times τ_P) after tetanus, at which time the PTP component should have become negligible.

We conclude that LTP is present in the sympathetic ganglion and is thus not a unique property of hippocampal synapses. The unique feature of LTP is the long duration of increased synaptic efficacy (hours) after brief (seconds) stimulation. Although this aspect of LTP is similar in the ganglia and the hippocampus, it is not known whether the underlying mechanisms are similar. The sympathetic ganglia should provide an easily accessible preparation with which to study this phenomenon and determine its role in nervous system function. The possible normal physiological role of activity-dependent synaptic plasticity in the sympathetic ganglion has been discussed elsewhere (*19*).

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10. We used 0.5-msec square voltage pulses with amplitudes 50 percent larger than those required to yield the maximal postsynaptic response. By using supramaximal stimulation, we hoped to minimize possible posttetanic recruitment of afferents.
11. In these experiments we used 0.5 to 1.0 m*M* $CaCl_2$ and 1.2 to 2.2 m*M* $MgCl_2$.
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14. The four parameters in Eq. 2 were obtained as follows. The terminal exponential decay of $I(t)$ was fitted by the expression $L\exp(-t/\tau_L)$ using a least-squares regression analysis. This gave what we have termed the magnitude L (the extrapolated zero-time intercept) of the slow component and its decay time constant τ_L. The values of this expression at earlier times were then subtracted from the original data and the resultant peeled differences were then similarly fitted by a second exponential $P\exp(-t/\tau_P)$. This yielded the magnitude P (zero-time intercept for the peeled differences) of the fast component and its decay time constant τ_P.
15. We have followed the convention of Magleby and co-workers (*8*, *13*) in identifying the kinetic component with a decay time constant on the order of a few minutes as PTP. We use the term LTP to refer to any increase in the efficacy of synaptic transmission that (i) can be produced by brief presynaptic tetanic stimulation (10 to 30 seconds) and (ii) is associated with a decay time constant or duration at least a decade longer than that associated with PTP (Table 1).
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Onset and Offset of Brain Events as Indices of Mental Chronometry

Abstract. *Analysis of single-trial electroencephalogram waveforms in a reaction time task demonstrated that the onset and offset values of event-related potentials can be used as indices of the duration of information processing. Two negative waves have been identified which peak at different times in different regions of the scalp, with the second overlapping the last part of the first. These waves are related in different ways to the duration of perceptual processing.*

Mental chronometry in humans is an important issue in cognitive psychology (*1*). Progress in its understanding has been made through electroencephalogram (EEG) studies, particularly those concerning the endogenous P300 or P3 wave (*2*). However, the P300 is preceded by a negative wave, N200 or N2. The peak latency of both waves was reported to covary with perceptual processing (*2–4*).

We report the existence of two types of N200 waves, which are related in different ways to the same behavioral response; the duration of one increases with reaction time, and that of the other remains constant. These results provide clues to the different functions of the waves and may help in the conceptualization of information processing in humans.

The N200 wave can be isolated for observation by removing the overlapping sensory P2 component; this can be accomplished by omitting an expected stimulus and rendering the omission relevant for the subject. However, even after the occurrence of a relevant stimulus, N200 can be isolated by subtracting the evoked potential obtained in a passive situation (*5–7*). Both subtraction and omission studies have shown that N200 may be a better index than P300 of the temporal course of information processing related to stimulus evaluation and sensory-motor decision. In contrast to P300, which sometimes peaks after the behavioral response, N200 always precedes the response (*3*, *4*). Furthermore, unlike the P300, the distribution of N200 on the scalp varies with stimulus modality (*6*, *8*, *9*).

Two types of N200 have been described for the visual modality: one is central and the other parieto-occipital. They were observed in both reaction time and counting tasks and therefore cannot be attributed to the movement-

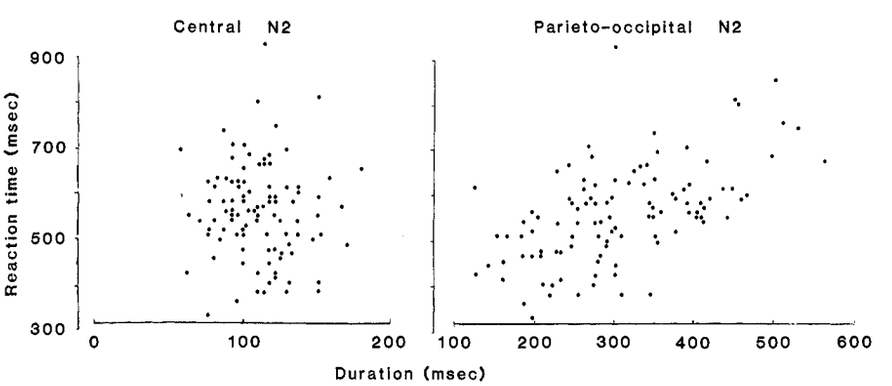

Fig. 1. Duration of Cz:N265 (left) and of POz:N220 (right) as a function of the reaction time of seven subjects during 107 trials.

