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Authors

Chapman, Robert M
Porsteinsson, Anton P
Gardner, Margaret N
et al.

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The Impact of AD Drug Treatments on Event-Related Potentials as Markers of Disease Conversion

Robert M. Chapman[*],[a], **Anton P. Porsteinsson**[b], **Margaret N. Gardner**[a], **Mark Mapstone**[c], **John W. McCrary**[a], **Tiffany C. Sandoval**[a], **Maria D. Guillily**[a], **Lindsey A. Reilly**[a], and **Elizabeth DeGrush**[a]

[a]Department of Brain and Cognitive Sciences, University of Rochester, Rochester, New York 14627, United States of America.

[b]Department of Psychiatry, University of Rochester Medical Center, and the Alzheimer's Disease Care, Research, and Education Program (AD-CARE), University of Rochester Medical Center, Rochester, New York 14620, United States of America.

[c]Department of Neurology, University of Rochester Medical Center, Rochester, New York 14620, United States of America.

Abstract

This paper investigates how commonly prescribed pharmacologic treatments for Alzheimer's disease (AD) affect Event-Related Potential (ERP) biomarkers as tools for predicting AD conversion in individuals with Mild Cognitive Impairment (MCI). We gathered baseline ERP data from two MCI groups (those taking AD medications and those not) and later determined which subjects developed AD (Convert->AD) and which subjects remained cognitively stable (Stable). We utilized a previously developed and validated multivariate system of ERP components to measure medication effects among these four subgroups. Discriminant analysis produced classification scores for each individual as a measure of similarity to each clinical group (Convert->AD, Stable), and we found a large significant main Group effect but no main AD Medications effect and no Group by Medications interaction. This suggested AD medications have negligible influence on this set of ERP components as weighted markers of disease progression. These results provide practical information to those using ERP measures as a biomarker to identify and track AD in individuals in a clinical or research setting.

Keywords

Alzheimer's disease (AD); AD Drug Treatments; Biomarker; Discriminant Analysis; EEG; Event-Related Potentials (ERP); Mild Cognitive Impairment (MCI); Neurophysiology; Prediction; Principal Components Analysis (PCA)

[*]To whom correspondence should be addressed. Postal Address: Department of Brain and Cognitive Sciences, 775 Library Road, University of Rochester, Rochester, NY 14627, USA. Telephone: (585) 275-8679. Fax: (585) 271-3043. rmc@cvs.rochester.edu.

Introduction

Event-Related Potentials (ERPs), which offer a noninvasive means to measure human electrical brain activity related to cognitive performance with high temporal resolution, have been shown to be useful biomarkers of Alzheimer's disease (AD) and its progression.[1–7] However, little work has been done to investigate the possible effect AD pharmacologic treatments may have on ERP biomarkers as tools to diagnose or predict AD in individual patients. Drug treatments, including cholinesterase inhibitors (rivastigmine, galantamine, and donepezil) and memantine, are often prescribed in clinical practice to patients who present with Mild Cognitive Impairment (MCI) [8]. This cognitive disorder is often characterized (in its amnestic form) with impairment in the domain of memory without significant impact on daily life. A significant proportion of individuals with MCI develop AD at a later time [8, 9], and predicting individual clinical outcomes is of vital importance both for timely application of therapeutic treatments and for adequate and appropriate enrollment in research [10, 11]. There is conflicting data on the efficacy of cholinesterase modifying medications in the treatment of AD and MCI [12, 13] and even less consensus on how these treatments may alter disease biomarkers and disease progression. It is essential, therefore, to determine how AD drug therapies influence biological measures of cognitive deterioration.

In this article, we will test the impact of AD drug treatments on a previously designed and validated multivariate ERP approach to predicting AD progression in MCI individuals. This multivariate system [2] used Principle Components Analysis (PCA) to untangle and separate the underlying and often times overlapping components of the ERPs, which were measured in response to a task with working memory and other cognitive demands. The ERP components were then combined into linear discriminant functions to discriminate between clinically defined Conversion-to-AD and Stable groups with associated confidence in the prediction for each individual. This ERP approach was cross-validated and demonstrated strong prediction accuracy with high confidence (88%) for most individuals (79%).

We will analyze classification scores (the measure of similarity to the Conversion-to-AD or Stable group) derived from discriminant analysis for MCI subgroups and determine if AD drug usage affected these scores (built from a weighted combination of ERP component markers). Simply speaking, these classification scores, which were derived from baseline ERP data, act as a scale between two clinically defined conditions: later developing AD or remaining stable over time. Each individual is placed along that scale according to the position of his or her classification scores. If AD drugs were exerting a positive effect, it should move the classification scores of those individuals who later develop AD and were taking the medications closer to those individuals who did not develop AD. This would appear in individual prediction outcomes as a "less confident" prediction of AD development (i.e., the individual lies between the Conversion and Stable groups rather than very close to the Conversion group not taking the drugs) or, ideally if the drugs were slowing or preventing progression, a prediction of cognitive stability. We will examine what influence AD medications may have on a multivariate system of ERP component biomarkers, which is of great practical interest for researchers and clinicians utilizing such a system to predict outcomes for individual MCI patients.

