ance component, statistical tests for paired comparisons were used, in which pairs of animals killed in the same triplets were matched when comparing two groups. Both nonparametric (signed-rank test, sign test) and parametric (*t*-test) paired comparisons showed an elevation of corticoids in the mid-aged groups over the young group ($P < .05$, two-tailed). Only one young animal exhibited higher corticoid values than its mid-aged paired animal. The aged group, however, was not found to be different in concentrations of corticoid from either of the other groups because of the extreme variance and bimodal distributions found in aged animals. Elevations in plasma corticosterone of rats with age have also been reported by three other research groups (*6, 9*) [see B. J. Winer, *Statistical Principles in Experimental Design* (McGraw-Hill, New York, 1962)].


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# Memory Impairment in Epileptic Patients: Selective Effects of Phenobarbital Concentration


Abstract. *Nineteen epileptic patients were tested first under medium (week 1) and then under high (week 2) therapeutic levels of phenobarbital. Relative to response times of 20 controls with equivalent practice but without medication, response times of patients in a short-term memory scanning task were strikingly slowed during week 2. However, increased phenobarbital did not slow responses in a task requiring access to information in long-term memory.*


In patients with recurrent epileptic seizures, the optimal daily dosage of anticonvulsant necessarily must represent a compromise between increased control of seizures and reduced information-processing capability. Although there are satisfactory ways of assessing both the patient's anticonvulsant level and his or her seizure frequency (*1*), no adequate measures have been advanced for evaluating drug-related cognitive impairment in epileptic patients (*2*). The present study was designed to assess the effect of one commonly prescribed anticonvulsant (phenobarbital) on specific parts of the memory system.

Cognitive theories distinguish two information stores in memory, a temporary short-term store and a more permanent long-term store (*3*). Much literature supports this dichotomy at the behavioral level (*4*) and, to a lesser extent, at the physiological level (*5*). Accordingly, we selected two tasks, each of which examines access to simple, highly familiar information in one of the memory stores. We were guided in our choice of tasks by previous investigations in our laboratory of the relation between verbal ability and memory (*6*).

Our measure of short-term memory performance was the Sternberg scanning task (*7*). In this procedure, a series of from one to six different digits is presented sequentially, followed after a brief pause by a probe digit (for example, 6 3 4 7 . . . 3?). The subject's task is to indicate as rapidly as possible whether the probe digit was in the memory set. The dependent variable is the reaction time (RT) required for the response, accuracy being perfect. Reaction time is typically found to be a linearly increasing function of the number of digits scanned.

There are several theoretical interpretations of this finding. The most straightforward is that the items are scanned one at a time in sequence. Under this interpretation, the slope of the linear function is taken as a measure of speed of access to information being held in short-term memory. Of course, other explanations are also possible. For example, one can develop models in which the search process takes place in parallel, and still account for the linear function (*8*). Other theorists have proposed memory strength models. However, for the purposes of this report, such distinctions are irrelevant. All the various models of the short-term memory scanning task assume that the slope of the linear function measures efficiency of access to information in short-term memory. That is all that we require. Slope values typically vary from 30 to 40 msec in normal, well-practiced college students.

As our measure of long-term memory performance, we used Posner's letter-matching task (*9*), a paradigm for investigating automatic access to name codes. On each trial, two letters are presented simultaneously and the subject judges whether the two letters have the same name. Thus, the correct response to "AB" or "Ab" is "different," while the correct response to "AA" or "Aa" is "same." Again, performance is essentially error-free.

This task can be used to measure the speed of access to long-term memory. Let us consider the simplest model of the task. It assumes that physically identical items (for example, "AA") can be responded to without the name even being determined; because the visual patterns are identical, the pattern names must be the same. On such trials, access to long-term memory does not involve the letter names. By contrast, detecting that "a" and "A" have the same name requires that the name codes of each pattern be retrieved from long-term memory and compared. Indeed, the RT on "name identity" trials is typically about 80 msec longer than the RT on "physical identity" trials when college students are used as subjects.

As is the case in the short-term memory scanning task, alternative models of the letter-matching task are also possible. For instance, the "horse race" (*10*) model assumes that visual patterns are always processed to a name level. In this model, the difference between name identity and physical identity trials is due to the extra processing required to deal with the entry of two nonidentical patterns into long-term memory. Once again, for the purposes of this report, the precise model for the task can be disregarded. All we claim for our task is that it is a measure of speed of access to information in long-term memory.

