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Evidence for terminal decline in the event-related potential of the brain

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Summary Precipitous decline (terminal decline) characterizes changes in the elderly just prior to death. The neurological and temporal parameters of terminal decline are not defined. The present study compared sensitive changes in the brain event-related potential (ERP) in 7 subjects who died within 1 year of evaluation with matched controls. Cross-correlation of annual ERPs revealed disorganization within and between subjects in response to memory dependent conditions but not in response to a novel stimulus (oddball). Motor reaction time to targets was not sensitive to decline. The changes associated with impending death were restricted to decline in reliability of the ERP within 1 year of death.

Key words: Event-related potential; Brain; Terminal decline; Precipitous decline; (Elderly)

Gradual decline during senium attributed to age is believed to be an artifact of cross-sectional design (Jarvik and Falek 1963; Riegel and Riegel 1972). Instead, changes among the elderly with advancing age are proposed to be precipitated by the “physical state or health” of the subject (Kleemeier 1962; Rowe and Kahn 1987). Since the initial observation of Kleemeier (1962), several studies (Birren 1965; Blum et al. 1973; Botwinick et al. 1978; Siegler et al. 1982; White and Cunningham 1988; Johansson and Berg 1989) have reported precipitous cognitive decline just prior to death (terminal decline). However, the specificity of terminal decline has not been determined. For instance some reports suggested that verbal abilities were uniquely sensitive to terminal decline (Blum et al. 1973; Siegler et al. 1982; White and Cunningham 1988), others (Kleemeier 1962; Botwinick et al. 1978) found that performance or psychomotor abilities deteriorated just prior to death, and some (Berg 1987) postulated that terminal decline was pervasive.

The sensitive interval for observing terminal decline is unknown. A comprehensive study by Johansson and Berg (1989) compared digit span in *groups* of elderly subjects tested at 5 year intervals. Performance declined for all groups during the 5 year interval before death regardless of the subject's age. Terminal decline also has been observed within a 2 year interval in both longitudinal (Kleemeier 1962) and cross-sectional

(White and Cunningham 1988) studies. Apparently shorter intervals have not been examined but White and Cunningham (1988) suggested that terminal decline may be evident in *individuals* before 2 years.

The present longitudinal study investigated cognitive changes within 1–3 years of death using the computer assisted analysis of the event-related potential (ERP) of the brain. An analysis sensitive to changes in the shape of EEG wave forms (phase) was used to detect evidence of terminal decline.

Methods

Subjects

Subjects were selected from 159 healthy elderly individuals participating in a study on effective aging. A non-survivor group (NSG) was comprised of 7 subjects who died during the study but had been tested for at least 2 consecutive years and within 1 year of death. At the time of testing and until the time of near death, these subjects were living independently and were healthy according to yearly physical examination. Cancer accounted for the cause of death in 5 cases, heart failure was the cause of death in the other 2 cases. A survivor group (SG) served as control. The SG consisted of 7 patients carefully matched with the NSG group for entry criteria including age, gender, time in the program and psychometric profile (see Table I).

Upon entry to the study all subjects were administered the digit span, digit symbol and vocabulary tests of the WAIS-R. There were no differences between

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TABLE I

Description of the subjects.

	ID number	Age	Sex
Non-survivors	34	72	F
	64	76	F
	82	78	F
	83	77	M
	101	73	F
	151	79	F
	192	70	M
Survivors	28	67	F
	63	73	F
	98	68	M
	103	78	M
	104	74	F
	144	77	F
	146	73	F

the groups on any of the tests (digit span: $t = 0.65$, $P = 0.53$; vocabulary: $t = 0.35$, $P = 0.73$; digit symbol: $t = 1.68$, $P = 0.12$).

Procedure

Subjects were tested in an electrically shielded, sound attenuating chamber and reclined in a comfortable chair as electrodes were applied to the scalp. Binaural headphones were placed over the ears and white noise (72 dB) from floor speakers masked extraneous noise. Subjects were monitored continuously with video and audio equipment. In a dual rare-event procedure (Sandman et al. 1990) target tones were presented either at predictable (Fixed, 450 Hz) infrequent intervals (every eighth tone), at identical (1:8 ratio), infrequent but unpredictable (Random, 600 Hz) intervals, or at frequent (Common, 550 Hz) intervals (6:8).

An example of the stimulus sequence is:

CCCRCCCCFCCCCCCCCFRRCRCCCCCF

where F = predictable infrequent (fixed); R = unpredictable infrequent (random); C = frequent (common).