Methods

Study Subjects

In this study, we used a subset of 30 elderly individuals diagnosed with MCI (Table 1) from a group previously used to develop ERP biomarkers as predictors of AD progression [2]. These subjects were recruited from the Memory Disorders Clinic at the University of Rochester and other affiliated University of Rochester clinics. All MCI subjects were evaluated by memory-disorders physicians and met consensus criteria for the amnestic subtype of MCI ("a-MCI") [8–10, 14]. Subsequent to this initial evaluation and baseline ERP data collection, each MCI subject was determined to either have converted to clinically defined AD (through the NINCDS-ADRDA criteria [15] and DSM-IV-TR criteria for Dementia of the Alzheimer's Type [16]) or to have remained stable with regard to cognitive state. These independent determinations were made through clinical follow-ups at a later date by the same memory-disorders physicians, who were blind to our study data so our ERP results had no bearing on their clinical judgments. Those subjects who converted were given the typical clinical assessment of "probable" AD (but referred to here as AD for brevity's sake). Chapman et al. [2] fully described the clinical assessment and follow-up of these MCI subjects. Of the 30 MCI subjects used in this paper, 15 subjects subsequently converted to AD and 15 remained cognitively stable.

We divided the Convert->AD (referred to as the Progress group in Chapman et al. [2]) and Stable groups into two subgroups: those who were treated with medications routinely prescribed in the treatment of memory impairment (including cholinesterase inhibitors and memantine) at the time of initial ERP data collection and those who were not. For information on time to conversion or drug duration, see Table 1. Our knowledge of which patients were or were not taking AD medications did not influence our measures. Irrespective of drug treatment, each subject underwent the same computer-controlled experimental paradigm. In addition, because the multivariate analysis and its parameters which produced the ERP component scores were ignorant of drug information [1, 2], all ERP measures were objective and "blind" to each subject's medication status. At the time of collecting baseline data, all of these subjects were classified as MCI, and it was impossible to know which subjects later would be placed in which clinical group.

In the Convert->AD group, 8 of the 15 individuals belonged to the AD Medications subgroup (Meds-Convert) and 7 belonged to the No AD Medications subgroup (NoMeds-Convert). Likewise, 8 of the 15 subjects in the Stable group belonged to the AD Medications subgroup (Meds-Stable) and 7 belonged to the No AD Medications subgroup (NoMeds-Stable). Two subjects (one in the Meds-Convert subgroup and one in the Meds-Stable subgroup) were taking both a cholinesterase inhibitor and memantine. Subjects taking donepezil were prescribed standard doses (5 mg – 10mg daily), with one subject in the Meds-Stable group taking 20 mg daily. Subjects taking galantamine were prescribed standard doses (16 mg or 24 mg daily). One subject was prescribed rivastigmine (through a transdermal system at 9.5 mg daily).

Though elderly subjects are very often afflicted with numerous health conditions, comorbid depression is of particular interest as its symptoms can mimic the cognitive impairments

seen in AD and MCI. Four subjects in the Convert->AD group (two in each medications subgroup) and six subjects in the Stable group (two in the Meds-Stable subgroup and four in the NoMeds-Stable subgroup) were also taking antidepressants (mostly Selective Serotonin Reuptake Inhibitors) at the time of ERP testing.

The sample of MCI subjects used in our analyses is one of clinical convenience. This is more advantageous in terms of better reflecting the myriad clinical presentations of MCI and AD with various comorbidities and demographic dissimilarities. However, demographic matching was difficult, and some demographic variables may require further study to fully elucidate how they interact with AD medications. We tested demographic variables for group, gender, and medications effects (and their interactions) (Table 1). There were no main effects concerning subject age, and there were no interactions. The Convert->AD group overall had a slightly higher number of years of education (F(1,29) = 5.10, $p < .05$), but this was the only significant result. We performed the Mini Mental State Examination (MMSE) [17] at baseline ERP data collection to ascertain if the medication subgroups had comparable levels of dementia at the time of enrollment in our study. This is an important aspect to examine, as a Medications effect might be attributed to those in the Meds-Convert group receiving treatment because they were further advanced toward AD than those in the NoMeds-Convert group. However, this was not found here where the Meds-Convert and NoMeds-Convert subgroups had the same MMSE mean scores (Table 1). The Stable group as a whole performed slightly better than the Convert->AD group (F(1,29) = 5.78, $p < .05$), but this difference is not important in assessing the Medications effect because members of both clinical groups are combined in that analysis (mean MMSE score for those taking AD medications = 26.4 and for those not = 26.7). Women also performed better than men (F(1,29) = 10.33, $p < .01$). Gender disparities on neuropsychological testing have been found in normal and cognitively impaired subjects [18]. However, there was no medication effect on MMSE performance or any interaction between medications and group or medications and gender, suggesting the medications subgroups had a comparable level of cognitive impairment at the time of baseline data collection. For a more complete neuropsychological assessment of these subjects, see Chapman et al. [2] and Table 1. There also were no main effects or interactions concerning performance on the Number-Letter task (NL Correct).

There were fewer women taking AD medications than men across both the Convert->AD and Stable groups (10 men, 6 women). There were also fewer women not taking medications across both groups (9 men, 5 women). Therefore, any Medications effect on ERP scores would not likely be attributable to gender, since the gender differences in the comparison were approximately the same.

