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Research Report

Electrophysiological and information processing variability predicts memory decrements associated with normal age-related cognitive decline and Alzheimer's disease (AD)

Michael J. Hogan[a,*], *Leigh Carolan*[b], *Richard A.P. Roche*[c,d], *Paul M. Dockree*[c], *Jochen Kaiser*[e], *Brendan P. Bunting*[f], *Ian H. Robertson*[c], *Brian A. Lawlor*[b]

[a]*Department of Psychology, NUI, Galway, Ireland*
[b]*Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland*
[c]*Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland*
[d]*Department of Psychology, NUI Maynooth, Co Kildare, Ireland*
[e]*Institute of Medical Psychology, Johann Wolfgang Goethe-University, Frankfurt am Main, Germany*
[f]*School of Psychology, University of Ulster, Magee campus, Londonderry, Ireland*

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ABSTRACT

Recent theoretical models of cognitive aging have implicated increased intra-individual variability as a critical marker of decline. The current study examined electrophysiological and information processing variability and memory performance in normal younger and older controls, and older adults with Alzheimer's disease (AD). It was hypothesized that higher levels of variability would be indicative of age-related and disease-related memory deficits. Results indicated both implicit and explicit memory deficits associated with AD. Consistent with previous research, behavioral speed and variability emerged as sensitive to age- and disease-related change. Amplitude variability of P3 event-related potentials was a unique component of electrophysiological activity and accounted for significant variance in reaction time (RT) mean and RT standard deviation, which in turn accounted for significant variance in memory function. Results are discussed in light of theoretical and applied issues in the field of cognitive aging.

There is a great deal of controversy regarding the predictive validity of standard neuropsychological assessments in identifying early cases of dementia (Ritchie and Lovestone, 2002; Ritchie and Touchon, 1992) and the underlying causal factors associated with age- and disease-related decrements in memory and cognition (Anderson and Craik, 2000; Grady and Craik, 2000; Hogan, 2004; Hogan et al., 2003). Theoretical models of neurological aging have implicated increased intra-individual variability as a marker of generalized cognitive decline (Li and Lindenberger, 1998). A number of studies have examined intra-individual variability in older adults using measures of reaction time (Hogan, 2003; Myerson and Hale, 1993; Myerson et al., 1990; Rabbitt and Lowe, 2000; Salthouse, 1993), sensorimotor ability (Li et al., 2001), and cognitive ability (Hertzog et al., 1992; Hultsch et al., 2002). Results support the conclusion that levels of intra-individual variability increase with advancing age.

* *Corresponding author.*
E-mail address: michael.hogan@nuigalway.ie (M.J. Hogan).

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Dementia patients are also reported to be more variable in performance than normal elderly (Hultsch et al., 2000), with some evidence for different levels of variability in different demential disorders (Ballard et al., 2001; Murtha et al., 2002; Walker et al., 2000). Cognitive aging researchers continue to work toward agreed operational definitions for the intra-individual variability construct (Nesselroade and Salthouse, 2004; Stuss et al., 2003); it is unclear if indicators derived directly from brain imaging, RT, sensorimotor, and cognitive performance are strictly comparable.

Given the excellent temporal resolution of electroencephalography (EEG), and the way in which EEG signals provide trial-by-trial data during the critical information processing stages of encoding and retrieval, it is likely that electrophysiological data can shed light on intra-individual variability–performance relations across the lifespan and across levels of ability within the older adult population. These data may be particularly useful for understanding critical periods of age-related decline marking the transition from normal to pathological aging.

Notably, the latency and amplitude of P3 event-related brain potentials (ERPs) reflect underlying brain dynamics associated with attentional and immediate memory processes (Donchin et al., 1986; Polich, 1986). These measures have been used to study age- and disease-related decline in cognitive efficiency, one significant finding being that P3 peak latency increases systematically with increases in cognitive dysfunction (Polich et al., 1986; deToledo-Morrell et al., 1991). Whereas both P3 component amplitude and latency are sensitive to early clinical signs of AD, the diagnostic utility of ERPs is less certain. For example, the abnormality rates for P3 latency from AD and other demented patients vary from 13% to 80% across reports (Polich, 1991, 1998a,b). At the same time, significant progress has been made in identifying factors that can contribute to this variable range (cf. Polich and Kok, 1995; Polich, 1996), so that biological and methodological factors that affect the P3 brain potential can be controlled to minimize external variability and maximize the differentiation of AD patients from normal control subjects (Pfefferbaum et al., 1990; Polich, 1997; Goodin, 1990).

To date, however, only one study has examined age-related and disease-related differences in EEG intra-individual variability. Patterson et al. (1988) examined latency variability of auditory event-related potentials (ERPs) in 15 demented, 8 depressed, and 15 normal older, and 12 normal young, participants. Latency variability measures from single trials were derived for the N1, P2, N2, and P3 components of the ERP. Dementia patients had longer P3 latencies and greater P3 latency variability than both control groups and the depressed group. However, regression analysis revealed that only 27% of the demented individuals were correctly classified using P3 variability, and 13% using P3 latency. The findings suggested that measures of ERP variability using the auditory oddball target detection paradigm were sensitive to group differences, but not sufficiently sensitive to be used in differentiating demented persons on an individual basis for clinical diagnosis.

In the current study, we examined variability in amplitude of ERPs. Unlike latency variability, assessment of amplitude variability (AmpV) does not involve subjective evaluation of peak amplitudes and pre-defined selection algorithms can be applied across individuals, groups, and study centers. The same single-trial ERPs (task-relevant ERPs in an implicit and explicit memory paradigm), which were used to generate the ERP amplitude mean (AmpM), were also used to generate the ERP amplitude variability measure. Because ERP amplitude means correlate with attention, stimulus identification, and memory (Friedman, 2000; Picton and Hillyard, 1974; Rugg, 1991), we assumed that amplitude variability would reflect the efficiency and stability of neural networks necessary for reliable encoding and retrieval of memories. For example, neuroimaging has demonstrated that regions of the right prefrontal cortex, including dorsolateral regions, fronto-polar areas, and frontal operculum, working in conjunction with temporal lobe areas, are key neuroanatomical correlates of an episodic "retrieval mode" (or REMO; Lepage et al., 2000). It is possible that age- and disease-related atrophy in prefrontal and temporal areas would lead to instability in REMO sites leading to a more variable electro-cortical signal indicative of poor fronto-hippocampal control.