The pure tones were 94 dB SPL with 100 msec duration and a rise time of 50 msec. Pretesting at each session determined that all subjects included in the analysis were able to discriminate the tones. Subjects were given practice to depress a hand held key each time they heard the random target (matched to the dominant hand) or the fixed target (matched to the non-dominant hand). They were instructed not to respond to common tones. Event-related potentials and reaction time (RT) were measured while the subjects listened to the tones with their eyes closed. They were monitored continuously with an audio/visual system.

EEG procedures. Recordings were made with a Grass polygraph, Model 79, with amplifier settings at 0.30 Hz and 100 Hz. Data were digitized and stored for off-line analysis on a MINC 11/23 computer (Digital

Equipment Corp). Tones were presented by a micro-computer interfaced with PDP system. Gold cup electrodes filled with EC-2 creme (Grass) were placed according to the international 10–20 system at Fz, Cz and Pz referenced to linked mastoids. Electrode impedances were matched within 1 k Ω and all were below 10 k Ω .

Event-related potential analysis. The EEG was sampled at 200 Hz. Baseline was determined by a 280 msec prestimulus average. Wave forms for 44 sequences of random, fixed and common tones were collected and averaged. Integrated wave forms were generated by averaging each cluster of four 200 Hz sampled points. Phase error was corrected by using a moving average. An analog filter conditioned the signal prior to digitization (12 dB/octave, 3 dB at 100 Hz), minimizing aliasing errors at 200 Hz and the phase error at 25 Hz.

Artifact rejection. Trials contaminated by eye movement were automatically rejected by computer software. The efficacy of the rejection system was determined by separately testing subjects asked to make lateral eye movements (eyes closed) to a series of 10 tones in each condition. Eye movement was verified by electrodes attached to the outer canthus and suborbit referenced to linked mastoids. The software system correctly identified 98.4% of the lateral eye movements in the EEG.

Trials were repeated automatically if reaction times to fixed or random target rare tones exceeded 1500 msec, if subjects pressed the wrong key or a key to the common tone, or because of artifact in the EEG. An artifact was defined as a response contaminated with eye-blinks or muscle movement or a response exceeding 50 μ V or less than 50 μ V. No subject had more than 3 trial sequences repeated and fewer than 2% (< 1 trial/subject) of the trials across all subjects were repeated.

Results

ERP wave form reliability

Reliability of the ERP for each subject was measured by cross-correlating waves (Pearson-Product Moment) for consecutive years at 16 msec intervals in each condition (i.e., fixed, random, common) at Pz (cf., Fabiani et al. 1987). Each subject had $n - 1$ (n = years tested) coefficients. High coefficients reflected stable phase (temporal) characteristics of the wave form over years independent of absolute amplitude.

Wave form stability declined the year before death for subjects in the NSG (Fig. 1). This reflects changes in the *shape* of the wave form within 1 year of death but not before. The wave forms of the SG were highly reliable (average $r = 0.87$) indicating that they remained highly stable over consecutive years. Coeffi-

Fig. 1. Reliability of the ERP on successive years calculated from Pz in fixed, random and common conditions. Each point on the abscissa represents the correlation of 2 years (e.g., years 1 with 2, years 2 with 3, etc.). The label "Years" refers to time in the study (number of successive years tested) not the time from death. The data presented are averaged cross-correlation coefficients for consecutive years for non-surviving and matched surviving elderly subjects. The results indicate that cross-correlation of the ERP dropped precipitously, especially in the common and predictable (i.e., fixed) conditions, as subjects approached death (see Fig. 2). Because subjects died at different points in the study there are different numbers of subjects as time increases (see Fig. 2).

cients were converted to *z* scores, across subjects and tested for differences between the NSG and SG. Wave forms of the non-survivor group matched with the SG group were significantly less reliable for the frequent tone ($t = 2.40$, $P = 0.03$, $df = 12$) and the infrequent fixed ($t = 2.67$, $P = 0.02$, $df = 12$) and random ($t = 2.54$, $P < 0.03$, $df = 12$) targets. This effect reflected the precipitous decline in reliability for *all* subjects in the NSG 1 year prior to death (Fig. 2) for the common tone and fixed target. Although the ERP to the random target was less stable in the non-survivors, it was more stable ($r = 0.82$) in this group than either the ERP to the fixed target ($r = 0.69$) or the common tone ($r = 0.53$). The ERP for *all* subjects in the SG either remained stable or increased in reliability over time. The apparent increase in stability in the NSG in the fixed condition at year 3-4 is a cohort effect due to subjects 34 and 64 who show a clear decline in their individual data (Fig. 2).

