possibility that benzodiazepines may selectively attach to subclasses of benzodiazepine receptors must be considered (*11*).

Early morning insomnia may not be unique to benzodiazepines, as rebound insomnia is (*2*); it may also occur with other sedative agents such as nonbenzodiazepine hypnotics with relatively rapid rates of elimination. Alcohol, which is known for its sedative properties and its short elimination half-life, also increases wakefulness during the second half of the night (*12*).

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5 November 1982

## Shadows of Thought: Shifting Lateralization of Human Brain Electrical Patterns During Brief Visuomotor Task

Abstract. *Dynamic spatial patterns of correlation of electrical potentials recorded from the human brain were shown in diagrams generated by mathematical pattern recognition. The patterns for "move" and "no-move" variants of a brief visuospatial task were compared. In the interval spanning the P300 peak of the evoked potential, higher correlations of the right parietal electrode with occipital and central electrodes distinguished the no-move task from the move task. In the next interval, spanning the readiness potential in the move task, higher correlations of the left central electrode with occipital and frontal electrodes characterized the move task. These results conform to neuropsychological expectations of localized processing and their temporal sequence. The rapid change in the side and site of localized processes may account for conflicting reports of lateralization in studies which lacked adequate spatial and temporal resolution.*

Many investigators have reported that brain activity is lateralized during cognitive tasks. Advanced radiological methods reveal relative localization and lateralization, but cannot resolve temporal sequencing because of the long time required for observation. Studies of ongoing, background electrical activity do not reveal split-second changes in neurocognitive patterns, and those that have reported lateralization of neurocognitive activity have been questioned on methodological grounds (*1–6*). Although the components of averaged event-related potentials (ERP's) may indicate the sequencing of some neurocognitive processes, they have not revealed consistent, robust signs of lateralization, even for language (*7*). Conclusions derived from patients with focal brain lesions or with "split-brains," cannot be directly extended to normal subjects. Lateralized processes inferred from reaction time differences to hemifield or dichotic stimulation have also been questioned on methodological grounds (*8*). These factors have undoubtedly contributed to conflicting reports of lateralization of brain activity.

To observe the spatial patterns and sequencing of neurocognitive activity, we have developed a new method called neurocognitive pattern (NCP) analysis. In NCP analysis the average ERP's of each person are used to determine the time intervals of task-related neural processes. Within these intervals the similarity of brain-potential waveshapes over the scalp is measured on a single-trial basis by computing the cross-correlation coefficient between paired combinations of electrodes. Although the neuroanatomic origin and neurophysiological significance of these correlations is not known, it has been suggested that cognitive activity may be associated with characteristic scalp correlation patterns (*9*). However, task-related electrical signals from the brain are spatially smeared in transmission to the scalp and are embedded in background activity. Since linear statistical methods were not effective in dealing with these obstacles, we used a more powerful analysis called trainable classification-network mathematical pattern recognition (*2, 3, 10–13*). For this method, artificial intelligence algorithms are used to extract patterns of correlation that differ between two conditions with no assumptions about the distribution of correlation values. The algorithm is first applied to a labeled subset of the experimental data called the training set, and the invariant patterns (classification functions) found are then verified on a separate unlabeled subset of data called the test set. If the classification functions can significantly separate the test set into the two conditions, the extracted patterns have intrinsic validity.

Previously we reported the existence of complex, rapidly changing patterns of brain-potential correlation involving many areas of both hemispheres that distinguished numeric and spatial judgments in a visuomotor task (*13*). Since the sequencing of neurocognitive differences between numeric and spatial processing is not definitely known, the complex patterns were difficult to interpret. The present experiment was designed to clarify this situation by highlighting presumably localized neural processes. In comparing two types of spatial judgment, the common activity of brain areas should cancel, revealing differences in the right parietal area presumed to mediate spatial judgments. The right-handed finger response in one task was designed to elicit lateralized activity of the left central motor area.

In this study a person estimated the distance a "target" should be moved to intersect a displayed arrow's trajectory. The "move" task required pressure of the right index finger on a transducer with a force proportional to that distance (*14*). In the "no-move" task the arrow pointed directly at the target, and no pressing was required (pseudorandom 20 percent of trials). Thus, the spatial judgment and response differed between tasks, while gross stimulus characteristics were the same.