Notably, both frontal lobe and temporal lobe areas are critical for understanding P3 generation; frontal lobe integrity is necessary for P3a generation (Knight, 1984; Knight et al., 1995); patients with focal hippocampal lesions have reduced P3a amplitude from novel distracters but normal P3b components from targets (Knight, 1996); P3 amplitude is affected by the temporal-parietal lobe junction, which may underlie component generation or transmission subsequent to hippocampal activation (Knight et al., 1989; Yamaguchi and Knight, 1992). In an earlier study, we observed a selective reduction in fronto-temporal coherence in a group of early AD patients compared with older controls (Hogan et al., 2003), which suggested reduced functional interaction between the two areas of the brain.

In the current study, three components of the ERP were examined: the N2; the anterior P3; and the posterior P3 (see below). The early N2 component is thought to represent the activity of early attentional and perceptual processes whereas the P3 reflect activity associated with higher-level identification and decision-making processes (cf. Rugg, 1991). We tested three groups: normal younger and older adults, and older adults with Alzheimer's disease (AD). EEGs were recorded during two memory tasks: one implicit and one explicit. In total, ERPs were available for 15 discrete conditions (i.e., 6 implicit encoding, 6 explicit encoding, and 3 explicit recognition events). The study had the following objectives:

(1) to examine if measures of AmpV can distinguish between younger and older adults and older adults with AD; and
(2) to model the direct and indirect effects of AmpM and AmpV on mean RT, RT SD, and cognitive performance.

1. Results

1.1. *Behavioral data*

1.1.1. *Implicit memory*

A series of 3 (group) × 6 (stimulus) ANOVAs were computed on accuracy, mean RT, and RT SD data. Only significant *p*-values

are reported here. For accuracy, there was a main effect of group ($p<0.01$), stimulus ($p<0.001$), and a group×stimulus interaction ($p<0.05$). Younger controls and older controls were more accurate than ADs ($p<0.01$). All groups had lower accuracy for animal words compared to control words and repeated words ($p<0.01$); the relative decrement in accuracy was largest for the AD group (see Table 1).

For RT mean, there was a main effect of group ($p<0.001$), stimulus ($p<0.001$), and a group×stimulus interaction ($p<0.001$). Young controls had faster RTs than did other groups for target (animal) words ($p<0.05$). Younger controls were significantly faster than ADs ($p<0.01$), but not older controls, when responding to control words and repeated words ($p<0.05$). Older controls were significantly faster than ADs across all conditions. All groups were faster at responding to the repeated words for lag=4 ($p<0.01$); all groups other than AD were faster at responding to repeated words for lag=12 ($p<0.01$). Repetition effects were larger for lag=4 when compared to lag=12; the difference was non-significant for younger controls and older controls, and significant for ADs ($p<0.05$).

For RT SD, there was a main effect of group ($p<0.001$) and stimulus ($p<0.001$). ADs were significantly more variable than other groups for all stimuli and all groups were less variable for repeated words ($p<0.01$; see Table 1).

1.1.2. *Explicit memory—encoding*

Results of a 3 (group)×3 (stimulus) mixed factor ANOVA on accuracy data revealed a main effect of group ($p<0.005$) and stimulus ($p<0.001$). ADs were less accurate than younger controls and older controls ($p<0.01$). Non-word accuracy was poorer than for neutral words ($p<0.01$) and learn words ($p<0.001$; see Table 2).

For mean RT, there was a main effect of group ($p<0.001$), and a group×stimulus interaction ($p<0.001$). Younger controls and older controls were faster than ADs ($p<0.01$); younger controls were faster than older controls ($p<0.05$) when responding to non-words. Younger controls were faster at responding to non-words when compared with neutral words and learn words ($p<0.01$); ADs showed the reverse pattern ($p<0.01$).

For RT SD there was a main effect of group ($p<0.001$) and a group×stimulus interaction ($p<0.001$). Younger controls did not differ from older controls overall but were more variable when responding to learn words than were older controls ($p<0.05$). Older adults were less variable than ADs ($p<0.01$). Younger controls were less variable to non-words when compared with neutral words and learn words ($p<0.01$); ADs showed the reverse pattern ($p<0.01$).

Table 1 – Implicit memory reaction time means and SDs and percentage accuracy across groups

	Young M (SD)	Old M (SD)	AD M (SD)
Accuracy (%)			
Animal	87.50 (8.56)	83.48 (16.06)	70.63 (12.63)
Control	94.55 (6.90)	93.41 (11.66)	87.92 (7.85)
4a	93.64 (10.93)	94.57 (8.25)	88.13 (12.89)
4b	93.64 (10.37)	96.09 (7.53)	90.00 (6.83)
12a	95.00 (7.24)	94.35 (7.43)	87.50 (11.83)
12b	95.23 (7.94)	93.91 (11.96)	91.25 (7.85)
RT mean			
Animal	0.83 (0.13)	0.98 (0.13)	1.34 (0.44)
Control	0.79 (0.17)	0.88 (0.14)	1.14 (0.38)
4a	0.80 (0.14)	0.91 (0.16)	1.16 (0.38)
4b	0.69 (0.13)	0.78 (0.11)	1.07 (0.37)
12a	0.78 (0.17)	0.86 (0.17)	1.07 (0.33)
12b	0.69 (0.14)	0.76 (0.10)	1.04 (0.35)
RT SD			
Animal	0.19 (0.09)	0.24 (0.11)	0.40 (0.19)
Control	0.21 (0.09)	0.23 (0.07)	0.39 (0.15)
4a	0.20 (0.08)	0.26 (0.1)	0.40 (0.18)
4b	0.16 (0.08)	0.18 (0.06)	0.33 (0.16)
12a	0.21 (0.09)	0.26 (0.13)	0.38 (0.15)
12b	0.14 (0.09)	0.16 (0.07)	0.31 (0.16)

Note. Animal=animal (target) words; Control=control (non-target) words; 4a=words to-be-repeated after 4 words; 4b=words repeated after 4 words; 12a=words to-be-repeated after 12 words; 12b=words repeated after 12 words.

