glutamyl-4-methoxy-2-naphthylamide, glycylglycine (free base), and Fast Blue BB as artificial substrate, peptide acceptor, and indicator, respectively (*11*).

In cocultures in which ME-2 cells were incubated upside down on C_6 cells, γ-GTP could be demonstrated in ME-2 cells within 24 hours (Fig. 1d). When the length of coculture incubation or the number of C_6 cells in the feeder layer or both were varied, the appearance and intensity of γ-GTP reaction were dependent on time and C_6 cell density. The enzyme concentration, as indicated by intensity of staining, increased with increasing incubation time and, for a standard induction period (24 or 96 hours), the enzyme concentration increased with increasing C_6 cell density. If cycloheximide (100 μg/ml) was present during coculture conditions that would normally give a high concentration of γ-GTP in ME-2 cells, the enzyme concentration could be reduced (Table 1); however, the enzyme was never completely abolished. In similar ME-2/C_6 cocultures in which parts of the C_6 monolayer were removed prior to coculture, the enzyme was detectable only in ME-2 cells that lay directly over C_6 cells; ME-2 cells that lay over empty areas of the dish were negative for γ-GTP (Fig. 1e). This result indicates that an intimate relationship is needed between the two cell types in order to induce the enzyme in the ME-2 cells.

In other experiments, the ME-2/C_6 cocultures were separated after 24 hours and the ME-2 cells maintained as a single cell type for various periods of time after being cocultured; the enzyme was shown to persist for at least 72 hours after coculture (Fig. 1f). However, in ME-2 monolayers 72 hours after coculture, there began a disappearance of γ-GTP on a per cell basis at a time coincident with renewed proliferation in the ME-2 cells. We interpret this to indicate that γ-GTP needs constant induction. All other coculture conditions used did not induce γ-GTP (Table 1).

We propose that the brain capillary endothelial cells require an inductive force to maintain high levels of γ-GTP activity. In coculture the glial cell can provide such an inductive force to the ME-2 cells, provided the two cell types are in close contact, a relationship that mimics the microanatomy in vivo. To our knowledge, this is the first demonstration of the glial cell inducing an enzyme in another cell type. This type of cellular interaction may be crucial to the normal development of the blood-brain barrier. It should be noted that the induction process is not species-specific, since the C_6 glial cells are of rat origin whereas the ME-2 vascular endothelial cells are isolated from the mouse. These findings pose many interesting questions related to mechanisms of interaction between a variety of cell types.

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Electrophysiological Signs of Split-Second Decision-Making

Abstract. *When young adults detected auditory stimuli at split-second intervals, different components of the event-related brain potentials showed markedly different speeds of recovery. The P_3 component (latency 300 to 350 milliseconds) was fully recovered at intervals of less than 1.0 second, while the N_1–P_2 components (latencies 100 to 180 milliseconds) were markedly attenuated with stimulus repetition even at longer interstimulus intervals. Thus, the N_1–P_2 recovers much more slowly than a subject's ability to evaluate signals, whereas the P_3 appears to be generated at the same high rates as the decision processes with which it is associated.*

Stimuli in all modalities elicit a succession of time-locked electrical waves from the human brain that can be recorded at the scalp as the evoked potential or event-related potential (ERP). The earlier waves in the ERP are generally regarded as exogenous or stimulus-bound, because their properties are determined primarily by the physical attributes of the stimulus. A number of components with longer latencies (including the P_3 wave at 300 to 500 msec) are highly sensitive to the processing demands of the task; these are considered to be endogenous in that they reflect cognitive operations triggered by relevant or significant stimuli (*1*).

Attempts to correlate human ERP components with specific psychological processes have met with varying success. In the case of exogenous ERP's, many of the psychophysiological relationships that have been reported are severely disrupted when the rate of stimulus delivery is changed (*2*). For example, the amplitudes of the long-latency components of the auditory evoked potential (N_1 and P_2 occurring at 100 and 180 msec, respectively) covary with perceived loudness when the interstimulus interval (ISI) is constant (*3*); however, shortening the ISI below about 10 seconds progressively reduces N_1 and P_2 amplitudes without a corresponding change in loudness (*4*) or reaction time (*5*).

The temporal recovery properties of endogenous ERP components have not yet been systematically investigated. Insofar as they index human cognitive processes, however, they should exhibit short refractory periods or recovery cycles like those of the cognitive operations with which they are associated.

We have examined the recovery properties of the P_3 wave, a long-latency (300- to 500-msec) endogenous potential associated with cognitive operations like decision-making, stimulus evaluation, and sensory detection (*1*, *2*). We now report that the P_3 wave exhibits a recovery cycle that parallels the speed with which accurate decisions can be made in a signal-detection paradigm, a recovery cycle much shorter than those reported for other long-latency ERP components.

