2.2. Sample of the present study

The present study included all patients ($n = 14$) from the Shankle Clinic (Newport Beach, CA) who participated in the Flurizan trial. These patients had total ADAS-Cog score data in addition to item response data for the WLM tasks of the ADAS-Cog and the MCIS. Such data were not available for the full Flurizan trial sample. Eight of the 14 patients received placebo, and six received Flurizan. Table 1 compares the characteristics of each treatment group. Nonparametric tests (median test for ratio variables and Pearson χ^2 for ordinal or nominal variables) were used to determine whether the treatment groups differed in any of the characteristics examined.

2.3. Analysis of ADAS-Cog total score data

Analysis of the ADAS-Cog total score data was performed using the intent-to-treat population, which consisted of the sample of 14 patients. These patients received at least 1 dose of study medication. Participants initially randomized to the 400-mg group were pooled with the 800-mg group. A last-observation-carried-forward method was used to impute missing data for the main change-from-baseline analysis of each ADAS-Cog total score end point. A missing value was replaced with a value that was the same number of standard deviations (SDs) from the treatment group mean at that time point as that participant's last observed value (z score = [observed value - treatment group mean]/treatment group SD). This imputation method accounts for AD being a progressive disease and for the data that may not be missing at

Table 1
Characteristics of the 14 Alzheimer's disease patients who participated in the Flurizan clinical trial

	All	Placebo	Flurizan	<i>P</i> value
Sample size*	14	8	6	.79
Age [†] , $\mu \pm \sigma$	73.2 \pm 9.5	72.4 \pm 7.9	74.4 \pm 12.6	.42
% Female*	53.9%	50.0%	60.0%	.73
Education [†] , $\mu \pm \sigma$	14.8 \pm 2.8	15.9 \pm 2.9	13.2 \pm 1.8	.10
Memory Performance	36.9 \pm 16.6	37.4 \pm 17.9	36.3 \pm 15.3	.57
Index score [†] , $\mu \pm \sigma$				
% Functional Assessment Staging Test stage 2,3 (n)*	3 (21.4%)	3 (37.5%)	0 (0.0%)	.24
% Functional Assessment Staging Test stage 4 (n)*	11 (78.6%)	5 (62.5%)	6 (100%)	.24
Pretrial duration [†] , $\mu \pm \sigma$	24.1 \pm 13.3	23.1 \pm 13.0	25.5 \pm 14.8	.59
Trial duration [†] , $\mu \pm \sigma$	16.5 \pm 3.4	17.6 \pm 1.1	15.2 \pm 4.9	.47
Posttrial duration [†] , $\mu \pm \sigma$	20.5 \pm 8.5	21.7 \pm 8.5	19.0 \pm 9.0	.59
Total duration [†] , $\mu \pm \sigma$	61.2 \pm 19.2	62.3 \pm 20.8	59.7 \pm 18.6	.59

Nonparametric tests were used to determine whether the treatment groups differed in any of the characteristics examined.

*Pearson χ^2 nonparametric test was used for ordinal or nominal variables.

[†]Median nonparametric test was used for ratio or integer variables.

random (i.e., patients who progress more quickly may be more likely to withdraw).

Change-from-baseline analysis was conducted using an analysis of covariance model, with the treatment group as a fixed effect and with the baseline score as the covariate. Analyses were conducted using the SAS GLM procedure (SAS Institute, Cary, NC) [7].

2.4. WLM tasks of the ADAS-Cog and MCIS

The item responses of the three immediate recall tasks and one delayed recall task of the ADAS-Cog and MCIS WLM tests were analyzed. All assessments of the ADAS-Cog and MCIS WLM tasks over the 18 months of the trial were included. The ADAS-Cog testing used four word lists administered over the seven assessments of the Flurizan trial. MCIS testing was performed at each patient's follow-up visit to the clinic. The MCIS test randomly selects among eight equivalent pairs of word lists without replacement, such that each patient must take the MCIS test nine times before being tested twice with the same word list. Each MCIS 10-word list was constructed to have a low interword associability for all pairs of words in the list. Each MCIS word list is matched with an equivalent distracter list that is used to test delayed recognition memory. This approach minimizes test-retest effects and the effects of the word lists themselves [6].