Exclusion criteria for all groups included clinical (or imaging) evidence of stroke, Parkinson's disease, HIV/AIDS, and reversible dementias, as well as treatment with benzodiazepines, antipsychotic, or antiepileptic medications. As an additional exclusion criterion, no subject had a previously clinically administered score of 20 or less on the MMSE. Our study received IRB approval from the University of Rochester Research Subjects Review Board, and informed consent was obtained from each subject.

The Number-Letter Paradigm

Subjects completed a Number-Letter paradigm [1, 2] while ERP data were collected. This task entails memory storage of one relevant stimulus in order to compare it with a second relevant stimulus. Two numbers and two letters were flashed individually in random order at intervals of 750 ms preceded and followed by a filled square comparable in size to the numbers and letters. All visual stimuli were white and presented briefly (~20 ms) on a dark background. On a number-relevant block of trials, the participant compared the two numbers in each trial for numerical order, the letters being irrelevant to the task. On another block of trials, the numbers were irrelevant and the task involved comparing the two letters for alphabetic order. At the end of each trial, the participant said "Forward", "Backward", or "Same" to indicate the numerical (or alphabetic) order of the two relevant stimuli.

EEG Recording

Scalp electrodes (O1, O2, OZ, T3, T4, T5, T6, P3, P4, PZ, C3, C4, CZ, F3, F4, and EOG with reference to linked earlobes) recorded electrical brain activity while the participant performed the Number-Letter task. The central midline site (CZ) is featured here because it provides a good view of many ERP components of interest [19–21] with the same paradigm used here.

Frequency bandpass of the Grass amplifiers was 0.1 to 100 Hz. Beginning 30 ms before each stimulus presentation, 155 digital samples were obtained at 5 ms intervals. Subsequently, the digital data were digitally filtered to pass frequencies below 60 Hz, and artifact criteria were applied to all channels based on the CZ and EOG channels to exclude those 750 ms epochs whose voltage range exceeded 200 μV or whose baseline exceeded ±250 μV (baseline was mean of 30 ms pre-stimulus). The ERPs were based on correct trials and data not rejected for artifacts. Mean artifact rejection rate for all MCI subjects was 5.6% (SD = 11.9%).

Measuring Classification Scores

In this analysis, classification scores represent similarity to clinically-defined groups based on a set of predictors (ERP components) (ure 1). Classification scores were computed through a series of multivariate procedures that transformed averaged ERPs into an empirically derived sum of weighted ERP component scores for each subject. ERPs were first derived for each subject from the EEG vectors (155 time points) by averaging each vector separately for each of the relevancy task conditions (relevant, irrelevant). Then the first multivariate procedure was applied to measure the latent component structure.

Principal Components Analysis—ERP components were identified and measured by Principal Components Analysis (PCA) [1, 2, 22–26] with Varimax rotation which allows the variations due to experimental conditions and individual differences in the data to define the ERP components [2]. We previously performed the PCA using a correlation matrix of the 155 time points on 48 individuals and their task conditions: 12 with clinically diagnosed AD, 12 MCI individuals, 12 elderly Controls, and 12 young subjects. Eight components were retained by Kaiser's Eigenvalue > 1 rule (accounting for 95% of the variance). The components included well-known components, such as C415, which is often called

parietally-loaded P3 [27–29], contingent negative variation (CNV) [30], memory "storage" component C250 [28, 31], C145 [32], as well as other early and late components. This set of components provided powerful discriminators of AD from normal aging [1] and predictors of progression to AD in these same MCI subjects [2].

PCA produces two important measures derived from the implicit structure of the ERP waveforms: component loadings and component scores. Both are essential to generating classification scores. The component loadings represent the temporal waveforms of each ERP component [1, 22]; a subset of these component waveforms appears in Figure 1. These component waveforms represent a vector of scoring coefficients for each component derived from the correlational relationships among the time points of the ERPs (this is something of a simplification to visually represent this mathematical procedure) [22]. This vector can be applied to the vector of ERP time points for each task condition (relevant, irrelevant) for each subject. The product of this multiplication is an ERP component score; each subject has a score for each component by each condition (component_condition).

Discriminant Analysis—Given this set of eight ERP components, a stepwise procedure determined which of the component_conditions had the greatest power in differentiating between the two clinically defined groups (Convert->AD, Stable). This was done before consideration of drug treatment. The selected ERP components are shown in Figure 1 (in the order they were chosen by the stepwise procedure). After selecting the predictor variables, discriminant analysis [33, 34] then determined an empirically derived discriminant function for classifying a subject into one or other group. This function is comprised of discriminant coefficients (or classification coefficients) for each ERP component_condition, and each coefficient can be considered the ERP component's weighted contribution to the discriminability of the function. The classification score is then derived by multiplying each ERP component score by its discriminant coefficient and summing these products and a constant (Figure 1). The subject is then assigned to one group or the other based on the computed value being higher or lower than zero, and posterior probabilities of group membership are then determined [34, 35]. A larger classification score implies that a subject is more confidently placed in either the Convert->AD group (positive) or the Stable group (negative) because of a strong similarity to one group, whereas a difference closer to zero suggests the subject is not strongly similar to either group. The individual prediction results of this analysis, including the associated probabilities, are discussed in detail in Chapman et al. [2]; in brief, this discriminant function was capable of predicting AD or cognitive stability correctly for most MCI individuals (79%), and the predictions were confident (88%). Here we are concerned with whether the classification success, engendered by the discriminant function, is influenced by AD drug treatments.