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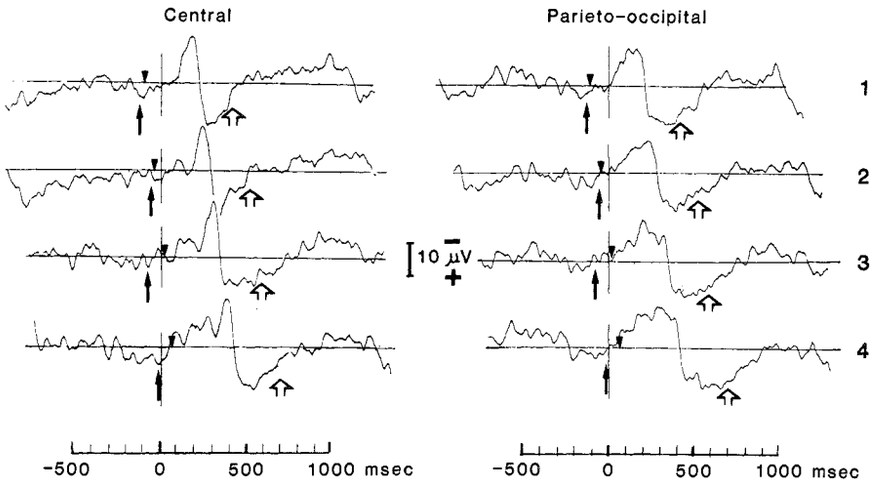

Fig. 2. Grand means of the EEG recorded at Cz (left) and POz (right) time locked to the offset of each N200 wave. Latency-corrected average potentials were obtained for each RT quartile (26 trials for 1 and 27 for 2, 3, and 4). On the time scale 0 indicates the onset of POz:N220. Onsets of Cz:N265 are from quartile 1 to 4: 101 msec, 187 msec, 214 msec, and 320 msec, respectively. The reproduced rhythm is indicated by the thin black arrows, the reaction time by the wide white arrows, and the time of the omission by the black triangles. The records illustrate (i) the covariation of the peak latency of Cz:N265 and of the duration of POz:N220 with RT, and (ii) the absence of variation of Cz:N265 duration as a function of RT.

related potentials (*4, 7–10*). Simson *et al.* (*6–8*) and Renault and Lesèvre (*4*) pointed out that the onset of the parieto-occipital N200 is simultaneous with the omission of the visual stimulus, but the two events have not been measured in the same experiment. We therefore studied the relation of the onset and offset of the two N200's and the time of the expected stimulus and the behavioral responses. We assumed that if one of the negative waves reflected the onset of information processing, then its onset would covary with the time when the stimulus was expected. In addition, to the extent that the peak latency or offset of this wave varies with the duration of the information processing, the duration of the N200 should increase when the behavioral output is delayed.

The onset and offset latencies of the two N200's were measured in experimental data previously reported (*4*). Seven normal adults were asked to fix their gaze on the center of a screen on which 20° checkerboards appeared for 22 msec at a rate of one per second. Ten percent of 450 stimuli were omitted randomly (no two were omitted in succession). The subject's task was to tap a rhythm in synchrony with the stimuli presented. Each tap provided an indication of when the subject expected the stimulus to occur—the expected stimulus time. In addition, the subject was required to flex a finger (*11*) as rapidly as possible after detecting an omission in the stimulus train—the reaction time (RT) to the omitted stimulus.

The N200's and P300's at Cz and POz (a point located midway between Pz and Oz) were measured in spatiotemporal maps of single trial EEG's by two independent investigators who were unaware of the subjects' behavioral responses. The N200's were identified in 85 percent of the trials. The 107 trials used for subsequent analyses were those on which the two investigators made identical measurements of two distinct N200 waves followed by two distinct P300 waves (*12*).