2.5. MCIS assessment phases

Because each patient receives MCIS testing at each follow-up visit to the clinic, MCIS data were available before (Pretreatment phase), during (Rx phase), and after (Post-Rx phase) the Flurizan trial. For the patients studied, mean follow-up durations before, during, and after the Myriad trial were 24.1 ± 13.3 , 16.5 ± 3.4 , and 20.5 ± 8.5 months, respectively. Mean number of MCIS assessments before, during, and after the Flurizan trial were 8.5 ± 4.3 , 11.0 ± 2.54 , and 7.9 ± 3.5 , respectively. Three of the 14 patients dropped out of the Flurizan trial after participating for 6, 13, and 15 months, respectively.

2.6. HBCP model for measuring underlying memory processes

Full details of the mathematics underlying HBCP methodology are described elsewhere [9]. Here, we will summarize the use of the HBCP model in measuring treatment effect, comparing different WLM tests, and evaluating changes in memory performance over the three assessment phases. All hierarchical Bayesian analyses were performed using the modeling software WinBUGS version 1.4.3 (MRC Biostatistical Unit, Cambridge, UK) [10].

The summary score of the ADAS-Cog represents a composite of different cognitive abilities, including memory, visual constructional praxis, and language. The ADAS-Cog WLM subtest is a sensitive measure for early detection of AD [8].

For the HBCP model, we constructed a simple two-parameter cognitive processing model of the free-recall item responses of the four recall tasks of the ADAS-Cog and MCIS WLM tests. The advantage of this approach is that it transcends a specific test's summary scores and focuses on measuring the underlying cognitive processes required to perform that test.

The basic features of the two-parameter memory model are shown in Figure 1. The first parameter is a primacy parameter (α), which controls the probability of recalling a word as a function of its proximity to the beginning of the list. This parameter reflects the amount of time available to encode or store each item (e.g., the first list word has the longest time available for encoding). The second parameter is a recency parameter (β), which controls the probability of recalling a word as a function of its proximity to the end of the list. This parameter reflects the likelihood of recalling an item from working memory during the learning trials (e.g., items at the end of the word list are more likely to be recalled from working memory). For the p th presented word in the 10-word list of the ADAS-Cog and MCIS tests, the primacy parameter has a recall probability α^p , and the recency parameter has a recall probability β^{10-p+1} . These terms combine to produce the probability of recalling word p on any given trial, so that $\theta_p = 1 - (1 - \alpha^p)(1 - \beta^{10-p+1})$. Therefore, the θ_p parameters predict the patient's probability of recall for each word (p) in each trial of the memory test.

To model memory performance for the patients analyzed from the Flurizan trial, we used separate θ_p parameters (θ_{ijtp}) for each patient (i), assessment (j), and recall task (t). The θ_{ijtp} parameters predict the observed item responses r_{ijtp} . These parameters were defined by embedding the memory

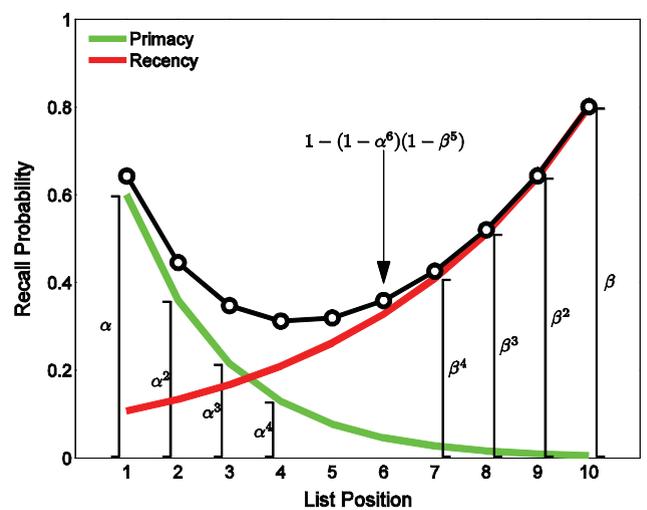


Fig. 1. Cognitive processing model used to describe recall curves at the level of individual patients. Two recall processes are involved, based on primacy (green) with parameter α for recalling words presented at the beginning of a list, and recency (red) with parameter β presented at the end of a list. The overall probability of a word being recalled is the probability it is recalled by one or both of these processes, and gives a characteristic serial position curve (black).