Table 2 – Explicit memory reaction time (RT) means and SDs and percentage accuracy across groups

	Young Mean (SD)	Old Mean (SD)	AD Mean (SD)
Accuracy (%)			
Word	94.09 (3.50)	95.52 (3.68)	87.34 (11.67)
Non-word	92.50 (13.18)	90.31 (17.97)	79.22 (20.85)
Learn word	99.43 (1.07)	98.85 (2.08)	92.03 (10.01)
RT mean			
Word	0.85 (0.12)	0.87 (0.14)	1.05 (0.32)
Non-word	0.71 (0.13)	0.82 (0.18)	1.20 (0.35)
Learn word	0.80 (0.14)	0.83 (0.17)	1.02 (0.30)
RT SD			
Word	0.27 (0.07)	0.22 (0.09)	0.38 (0.17)
Non-word	0.17 (0.08)	0.21 (0.09)	0.42 (0.19)
Learn word	0.29 (0.11)	0.22 (0.07)	0.33 (0.18)

1.1.3. *Recognition*

Younger controls had better recognition memory than older controls ($p<0.05$) and ADs ($p<0.01$). Older controls had better memory than ADs ($p<0.01$). Younger controls and older controls showed better recognition to learn words when compared with neutral words ($p<0.05$); ADs did not. At the same time, the benefit of a learning cue was significantly greater in the younger control group when compared to older controls ($p<0.01$) (Fig. 1).

1.2. *Group differences in ERP factor scores*

Using the 36 ERP variables derived from the implicit memory task, factor analysis was used to test the hypothesis that AmpM and AmpV for the N2, anterior P3, and posterior P3 ERP components represented separate dimensions of brain activation. Six factors with eigenvalues >1 were extracted, accounting for a total of 82.92% of the sample variance. All variables with a factor loading greater than or equal to 0.60 on one or other of the six factors were retained for interpretation.

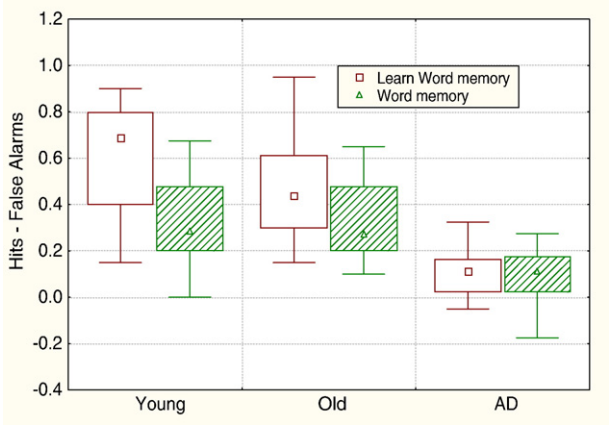

Fig. 1 – Recognition memory of younger and older adults to Learn Words and Words (i.e., words seen but not explicitly learnt).

Factors 5 and 6, which together accounted for 9.77% of the sample variance, were dropped from the model as they comprised a collection of weak factor loadings. The four remaining factors clearly distinguished AmpV from AmpM. Factors 1 and 4, accounted for a total of 45.81% of the sample variance. These two factors included all 18 AmpV indicators—factor 1 included all 12 anterior P3 and posterior P3 AmpV indicators and accounted for 40.25% of variance; factor 4 included all 6 N2 AmpV indicators and accounted for 5.56% of variance. Factors 2 and 3 accounted for a total of 29.68% of the sample variance, and these factors included all 18 AmpM indicators—factor 2 included the 12 anterior P3 and posterior P3 indicators and accounted for 19.57% of variance; factor 3 included the 6 N2 indicators and accounted for 10.11% of variance.

Given the specificity of the 4 factors, we computed factor scores for each participant and conducted a series of one-way ANOVAs to examine group differences, one for each factor. Results indicated no main effect of group for factors 2, 3, and 4, but a significant group effect for factor 1 (P3 variability), $F(2,59)=3.90$; $p<0.025$. ADs were more variable than young controls ($p<0.001$); however, pairwise differences between young controls and older controls and between older controls and ADs did not reach significance.

Using the 36 explicit memory ERP indicators and the same factor analysis logic as above, the following pattern was observed. Six factors with eigenvalues >1 emerged; all variables except one (P3b variability for non-words) had unique loadings greater than 0.60, and unlike the implicit memory task all 6 factors required interpretation. Together the 6 factors accounted for 78.74% of the sample variance. Factors 1, 3, and 6 included the 17 remaining AmpV indicators and accounted for 35.82%, 9.42%, and 4.28% of the variance, respectively. Factor 1 had seven anterior P3 and posterior P3 loadings; factor 3 had six N2 loadings; factor 6 had four anterior P3 and posterior P3 loadings. Factors 2, 4, and 5 included all 18 AmpM indicators and accounted for 15.88%, 8.11%, and 5.31% of the variance, respectively. Factor 2 had six anterior P3 and posterior P3 loadings; factor 4 had six anterior P3 and posterior P3 loadings; factor 5 had six N2 loadings. Again, factor scores were extracted and group differences examined.

A series of one-way ANOVAs revealed no effect of group for scores on factors 2, 3, 4, and 5, but significant effects for factor 1, $F(2,59)=4.62$; $p<0.015$, and factor 6, $F(2,59)=5.07$; $p<0.01$. For factor 1, which includes anterior P3 and posterior P3 AmpV for words ($n=6$) and posterior P3 for the cue to learn (L), ADs were more variable when compared with younger controls and older controls ($p<0.015$ for both). For factor 6, which includes anterior P3 and posterior P3 AmpV for central fixation X ($n=3$) and for words to-be-learnt, older controls had significantly more variability than did younger controls ($p<0.001$); older controls and ADs and younger adults and ADs differences were non-significant ($p>0.05$ for both).

Finally, we examined the factor structure of the 18 explicit recognition ERP indicators. Five factors with eigenvalues >1 emerged, each with factor loadings greater than 0.60. Three variables – N2 to Learn Words and anterior P3 and posterior P3 to words not seen before – with weak factor loadings were excluded as non-specific. A principal components model, using the remaining 15 variables, resulted in a six-factor solution that accounted for a total of 88.58% of the sample variance. Factor 1 (40.03%) included all 6 anterior P3 and posterior P3 AmpV indicators; factor 2 (20.04%) included N2, anterior P3, and posterior P3 AmpM to words not seen before; factor 3 (12.43%) included anterior P3 and posterior P3 AmpM to Learn Words; factor 4 (8.72%) included N2 AmpM and N2 AmpV to words not seen before; and factor 5 (7.35%) included AmpV N2s for Words and Learn Words.

ANOVA revealed an effect of group for factor 1, $F(2,59)=5.09$; $p<0.01$; ADs were significantly more variable than younger controls ($p<0.005$). The young controls – older controls and the older controls – ADs comparisons were not significant.