Nine right-handed, healthy adults (eight males, one female) participated in the study. The average response initiation (muscle potential onset) time for the move trials was 0.59 second (standard deviation, 0.19; mean of standard deviations within persons, 0.24). Brain potentials were recorded from 15 scalp electrodes and referenced to linked mastoids (Fig. 1A) (*15*). Vertical and horizontal eye movements, muscle potentials from the responding finger, and the output of the force transducer were also recorded. The data were edited to remove trials with artifacts, and a set of 1612 correct, representative trials (839 move, 773 no-move) was formed. Averaged ERP's were computed for all electrodes (Fig. 1B), and *t*-tests and analyses of variance (ANOVA's) were performed (*16, 17*).

Cross-correlations were computed between 91 paired combinations of the 15 electrodes for each trial in each of three 175-msec intervals (Fig. 1B). Two intervals spanned the N100–P200 and P300 ERP peaks, and the third (RP) interval spanned most of the readiness potential (in the move task). The centerpoint of each interval was determined for each person (*18*). The correlations were standardized within persons, within electrode pairs (mean, 0; standard deviation, 1), and then grouped across people. The *t*-tests and ANOVA's of single-trial correlations did not distinguish meaningful differences in between-task spatiotemporal patterns.

Mathematical pattern classification was then applied to the single-trial correlations of all nine people to search for subtle between-task differences in each interval. To make the results anatomically interpretable, we performed the search separately on each of 15 sets of electrode pairs. Each set consisted of the correlations of a particular electrode with ten other electrodes (Fig. 1C). For each interval, the electrode set that distinguished conditions on the test set with the highest significance level (*19*), and the most prominent correlations for that electrode set (*20*), were diagramed.

In the N100–P200 interval, correlations of the midline parietal electrode distinguished the tasks ($P < .001$) (Fig. 2A). In the P300 interval, correlations of the right parietal electrode with the midline occipital and precentral electrodes were greater in the no-move task, while correlations of the right parietal with the right central electrode were greater in the move task ($P < 5 \times 10^{-5}$) (Fig. 2B). In the RP interval, correlations of the left central electrode with the midline frontal and occipital electrodes were greater in the move task, while correlations of the left central electrode with the midline parietal electrode were greater in the no-move task ($P < 5 \times 10^{-6}$) (Fig. 2C).

The right parietal locus of between-task difference in the P300 interval may reflect a lateralization of activity distinguishing the two types of spatial judgment (*21*) or the difference between movement estimation in the move task and the cancellation of response in the no-move task. The left central focus of difference in the RP interval 135 msec later may reflect the preparation and initiation of the movement of the right index finger. In contrast, the pattern of difference in the N100–P200 interval was not lateralized.

These results may help explain conflicting reports of brain-potential lateralization. In many studies, various "verbal-analytic" and "spatial" tasks 1 minute or more in duration have been associated with relative left and right hemisphere EEG activity (*1–6*). However, it

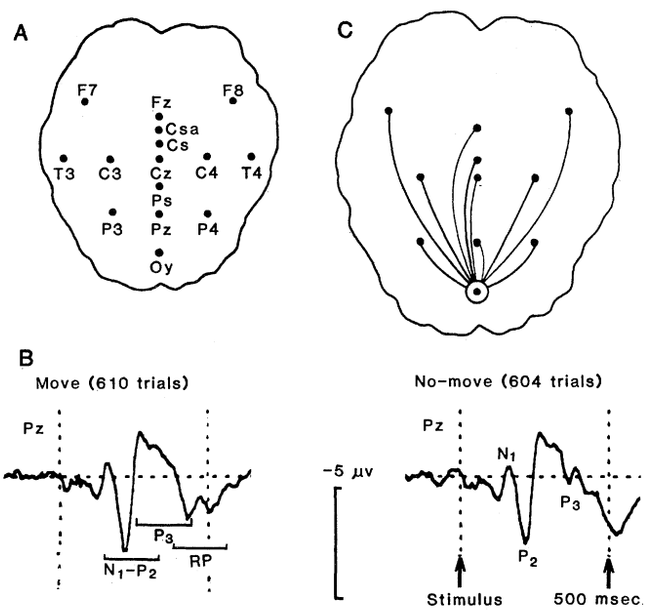


Fig. 1. (A) Montage of 15 electrodes. Nonstandard placements are intended to overlie cortical areas of particular interest: anterior occipital (*Oy*), anterior parietal (*Ps*), midline precentral (superior edge-*Cs*), and midline premotor (*Csa*) areas. (B) Composite average event-related potentials (ERP's) from four persons (75 percent of the total data from nine persons) for the Pz electrode, showing the major ERP peaks and corresponding single trial correlation analysis intervals. The P300 ERP peak is larger in the infrequent no-move trials. (C) One of the 15 sets of ten electrode pairs into which the 91 paired correlations were grouped. The anterior occipital (*Oy*) set is shown. In Fig. 2 the principal electrodes of differing sets are circled and the most prominent correlations are indicated as solid and dotted lines.