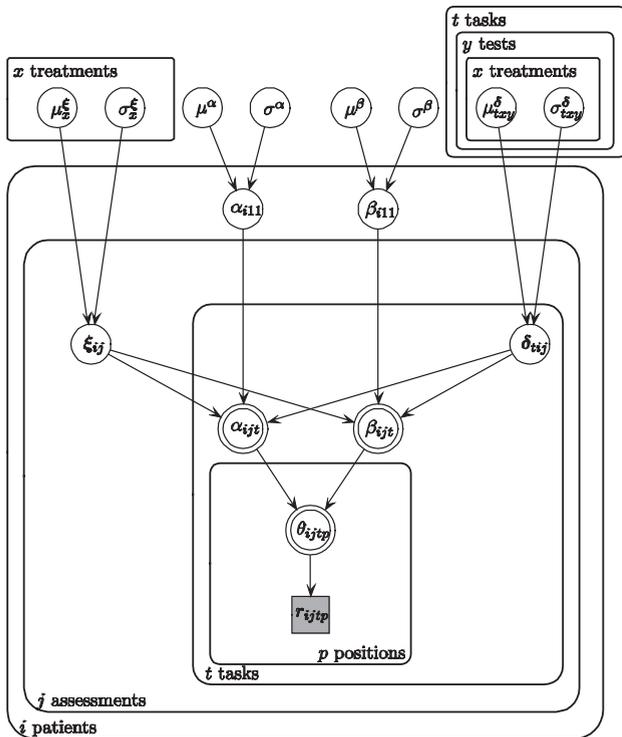


Fig. 2. HBCP model using 2 parameters of the underlying cognitive processes involved in performing the ADAS-Cog and MCIS WLM tests. These parameters reflect processes of memory storage (α_{ijt}) and retrieval (β_{ijt}) for each patient (i), assessment (j), and recall trial (task; t), and are used to estimate the probability (θ_{ijtp}) that the p th presented word in the 10-word list will be recalled. Mathematically, the probability of recalling a word p for a given patient, assessment, and recall trial is: $\theta_{ijtp} = 1 - (1 - \alpha_{ijt})^p (1 - \beta_{ijt})^{10-p+1}$. The initial values of α_{ijt} and β_{ijt} are set by previous information about the memory storage (μ^α , σ^α) and retrieval parameters (μ^β , σ^β), which are then updated for each patient by their recall performance on learning trial 1 of the baseline assessment (α_{i11} and β_{i11}). Subsequent parameter values of α_{ijt} and β_{ijt} for the remaining baseline assessment recall trials and for all postbaseline assessment recall trials are influenced by treatment effects (ξ_{ij}) and by the WLM test used to measure memory performance (δ_{ij}). For the MCIS WLM test, additional item response data were available for assessment phases before (Pre) and after (Post) the Flurizan trial covering the years 2002 to 2009. These assessment phases were modeled as already described for the Flurizan trial assessment phase (Treat), except that they had no Flurizan or placebo treatment effects and no ADAS-Cog WLM test effects.

model into a hierarchical Bayesian analysis, which is shown as a graphical model in Figure 2.

Therefore, there are separate cognitive processing parameters (α_{ijt} and β_{ijt}) for each patient (i), assessment (j), and recall task (t), which are used to estimate θ_{ijtp} .

The α_{ijt} and β_{ijt} parameters are influenced by

1. Previous knowledge about the memory storage (μ^α , σ^α) and retrieval parameters (μ^β , σ^β);
2. α_{i11} and β_{i11} , the i th patient's memory storage and retrieval strengths, respectively, on their first recall task of their initial (baseline) assessment;
3. ξ_{ij} , the effect of treatment on the i th subject, the j th time they are assessed, which is a function of the time between the initial and the j th assessment; and

4. δ_{ij} , the interaction effect, which can be thought of as the sensitivity of the cognitive test (ADAS-Cog or MCIS) to the treatment (Flurizan or placebo) for subject i , at assessment j , on task t .