1.3. *AmpM and AmpV as independent performance predictors*

The principal component solutions were useful for observing and testing the nature of the distinct clusters for the AmpM and AmpV variables which were taken as a tentative solution given the sample size. Further, although the principal component solutions and a number of factor analytic models using maximum likelihood with a promax solution presented somewhat similar solutions, it is important to keep in mind that these different approaches partition the variance in different ways. Hence, given the restrictive nature of the present sample, the factor solutions are tentative but nevertheless are highly suggestive.

In the next part of the analysis, information based on the previous analysis is used to examine possible predictors of behavior performance using path analysis within a structural equation modeling framework (AMOS v.5.0). This will allow us not only to test our models but to introduce both direct and indirect effects into the patterns of relationships between the exogenous and endogenous variables. Here we focus on possible explanatory factors that are thought to be related to the performance outcomes of explicit memory recognition for (a) words (seen but not learnt) (b) learnt words and (c) the Wechsler Logical Memory Test (WLM). For each of these outcomes, we examined the direct effects of AmpM and AmpV on the mean RT and RT SD and, in turn, whether these

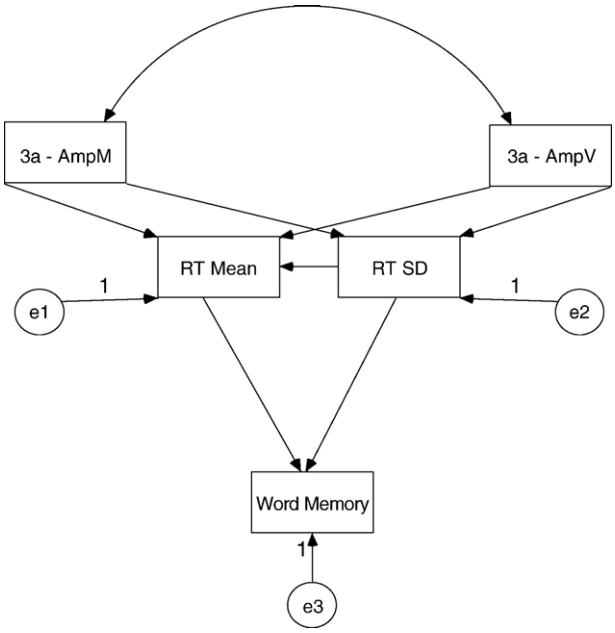

Fig. 2 – Best-fitting structural equation model describing the relationship between AmpM, AmpV, RT mean, RT SD, and explicit memory outcomes.

latter two measures directly predicted the scores on explicit memory recognition tasks and the WLM test. Through an examination of the indirect effects, it is also possible to establish the effects of AmpM and AmpV on the outcome measures (explicit memory recognition tasks and WLM).

Three identically structured models were analyzed (see Fig. 2), one with Learn Word memory as outcome, the second with Word memory as outcome (i.e., hits minus false alarms for words seen-and-learnt and words seen but not learnt), the third with WLM test scores as outcome. In all three models, we used the mean of anterior P3 AmpM and AmpV and mean RT and RT SD to all word types during encoding (i.e., Words, Learn Words, and Non-Words).[1]

The three outcome measures (WLM, Word memory, and Learn Word memory) all had the same pattern of direct and indirect predictors. These identically structured models all produced a reasonably good fit for the data (chi-square values with a probability of 0.05 or greater). The predictors were set up so that AmpM and AmpV, while correlated with each other, had a direct effect upon RT mean and RT SD, and RT SD itself had a direct effect upon RT mean (see Fig. 2). The correlation between P3 AmpM and AmpV was 0.63. The effect of AmpM on both RT mean and RT SD was not statistically significant (0.05 level). Conversely, the effect of AmpV on both RT mean and RT SD was statistically significant ($p<0.025$) and the path from RT SD to RT mean was highly significant ($p<0.001$). These results are shown in the first five rows of figures reported in Table 3. The introduction of a direct effect from RT SD to RT mean was decided on two grounds: (a) it is suggested by Eysenck (1982) and Jensen (1992),[2] and (b) it provides a stronger explanation for the sample correlation between RT mean and RT SD. For some this may be a step too far, and as such they might prefer that the residual variances in both measures were simply allowed to correlate. This would produce an identical fit for the model but would reduce the impact of the RT SD on each of the three outcome measures.

In the next three parts of Table 3, the effects of RT mean and RT SD on the three outcomes measures (WLM, Learn Word Memory, and Word Memory) have been reported. These results show that RT mean had a significant direct effect on two of the three outcome measures (WLM and Learn Word memory), but not on Word memory (see Table 3). RT SD did not have a statistically significant (0.05 level) impact on any of the three outcome measures.

However, a measure although not having a direct effect on an outcome (endogenous) measure may, nevertheless, due to its impact on other variables, i.e., indirect effects, in the model have an important total effect on the outcome measure(s). The total effects, comprising the (a) indirect effects and (b) direct effects, are given in Table 3 under the column labeled Total Effects. These total effects show a moderate to strong effect for RT SD on the three outcome measures [WLM (−0.460), Word memory (−0.369), and Learn Word memory (−0.389)]. It would appear that RT SD is having a roughly similar impact on all three outcome measures and in the same manner, i.e., as RT SD increases, the scores on all three outcome measures are reduced. Of the two exogenous measures, AmpV had a moderate but negative impact on all three outcome measures (AmpV effect on WLM, Words, and Learn Words were −0.299, −0.193 and −0.263, respectively). The other exogenous measure, AmpM, had low but positive total effects on the same corresponding three outcome measures: 0.122, 0.069, and 0.112.

In all three models, the variance explained for the RT mean was 67% (this value is the same across all three models because the same predictors have been used). The variance explained for the three outcome measures were 32% (WLM), 15% (Word memory), and 24% (Learn Word memory).

2. Discussion

We examined behavioral and electrophysiological responding of younger adults, older controls, and older adults with

[1] A series of alternative models was also tested. The anterior P3 measures were removed from the model and replaced, first by the posterior P3 measures, and second by the N2 measures. All of the models were run again, using the same structure for the path analysis. These models were a good fit to the data. In no case did the introduction of these predictor measures (in place of those included within the current analysis) lead to a better predicted explanation of the three exogenous measures.