Factorial ANOVA—We used analysis of variance (ANOVA) on the relation of ERP classification scores to two factors, clinical Groups (Convert->AD, Stable) and AD Medications (Taking, Not Taking) in a two-way factorial design. This provided an efficient way to utilize the sample to separately test two main effects (with 14 subjects per group or greater) and their interaction.

We anticipated a significantly large Group effect, based on previous strong results with individuals in predicting clinical group membership [2]. A hypothetical positive drug effect should be fairly large to influence ERP biomarkers as predictors of AD conversion. We assumed that AD drugs would have the effect of making individuals more Stable (i.e., make difference scores more negative). We estimated a mean difference score between the Convert->AD group and the Stable group of 3.75, which meant we had power > 0.9 to detect a main clinical Group effect at alpha = 0.05. We estimated an AD Medications effect might be smaller than the clinical Group effect and chose a mean difference score of 2.25 between those taking medications and those not. Given the sample size, we would be able to detect a Medications main effect with power = 0.89 and a Group × Medications interaction with power = 0.42 (see Discussion for explanation of actual results).

Statistical Analysis

All statistical procedures were performed with SAS 9.1.3 [36]. The FACTOR and SCORE procedures were used to generate the ERP component solution and calculate ERP component scores for the MCI groups. The STEPDISC and DISCRIM procedures were used to build the discriminant functions. All ANOVAs were performed using the GLM procedure. Power calculations were performed with the GLMPOWER procedure.

Results

Group mean differences among the classification scores of the clinically defined Convert->AD and Stable groups and their medications subgroups were examined with ANOVA. The effects of interest were the main effects of clinical Group and of AD Medications (referred to simply as "Medications" for brevity's sake) and the interaction between Group and Medications. "Group" in this case refers to the clinical group (whether or not the subject actually did develop AD or remain stable) rather than the outcome predicted by the ERP measures (represented by the classification scores).

Mean classification scores (Table 2) indicate that the Convert->AD group showed larger positive classification scores, whereas the Stable group showed negative classification scores. This reflected the large significant Group effect in that most individuals received a correct baseline classification score (prediction) relative to their eventual clinical diagnosis (Convert to AD or Stable) (Table 3). This was expected given the strong predictive outcomes for individuals discussed in other work [2]. Of greater interest for this paper is the Medications effect and its interaction with Group. For the Medications main effect, there was no significant difference between those taking medications and those who were not. Additionally, there was no significant interaction between Group and Medications.

Graphing the classification difference score for each subject clearly depicts the large Group effect (Figure 2) in that most of the subjects in the Convert->AD group lie on the positive side above the zero line. This indicates the ERP predictions of who would convert to AD were mostly correct. Most of the subjects in the Stable group are below the zero line, again showing the accuracy of the ERP predictions of who would remain stable as MCI. Those subjects taking AD medications appear randomly among those not taking medications rather than grouped, indicating AD medications had no effect on ERP classification score. This

was true for both clinical groups, confirming the lack of significant interaction between Medications and Group.

Although few subjects were taking antidepressants (Table 1), we examined the effect of antidepressants since psychiatric medications are often prescribed for the elderly. The same large clinical Group effect was found ($F(1,22) = 21.77$, $p = 0.0001$). However, the main effect of Antidepressants ($F(1,22) = 2.74$, $p = 0.11$) was not significant, nor was there an Antidepressant by Group interaction ($F(1,22) = 0.05$, $p = 0.83$). There was also no main AD Medications effect ($F(1,22) = 0.50$, $p = 0.49$), no significant interaction between Antidepressants and AD Medications ($F(1,22) = 0.32$, $p = 0.57$), and there was no significant three-way interaction ($F(1,22) = 0.97$, $p = 0.34$).

Discussion

We have shown in previous work that ERP components can function as biomarkers of AD in individuals [1] and can predict with good accuracy the future occurrence of AD in MCI individuals [2]. In this article, we examined a pertinent question: do AD pharmacologic treatments taken by MCI individuals at baseline affect ERP components as predictors of AD decline? This is a practical issue as any diagnostic system implemented for clinical use must be sufficiently robust and accurate to withstand the numerous variations among patients. There are also theoretical implications about the efficacy of AD drug regimens as a means to slow or prevent the progression of dementia.

