An eigenvector-based EEG analysis method for diagnosing neurodegenerative and neuropsychiatric diseases and for monitoring and assessing treatment response

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Background

The importance of biomarkers in diagnosing Alzheimer's disease (AD) is well known, but the use of biomarkers for tracking disease progression has been challenging due to complex relationships between biomarkers and clinical endpoints in treatment trials. Abnormalities in the electroencephalogram (EEG) and specifically event related potentials (ERPs) associated with AD show promise as diagnostic, prognostic and progression biomarkers of AD due to their closer association with cognition and other clinical manifestations of the disease. To evaluate ERPs in AD, we used a patented eigenvector-based method on data in patients with AD and in healthy controls.

Initial testing demonstrates that the method has substantial power in discriminating between experimental conditions within a single subject and within a single brain location. F-ratios within-subject tests are very high (up to 37020.4 as shown in Table 1), indicating that the error term is a tiny fraction of the signal. This indicates that diagnosis through electrical signal processing may be possible with EEG/ERP. In addition, it suggests that this method could be used to discriminate between populations of subjects .

Table 1: Analyses showing within patient variability for a typical male (male A) and a male with low ML performance at 3 locations (red circle)

Table 1
Twenty MANOVA Analyses of the Effects of the Experimental Conditions, ML and PA, at Each of the Five Electrode Locations for Each of the Four Male Subjects (Note the relatively low ML performance for Male B at three locations.)

			Cz			Fz			Oz			T3			T4		
Subject	DepVar	Ind Var	F/L*	*p*	R^2	F/L*	*p*	R^2	F/L*	*p*	R^2	F/L*	*p*	R^2	F/L*	*p*	R^2
Male A	rasd1(ml)	ML	1272.3	<.0001	.9964	12338.2	<.0001	.9997	9028.5	<.0001	.9993	66.5	<.0001	.9476	137.1	<.0001	.9747
		PA	0.0	.8411	.0000	0.0	.9474	.0000	1.5	.2729	.0001	0.0	.9286	.0001	0.0	.8414	.0002
	rasd2(pa)	ML	0.2	.8318	.0009	0.3	.7896	.0009	0.0	.9614	.0007	0.2	.7975	.0001	0.1	.9112	.0002
		PA	426.2	<.0001	.9849	515.6	<.0001	.9843	93.5	<.0001	.8692	7303.9	<.0001	.9989	1061.9	<.0001	.9912
	Multivariate	ML		.00147	<.0001	.9985	.00020	<.0001	.9998	.00005	<.0001	1.0000	.00053	<.0001	.9995	.00647	.0005	.9935
		PA		.00924	.0002	.9908	.01053	.0002	.9895	.00754	.0001	.9925	.00001	<.0001	1.0000	.00172	<.0001	.9983
Male B	rasd1(ml)	ML	19.6	.0023	.7974	51.1	.0002	.9228	16.5	.0036	.7744	620.4	<.0001	.9932	11.2	.0095	.6463
		PA	0.0	.9617	.0001	0.0	.9722	.0000	0.0	.9820	.0000	0.1	.7277	.0001	0.1	.8069	.0019
	rasd2(pa)	ML	1.0	.4350	.0001	0.5	.6297	.0003	0.7	.5276	.0001	0.2	.8367	.0009	1.6	.2733	.0091
		PA	37020.4	<.0001	.9997	3646.9	<.0001	.9978	11526.3	<.0001	.9993	395.1	<.0001	.9832	337.7	<.0001	.9469
	Multivariate	ML		.06591	.0413	.9341	.03868	.0160	.9613	.11895	.1120	.8810	.00028	<.0001	.9997	.12851	.1269	.8715
		PA		.00010	<.0001	.9999	.00143	<.0001	.9986	.00051	<.0001	.9995	.00097	<.0001	.9990	.01632	.0005	.9837

Analyses were performed to discriminate the following populations:
1) Males vs Females (Figure 1A and Figure 1B)
2) Clinical Depression vs Normal Individuals (Figure 1C)
3) Individuals with OCD vs Normal Individuals (Figure 1D)

Two different cognitive tasks were used to elicit responses:
A) Sternberg Memory-Search Paradigm (Difficult), and
B) Visual Oddball Paradigm. (Easy)