[2] Both researchers hold the view that RT median or RT mean are merely consequences of whatever basic process is reflected by RT SD. The particular process hypothesized by Eysenck is random errors in the transmission of information in the brain, or what might be called "neural noise". Jensen (1992) argues that oscillation in response speed will cause a positive skew in the distribution of RTs obtained in a large number of trials. The greater the oscillation, the larger will be RT SD, but the RT mean (and, to a lesser extent, RT median) is also increased by the positive skewness of the total distribution of RTs.

Table 3 – Path model coefficients (standardized and un-standardized) and total effects for three models relating to memory recognition tasks

			Estimate	SE	CR	*p*	Std estimate	Std total effects
RT SD	←	AmpM	−0.013	0.018	−0.707	0.480	−0.110	−0.110
RT SD	←	AmpV	0.048	0.018	2.661	0.008	0.414	0.414
Mean RT	←	AmpV	0.050	0.022	2.284	0.022	0.231	0.539
Mean RT	←	AmpM	−0.034	0.021	−1.618	0.106	−0.156	−0.238
Mean RT	←	RT SD	1.380	0.146	9.425	0.000	0.744	0.744
Additional effects for Weschler Logical Memory (WLM)								
WLM	←	Mean RT	−37.559	14.520	−2.587	0.010	−0.455	−0.455
WLM	←	RT SD	−20.034	26.939	−0.744	0.457	−0.131	−0.469
WLM	←	AmpV						−0.299
WLM		AmpM						0.122
Additional effects for words seen but not learnt								
Words	←	Mean RT	−0.148	0.168	−0.881	0.378	−0.173	−0.173
Words	←	RT SD	−0.382	0.312	−1.227	0.220	−0.240	−0.369
Words	←	AmpV						−0.193
Words	←	AmpM						0.067
Additional effects for memory for learnt words								
Learn words	←	Mean RT	−0.550	0.231	−2.383	0.017	−0.442	−0.442
Learn words	←	RT SD	−0.139	0.428	−0.325	0.745	−0.060	−0.389
Learn words	←	AmpV						−0.263
Learn words	←	AmpM						0.112

Note: SE = standard error; CR = critical ratio; *p* = probability; Std = standardized.

Alzheimer's disease (AD) during an implicit and explicit memory task. When compared with the effects of aging on explicit memory, research suggests significant implicit memory resilience (Fleischman et al., 2004), even during the early stages of AD (Camus et al., 2003; Eldridge et al., 2002). This is perhaps due to the lower resource demands of implicit memory tasks when compared with explicit memory tasks (Craik et al., 1987), and the distributed and spared nature of priming processes in the aging brain (Cabeza, 2001). Largely consistent with this view, the current study observed that ADs demonstrated significant repetition priming effects for lag=4 but not for lag=12, suggesting a possible limit to implicit memory resilience in the face of disease.

Conversely, explicit memory, as tested using a word recognition test, showed a clear pattern of group difference. Older controls had significantly better memory when compared with ADs, and all groups other than ADs showed better recognition to words where a cue to learn preceded word presentation. Craik and Jennings (1992) have argued that, due to limitations in processing resources, the ability to self-initiate optimal processing functions at both encoding and retrieval is particularly problematic for older adults. As a result, older adults do not spontaneously engage in cognitively demanding processes such as deep, semantic encoding and thus retain less. For example, Craik and Byrd (1982) and Craik and Simon (1980) reported a series of experiments in which age-related decrements were greatest in conditions that demanded self-initiated learning but were minimized or eliminated when deep encoding was encouraged by semantic orienting tasks. Our results confirm these earlier findings and also suggest that whereas older adults' self-initiated learning strategies are *less* effective than younger adults', attempts by AD patients to self-initiate learning were ineffective.

Modeling aging memory involves modeling its neurological and information processing resource base. Anderson and Craik (2000) proposed that the age-related neurological alterations occurring in the frontal lobes with increasing age mediate two general cognitive changes: a reduction in the amount of attentional resources available for complex cognitive tasks, and a reduction in the processing speed of elemental cognitive processes. According to Anderson and Craik, age-related reductions in cognitive resources and age-related cognitive slowing act to reduce overall cognitive control. These decrements in cognitive control are clearly accentuated when age-related decrements are compounded by disease-related decrements like those observed in AD, where frontal and temporal lobe atrophy reduces coherence between the two cortical sites (Hogan et al., 2003) and negatively impacts upon controlled access to encoded representations. Consistent with previous research, we observed age- and disease-related slowing of behavioral performance (Crossley et al., 2004). Further, the reaction times (RTs) of Alzheimer's patients were significantly more variable than all other groups (see also, Hultsch et al., 2000), particularly during the implicit memory word categorization task.

Modeling the structural and functional age- and disease-related neurological changes that undergird speed and variability of behavioral performance is an ongoing challenge (Hogan, 2004). At the same time, it is clear that these basic parameters of information processing efficiency account for a large portion of the age- and disease-related variance in higher-level cognitive ability (cf. Salthouse, 1996; Hultsch et

al., 2000). One important question is whether or not RT mean and RT SD are best conceptualized as sharing common brain generators or having distinct brain generators. Notably, both Eysenck (1982) and Jensen (1992) hold the view that RT median or RT mean are merely consequences of whatever basic process is reflected by RT SD, and the particular process hypothesized by Eysenck is random errors in the transmission of information in the brain, or what might be called "neural noise". Conversely, Hale et al. (1988) have argued that general slowing is the root of the greater variability in response time (RT) of older samples. Hale et al. used Brinley plots to examine the relationship between group mean RT and group mean RT standard deviation (SD). They found that the correlation between speed and variability is positive ($r=0.91$–0.94) and is practically identical for younger and older samples (see also, Myerson and Hale, 1993).

However, it has been argued that the dependence of Brinley plots on the comparison of group means prohibits a thorough test of the Generalized Slowing Model (Sliwinski et al., 1994). A group mean may not be representative of the distribution from which it was computed, and the mean size is determined by the sample size and the distribution of scores. Therefore, Brinley plots that combine reaction time means across groups without regard to the task, the specific experimental manipulation, or to individual differences, may be less sensitive in the identification of task-, process-, or domain-specific effects of aging (Fisk et al., 1992; Fisk and Fisher, 1994; Mayr and Kliegl, 1993; Sliwinski et al., 1994).