In contrast to the P300's, the N200's always preceded the motor response. In spite of the overlap in space and in time, the two waves labeled POz:N220 and Cz:N265 (*13*) differed significantly in mean (± standard deviation) onset latencies (16.2 ± 112.6 and 197.6 ± 91.7 msec), mean peak latencies (218.7 ± 109.7 and 264.9 ± 93.6 msec), mean peak locations (22.3 ± 7.3 and 52.4 ± 10.5 percent), and mean durations (305.7 ± 87.2 and 112.5 ± 30.3 msec) (*14*). The onset of POz:N220 varied from −182 msec before the stimulus omission time to 286 msec after it; the corresponding time of the reproduced rhythm ranged from −226 to 220 msec (mean, −54.9 ± 104.1 msec).

To test the apparent covariation of the two measures, product-moment correlations of the onsets of POz:N220 and of that of the reproduced rhythm were computed. For all subjects and all single trials pooled, the correlation coefficient (r) was .61 (*15*). Except in two instances Cz:N265 began after POz:N220. The interval between the onset of the N200 waves ranged from −30 to 434 msec (mean, 181.4 ± 96.3 msec); both waves ended at approximately the same time, with the difference between their offsets ranging from −152 to 160 msec (mean, 11.8 ± 49.9 msec). Furthermore, there was only a small correlation between the time of the rhythm and the Cz:N265 onset, whereas the onset and offset of POz:N220 and those of Cz:N265 were highly correlated (*16*). Therefore, the stage of information processing that starts with the reproduced rhythm seems to initiate the generation of POz:N220, and the underlying proceses reflected by this wave lead in turn to the generation of Cz:N265, which develops concurrently with the end of the POz:N220. An alternative explanation suggesting independent, parallel initiation of the POz:N220 and the Cz:N265 from the time of the reproduced rhythm is not consistent with the fact that the onset of the Cz:N265 did not covary highly with the time of the rhythm.

These results indicate that the beginning of the process that leads to omission detection is associated with the onset of POz:N220. Therefore, RT's were measured from this point. Product-moment correlations between RT's thus calculated and the trial-by-trial duration of each negative wave were computed (Fig. 1). Across subjects and trials, r = .57 and .09 for POz:N220 and Cz:N265, respectively (*17*). Measures of RT from the omission and the reproduced rhythm were also computed; in both cases correlations across subjects and trials were markedly reduced (*18*). This finding is consistent with the suggestion that the beginning of the information processing leading to a motor response is marked by the onset of POz:N220 and not by the omission or the reproduced rhythm. Besides, neither the duration or offset latency of Cz:N265 and POz:N220 nor the RT was consistently correlated with the time of the reproduced rhythm. We conclude that (i) the expected stimulus time of the subject determines only the onset of POz:N220, and (ii) POz:N220 provides an index of the duration of information processing, since its duration appears to be a determinant of RT.

Subtraction studies by Ritter (*19*) and Harter and Guido (*7*) indicated that a component resembling POz:N220 was associated with visual perception. In the case of the omission response, the processes underlying the behavioral output probably involve verification of the time estimation, identification of the stimulus, template matching, and response selec-

tion. The onset of POz:N220 occurred on the average 71.1 msec after the reproduced rhythm, and we assume that this interval included the verification of the 1 second that elapsed from the preceding visual stimulus. Therefore, the onset of POz:N220 might mark the beginning of the identification stage, and its offset either the end of template-matching or response selection (*20*). Thus the duration of POz:N220 may be considered an independent variable indicating on-line perceptual processing before P300 generation.

Although the duration of Cz:N265 did not vary with RT, its onset, peak, and offset latencies did (r = .58, .57, and .56, respectively). To show the effect of increasing RT on POz:N220 and Cz:N265 more clearly, the trials were averaged according to RT quartiles. The duration of POz:N220 and the peak latency of Cz:N265 were nearly twice as long in the fourth quartile as in the first (Fig. 2). It also appears that Cz:N265 (central sharp peak) occurred at the end of the parieto-occipital wave, which appeared between the reproduced rhythm and the subject's motor response.

The temporal relations between POz:N220 and Cz:N265 might aid in choosing between serial and parallel models of human information processing. Whatever underlying process is reflected by Cz:N265, probably orientation (*21*), it appears to be concurrent with the processes reflected by the last part of POz:N220 and sometimes with those responsible for the central initiation of the movement. However, these parallel processes are not independent since the onset and offset values of POz:N220 and Cz:N265 covary and are related to the motor response. Thus, from a theoretical point of view, the relationships between these cerebral and behavioral events support parallel contingent or cascade types of models (*22*). In the cascade model all processing stages operate continuously, and information, as it becomes available, is transferred from one to the next. In our view, a part of these information transfers and their subsequent processing could be reflected by the brain waves we have described.