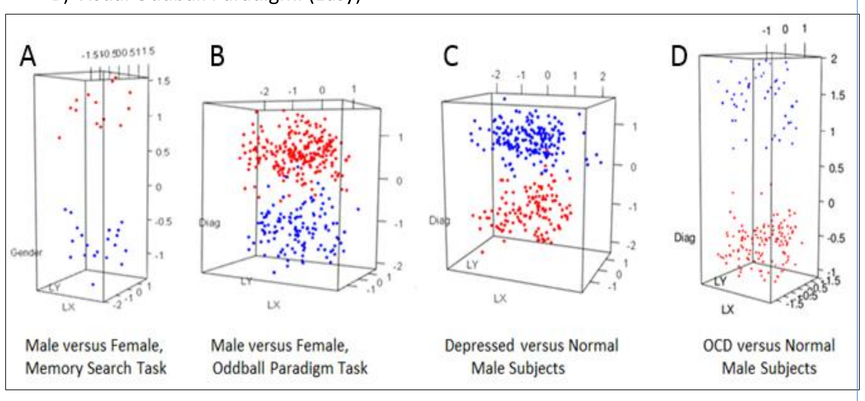

Figure 1. 3D scatterplots A and B are comparisons of the differentiation of male and female subjects. Scatterplot B is an oddball paradigm task which is compared to scatterplot A's more cognitively demanding memory search task. Scatterplots C and D show discrimination with the oddball task for clinically depressed versus normal (C) and OCD versus normal.
The vertical dimension in each figure is factor scores on the relevant detection dimension (male vs female; depressed vs normal; OCD vs normal), and the two horizontal axes are left vs right electrode location (LX) and front vs back location (LY).

Figure 1 shows significant discrimination between persons of various categories, particularly with a strong cognitive task, like the Sternberg memory-search paradigm. Panel A of Figure 1 shows that males have a substantially different cognitive process in memory search than do females, $F(1,33)=579.84$, $p<.0001$, $R^2=.946$. Panel B of Figure 1 shows that the discrimination between females and males is not nearly so strong for the simpler and weaker oddball paradigm task, $F(1,382)=1556.54$, $p<.0001$, $R^2=.803$, although the discrimination is still very strong. When testing clinically depressed males compared to healthy males using the oddball task, we see in Panel C of Figure 1 that the discrimination between the two groups is very strong, $F(1,318)=1802.31$, $p<.0001$, $R^2=.850$, and the discrimination between OCD males and healthy controls is even stronger, even though it is here tested with the weaker task (oddball paradigm), $F(1,178)=1939.76$, $p<.0001$, $R^2=.916$.

An additional analysis has been performed to discriminate:
4) High Performing Students vs. Low Performing Students using the Visual Oddball Paradigm.

The method discriminates even more subtle differences between subjects, as shown in Figure 2, where we see a high level of discrimination between college students with GPAs above 3.5 and those on academic probation. The difference between groups is somewhat strong for females [$F(1,574)=831.29$, $p<.0001$, $R^2=.592$], but substantially stronger for males [$F(1,702)=2178.69$, $p<.0001$, $R^2=.756$].

Figure 2: Discrimination of High and Low Performing Students at BYU

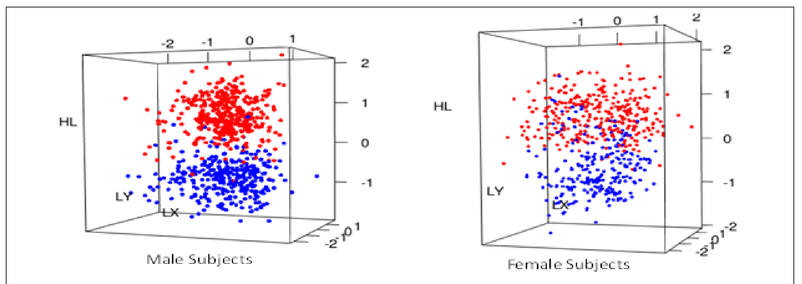

Figure 2. Three-dimensional scatterplots of male and female subjects from the Wolf study of the differentiation of high performing students (3.5 GPA and above, red data points) and low performing students (academic probation, blue data points) using a simple oddball paradigm task. The vertical dimension in each graphical object is factor scores on high vs. low academic performance, and the two horizontal dimensions are the factor scores on left vs. right electrode location (x axis) and front vs. back location (z axis).