Other researchers have highlighted the more complex relationships between response distributions, task parameters and individual differences (Balota and Spieler, 1999, Logan, 1992; Van Breukelen, 1995). Without further application of more advanced experimental and statistical techniques, it would be hasty to conclude that RT SD is less important than RT mean, particularly given that there are theoretical reasons for assuming that RT SD may be more sensitive to the effects of aging than mean RT. For example, early theories of cognitive aging (Crossman and Szafran, 1956; Welford, 1959) attributed the cause of cognitive aging deficits to age-related increase in neural noise in the central nervous system. More recently, using a neural network model of cognitive aging, Li and Lindenberger (1998) demonstrated that a series of benchmark phenomena of cognitive aging, ranging from general slowing, susceptibility to interference, and age-related increase in inter-individual and intra-individual variability can all be accounted for by a single parameter, which increases the level of intra-network variability via lowering the signal-to-noise ratio of the processing units (see also, Li et al., 2000).

In the current study, we modeled the relationship between the mean amplitude and amplitude variability of ERPs, the speed and variability of behavioral performance, and memory performance. Trial-by-trial data during fifteen critical information processing stages of encoding and retrieval were examined. Because ERP mean amplitudes correlate with attention, stimulus identification, and memory (Friedman, 2000; Picton and Hillyard, 1974; Rugg, 1991), we assumed that intra-individual variability in mean amplitude of ERPs would reflect the efficiency and stability of neural networks necessary for reliable encoding and retrieval of memories and that age- and disease-related atrophy would lead to greater electrocortical signal instability indicative of poor fronto-hippocampal control.

Across three conditions – implicit memory, explicit memory encoding, and explicit memory recognition – using a total of 90 ERP indicators (45 AmpM and 45 AmpV), we found that AmpM and AmpV clustered as unique factors in factor analysis. Using AmpM and AmpV factor scores as individual difference variables, we found that AmpV consistently distinguished younger adults from ADs. AmpV factor scores did not, however, distinguish older controls from ADs. At this level of analysis, our results are consistent with those of Patterson et al. (1988). They found that measures of latency variability of auditory ERPs were sensitive to AD, but not sufficiently sensitive such that variability indicators could be used to differentiate demented persons on an individual basis for clinical diagnosis.

At the same time, we recognized that principal component analysis (PCA) factor scores are somewhat blunt as indicators, and a series of separate post hoc analyses comparing the three groups on specific target ERPs did produce some interesting effects. For example, during explicit recognition ADs had greater anterior P3 non-target variability when compared with both younger adults and older controls, $p<0.05$. A tentative interpretation of this finding is that greater fluctuation in signaling during attempts to recognize words as non-targets may be associated with increased (but more variable) efforts to retrieve weak memory traces and engage comparison processes aimed at maximizing 'hits' and minimizing 'false alarms'. At the same time, because of the specificity and complexity of this issue we have decided to examine it in more detail in a follow-up report using a combination of spectral power analysis, coherence analysis, and ERP analysis.

Central to the current study was the application of structural equation modeling (SEM) to test the direct and indirect effects of AmpM and AmpV on memory performance via their influence on mean RT and RT SD. For each of three explicit memory outcomes – Weschler Logical Memory (WLM), Word memory, and Learn Word memory – we found that anterior P3 AmpV but not AmpM accounted for significant variance in RT SD and RT mean. From here, our best fitting model suggested that RT SD accounted for significant variance in RT mean, and RT mean, in turn, accounted for significant variance in two of the three outcome measures (WLM and Learn Word memory). Total effects analysis indicated that AmpV had a small to moderate impact on all three outcome measures, whereas RT SD had a moderate to strong effect. The model we used accounted for more variance in WLM (32%) than in either Learn Word memory (24%) or Word memory (15%).

Overall, the results of the current study point to the value of examining amplitude variability of ERPs as a distinct marker of neurological function. Notably, AmpV was found to be a good predictor of behavioral speed and variability, which in turn were found to predict memory performance. These results suggest that AmpV may be a marker of neural network efficiency. Higher levels of AmpV predict more variable RTs and slower RTs. At the same time, as measured in the current study, AmpV was not generally sensitive enough to help us to

distinguish normal age-related cognitive decline from the pattern of cognitive decline observed in AD patients. Future research will do well to explore the functional correlates of AmpV in a broader range of experimental conditions and in other clinical groups, particularly those clinical groups for whom regulation over specialized neural networks is assumed to be a critical factor in any cognitive, emotional, motivational, or behavioral difficulties they are experiencing.

The idea that ERP amplitude variability may be of general functional significance comes from studies that have found increased ERP amplitude variability to be associated with attentional and behavioral problems in ADHD (Lazzaro et al., 1997) and schizophrenia (Anderson et al., 1991, 1995). Therefore, although increased amplitude variability is not a marker of dysfunction *specific* to old age, it may prove to be a *sensitive* marker under specific testing conditions. Further, for the purposes of modeling age- and disease-related slowing and behavioral variability (Hultsch et al., 2000), the current study suggests that measures of ERP amplitude variability may prove useful, offering an indicator of functional dynamics complementary to other measures of neural function.

We suggest that continued application of structural equation modeling to the relation between a variety of EEG measures and behavioral performance indicators will help tease apart the functional significance of different EEG measures. The only caveat is that this research strategy, if it is pursued, will require large sample sizes in order to successfully model the data. We recognize this as a limitation in our own study. We also recognize that, unlike the more specific, temporally sensitive indicator of amplitude variability used in other studies (e.g., Anderson et al., 1991, 1995), the measures of amplitude variability used in the current study reflect the total amount of variability in a broad time window. Also, although we adopted the reasoned strategy of measuring AmpM and AmpV for each participant at the sites where the amplitude power peaked, by restricting our analysis to one site alone we did not ascertain whether or not ERP variability in other sites was more or less sensitive to age-related decline. Further research with older adult should focus on extracting a range of more specific indicators of EEG variability across multiple sites, such that the functional significance of each can be assessed.

Ultimately, understanding how intra-individual variability affects learning and memory may be crucial for the design of cognitive rehabilitation programs in older adult populations (Robertson and Murre, 1999). If, for example, we can identify the neurological dynamics underlying behavioral and performance fluctuations as people age, this may help us to conceive of novel neurocognitive interventions that act to enhance neural network stability, facilitate awareness and self-management skills for those experiencing altered performance dynamics, and so on.

Conversely, a focus on average performance alone, rather than a focus on both average performance and the variations in performance over time, is destined to fall short of the mark; it will inhibit the development of process-oriented models of cognitive aging and the dynamic systems thinking that is needed to develop such models; it will overlook the potential for complementary analyses available in many data sets; it will limit developments in our understanding of the relations between intra- and inter-individual differences; and it will constrain the thinking of those people working directly with older adults and adults in the early and later stages of dementia. Further research in this area should seek to develop novel electrophysiological strategies that record time- and performance-related changes in brain activity. In this way, we can work to develop a better understanding of the brain dynamics undergirding individual differences in both average performance and performance fluctuations.