For all the influences on the memory parameters (α_{ijt} and β_{ijt}), we included a random effect that assumes they are not constant but rather are drawn from a Gaussian distribution. This means, for example, the patient's memory storage and retrieval parameters (α_{i11} and β_{i11}) are different for different patients because they are drawn from a Gaussian distribution. Similarly, the effects of treatment and test are not assumed to be constant across patients, assessments, or tasks, but are drawn from a Gaussian distribution with the means and SDs specified in Figure 2.

2.7. Comparing treatment groups

For the MCIS and ADAS-Cog WLM tests, treatment group effects due to Flurizan and placebo were determined by using each assessment after the baseline to estimate the change in the memory parameters α and β , due to the treatment group. Different time durations between the assessments were handled by modeling the change in the memory parameters, including their dependency on the duration between the baseline and assessment dates. Each assessment after the baseline was assumed to estimate the memory parameters as being randomly drawn from the Gaussian distribution of the mean change in the cognitive parameter per unit time. For each recall task, WLM test, and treatment group, the means of the Gaussian distributions for the change in primacy and recency parameters were then examined. The posterior distributions of this measure of mean change are shown in Figures 3 and 4.

2.8. Handling of missing data

Hierarchical Bayesian models use all the available data and do not need to impute or otherwise substitute missing data. When data are missing, the results are simply inferred from the estimates derived by the available data. Therefore, a broad range of missing data patterns are handled automatically without resorting to special methods of restricting or constraining the data to be analyzed.

3. Results

Table 1 shows that there were no significant differences between Flurizan and placebo treatment groups for any of the characteristics examined.

Table 2 shows the results of the covariance analysis of the ADAS-Cog total score data. The mean treatment group difference in the change in the ADAS-Cog total score from baseline to 18 months was 6.31 points in favor of placebo (95% CI = -6.4 to 19.1). However, this treatment group difference was not significant ($P = .2982$).

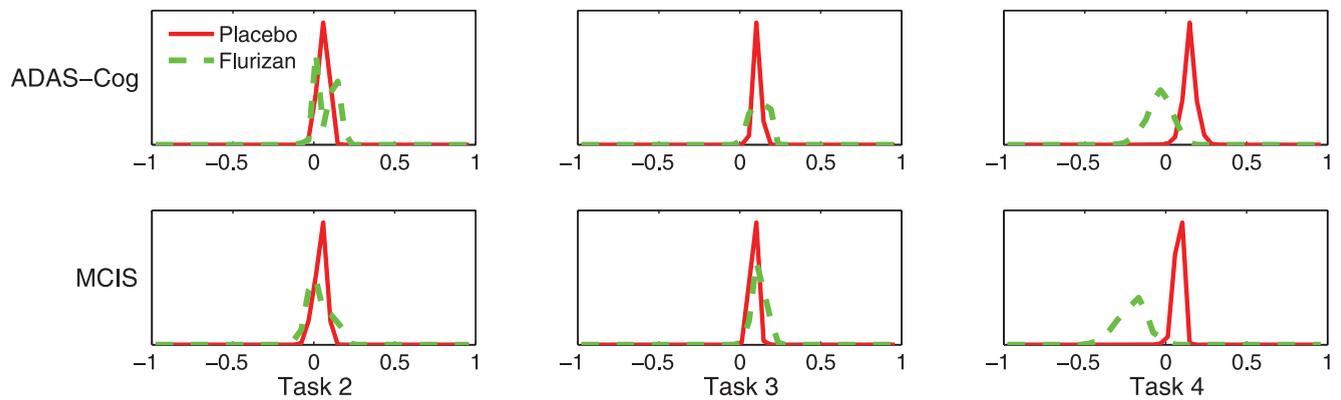


Fig. 3. Distributions of the mean changes in the memory storage parameters (α_i) for recall tasks 2 to 4, for each treatment (Flurizan = green dashes, placebo = red line), and for each WLM test (row 1 = ADAS-Cog, row 2 = MCIS). Both ADAS-Cog and MCIS WLM tests show that the Flurizan group experienced a greater decline in memory storage associated with the delayed recall trial than the placebo group. The WLM test of the MCIS discriminated this harmful treatment effect 39% better than that of the ADAS-Cog.