We elicited sequences of P_3's by requiring subjects to tally near-threshold or suprathreshold (70-dB sound level) tones presented at short ISI's. As many as three such tones (all 1.0 kHz and 50 msec long) could be presented on a single trial during a 1200-msec interval (*6*).

Each trial began with a faint warning flash, which was followed by three positions where tones might or might not be presented, according to a random sched-

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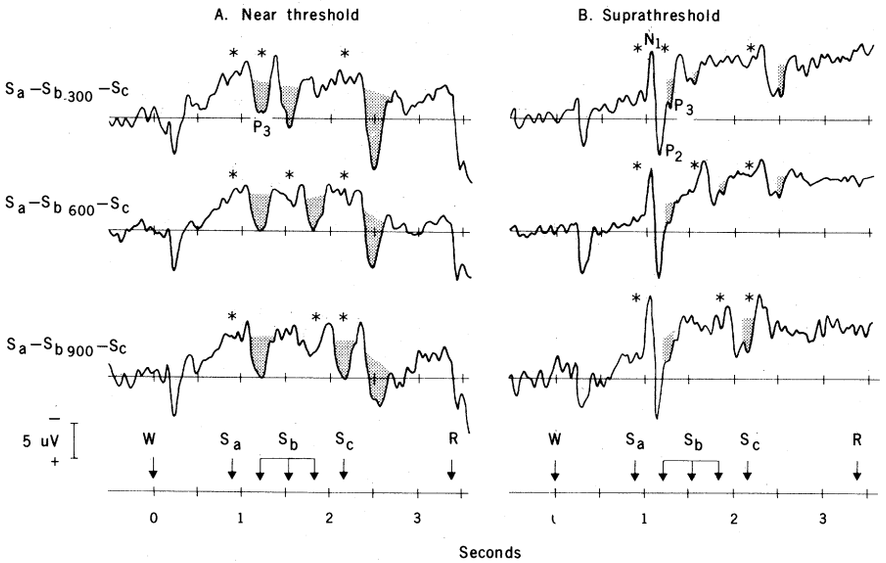

Fig. 1. Event-related potentials from the vertex to correctly detected triplet trials (three tones presented) in near-threshold (left, group 1) and suprathreshold (right) conditions. Asterisks indicate the time of stimulus delivery. Shaded areas show P_3 components relative to sloping baselines.

ule. The first and third positions (termed S_a and S_c) were fixed in time and followed the warning cue by 900 and 2100 msec, respectively. The second tone (S_b) could occur either 300, 600, or 900 msec after S_a (Fig. 1).

Tones were presented independently with a probability of .5 in each position, with the stipulation that a tone could occur at only one of the S_b positions on any trial. Thus one-eighth of the trials contained no tones at all, and one-eighth contained three tones. The three possible S_a–S_b intervals were given in random order from trial to trial, with each equiprobable. A second flash occurring 1.2 seconds after the S_c position cued subjects to report orally the number of tones detected during that trial. Intertrial intervals averaged 7.2 seconds (range 4.0 to 15.0 seconds).

Twelve blocks of 25 trials each were presented during a 1.5-hour test period. Electroencephalographic data from each subject were recorded from three midline scalp sites (F_z, C_z, and P_z), stored on f-m tape, and analyzed off-line (*7*). The amplitude of the individual P_3's within a trial was quantified according to a sloping baseline-peak measure (*8*); N_1-P_2 amplitudes were measured from peak to peak using suprathreshold data only.

Subjects' detection performance was consistently accurate in both near-threshold (91.3 percent of the trials were correctly reported) and suprathreshold (more than 99 percent correct) tasks and did not vary systematically in either experiment as a function of ISI.

Figure 1 shows ERP's recorded at the vertex to correctly detected triplet trials (*9*). The detection of each near-threshold tone was accompanied by a prominent P_3 wave, largest over central and parietal sites, whereas the detection of suprathreshold tones was accompanied by prominent N_1-P_2 components and a smaller P_3. The P_3 had recovered after 900-msec ISI's for both conditions, while the N_1-P_2 (evoked in suprathreshold conditions only) was greatly diminished in amplitude at all ISI's within the trial (Fig. 1).