3. Experimental procedures

3.1. *Participants*

Twenty-four young, 24 old, and 16 ADs (mean age=21.5, 72.8 and 77 years, respectively) were recruited with informed consent. All participants who attend the Mercer's Institute for Research on Aging receive a comprehensive medical and neuropsychological assessment (Swanwick et al., 1996; Hogan et al., 2003). Individuals with depression as evidenced by a score of ≥5 on the GDS-15 (Skeikh and Yesavage, 1986) were excluded. All AD patients met NINCDS-ADRDA criteria for AD (McKhann et al., 1984). Neuropsychological screening tests included WAIS Vocabulary and Logical Memory (Wechsler, 1987); The Clock Drawing Test (Shulman and Feinstein, 2003); The Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983); and The Mini Mental State Examination (Folstein et al., 1975). Ethical approval was obtained from the St. James's Hospital ethics board.

The number of years in formal education was significantly longer in the younger group compared with the other two groups ($p<0.01$; see Table 4 for means and standard deviations). Younger controls scored higher than older controls and ADs on the Wechsler Vocabulary Scale ($p<0.01$). Younger controls differed from all other groups on the Mini Mental State Examination ($p<0.01$); older controls performed better than ADs ($p<0.001$).

Younger and older controls did not differ on the Clock drawing test, but both groups performed better than ADs

Table 4 – Means and standard deviations (SD) for the screening measurements

	Young		Old		AD	
	Mean	SD	Mean	SD	Mean	SD
Education	16.17	1.61	11.71	2.99	12.88	2.73
WAIS	57.71	5.58	50.96	8.00	47.68	11.83
LM1—immediate	36.41	3.85	24.95	4.78	9.5	5.78
LM1-Story B slope	5.96	2.22	4.29	2.26	2.19	1.97
LM2—delayed	40.37	3.21	25.42	5.56	4.06	6.24
Clock Drawing Test	5	0	4.67	0.56	4.06	1.71
HAD/GDS	8.46	4.54	5.00	3.56	5.87	4.17
MMSE	29.83	0.38	28.88	1.03	23.62	3.15

Note. WAIS=Wechsler Vocabulary Scale; LM=Logical Memory; HAD=Hospital Anxiety and Depression Scale; GDS=Geriatric Depression Scale; MMSE=Mini Mental State Examination.

($p<0.05$). Older controls and ADs did not differ on the GDS. Younger controls had better logical memory than both older controls and ADs ($p<0.001$); older controls performed better than ADs ($p<0.001$).

3.2. EEG tasks

3.2.1. Implicit memory

Implicit memory was assessed using a measure of repetition priming. A total of 160 words were presented sequentially on a computer screen. They consisted of 20 animal words, and 140 non-animal words, of which 60 were *control* words, 20 were words *to-be-repeated* after 4 trials (and *repeated* on the 4th trial), and 20 were words *to-be-repeated* after 12 trials (and *repeated* on the 12th trial). Participants were instructed to press "1" if the word was an Animal or "2" if it was not. Words were presented for 300 ms in large (24-point) font with an interstimulus interval of 1000 ms. Repetition priming for lag=4 and lag=12 was computed for each participant by subtraction of mean reaction times to words on first and second (repeated) presentation.

3.2.2. Explicit memory

Eighty words and 40 non-words were presented for 1000 ms, in white on a black background. Participants were instructed to press "1" if the stimulus was a word and "2" if it is a non-word. A central fixation "X" presented for 1000 ms preceded all 40 non-words and 40 of the words. The other 40 words were preceded by a central fixation "L" presented for 1000 ms, a cue that informed participants to learn words that followed.

A total of 80 words were presented during the recognition phase; 20 words that the participants had been asked to learn during encoding (i.e., preceded by an "L"), 20 words that participants had not previously been asked to learn (i.e., preceded by "X"), and 40 words not previously seen. Participants were asked to press "1" if they thought the word presented was any one of the words presented during encoding stage (i.e., including those learnt and not learnt) and "2" if they thought that it had not been presented previously.

3.3. EEG recordings

Electrophysiological data were recorded in AC mode with a gain of 500 and a band pass of 0.15–30 Hz. The A/D conversion rate was 500 Hz and the range was 11 mV. Each participant wore a Quikcap EEG recording cap connected to the Neuroscan Synamps (Scan 4.1) ERP recording system (Medtech Systems Ltd., Horsham, UK) for the duration of the tasks, and EEG activity was recorded. Scalp potentials were obtained using a 32-channel array with linked ear reference electrodes and an anterior scalp ground (Afz). The electrode array conformed to the International 10-20 System (American Encephalographic Society, 1994b). Vertical eye movements were recorded with two electrodes placed above and below the left eye, whereas electrodes at the outer canthus of each eye recorded horizontal movements. Silver/silver-chloride (Ag/AgCl) electrodes were used at all sites. Recording commenced when electrical impedance had been reduced to less than 10 kΩ by light abrasion of the scalp. All recordings were referenced to linked mastoids with an additional mastoid placement used as ground electrode.

3.3.1. Overall analysis strategy

This analysis does not focus on group differences in every ERP component, that is, amplitude mean (AmpM) and amplitude variability (AmpV) for N2, anterior P3, and posterior P3 across each stimulus condition (6 implicit, 6 explicit encoding, and 3 explicit retrieval). We are pursuing this analysis in a separate paper. In the current analysis, by extracting N2 and P3 across a range of different stimulus conditions, our intention was, first, through factor analysis, to distinguish amplitude mean from