The epileptic patients performed the two tasks during week 1 under a medium maintenance level of medication (8 to 15 $\mu$g of phenobarbital per milliliter of blood) and during week 2 under a higher level (20 to 32 $\mu$g/ml). These dosages are representative of the levels used clinically. Approximately 30 percent of all epileptic patients are prescribed maintenance dosages at our lower level and 40 percent at our higher level. The medium dosage consistently preceded the high dosage because of the long half-life of phenobarbital, the hospital schedules, and the time which the patients had available. There were 3 days of testing on these tasks at each level of medication, separated by 5 days to permit the increased level of phenobarbital to stabilize. Day 1 of each week was considered to be a practice day, and the data were discarded. On days 2 and 3, several practice trials preceded each task to help reduce warm-up effects.



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On each day, the short-term memory task consisted of 100 trials. On half of these trials, the probe was positive (that is, in the memory set) and on the other half the probe was negative (not in the memory set). There was an approximately equal number of trials at each of the set sizes one through six, presented in random order. The items in each memory set were drawn at random from the digits 0 to 9, without replacement. The memory set digits were presented individually at a 1.2-second rate with a 2-second delay before the probe. To indicate that the probe item had appeared in the memory set, subjects depressed a response key with their right index finger. The left index finger was used to depress a key indicating that the probe had not appeared in the memory set. After each trial subjects were informed of their RT.

The long-term memory task consisted of 128 trials daily; 64 "different" trials, 32 "name identity" trials, and 32 "physical identity" trials. Trial types were presented in random order. The five letters A, B, N, E, and R were used as stimuli because of their distinct type forms in both uppercase and lowercase. Subjects again used their right index fingers for the positive response and were given both accuracy and RT information after every trial.

The 19 epileptic patients (*11*) were all males ranging in age from 20 to 55 years (mean = 37). All had grand mal seizures with a frequency of not more than eight per year. None had clinical evidence of neurological brain lesion. During week 1, the patients were tested at the level of medication they had been receiving when admitted to the hospital. The mean concentration of phenobarbital in the serum at this time was 15.8 $\mu$g/ml, with a standard deviation of 4.77. After the last testing session in week 1, the phenobarbital dose of 17 patients was increased to 2 to 2.4 mg per kilogram of body weight per day, an increase of about 60 to 100 percent of the dosage during week 1. The remaining two patients were taking primidone during week 1 and, since a substantial portion of primidone is converted in the body to phenobarbital, their daily dosage of primidone was increased to 14.5 mg/kg in week 2. This again represented an increment of about 100 percent over the dosage during week 1. During week 2, the mean concentration of phenobarbital in the serum was 26.2 $\mu$g/ml, with a standard deviation of 7.89.

There was an overlap between the concentrations of drug in the serum in weeks 1 and 2 (although obviously not in the same subject). In 6 of the 19 epileptic patients, the concentration in week 1 was higher than the lowest concentration observed after the dosages were increased. Thus, the increased dosage did not represent an extrapolation far beyond currrent medical use.

Table 1. Access time to long-term memory code. Mean reaction time (in milliseconds) for name identity (NI) trials and physical identity (PI) trials, together with the difference score (NI − PI), shown as a function of group and week of testing.

| Measure | Week 1 | Week 2 |
|---|---|---|
| | *Epileptics* | |
| NI | 739 | 741 |
| PI | 600 | 620 |
| NI − PI | 139 | 121 |
| | *Controls* | |
| NI | 558 | 528 |
| PI | 472 | 446 |
| NI − PI | 86 | 83 |

The control group consisted of 20 males ranging in age from 20 to 32 years (mean = 24). Although ideally the control group would have consisted of epileptic patients without drug treatment, this was not possible because of the limited availability of such patients. Consequently, subjects in our control group received no medication and were included solely as a control for practice effects. All patients and control subjects had at least a high school education.

For testing and data collection we used computer-controlled visual displays and response keyboard located in individual isolated booths. The patients were tested in small groups (one to four patients) in the morning (about 1½ to 2 hours after they received medication); control subjects were tested in the afternoon. To aid in reducing warm-up effects, a simple RT and a choice RT task preceded the two memory tasks every day. The long-term task always preceded the short-term task, with brief intertask breaks to reduce fatigue. Testing was done on Monday through Wednesday of week 1 and on Tuesday through Thursday of week 2 (*12*).