Figure 3 shows the inferred posterior distributions of the mean change per unit time in the memory storage (primacy) parameters (α_i), from baseline to subsequent assessments, for recall tasks 2 to 4 for each treatment (Flurizan = green dashes, placebo = red lines) and each test (ADAS-Cog, MCIS). The distributions for Flurizan versus placebo are virtually identical for recall tasks 2 and 3 for both cognitive tests. However, for delayed recall task 4, both the ADAS-Cog and MCIS WLM tests show that the Flurizan group experienced a greater decline in memory storage than the placebo group over the course of the trial. In terms of the differences between the WLM tests, the MCIS discriminated this harmful treatment effect on memory storage 39% better than the ADAS-Cog. Figure 3 indicates that Flurizan worsened the memory storage associated with delayed recall.

Figure 4 shows the inferred posterior distributions of the mean change per unit time in the working memory capacity parameters (β_i), from baseline to subsequent assessments, for recall tasks 2 to 4, for each treatment (Flurizan = green

dashes, placebo = red lines) and each test (ADAS-Cog, MCIS). The distributions of the memory retrieval parameters for Flurizan versus placebo are virtually identical in each recall task and for each cognitive test. Figure 4 indicates that there is no treatment group difference in the change in working memory capacity as measured by either the ADAS-Cog or MCIS WLM test.

Figure 5 shows, for each recall task of the MCIS test and for each treatment group (Flurizan = green dashes, placebo = red lines), the inferred posterior distributions of the mean change in the memory parameters per unit time, from baseline to subsequent assessments of each assessment phase (Pre = before, Treat = during, and Post = after the Flurizan trial). Such data were only available for the MCIS test. The memory parameter changes for recall tasks 2 and 3 are similar for Flurizan and placebo groups during the Pre assessment phase, but show differences in favor of the placebo group during the Treat and Post assessment phases. For the delayed recall task, the Flurizan group showed somewhat greater decline in memory storage than the placebo

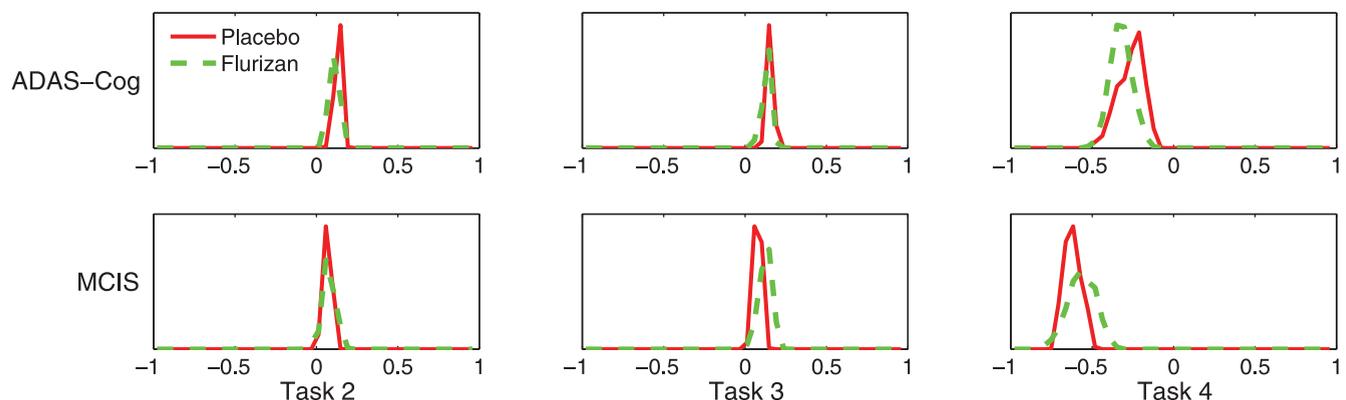


Fig. 4. Distributions of the mean changes in the working memory capacity parameters (β_i) for recall tasks 2 to 4, for each treatment (Flurizan = green dashes, placebo = red lines), and for each WLM test (row 1 = ADAS-Cog, row 2 = MCIS). There are no clear treatment group differences.