We have found that this weighted combination of ERP component measures was not significantly affected by AD drug treatments. Our analysis made use of the classification score for each MCI individual. Selecting this measure provided some key advantages: 1) the ERP classification score is a direct measure of how similar an individual is to either group (Convert->AD or Stable), 2) this score allows the selected ERP components to contribute to the classification through empirically derived weights (discriminant coefficients), and 3) degrees of freedom considerations suggest usage of fewer measures (and thus fewer analyses). ANOVA results showed a significant main clinical Group effect, which was expected given this weighted combination of ERP components discriminated MCI individuals with statistically significant accuracy in previous work [2]. We found no significant Medications effect (suggesting that AD drugs across both the groups produced little effect on the ERP component scores). Most importantly, there was no significant Group by Medications interaction. These results are strikingly depicted in Figure 2, where nearly all of the clinically-diagnosed Convert->AD group lie above the midline (where the classification difference = 0) and nearly all of the Stable group lie below the midline. This represents the large and significant Group effect at the level of individuals ($p < 0.0001$, $df = 1, 26$). If there was a beneficial Medications effect, it should manifest in the subjects taking AD treatments having more negative classification scores (more Stable-like) than those not taking AD drugs. Furthermore, if there was an interaction between Group and Medications, medication users might appear differently in each clinical group. However, subjects who were taking AD medications (subjects marked with an "X") are fairly randomly distributed within each group, confirming that AD medications had very little influence on ERP classification scores. Thus we conclude that regardless of whether or not an MCI individual

was taking AD medications at the time of baseline testing, these ERP components were unaffected as disease predictors.

This result is further affirmed by analyzing the misclassified subjects from our previous work [2]. ERP components were capable of correctly classifying 79% of those taking medications in both the Stable and Conversion groups (χ^2 (1, N = 14) = 4.71, $p < .05$). They also correctly classified 81% of those not taking medications in both groups (χ^2 (1, N = 16) = 6.30, $p < .05$). Moreover, they performed with the same accuracy in predicting clinical outcomes in individuals regardless of medications (χ^2 (1, N = 30) = 0.03, $p = .85$).

There are few published studies discussing how cholinesterase inhibitors affect ERP components in the literature. Some work has suggested that donepezil and rivastigmine reduce P300 latency abnormalities in AD [37–39]. These studies were generally conducted using individuals with moderate-severe AD and therefore drug effects may be more pronounced. Also, we have examined amplitude changes in this work rather than latency shifting. Some research has been done on cholinesterase modifying drugs regarding early somatosensory and visual ERPs in MCI subjects and found drugs effects concerning very early somatosensory ERPs (N20, P50) but no effects on early visual ERPs (N70, P100, N150) [40]. Our result concurs that later post-stimulus ERPs (visual and cognitive processing) do not seem to be affected by cholinesterase treatments to the extent of altering ERP assessment of clinical status.

We also examined the effect of antidepressants. Though the sample sizes of the users and non-users subgroups were not balanced for this variable and were very small, our results indicated that antidepressants also failed to exert a significant effect on our ERP measures. We believe this is the first demonstration of this result concerning ERPs, though it requires validation with larger sample sizes.

If AD drugs were exerting a positive effect to reduce AD decline (and thus move the Meds-Convert group closer to the Stable group in terms of weighted ERP component scores), the interaction between Group and AD Medications would be significant. This was not the case. In fact, the mean classification scores (Table 2) and group mean ERPs (Figure, Supplemental Figure 1) suggested an unexpected outcome. The Meds-Convert group actually showed the largest positive score (indicating the subjects were more likely to convert to AD), larger than both Stable groups and the NoMeds-Convert group. This indicates these individuals moved the mean classification score for the Convert->AD group *further* from that of the Stable group, which might be the opposite effect of what the AD medications would hopefully do. However, these differences were not statistically significant (between Meds-Convert and NoMeds-Convert: $t(1,15) = -0.97$, $p = .35$; between Meds-Stable and NoMeds-Stable: $t(1,15) = 0.23$, $p = .82$).

Because this study employed a clinical sample of convenience, control over demographic effects was limited. In addition, sample sizes were small. The results concerning our analysis of antidepressant use should be considered tentative and in need of validation in light of the small group sizes. We also successfully detected the clinical Group effect (at alpha <0.0001, Table 3) with the sample size we had in this analysis. We aim in this paper to

determine if an AD medications effect exists with a magnitude large enough to influence ERP components as predictors of AD conversion. In this set of data, a magnitude of difference between the Convert->AD group and Stable group mean scores of 3.4 was large enough to produce a significant main effect at alpha < 0.0001. At alpha = 0.05, the same subjects and same dependent variable (ERP scores) would require a mean difference of only 1.4. Thus a significant main effect at this alpha level would be 60% smaller than our main clinical Group effect. We failed to find a significant main Medications effect; we actually obtained a mean difference between those subjects taking medications and those not of −0.38, and this small difference is in the wrong direction. This suggests that if a Medications effect did exist, it would be trivial and of much smaller magnitude than the main Group effect [41]. Therefore, the influence of AD medications on the ERP prediction outcomes would be small and irrelevant. Additional research is of course required to better determine the reliability and generalizibility of our results. This paper is a first stroke at attempting to quantify the effects of AD medications on a set of AD biomarkers that has been shown to accurately predict AD conversion in MCI individuals, and these results must be confirmed with a significantly larger sample size.