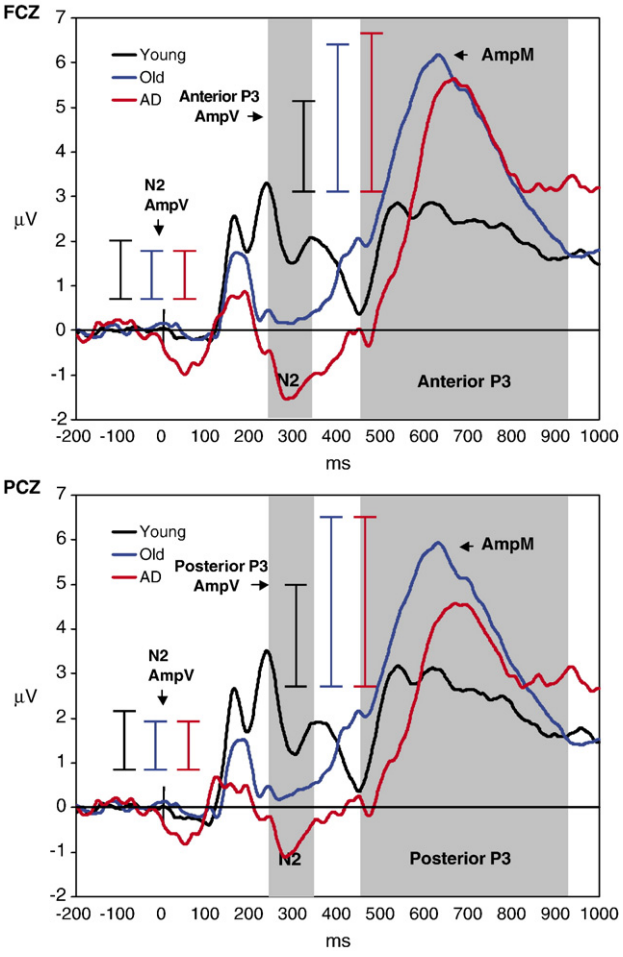

Fig. 3 – Grand-averaged waveform morphologies in fronto-central (FCZ) and parieto-central (PCZ) scalp regions for the young, old, and Alzheimer's disease groups, respectively. Grey shaded areas represent the time window of each component of interest (N2, Anterior P3 and Posterior P3) that are maximal over fronto-central and parieto-central scalp. AmpM represents the mean amplitude within the latency window for each component of interest. AmpV represents the standard deviation of the mean for each component of interest. AmpV is represented schematically as an error bar for each participant group at FCZ and PCZ, thus the relative variance across groups can be compared. Note: For each individual, each component was analysed at the electrode where the component was maximal on scalp topographical maps. Group differences are reported in Results.

amplitude variability. Because AmpM and AmpV measures clustered on different factors (see below), we decided to compute factor scores for each and examined group differences using these factor scores rather than do multiple comparisons across all measures. This strategy reduced the potential for Type 1 error and offered a relatively succinct and integrative analysis of the data. In the second stage of data analysis, we used AmpM and AmpV as discrete measures in a structural equation modeling context to examine the relationship between ERPs, RT, and memory functioning.

3.4. *Procedure*

Medical/neuropsychological and electrophysiological/information processing assessments took place on two separate days. On first arriving in the testing room, participants completed the paper and pencil and memory tests. During the second session, participants were prepared for the EEG tasks and provided with an opportunity to practice using the computer interface prior to each task. Participants completed the implicit and explicit memory tasks with a rest interval of 3 min between each.

3.4.1. *Electrophysiological data analysis*

Bad channels caused by faulty connections were deleted manually from the continuous EEG recordings. Sweeps in which amplitudes exceeded ±100 μV at any scalp electrode were automatically rejected. All sweeps were baseline corrected using the prestimulus interval as the baseline interval and epoched into single sweep recordings, from −250 ms prestimulus to 950 ms post stimulus. Incorrect responses and non-responses were manually selected from these EEG sweeps and were excluded from the subsequent analysis. The remaining epochs were separated into stimuli category for each task and these averages were combined to produce grand average waveforms.

Waveform component structure was defined in an a priori manner without any knowledge of effects that may be in the data. For each electrode, an overall grand average waveform for the entirety of each task was generated by collapsing across conditions for each group. In this way, the latency of the components of interest (in this case the N2 and P3) could be identified through visual inspection. Notably, the morphology of the P3 component was represented topographically as a broad, elongated field pattern extending over parietal, central, and frontal scalp sites. We reasoned that the elongated field pattern is likely the result of multiple and distributed cortical generators—possibly located in both frontal and parietal areas. Consequently, we selected, on an individual basis, maximal locations over posterior scalp and frontal scalp to reflect the potential diverse generators for this component. Hereafter, we refer to posterior P3 and anterior P3 to reflect this. And although there was no difference in the latency window for the anterior and posterior P3 when analyzed in this way, we wanted to examine mean amplitude and amplitude variability in both, as both anterior and posterior sites could potentially reveal different functional relations. The N2 was found to peak at 288 ms, and a latency window of 240–317 ms was defined for this component; the latency window for the P3 in this task was 470–940 ms. For the purposes of presentation, grand average waveform morphologies are presented a two midline sites (FCZ and CPZ, see Fig. 3).

ERP components are the summation of many simultaneously active cortical generators that will not be evoked in the same spatially distinct location for each individual (Foxe and Simpson, 2002; Murray et al., 2001). In the current study, each component was analyzed at the electrode where the component was maximal on scalp topographical maps. Despite some spatial variations in the topography of individual componentry, a central field pattern was consistent for the N2, anterior P3, and posterior P3. The data at each electrode site were averaged across the appropriate latency window and the mean amplitude and mean standard deviation was extracted for each electrode, for each stimulus, for each individual. The amplitude measure (AmpM) and standard deviation measure (AmpV) were then used as the variables in factor analysis and structural equation modeling.

Factor analysis was used to test the hypothesis that AmpM and AmpV for the N2, anterior P3, and posterior P3 ERP components represent separate dimensions of brain activation. A six-factor solution was extracted using a principal component factor analysis with varimax normalized rotation. This analysis was undertaken separately for the implicit memory task, the explicit memory encoding task, and the explicit memory recognition task.

For both the implicit memory task and the explicit memory encoding task, a total of 36 ERP variables [2 markers (AmpM, AmpV)×3 components (N2, anterior P3, posterior P3)×6 stimuli] were entered as normalized z-scores. Factor analysis on the explicit memory recognition task was performed using 18 ERP variables. Because AmpM and AmpV variables tended to cluster on unique factors (see Section 2 below), factor scores were computed for each participant and the three groups compared. Using information based on the factor analysis, we also examined ERP predictors of behavioral performance using structural equation modeling (AMOS v.5.0). This allowed us to examine both direct and indirect effects in the patterns of relationships between the exogenous and endogenous variables. Here, we focus on three outcome measures: explicit memory recognition for both Words and Learn Words and performance on the Weschler Logical Memory Test (WLM). For each of these outcomes, we examined the direct effects of AmpM and AmpV on the mean RT and RT SD and, in turn, whether these latter two measures predicted the scores on explicit memory recognition and the WLM test.

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