

dromes, animals show an increased capacity to convert even restricted amounts of food into lipid (3, 5, 6). Further, this food, once stored, is released much more slowly in the homozygous obese (*ob/ob*) or diabetes (*db/db*) mutants, which leads to greatly increased food efficiency and remarkable ability to withstand a fast (up to 40 days) (9). This report indicates that the heterozygous "normal" carriers have more efficient pathways of metabolism intermediate between those of homozygous mutant and the homozygous normal mice. This thriftiness trait, if manifested in wild populations, could provide the heterozygote with a selective advantage when food was scarce and yet not be deleterious when food was abundant. The existence of this trait in mice heterozygous for one mutant allele for either of two obesity-diabetes syndromes lends credence to the thrifty genotype etiology of diabetes (1).

Such mechanisms may have played a role both in the development of diabetes-susceptible human populations (various Indian and primitive cultures) and the persistence of diabetes susceptibility in the population despite negative selection pressures. The metabolic abnormalities controlling thriftiness should be more amenable to analysis in genetically defined models where the effects of one gene can be studied rather than in genetically ill-defined human populations where the interaction among many "thrifty" genes (both heterozygous and homozygous) may make interpretation impossible.

DOUGLAS L. COLEMAN

Jackson Laboratory,  
Bar Harbor, Maine 04609

#### References and Notes

1. J. V. Neel, *Am. J. Hum. Genet.* **14**, 353 (1962); D. L. Coleman, *Nutr. Rev.* **36**, 129 (1978).
2. L. Herberg and D. L. Coleman, *Metabolism* **26**, 59 (1977).
3. D. L. Coleman, *Diabetologia* **14**, 141 (1978).
4. G. S. Cuendet, E. G. Loten, D. P. Cameron, A. E. Renold, E. B. Marliss, *Am. J. Physiol.* **228**, 276 (1975).
5. L. G. Alonso and T. H. Maren, *ibid.* **183**, 284 (1955).
6. J. E. Cox and T. L. Powley, *J. Comp. Physiol. Psychol.* **91**, 347 (1977).
7. D. L. Coleman and K. P. Hummel, *Diabetologia* **3**, 238 (1969).
8. K. P. Hummel, D. L. Coleman, P. W. Lane, *Biochem. Genet.* **7**, 1 (1972); D. L. Coleman and K. P. Hummel, *Diabetologia* **9**, 287 (1973).
9. D. L. Coleman, unpublished data.
10. P. R. Flatt, C. J. Bailey, T. W. Atkins, A. J. Matty, *Diabetologia* **13**, 393 (1977).
11. T. T. Yen, L. Lowry, J. Steinmetz, *Biochem. Biophys. Res. Commun.* **33**, 883 (1968).
12. P. Trayhurn and W. P. T. James, *Pfluegers Arch. Gesamte Physiol. Menschen Tiere* **373**, 189 (1978); T. T. Yen, R. W. Fuller, D. V. Pearson, *Comp. Biochem. Physiol.* **49A**, 377 (1974).
13. Supported in part by NIH grants AM 14461 and AM 20725 and by a grant from the Juvenile Diabetes Foundation. The Jackson Laboratory is fully accredited by the American Association of Laboratory Animal Care.

5 July 1978; revised 22 September 1978

## Electroencephalogram Correlates of Higher Cortical Functions

**Abstract.** By means of two-stage, nonlinear multivariate pattern recognition, electroencephalograms (EEG's) were analyzed during performance of verbal and spatial tasks. Complex scalp distributions of  $\theta$ -,  $\beta$ -, and, to a lesser extent,  $\alpha$ -band spectral intensities discriminated between the two members of a pair of tasks, such as writing sentences and Koh's block design. Small EEG asymmetries were probably attributable to limb movements and other uncontrolled noncognitive aspects of tasks. Significant EEG differences between cognitive tasks were eliminated when controls for inter-task differences in efferent activity, stimulus characteristics, and performance-related factors were introduced. Each controlled task was associated with an approximately 10 percent reduction, as compared with visual fixation, in the magnitude of  $\alpha$ - and  $\beta$ -band spectral intensity. This effect occurred bilaterally and was approximately the same over occipital, parietal, and central regions, with some minor difference over the frontal region in the  $\beta$  band. With these controls, no evidence for lateralization of different cognitive functions was found in the EEG.