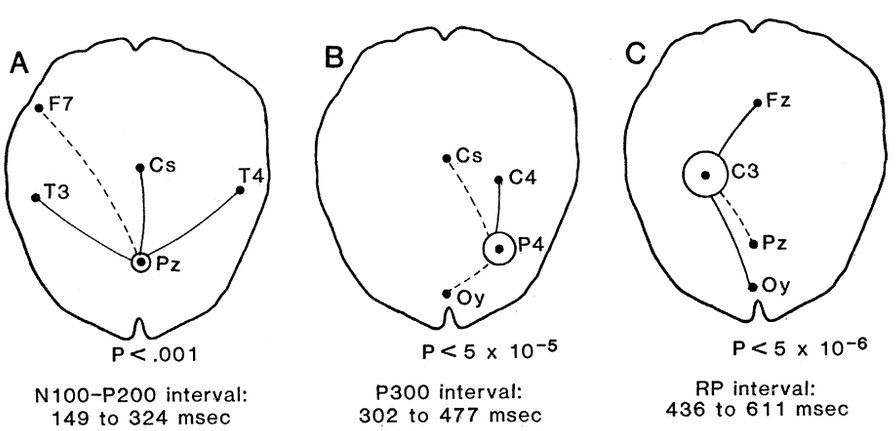


Fig. 2. Diagrams of between-task differences in the (A) N100–P200, (B) P300, and (C) RP intervals generated by neurocognitive pattern (NCP) analysis. The most significantly differing electrode sets, their significance level, and the most prominent correlations within the set are shown. A solid line between two electrodes indicates that the correlations were higher in the move task, while a dotted line indicates higher no-move task correlations.

is not clear whether this activity is associated with mental aspects of tasks or with sensorimotor components, or with artifacts. In a previous study we found no topographic differences in EEG spectra between 15-second arithmetic, block rotation and letter substitution tasks after rigorously controlling other-than-cognitive factors (*2–4*). However, such heterogeneous tasks cannot be resolved into serial components reflecting different neurocognitive processes. We therefore refined our approach by using short (less than 1 second) tasks, using time references based on person-specific average ERP measurements, computing correlations between channels on a single-trial basis, and using mathematical pattern classification to reveal split-second sequential processing. This yielded a sequence of clear-cut between-task difference patterns involving split-second changes in the localization and lateralization of mass neural activity. Appropriate studies of neurocognitive functions should take into account this rapidly shifting network of localized and lateralized processes.