Table 2
Analysis of covariance of the change in Alzheimer's Disease Assessment Scale—Cognitive subscale total score (z score) from baseline to 18 months for each treatment group

Treatment group	n	Mean change	95% Confidence interval	P value
Flurizan	6	10.78	1.77 to 19.79	0.2982
Placebo	8	4.47	–3.15 to 12.08	

No significant treatment group difference was detected ($P = .2982$).

group during the Pre assessment phase, but showed much greater decline than the placebo group during the Treat and Post assessment phases.

4. Discussion

The three purposes of the present study were

1. To compare the results of the covariance analysis of the ADAS-Cog total score data with the HBCP modeling analysis of the WLM item response data for the same sample of subjects.
2. To compare the differences in the sensitivity of the ADAS-Cog and MCIS WLM tests for detecting treatment group differences.

3. To examine the changes in primacy and recency memory performance parameters before, during, and after the Flurizan trial.

This study showed that HBCP modeling identified a harmful effect of Flurizan on the primacy parameter during the delayed recall task. In contrast, covariance analysis of the change in ADAS-Cog total scores did not detect this effect, which is consistent with the findings of the Flurizan full trial analysis of 1649 mild AD patients. Support for a harmful effect of Flurizan comes from two sources. First, in the original Flurizan trial analysis, the CDR Sum of Boxes score showed greater decline in dementia severity for the Flurizan group compared with the placebo group (the difference reached significance, $P = .046$, only after 18 months of the trial) [2]. Second, two large phase III clinical trials of the γ -secretase inhibitor semagacestat in mild-to-moderate AD patients were stopped because patients receiving semagacestat showed greater cognitive and functional decline than those receiving placebo. The ability of HBCP modeling, but not covariance analysis, to detect this harmful effect on a sample of just 14 AD patients shows the potential power of this method. The comparison of these two methods is partly confounded because covariance analysis cannot be performed on the WLM item responses.