Our results may mirror findings by others that AD therapeutic treatments have little positive effect in preventing disease progression [13]. Subjects in both our Meds-Convert and NoMeds-Convert groups still developed AD from comparatively the same state of cognitive impairment in roughly the same amount of time (though our study lacks the statistical power to examine if the drugs slowed disease development). More importantly, our ERP components were able to predict these clinical outcomes accurately from baseline and despite any AD medications the subjects were or were not taking at the time. However, it should be noted that these drugs are not currently FDA approved for use in MCI and while their off-label use is common, their disease modifying effects are not completely known. Interestingly, one recent study has reported reduced conversion of MCI to AD with donepezil, but only in patients with concomitant depression [42]. The conflicting body of evidence regarding these treatments in MCI indicates that the interaction between depression and AD needs much closer investigation. A more in-depth, longitudinal analysis is also needed to determine if the AD drugs slowed disease progression over time, and more research parsing the effects of the individual types of cholinesterase inhibitors would be beneficial. With only two subjects taking memantine along with a cholinesterase inhibitor, we can make no conclusions about its impact.

Beyond this practical application, there are theoretical conclusions that can be drawn from these results. The ERP components most important for measuring disease progression (including C250 (the "memory storage component") and C415 (P300)) do not seem to be affected by AD drugs. This thought should be tempered by an important realization: we examined only the weighted result of the discriminant function, not each ERP component individually. This was done to focus on the practical utility of the ERP biomarkers and to avoid "picking and choosing" which components to analyze. However, this approach limits the interpretability of the result for individual components. Further research is required to examine any effects (the type and directionality) AD drugs or other medications commonly prescribed AD and MCI patients have on specific ERP components.

Conclusion

We have found that AD medications produced no statistically significant effects on a multivariate, weighted combination of ERP measures used as biomarkers of AD conversion in MCI individuals. These ERP measures were significant predictors of which MCI individuals would later develop AD, but whether or not these individuals were taking commonly prescribed AD medications at baseline made no difference in these predictions. This suggests that AD medications have little impact on this system of ERP biomarkers and their utility in diagnosing and predicting AD in individuals. Additionally, our results add to a mounting body of evidence that AD medications may produce little significant effect in preventing AD progression in MCI patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

AD	Alzheimer's Disease
AMNART	American National Adult Reading Test
ANOVA	Analysis of Variance
ERP	Event-Related Potential
GDS	Geriatric Depression Scale
MCI	Mild Cognitive Impairment
MEDS-CONVERT	Conversion->AD group taking AD medications at baseline
MEDS-STABLE	Stable group taking AD medications at baseline

MMSE	Mini-Mental State Examination
NOMEDS-CONVERT	Conversion->AD group not taking AD medications at baseline
NOMEDS-STABLE	Stable group not taking AD medications at baseline
PCA	Principle Components Analysis

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Linear Discriminant Function for Classifying (Predicting) a Subject in the Conversion or Stable Group (Weighted Sum of ERP Component Scores)
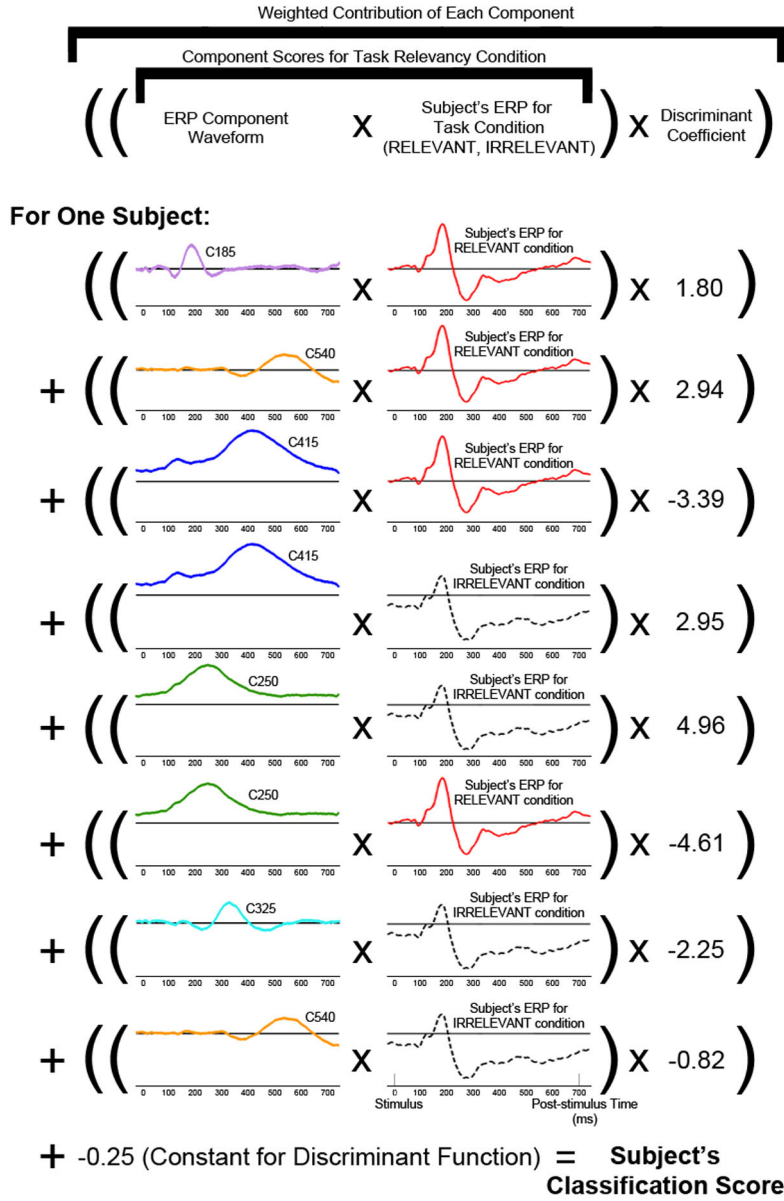