Wave form differences

Two exploratory, stepwise discriminant function analyses (SDFA) of the ERP were computed. The purpose of the first analysis was to determine if the two groups could be distinguished, and what part of the wave contributed to the separation. The ERP within 1 year of death in the NSG was compared with the ERP of the matched SG at Pz and Fz. The results are presented in Fig. 3 and Table II. Separation of the groups based on the ERP was significant for the fixed target at both Fz and Pz. Only one subject in the NSG was mis-classified. The difference between the groups was due primarily to smaller early components (within 100 msec) over Fz and smaller late components over Pz

Fig. 2. These data are identical to Fig. 1, except they are presented for each individual subject. This figure illustrates the precipitous drop in correlation for *every* non-surviving participant. The last point on the graph for non-surviving subjects indicates the year that they died. For instance, subject 82 died during year 3 (thus has correlations between years 1 and 2, and between years 2 and 3). Subject 34 died during the fourth year of the study and has 3 correlation coefficients plotted. From this figure it is clear that surviving subject 28 is responsible for the slightly lower correlation between years 1 and 2 among survivors in the Fixed condition presented on Fig. 1. However, unlike the non-surviving subjects, the correlation increases over time in subject 28.

Fig. 3. Group averaged event-related potentials over Pz and Fz for the non-survivors 1 year prior to death ($n = 7$) and the matched survivors ($n = 7$) for the fixed, random and common condition. The numbers along the wave form reflect the order of the intervals selected as determined by stepwise discriminant function analysis (e.g., an interval with a "1" is the first variable to enter the equation, "2" is the second variable to enter, etc.). An * indicates that the variable is statistically significant (see Table II).

TABLE II

Stepwise discriminant function, NSG 1 year prior to death (n = 7) and matched SG (n = 7).

Pz	Significance	Fz	Significance
<i>Fixed condition (msec)</i>			
576	0.05	80	0.05
528	0.05	192	0.05
400	0.05	16	0.01
256	0.001	64	0.01
<i>Correct classification (%)</i>			
	NSG		NSG
NSG	85.7		85.7
SG			100
	SG		100
<i>Random condition (msec)</i>			
256		528	
432	0.05	544	0.05
144	0.05	256	0.05
192	0.05	224	0.05
<i>Correct classification (%)</i>			
	NSG		NSG
NSG	71.4		85.7
SG			71.4
	SG		85.7
<i>Common condition (msec)</i>			
592	0.05	464	
112	0.05	192	
48	0.05	224	
608	0.05	240	0.05
<i>Correction classification (%)</i>			
	NSG		NSG
NSG	71.4		85.7
SG			71.4
	SG		71.4

in the NSG. ERPs to the frequent tone distinguished the groups only at Pz involving larger early (P1) and smaller late components in the NSG.

Fig. 4. Group averaged event-related potentials over Pz and Fz for the non-survivors 1 year and 2 years prior to death (n = 7) in the fixed, random and common condition. The numbers along the ERP indicate the order of variables selected to discriminate between 1 and 2 years before death. An * indicates that the variable selected is statistically significant (see Table III).

TABLE III

Significant stepwise discriminant function, NSG 1 year (n = 7) and NSG 2 years (n = 7) prior to death.

Pz	Significance	Fz	Significance
<i>Fixed condition (msec)</i>			
80	0.05	80	0.05
400	0.05	496	0.05
		224	0.01
		288	0.01
		240	0.01
		176	0.01
<i>Correct classification (%)</i>			
	1 yr	2 yrs	1 yr
NSG 1 yr	85.7		85.7
NSG 2 yrs		85.7	
			85.7
<i>Common condition (msec)</i>			
112	0.05		
192	0.05		
464	0.001		
432	0.001		
368	0.001		
48	0.001		
<i>Correct classification (%)</i>			
	1 yr	2 yrs	1 yr
NSG 1 yr	100		85.7
NSG 2 yrs		100	
			85.7

The second SDFA compared the ERP of the NSG 1 and 2 years before death. As illustrated in Fig. 4, amplitude of early components of the ERP to the fixed target was smaller 1 year from death at both Fz and Pz (Table III). Consistent with the first SDFA, significant differences were apparent at Pz but not Fz to the frequent tone, and the ERP was not influenced by proximity to death in the random condition.

Reaction time analysis

Reaction times to the fixed and random targets were not significantly different between groups and were not significantly different 1 and 2 years before death in the NSG (Table IV).