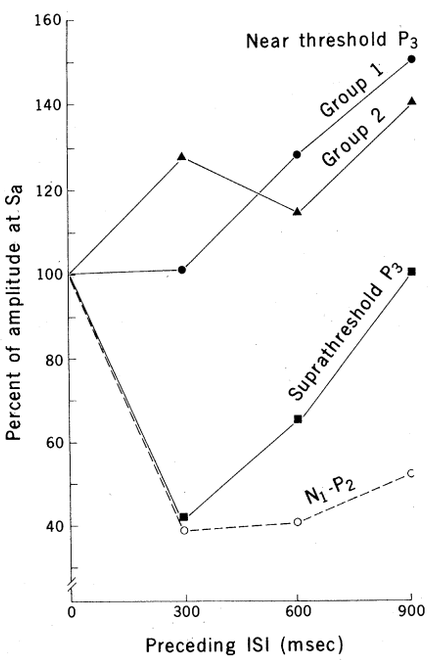

Fig. 2. Recovery functions of P_3 and N_1-P_2 components. Component amplitudes (relative to their amplitude to S_a tones) are plotted as a function of the preceding ISI. The data shown are averaged over S_b and S_c positions in triplet trials.

The divergent recovery cycles of P_3 and N_1-P_2 are shown in Fig. 2. The N_1-P_2 amplitudes were markedly reduced by stimulus repetition at all intervals during the signal delivery period, consistent with previous reports of prolonged refractory periods of these components (*10*). For example, at 900-msec intervals N_1-P_2 amplitudes had recovered to about 50 percent of amplitudes at S_a. In contrast, near-threshold P_3's were as large after 300-msec ISI's as at trial onset and were actually larger at longer intervals. Suprathreshold P_3's were decremented after 300- and 600-msec ISI's but were completely recovered by 900 msec (*11*). Both near-threshold and suprathreshold P_3's were more fully recovered than N_1-P_2's after 900-msec intervals ($P < .01$ for all comparisons). The latency of P_3 also varied with preceding interval; P_3 latencies were longer after 300-msec ISI's than at S_a (*12*).

These results indicate a basic dichotomy in the speed of recovery of the N_1-P_2 (exogenous) and P_3 (endogenous) waves. Since the refractory periods of exogenous components generally increase as a function of their latencies (*13*), an exogenous component with a latency comparable to that of P_3 would presumably have a refractory period longer than the 10 to 20 seconds ascribed to N_1-P_2 (*10*). The fact that the recovery cycle of the P_3 was more than an order of magnitude faster than this indicates that it probably arises from neural generators with fundamentally different properties than those responsible for exogenous components. How these generators differ in their pharmacological and physiological characteristics is a question for further study.

Despite their rapid recovery, the generators of P_3 were apparently being taxed at the 300-msec ISI, because P_3 latencies at this ISI were prolonged in comparison with S_a, and amplitudes were reduced in relation to P_3's produced at the longer ISI's. This result parallels those of studies of the psychological refractory period, which show that the reaction time for the second of two decisions is prolonged at ISI's shorter than about 500 msec (*14*).

The rapid recovery of P_3 in this and related experiments (*15*) suggests that it is generated by neural subsystems that share the recovery functions of psychological decision processes. By contrast, the prolonged refractory period of N_1-P_2 implies that it is a sign of processing operations that change markedly with repetition. Indeed, the refractory properties of N_1-P_2 have been ascribed to short-

term habituation or to the different levels of activation required to excite short-term memory traces (*16*).

The short recovery cycle of P_3 may also be characteristic of other endogenous components associated with human information processing (*17*). If so, studies of refractory properties may provide a basic criterion for linking ERP components to specific perceptual and cognitive processes.

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7. Two different groups of subjects were run in the near-threshold condition. Subjects in group 1 (three female and two male, ages 18 to 25) each participated in two successive test periods (600 trials). The EEG data from these subjects were amplified by chopper-stabilized d-c amplifiers (bandpass 0 to 40 Hz), and averaged and quantified by computer (PDP 11/45). Subjects in group 2 (five female and three male, ages 18 to 34) participated in a single test period. Their EEG's were amplified by low-frequency-sensitive a-c amplifiers (bandpass, 0.15 to 150 Hz), averaged on a signal averager and quantified from *x-y* plots with a ruler. In the suprathreshold experiment, five subjects (all female, 19 to 32 years old) reported the number of tones presented on each trial, as in the near-threshold experiment; stimulus delivery was controlled by the same tape-recorded sequence of trigger pulses. Procedures for data recording, analysis, and quantification were identical to those for group 1 subjects.
8. The P_3 was measured with respect to a baseline connecting the mean voltage during the 200 msec before stimulus delivery with the mean voltage from 450 to 600 msec after the stimulus. This baseline was chosen to minimize the possible influence of slow potential shifts on P_3 amplitude. Other measures (including prestimulus baseline-peak and P_3 area) provided results consistent with those reported here.
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11. Recovery cycle calculations for near-threshold P_3's were complicated by the fact that P_3's to unpreceded tones at S_a were slightly smaller (20 to 25 percent) than P_3's to unpreceded tones at other positions [$F(1,16) = 5.914$, $P < .05$]. Hence, while near-threshold P_3's following 300-msec ISI's were as large as those at S_a, they were slightly smaller than P_3's following unpreceded stimuli at the $S_{b_{300}}$ and S_c positions [$F(1,16) = 5.49$, $P < .05$ combined over S_b and S_c positions]. However, near-threshold P_3's to tones preceded by 900 msec ISI's were not only much larger than those at S_a, but were also larger than those following unpreceded stimuli at other positions ($P < .05$ for all comparisons). Although unpreceded suprathreshold P_3's did not differ in amplitude as a function of position, suprathreshold P_3 recovery cycles were complicated by the possible influence of the quantification procedure on the small P_3 component. In particular, with 300-msec ISI's the sloping baseline included portions of the preceding P_2-P_3 complex. Hence, at these intervals, the baseline may have been shifted positively, thereby reducing the measured suprathreshold P_3 amplitudes. Thus, the data in Fig. 2 may underestimate the extent of suprathreshold P_3 recovery at 300-msec ISI's.
12. For near-threshold P_3's, this latency difference averaged 26 msec [$F(1,16) = 13.57$, $P < .01$]; for suprathreshold P_3's, it was 20 msec [$F(1,16) = 4.49$, $P < .05$].
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17. For example, the attentional modulation of the N_1-P_2 during selective attention tasks has a recovery cycle much shorter than that of the N_1-P_2 itself. In fact, attention-related ERP enhancement is largest at ISI's below 500 msec [V. Schwent, S. A. Hillyard, R. Galambos, *Electroencephalogr. Clin. Neurophysiol.* **40**, 604 (1976)].