Figure 1.
Linear discriminant function. Component scores are generated by multiplying the vector of component scoring coefficients (measured with PCA) with the subject's vector of ERP time points for task conditions (in this case, Number-Letter stimuli relevant or irrelevant to the task). It should be noted that the component waveforms depicted above are a vector of component loadings (shown for simplicity's sake and mathematically similar to the scoring coefficients) with the metric restored by multiplying the loading at each time point by the standard deviation of the dataset at that corresponding time point [2, 22]. The voltage scale

of the component and ERP waveforms is identical. The ERP component_conditions are shown in the order they were selected by the stepwise discriminant procedure. The ERP component scores are then multiplied by discriminant coefficients. These coefficients were derived by subtracting the classification coefficients developed for the Stable group from those developed for the Conversion group [34, 35]. After applying discriminant coefficients, the results are summed and then added to a constant (which is also a difference between the Conversion and Stable group constants) to produce a classification score for each subject. A list of the classification coefficients for each of the groups was presented in previous work [2].
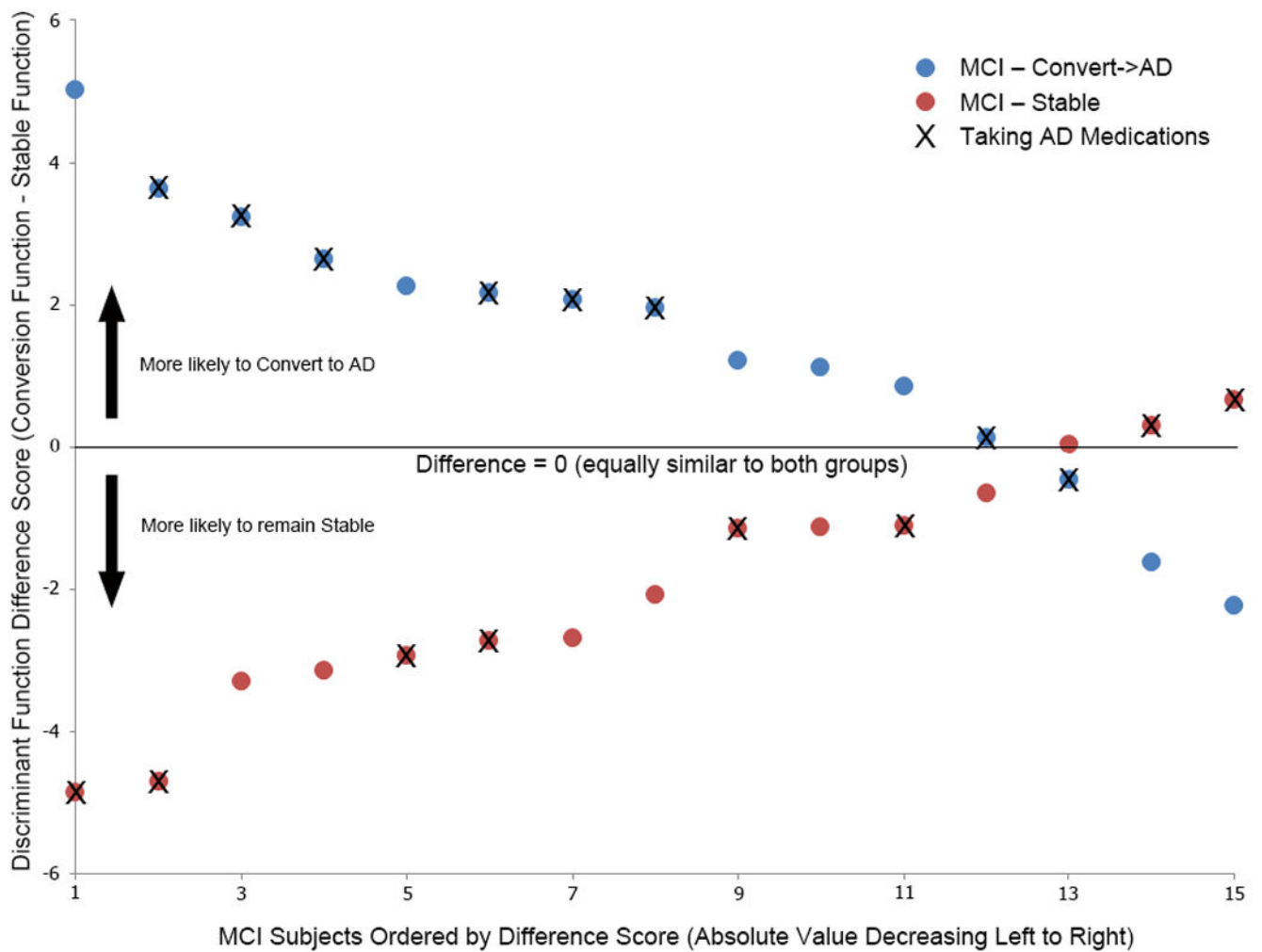
Figure 2.
ERP classification difference scores. The 30 MCI subjects (15 later Convert->AD, 15 remain Stable) are ordered by the absolute value of their difference scores (decreasing from left to right). The midline represents a difference score of 0 (not similar to either group). Subjects above this line were predicted to convert to AD. Subjects below this line were predicted to remain stable. The six subjects that were misclassified [2] fall on the "wrong side" of the midline for their clinical group (see x-axis 13–15). Subjects marked by an "X" were taking AD medications at the time of baseline ERP data collection.