TABLE IV

Reaction time 1 yr prior to death in the NSG compared with matched

	NSG	SG	P value
Fixed	740.2286 ± 280.5322	654.6429 ± 183.1752	0.5140
Random	788.7286 ± 195.2349	727.8428 ± 165.0090	0.5407

Reaction time in the NSG 1 yr and 2 yr prior to death

	1 yr prior	2 yr prior	
Fixed	740.5586 ± 280.5322	674.6286 ± 195.4500	0.6220
Random	788.7286 ± 195.2349	762.7429 ± 115.6944	0.7683

Discussion

The ERP is typically very reliable over days (Fabiani et al. 1987), months (Lewis 1984; Karniski and Blair 1989) and even years as reported for the control group in this study. Cross-correlation of the ERP wave form produces an objective measure of stability independent of specific components and of subjective scoring criteria (Lewis 1984). Loss of reliability within subjects typically suggests the presence of *structural or systemic influences* and not random fluctuations in measures of brain activity (Fabiani et al. 1987; Kileny and Peters-Kripal 1987; Karniski and Blair 1989).

In the current study, longitudinal analyses of ERP reliability produced new evidence in support of terminal decline. Decreasing reliability of the ERP characterized responses of all the non-survivors the year prior to death in conditions with predictable or frequent stimulation. The ERP was extremely reliable and even increased in the carefully matched survivors. Imminent death possibly was the *systemic influence* in the NSG and apparently was responsible for the change in ERP organization.

ERP stability was fragile and sensitive to decline in response to both targets and to the frequent tone. Stable responses were evident 2 years before death in NSG and for all comparisons in the SG. However, the ERP of the NSG became disorganized and unstable the year before death. The ERP to the random target was significantly more stable in the SG, however, compared with the fixed target and the frequent tone, responses to novelty were significantly more reliable across years including the year before death. These findings are consistent with the report of higher reliability of the ERP when challenged with rare or target tones, probably because of a more favorable signal-noise ratio compared with frequent or predictable targets (Fabiani et al. 1987). The ERP was most reliable and least affected by terminal decline in the random condition which had both rare and target tone features suggesting that the nervous system even in decline apparently can respond to a novel challenge.

However, the cross-correlation method may lead to erroneous conclusions about imminent death. For instance subject 144 in the survivor group (see Fig. 2) exhibited the instability pattern of the non-survivors. Subsequent follow-up revealed a very active 80-year-old woman who, shortly after the last test, lost her husband. It is conceivable that the ERP is sensitive to significant life stress including imminent death of a spouse. If the usual pattern of stress surrounding imminent death is followed (Datan et al. 1987), subject 144 is at risk for decline.

The application of exploratory stepwise discriminant analysis of the wave form differences in this small sample produced marginal indications for terminal de-

cline. Compared with the NSG, ERPs of the survivors maintained late positivity at Pz in all conditions. As expected (Pfefferbaum et al. 1984), in response to the novel target, the survivors had greater positivity over Pz. The decrease in positivity and loss of topographic identity in the NSG are consistent with lifespan trends that may reflect structural changes (Pfefferbaum et al. 1980).

Early positivity (around the latency of P1) was larger at both Fz and Pz for the non-survivors in the common condition. Increasing P1 has been reported in normal aging to reflect reduced cortical inhibition and decreased ability to habituate (Shagass 1972; Dustman and Shearer 1987). The effect in the NSG may be an exaggeration of this observation and indicate that previous studies of normal aging included subjects near death.

There were no differences between survivors and non-survivors on any of the behavioral measures. Reaction time to the target tones and the WAIS-R subtests (digit span, digit symbol, vocabulary) did not distinguish the survivors and non-survivors. Other studies of decline using these measures typically reported group effects in very large samples. It is possible that either these tests are not sufficiently sensitive to terminal decline to detect changes in individuals or their discriminating power is absorbed by normal aging (Birren 1965; Jarvik and Blum 1971; White and Cunningham 1988).

Although the sample was small, the reliability of the ERP declined just prior to death for *all* 7 non-survivors. This evidence of terminal decline was in contrast to the robust stability of the ERP in the survivor group. The parameter of reliability that was sensitive to terminal decline related to perception of usual events. However, responses to stronger, perhaps biologically significant (Lynn 1966), novel stimulation remained relatively reliable even as the subject approached death. Future studies should evaluate carefully the nature of environmental challenges before concluding the presence or significance of terminal decline among the elderly.

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