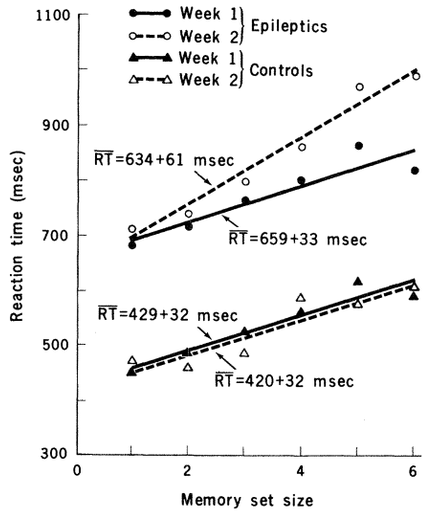


Fig. 1. Scanning in short-term memory. Mean reaction time (*RT*, in milliseconds) to probe digits as a function of memory set size (1 to 6 digits). The data are collapsed over positive and negative probe types, with the equations representing the slope and zero-intercept of the least-squares best-fitting line. The curves are a function of group and week of testing.

Because scores were high on the first day of each week, we used for our analyses only the data from days 2 and 3, collapsed over days for each subject. The basic analyses reported are group (patient versus controls) by week (first versus second) analyses of variance with RT being used as the dependent variable. The critical dependent variables in the two tasks were uncorrelated for each group in both weeks. This reinforces the notion that the two paradigms were measuring independent memory processes, as intended.

The results from the short-term scanning task are shown in Fig. 1. The pattern of main effects is straightforward (*13*). As is typically the case, RT's to negative probes (zero-intercept of 594 msec) were considerably longer than RT's to positive probes (zero-intercept of 483 msec) (*14*). However, probe type did not interact with any of the other variables, so for further analyses we used data averaged over probe type for each subject. The performance of the control subjects was remarkably consistent from week 1 to week 2 in both scanning rate (slope) and response-production time (zero-intercept), evidence for the successful elimination of practice effects. The performance of the epileptic patients, however, changed dramatically in week 2. Their zero-intercept values showed no reliable change, but their slope values nearly doubled, a highly reliable increase. These effects are supported by the respective groups by weeks interactions, which are significant for slopes ($F = 8.8$; d.f. = 1, 35; $P < .01$), but not for zero-intercepts ($F < 1$) (*15*). Thus, scanning of information in short-term memory is highly sensitive to increased phenobarbital concentration.

The data on access to long-term memory codes, shown in Table 1, consist of mean RT to name identity and mean RT to physical identity, together with the difference score (name identity minus physical identity) which indicates the ad-

ditional time needed to complete a task that requires retrieval of a letter's name in long-term memory (*16*). Again the pattern is straightforward, although quite different from the data for the short-term memory task. Epileptic patients take longer to complete either task; furthermore, the difference between name and physical identity RT is greater in the epileptic than in the control group. (Both the groups and the groups by task interaction are significant at the $P = .01$ level.) Our main interest, however, is the difference between name identity and physical identity RT's. This remains constant over weeks in the control subjects and actually decreases (insignificantly, $P > .10$) in the epileptic group. In fact, the decrease is associated with a rise in physical identity RT, the task requiring the least involvement of long-term memory. Thus the effects, if reliable at all, are in the opposite direction to what one would expect if the increase in drug dosage affected access to information in long-term memory.

The patients uniformly demonstrated a greater difference between name identity and physical identity RT's than did the controls, although the size of this difference did not increase with increased dosage (Table 1). One cannot argue from this alone, however, that epilepsy itself impaired access to long-term memory—this difference score has been shown to increase with age beyond adulthood, and to decrease with increases in intelligence (*17*). Unfortunately, the two groups, controls and patients, could not be matched perfectly on a number of variables, so any interpretation of this difference would be speculative.

Our data indicated that speed of access to information in short-term memory was sensitive to phenobarbital concentration, whereas speed of access to information in long-term memory was not. These results suggest that phenobarbital selectively impairs short-term memory functioning, a conclusion strengthened by the fact that memory scanning rate for different kinds of material is almost a perfect predictor of immediate memory span (*18*). Of course, it would be desirable to extend our finding to other measures of short- and long-term memory, to increase their generalizability. In particular, analogous measures of accuracy would be a good complement to our measures of speed.