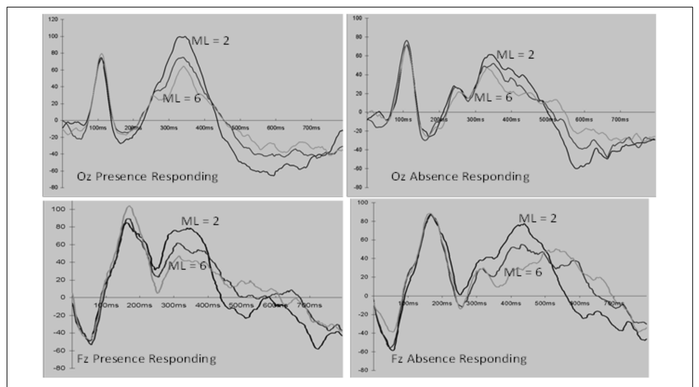

Figure 4. Summary averages over all seven subjects, showing the effects of memory load (ML=2, 4, or 6 digits). The two left panels show the effects of ML for presence responding, the Oz location on top and the Fz location on the bottom. The right two panels show the same information for the absence responding condition.

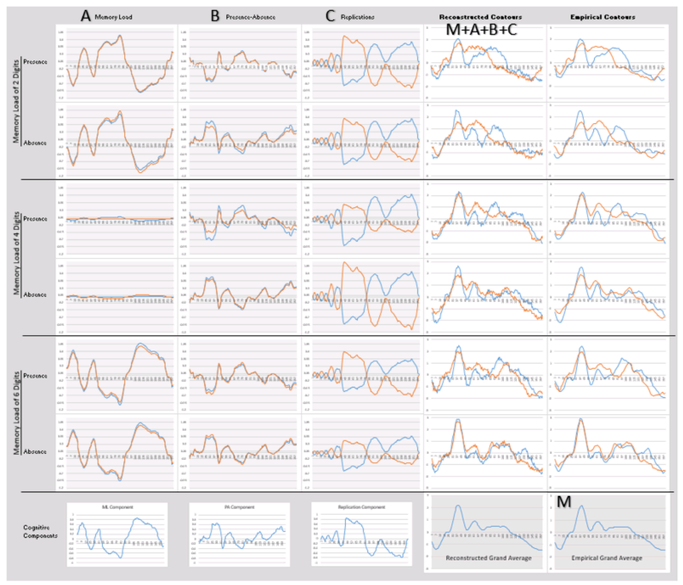

Figure 5. Decomposition table of graphs for subject Male A, electrode location Cz, showing the decomposition and reconstruction of the twelve empirical waves from the three cognitive components, memory load (ML), presence versus absence responding (PA), and replications. The shapes of the three cognitive components for this subject at this location are shown in the bottom left three graphs. These cognitive components have strong diagnostic capabilities.

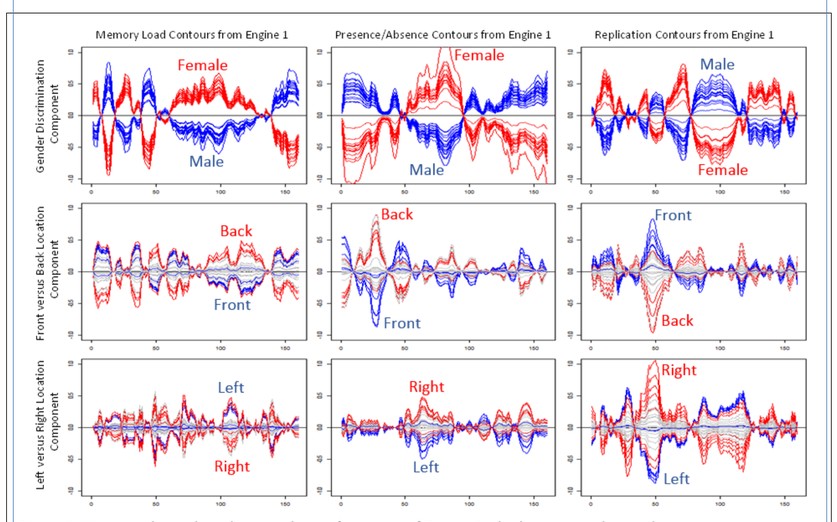

Figure 6. Nine envelope plots showing the performance of Engine 2, the between-subjects diagnostic engine, in discriminating between male and female subjects, front versus back electrode locations, and left versus right electrode locations, in the Sternberg memory search study. Each envelope plot has thirty-five contours, color coded to highlight each contrast (male/female, front/back, and left/right).

Methods

Subjects: The original sample was obtained from Neuronetrix and consisted of 99 subjects with probable mild AD diagnosed according to NINCDS-ADRDA criteria and 100 age-matched healthy controls. Inclusion criteria for the AD cohort included MMSE 21-26, CDR 0.5, 1 or 2, and low performance on education adjusted Wechsler Logical Memory II. Inclusion criteria for the HC cohort were MMSE 27+, CDR 0 and normal performance on education adjusted Wechsler Logical Memory II.