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Buprenorphine Suppresses Heroin Use by Heroin Addicts

Abstract. *Heroin-dependent men were given buprenorphine (a partial opiate agonist-antagonist) or a placebo under double-blind conditions on a clinical research ward where they could acquire heroin (21 to 40.5 milligrams per day, intravenously). Buprenorphine significantly ($P < .001$) suppressed the self-administration of heroin over 10 days. Control subjects took between 93 and 100 percent of the available heroin. The effects of buprenorphine were dose-dependent; a dose of 8 milligrams per day reduced heroin use by 69 to 98 percent; a dose of 4 milligrams per day reduced heroin use by 45 percent. Termination of buprenorphine maintenance did not result in opiate withdrawal signs or symptoms. The subjects liked buprenorphine and indicated that it was preferable to methadone or naltrexone. Buprenorphine should be a safe and effective new pharmacotherapy for heroin dependence.*

Buprenorphine is a new oripavine derivative (*1*) with 25 to 40 times the analgesic potency of morphine and an equivalent duration of action (*2*). The subjective effects of buprenorphine also resemble those of morphine, and former heroin addicts report that they like morphine and buprenorphine equally well (*3*). In addition to its morphinelike agonistic properties, buprenorphine is also an opiate antagonist that effectively antagonizes high doses of morphine for 24 to 36 hours (*3*). Since buprenorphine is a partial opiate agonist-antagonist, it combines in one drug the characteristics of two of the leading pharmacotherapies for heroin addiction. It is equivalent to the antagonist naltrexone in potency and duration of narcotic blockade (*4*), and its opiate agonist properties resemble those of methadone in terms of reported positive subjective effects. However, termination of maintenance with high doses of buprenorphine does not result in the severe and protracted withdrawal signs and symptoms (*3*) that occur when methadone treatment is ended. A mild, almost negligible withdrawal syndrome was detected about 2 weeks after abrupt cessation of maintenance on buprenorphine (*3*).

Table 1. Sequence and duration of experimental conditions.

Drug condition		Duration (days)
Buprenorphine	Placebo	
Baseline (drug-free)	Baseline (drug-free)	5
Buprenorphine (0.5 to 8 mg/day)	Placebo	14
Buprenorphine and heroin	Placebo and heroin	10
Buprenorphine detoxification (7 to 1 mg/day)	Methadone detoxification (25 to 5 mg/day)	5
Baseline (drug-free)	Baseline (drug-free)	3
Naltrexone (10 to 50 mg/day)	Naltrexone (10 to 50 mg/day)	3

Since buprenorphine has some desirable properties as an opiate agonist, does not induce physical dependence, and antagonizes the effects of other opiate agonists, it could be an effective pharmacotherapy for heroin addiction. This report describes the effect of buprenorphine (or placebo) maintenance on self-administration of heroin by male opiate addicts studied on a clinical research ward under double-blind conditions. Ten volunteers 24 to 32 years of age (mean, 28.6 years) and with a 1- to 19-year history of heroin use (mean, 10.4 years) gave informed consent for their participation in these studies. Each subject had been treated for heroin addiction in conventional programs but had failed to maintain abstinence from opiates. Each volunteer was in good physical health, as determined by appropriate medical, psy-

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