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14. The stimulus subtended a visual angle of less than 2 degrees. The vertical position and side of screen of the target changed randomly across trials for both tasks, as did the horizontal angle and direction of the arrow. Response was made on a Grass isometric force transducer and varied randomly across trials from 0.1 to 1 kg. An individual trial consisted of a neutral warning that was followed after 2 seconds by the stimulus. One second after its completion the response was displayed.
15. Brain potentials were amplified with a Bioelectric Systems model AS-64P and Beckman Accutraces with a passband of about 0.1 to 50 Hz. Electroculogram and muscle potentials were amplified by a Grass model 6 with similar filter settings. All signals were digitized to 11 bits at 128 samples per second, and a 12-Hz, 15-point nonrecursive digital low-pass filter was applied.
16. A task-by-electrode-by-person analysis of variance of the P300 peak voltage revealed a significant task effect [$F(1, 8) = 29.0$, $P < .001$] and task-by-electrode interaction [$F(13, 104) = 2.9$, $P < .005$]. Correlated $t$-tests revealed P300 voltage enhancements in the no-move task for all but the lateral temporal electrodes; the most significant difference ($P < .0005$) was at the anterior midline parietal electrode. When corrected for multiple comparisons by the Bonferroni method only the right central, anterior, and posterior midline parietal electrodes reached significance ($P < .05$). P300 ERP peak amplitude increases have been associated with similar go versus no-go decisions [R. Simson, H. Vaughan, W. Ritter, *Electroencephalog. Clin. Neurophysiol* **43**, 864 (1977)] and with the perception of a novel or relevant stimulus. This study differs from typical P300 studies in that a difficult motor response is required to the more frequent stimulus.
17. A task-by-electrode-by-person analysis of variance of the slope of a straight line fitted to the slow-potential shift across the RP interval revealed a significant task effect [$F(1, 8) = 5.6$, $P < .05$], electrode effect [$F(14, 112) = 1.9$, $P < .05$], and task-by-electrode interaction [$F(14, 112) = 2.7$, $P < .005$]. Correlated $t$-tests showed larger move task slopes for nine electrodes; the most significant difference ($P < .005$) was at the left central electrode. When Bonferroni-corrected, no electrode reached significance at $P < .05$.
18. The N100–P200 and P300 centerpoints in milliseconds for each of the volunteers were: V1 (218, 452); V2 (200, 388); V3 (228, 482); V4 (210, 462); V5 (203, 398); V6 (208, 298); V7 (212, 368); V8 (181, 318); and V9 (203, 358). The RP interval was centered 135 msec after the P300 centerpoint.
19. The functions were derived from two-thirds of the data and were tested on the remaining one-third. This was repeated three times and the average test-set classification accuracy was computed. A test-set classification accuracy of 55 percent corresponds to $P < 5 \times 10^{-5}$. This is more than 3.8 standard deviations above the mean classification accuracy of 48 classifications using 1612 randomly labeled move and no-move trials. Mean accuracy on the randomly labeled data was 50.6 percent, with a standard deviation of 1.1 percent, an accuracy that could have occurred by chance with $P = .32$ according to the binomial distribution. High classification accuracy was not the objective. Rather, the relative classification accuracy of each electrode set was used as an indicator of anatomic and temporal localization of task-related patterns. The classification accuracy of the P300 and RP intervals assessed on each individual was at the chance level for only two of the nine people. Their data comprised only 9 percent of the total data set. When the entire analysis was performed on the data of one person (V7) in the P300 interval, the P4 electrode set again achieved the highest classification accuracy.
20. To select the most prominent correlations from significant classification functions, the pattern recognition analysis was applied recursively on the highest weighted correlations. Test-set classification accuracy based on the final three or four correlations was significant at $P < .001$ or better in each interval.
21. The P300 ERP peak has not been found to vary in lateralization specifically as a function of cognitive task (*1*). J. Desmedt [*Proc. Natl. Acad. Sci. U.S.A.* **74**, 4037 (1977)] reported a qualitative change in the ERP over the right hemisphere in a somatosensory-motor task, but the effect was general and was not present in the P300 peak.
22. We thank the late Gobind B. Lal for the "shadows of thought" metaphor; H. Currens for manuscript preparation and artwork; G. Gilcrease and J. Ghannam for assistance with recordings and analysis; R. Adey, M. Aminoff, P. Bach-y-Rita, F. Benson, E. Callaway, J. Engel, B. Garoutte, W. Gersch, R. Halliday, E. Roy John, B. Libet, J. Mazziotta, M. Mesulam, K. Pribram, J. Roumasset, A. Salamy, C. Skomer, J. Spire, H. Vaughan, D. O. Walter, C. Woods, and J. Vidal for valuable comments; J. Miller (Air Force School of Aerospace Medicine), D. Woodward (Office of Naval Research), A. Fregly (Air Force Office of Scientific Research), J. Fetzer, and M. Bachman-Hoffman for research support.

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## A Functional Role for an Opiate System in Snail Thermal Behavior

Abstract. *The terrestrial snail* Cepaea nemoralis, *when placed on a 40°C hot plate, lifts the anterior portion of its foot. The latency of this response is influenced by morphine and by naloxone in a dose-dependent and time-dependent manner. Morphine increases the time taken to respond, whereas naloxone reduces it. Furthermore, naloxone abolishes the effect of morphine. These results indicate that an opiate system may have a role in this behavior, which resembles that reported in vertebrates.*

Although the importance of opiate systems in mediating behavioral and physiological activities is recognized in vertebrates (*1*), the role of opiate systems in invertebrates has only recently become apparent (*2–4*). Evidence for electrophysiological and biochemical effects of opiates, their agonists, and antagonists and the demonstration of specific opiate receptors in molluscs (*3*), have resulted in the suggestion that opiate receptors and their effectors play a role in the regulation of transmitter release in invertebrates (*4*). We present evidence that opiate systems have a functional role in determining the thermal behaviors of the terrestrial snail *Cepaea nemoralis*.

The snails were maintained as sepa-