The reactions of memory processes to drugs that we report differ markedly from the pattern observed in previous studies of the association between information-processing abilities and conventionally defined verbal intelligence. In those studies, lower verbal intelligence was associated with longer access time to well-known information in long-term memory (*6*, *17*). Short-term memory scanning, on the other hand, has not proved sensitive to differing verbal ability. This is precisely the reverse of the pattern we report for phenobarbital, in which only short-term memory was sensitive to the drug effect. Taken together, these findings provide further confirmation for the dichotomy between short-term memory and long-term memory.

Phenobarbital is one of a very large array of drugs used to control the physical manifestations of disorders of the nervous system. The cognitive side effects of such drugs should be carefully assessed. For example, impairment of short-term memory may critically influence a person's ability to maintain attention, a crucial ability when one is trying to acquire new information. Given the large number of school-age children who suffer seizures, this could be a problem of considerable clinical significance. More generally, physicians require a more sensitive technology for assessing the cognitive side effects of medication, so as to better establish the optimum trade-off between control of physical symptoms and impairment of mental efficiency.

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11. One of the original 20 epileptic patients is not included in this report. Motor problems made it difficult for him to perform the tasks; consequently, his RT's were not representative.
12. Additional practiced tasks were performed after the memory tasks each day, and several unpracticed tasks were conducted on the fourth day each week. The memory data reported here are part of a larger study of phenobarbital effects on cognitive performance in a broader set of tasks. Subsequent reports elsewhere will examine performance on these other cognitive tasks.
13. For slopes, the groups effect ($F = 7.0$; d.f. = 1, 35; $P < .01$) and the weeks effect ($F = 8.8$; d.f. = 1, 35; $P < .01$) were both significant. For zero-intercepts, only the groups effect ($F = 11.1$; d.f. = 1, 35; $P < .01$) and not the weeks effect ($F < 1$) was significant (the 95 percent confidence interval for the 25-msec intercept difference between week 1 and week 2 in the epileptic group was $25 \pm 88.6$ msec). The zero-intercept data simply reflect the overall slower response production of the epileptic patients in both weeks. This constant zero-intercept difference between groups is not relevant to our arguments, because our primary interest concerns within-group comparisons. The patients may take longer to respond in general because of some combination of the following three factors: (i) the patients are older than the control subjects, (ii) the patients have epilepsy, and (iii) the patients began the study under medication.
14. The problem of a speed-accuracy trade-off was absent in these data. The mean percentage of errors over both groups of subjects and both weeks was 3.4 percent. In a three-way analysis of variance (group by week by set size), there were only two significant effects. The first was week ($F = 6.9$; d.f. = 1, 35; $P < .01$), with all subjects making slightly more errors in the second week than in the first week. More important, the effect of set size was highly significant ($F = 10.7$; d.f. = 5, 175; $P < .001$), increasing from 2.4 percent at size 1, to 5.1 percent at size 6. Percentages of errors and mean correct RT's were uncorrelated.
15. Because of computer failure in the first week of testing for two of the control subjects, the short-term memory data include only 18 of the 20 controls. Similarly, the long-term memory data include only 18 of the 19 patients.
16. The problem of a speed-accuracy trade-off did not arise in these data. The mean percentage of errors over both groups of subjects and both weeks was 8.0 percent. In a three-way analysis of variance (group by week by identity condition), only the identity condition effect was significant ($F = 88.6$; d.f. = 1, 36; $P < .001$). There were more errors on name identity trials (13.2 percent) than on physical identity trials (2.8 percent). Percentage of errors and mean correct RT's were uncorrelated.
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19. We thank J. Davidson and C. McKee for assistance in testing the subjects and analyzing the data; J. K. Steusing for assistance in determining drug concentrations in body fluids; the medical and nursing staff at the Seattle Veterans Administration Hospital for help with many procedural problems; and our colleagues at the University of Washington and the National Institutes of Health for their comments. This research was partially supported by NIMH grant MH-21795 to the University of Washington. Address reprint requests to C.M.M., Division of Life Sciences, Scarborough College, University of Toronto, West Hill, Ontario, Canada M1C 1A4.

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