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12. A number of maps did not show all four waves well; however, two negative foci followed by two positive foci appeared in the grand mean of 294 trials (free of artifact and eye movements), although they were not clearly differentiated. Because of the rapid potential changes between N200's and P300's, the offsets (zero crossing) of N200's were easily recognized. The parieto-occipital N200 onset was always the baseline zero crossing. The central N200 onset was more difficult to determine since this wave developed concurrently with the end of the parieto-occipital one. Thus both potentials added partially and the longer the parieto-occipital N200 lasted the more the onset of the central N200 was shifted away from the baseline. For this reason the beginning of the sharp central peak was not always a zero crossing.
13. These waves were labeled as recommended by E. Donchin, W. Ritter, and W. C. McCallum [in *Event-Related Brain Potentials in Man*, E. Callaways, P. Tueting, S. H. Koslow, Eds. (Academic Press, New York, 1978), p. 349].
14. The POz:N220 showed a significant statistical difference from the Cz:N265 (correlated, paired t-tests, $n - 1 = 106$) for onset latency (t = 12.9, $P < .001$), peak latency (t = 3.31, $P < .005$), peak location (t = 24.3, $P < .001$), and duration (t = 21.6, $P < .001$).
15. The correlation, number of trials, and two-tailed P values, when statistically significant, for each subject were: M.M., .81, 22, $P < .001$; H.L., .36, 14; J.F., .39, 14; J.P.J., .69, 8; C.M., .26, 18; R.R., .21, 21; B.R., .25, 10; and all trials, .61, 107, $P < .001$.
16. Correlations between rhythm and Cz:N265 onset: M.M., .30; H.L., .39; J.F., .27; J.P.J., .68; C.M., −.19; R.R., .22; B.R., .55; and all trials, .33. Correlations between onsets of both Cz:N265 and POz:N220: M.M., .49 ($P < .05$); H.L., .46; J.E., .56 ($P < .05$); J.P.J., .82 ($P < .05$); C.M., .52 ($P < .05$); R.R., .34; B.R., .50; all trials, .57 ($P < .001$). Correlations between offsets: .48, .46, .42, .89, .57, .41, .40, and .57 for all trials.
17. Correlations for POz:N220 and Cz:N265, respectively: M.M., .65 (P = .001), .04; H.L., .57 ($P < .05$), .06; J.F., .57 ($P < .05$), .51; J.P.J., .63, −.81 ($P < .05$); C.M., .48 ($P < .05$), −.26; R.R., .77 ($P < .001$), .38; B.R., .46, .09; and all trials .57 ($P < .001$), .09.
18. The values of r were −.04 and .33 for POz:N220 duration and .11 and .24 for Cz:N265.
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Dietary Restriction in Mice Beginning at 1 Year of Age: Effect on Life-Span and Spontaneous Cancer Incidence

Abstract. *Lifelong dietary restriction beginning at 3 to 6 weeks of age in rodents is known to decelerate the rate of aging, increase mean and maximum life-spans, and inhibit the occurrence of many spontaneous cancers. Little is known about the effects of dietary restriction started in middle age. In the experiments now reported the food intake of 12- to 13-month-old mice of two long-lived strains was restricted by using nutrient-enriched diets in accordance with the concept of "undernutrition without malnutrition." The mice on the restricted diet averaged 10 to 20 percent increases in mean and maximum survival times compared to the control mice. Spontaneous lymphoma was inhibited by the food restriction.*

Rats and mice given restricted diets from about the age of weaning (3 to 6 weeks) show extended mean and maximum survival times (*1*) and a decreased incidence or delayed onset of several diseases of old age (*2*). Other strategies for delaying aging in rodents (for example, administration of antioxidants or hormones) differ from weaning-initiated dietary restriction in that they do not cause clear-cut increases in maximum longevities (*3*) or inhibit age-related increases in mortality rates (*4*). Old rodents that have been subjected to restricted diets since weaning show more youthful physiologic (*5*) and immunologic (*6*) responses than do age-matched controls. Although underfed rodents consume fewer calories than control animals (25 to 50 percent less in most studies), intakes of other essential nutrients (such as vitamins, salts, and protein)

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