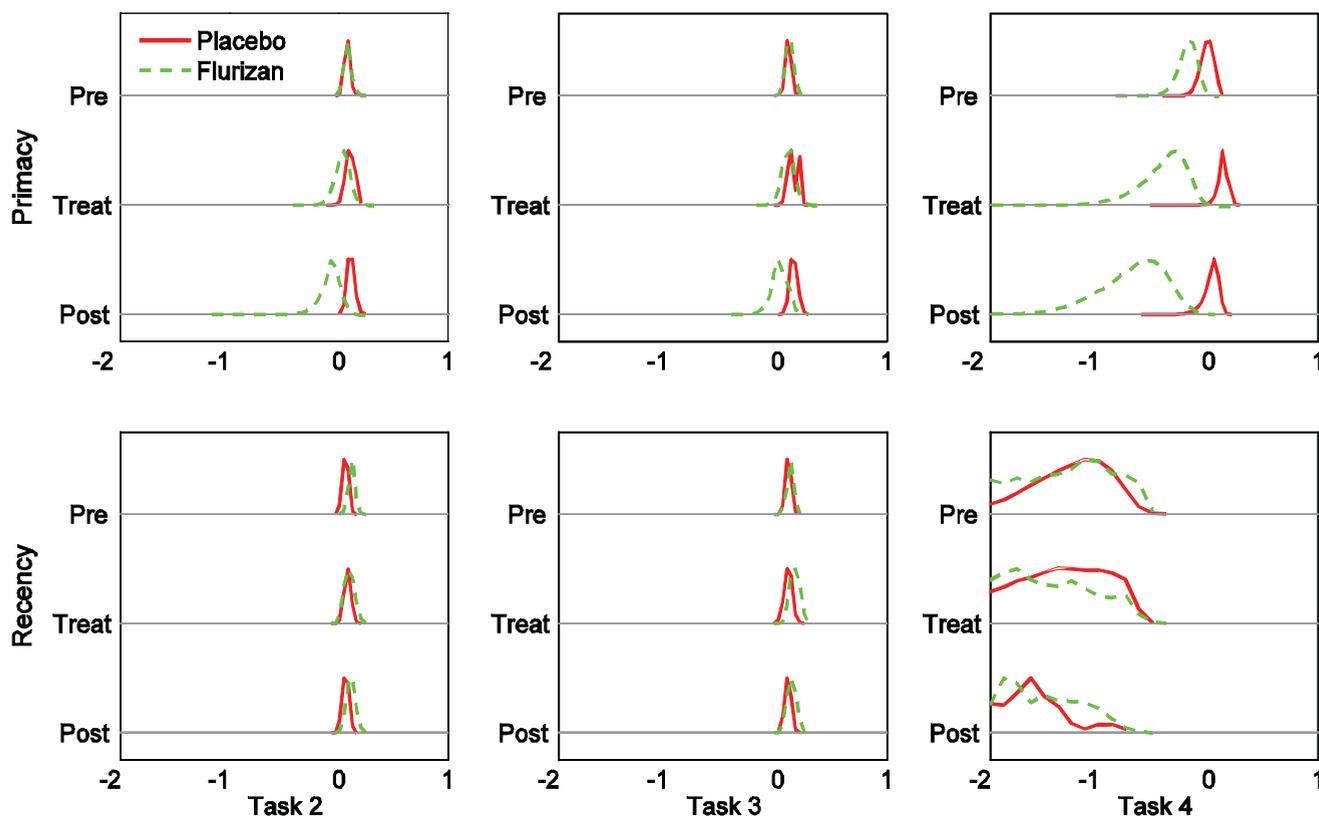


Fig. 5. Distribution of the mean change in the MCIS test's memory storage and working memory capacity parameters for recall tasks 2 to 4, for each treatment (Flurizan = green dashes, placebo = red lines) and each assessment phase (Pre = before, Treat = during, and Post = after the Flurizan trial). Such data were not available for the ADAS-Cog.

Because the primacy parameter relates to the improved recall of words presented early in lists, we hypothesize that it reflects some combination of memory storage and metacognitive processes like rehearsal. Because the harmful effect of Flurizan on the primacy parameter was specific to the delayed recall task (which is most reliant on hippocampal encoding), and did not affect the immediate recall tasks (which is more reliant on working memory capacity than is delayed recall), Flurizan may interfere with hippocampal memory storage.

This HBCP modeling results showed that the MCIS WLM test is about 39% more sensitive than the ADAS-Cog WLM test, at least in terms of detecting treatment group differences. This is likely to be due to a difference in the method of test administration—the ADAS-Cog WLM changes the order of the presentation of the 10 list words over the three learning tasks, whereas the MCIS does not. Changing word presentation order across learning tasks may interfere with associative encoding of the temporal order of the stimuli (words), thereby reducing the amount of information that can be extracted into the primacy and recency parameters.

Finally, the study showed that the harmful effect of Flurizan on the memory storage parameter for delayed recall (possibly reflecting hippocampal encoding) persisted and got larger after Flurizan was discontinued. In contrast, those treated with placebo did not show such a worsening of the primacy parameter after its discontinuation. These findings suggest that γ -secretase modulators may irreversibly harm hippocampal memory storage, with acceleration of memory decline even after their discontinuation.

The findings from the present study suggest that analytical methods that can use the item response data from clinical trials and model underlying cognitive processes involved in generating cognitive test scores can detect treatment group differences in much smaller samples than has been previously required.

Bayesian methods have often been applied to clinical trial analysis, including longitudinal studies [11]. The innovative part of our approach is to combine hierarchical Bayesian methods of data analysis with cognitive models of memory so that inference is done using meaningful parameters based on models of assessment task performance. To our knowledge, HBCP methodology has not been previously applied in AD research.

HBCP models can be extended to incorporate neurobiological parameters, such as structural and functional biomarker measures, to provide a more cohesive picture of how Alzheimer's pathophysiology impacts brain function.

5. Conclusions

The present article showed that HBCP models detected treatment effects from very small patient samples that were heretofore undetected from much larger samples. In both samples, the standard method (covariance analysis)

did not detect any treatment effect. HBCP models also permit different tests of a similar cognitive ability to be compared in terms of their discriminative power. HBCP models may be important in evaluating results of phase I and phase II FDA trials before larger more costly phase III FDA trials are considered.

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