EEG: We used EEG data from three conditions obtained from seven electrode locations (Fz, Cz, Pz, F3, F4, P3, P4, 10-20 International System) collected at eight ms intervals over 1184 ms, starting 240 ms before an auditory oddball stimulus and ending 944 ms after the stimulus. We extracted three cognitive components for each subject, one for the contrast between the target stimulus and the other two stimuli, one for front versus back electrode locations, and one for left versus right electrode locations. We next analyzed these eigenvectors to extract second-level cognitive components showing the differences between AD subjects and healthy controls for each of the three conditions.

Results

The final sample consisted of 75 AD subjects and 95 healthy controls. All three second-level cognitive components discriminated between AD and healthy controls - target versus others: $F(1,168)=81.02$, $p<0.0001$, $R^2=.3254$, front versus back: $F1,168)=53.24$, $p=0.0001$, $R^2=.2406$, and left versus right: $F(1,168)=123.07$, $p<0.0001$, $R^2=.4228$. A multivariate test of the three-dimensional pattern of these combined cognitive components also discriminated between the two groups: Wilks' lambda = .4297, $p<0.0001$, $R^2=.5703$.

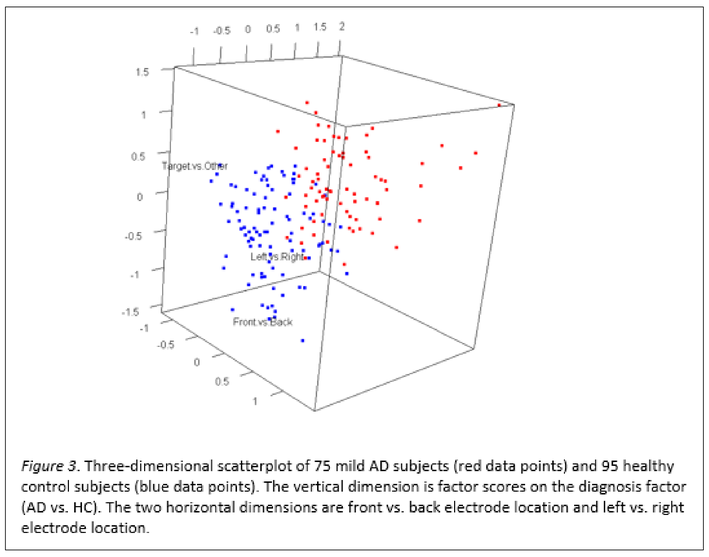

Figure 3. Three-dimensional scatterplot of 75 mild AD subjects (red data points) and 95 healthy control subjects (blue data points). The vertical dimension is factor scores on the diagnosis factor (AD vs. HC). The two horizontal dimensions are front vs. back electrode location and left vs. right electrode location.

Visual inspection of the scatterplot in Figure 3 shows that the best separation between the AD subjects and the healthy controls is along the axis corresponding to left versus right electrode location. The next best separation is along the vertical axis, the one corresponding to target stimulus versus other. The separation is substantially weaker along the third axis, the one extending from the back of the figure to the front, and corresponding to front versus back electrode location.

By multiplying the vectors for the contours of the three components by the mean coefficients of the AD and healthy controls, we constructed envelope plots for each of the three second-order cognitive components calculated to maximally discriminate between the AD and the HC groups. The envelope plots show the points of major and minor contrast between the AD and HC group at each temporal location along the X axis. The major contrast for the cognitive component based upon target versus other (Panel A) is in the region between 336 and 640 ms, which is slightly to the right of the common location for P300. The major contrast for the component based upon front versus back electrode location is to the right of 752 ms and is negative for AD. For the component based upon left versus right electrode location, major contrasts are located in two adjoining regions, the first between 360 and 632 ms and the second from 632 ms to about 832 ms.

Conclusions

This eigenvector-based method of analyzing ERPs accurately discriminated between subjects with mild AD and healthy age-matched controls and may be a useful biomarker to identify and potentially track AD. The discrimination between subjects based on the target stimulus suggests a difference in cognitive processing between the two groups. The left-right location discrimination could be due to asymmetrical pathological changes between right and left cortical areas or to pathological changes in neural connections between the two cerebral hemispheres, whereas the front-back location discrimination suggests the possibility of cortical disconnection. Results should be substantially better with a more complex task such as Memory Search.

Further research investigating this method longitudinally as well as in healthy subjects at risk for AD and subjects with mild cognitive impairment is needed.