Table 1

MCI subject baseline demographics. Values appear as mean (SD) unless otherwise specified.

	Convert->AD (n = 15)		Stable (n = 15)	
	Meds (n = 8)	NoMeds (n = 7)	Meds (n = 8)	NoMeds (n = 7)
Gender (M/F)	7/1	5/2	3/5	4/3
Age[a]	78.7 (5.5)	77.0 (1.4)	72.7 (8.4)	76.1 (4.9)
Education[a]	17 (1.3)	16.0 (1.5)	14.0 (0.8)	13.0 (1.3)
Follow-up Time[b]	1.3 (0.42–3.9)	0.9 (0.3–3.4)	2.8 (1.9–4.8)	2.8 (1.9–4.5)
Drug Duration[c]	2.5 (1–23)	0	4.5 (1.5–18)	0
NL Correct[d]	93.9 (4.3)	96.4 (2.6)	97.4 (1.9)	95.2 (3.6)
Antidepressants (n)	2	2	2	4
Neuropsychological Assessment				
MMSE[e]	25.7 (2.7)	25.7 (3.0)	27.0 (2.6)	27.7 (1.5)
GDS[f]	3.6 (2.5)	9.5 (9.1)	5.4 (3.3)	8.3 (5.3)
Blessed[g]	1.3 (0.9)	2.6 (2.7)	1.3 (1.4)	0.9 (0.7)
AMNART[h]	37.8 (10.6)	38.4 (4.8)	37.4 (6.9)	37.0 (5.9)

[a]Median in years (semi-interquartile range in parentheses). Two subjects did not provide education information in the NoMeds Convert->AD subgroup.

[b]Median number of years (range in parentheses) between initial diagnosis of MCI and subsequent diagnosis of AD (Conversion group) or median number of years between initial diagnosis and last clinical work-up (Stable group).

[c]Median number of months (range in parentheses) subjects took AD medications prior to baseline ERP data collection.

[d]Percent of correctly answered trials on the Number-Letter task. All subgroups were similar to like-age, cognitively normal Controls (96.0%, SD = 2.6%). Only correct trials were used in subsequent ERP analyses.

[e]Mini Mental State Examination [17]. A higher score (out of 30) indicates more intact cognitive state. This test was performed at baseline ERP data collection.

[f]Geriatric Depression Scale [43]. A higher score indicates a greater degree of depression (as subjectively reported by the subject). A measure less than 10 is considered not depressed. ANOVA revealed no main Group effect, no Medications effect, and no Group by Medication interaction, indicating the four subgroups were equally affected by depression. This test was performed at baseline ERP data collection.

[g]Blessed Dementia Scale [44]. A higher score indicates a greater negative impact of MCI on activities of daily living. ANOVA revealed no main Group effect, no Medications effect, and no Group by Medication interaction, indicating memory impairment equally affected the daily activities of the four MCI subgroups. This test was performed at baseline ERP data collection.

[h]American National Adult Reading Test [45]. ANOVA revealed no main Group effect, no Medications effect, and no Group by Medication interaction, indicating the four subgroups had roughly the same pre-morbid verbal intelligence. This test was performed at baseline ERP data collection.

Table 2

Mean ERP classification scores (SD) for the MCI groups and subgroups. These scores are calculated through a weighted combination of ERP component scores. A discriminant function was created by the discriminant procedure to classify each individual as an eventual member of the Convert->AD group or the Stable group based on baseline ERP data. Component scores are similar to z-scores. See Table 3 for ANOVA results concerning these mean scores.

	Classification Score (Conversion vs. Stable from ERP Prediction)
Clinical Group	
Conversion (n = 15)	1.47 (1.94)
Stable (n = 15)	−1.96 (1.70)
AD Medications	
Taking (n = 16)	−0.07 (2.68)
Not Taking (n = 14)	−0.45 (2.36)
Group × Medications	
Meds-Convert	1.92 (1.42)
NoMeds-Convert	0.95 (2.42)
Meds-Stable	−2.06 (2.09)
NoMeds-Stable	−1.85 (1.29)

Table 3

ANOVA on the relation of ERP classification scores to two factors, clinical Group (Convert->AD, Stable) and AD Medications (Taking, Not Taking) in a two-way factorial design. These analyses were performed using the subjects' classification difference scores (the result of the Conversion function – the result of the Stable function).

Source	df	F	p
Group (Conversion, Stable)	1, 26	25.42	<0.0001
AD Medications (Taking, Not Taking)	1, 26	0.32	0.58
Group × AD Medications	1, 26	0.76	0.39