For several years, researchers have reported correlations between interhemispheric asymmetries of ongoing brain electrical activity (EEG) and differences between "cognitive" tasks (1, 2). These results have been interpreted to reflect the functional specialization (in right-handers) of the left and right cerebral hemispheres, respectively, for sequential-analytical (verbal-logical) and simultaneous-holistic (spatial) cognitive processes. Frequently, interhemispheric EEG  $\alpha$ -band asymmetries were the only indices studied, the assumption being that such asymmetries were associated with the cognitive aspects of the tasks. In fact, it has never been established that asymmetries or other EEG features are directly related to cognitive activities. In addition to their cognitive differences, the tasks used in most of these studies have involved differences in stimulus characteristics, efferent activities (limb and eye movements), and performance-related factors (task demands and a subject's ability and effort). These noncognitive factors, which are known to affect the EEG, have not been adequately controlled in previous experiments.

Using two-stage, multivariate, nonlinear pattern recognition, we have searched for sets of EEG features, including but not limited to asymmetries, which might discriminate between commonly employed verbal-logical and spatial tasks (1, 2). Initially, several strongly discriminating features, not related to asymmetry, were found. While weak asymmetry effects were also found, it seemed likely that they were attributable to limb movements and other uncontrolled noncognitive aspects of the tasks. When limb movement was not required during task performance, and when stimulus characteristics and performance-related differences between tasks were relatively controlled, our analytical procedures did not uncover EEG patterns of any sort that could significantly distin-

guish between logical and spatial cognitive tasks. Each of the controlled tasks was associated with an approximately 10 percent reduction, as compared with visual fixation, in the magnitude of  $\alpha$ - and  $\beta$ -band spectral intensity. This effect occurred bilaterally and was approximately the same over occipital, parietal, and central regions with some minor difference over the frontal region in the  $\beta$  band. With these controls, asymmetry differences between the tasks were all but absent.

The results reported here were derived from two experiments in which EEG's were recorded from normal, right-handed (as assessed by questionnaire; siblings and parents were also right-handed) subjects while they performed batteries of randomly ordered cognitive and control tasks.

In the first experiment, 23 adults (18 males and 5 females) performed two or three 1-minute trials of reading, writing a summary of the previously read material from memory, Koh's block design, mental paper folding (the reconstruction of a cube from a flat pattern), scribbling, undirected block manipulation, and visual fixation on a spot (3). Reading and writing from memory have previously been used as examples of verbal-logical tasks, and Koh's block design and mental paper folding as spatial tasks (1, 2). Scribbling, undirected block manipulation, and visual fixation served as control tasks.

Experiment 2 was intended to separate possible EEG patterns associated with the cognitive aspects of tasks from those associated with efferent components, stimulus characteristics, and performance-related factors, all of which are intermixed in complex tasks such as those used in experiment 1. In this experiment, 32 adults (23 males and 9 females) (4) each performed 30 trials of shorter, simplified tasks, including: (i) mental rotation of block structures, a spatial task;

(ii) addition of a column of six to eight signed integers, a logical task; (iii) letter substitution, another logical task; and (iv) visual fixation on a spot, a control task (5). Each trial in experiment 2 lasted 6 to 15 seconds. Stimulus characteristics were better controlled than in experiment 1, and no motion of the limbs was required (6). For each subject, the amount of time to achieve the task and the degree of accuracy were assessed. Within- and between-subject differences in these performance-related factors were adjusted by selecting a subset of tasks for each subject that he or she would be expected to perform correctly about 80 percent of the time, in an average of approximately 7 seconds. This subset of tasks was selected for each subject on the basis of his or her performance during a practice session (7).

In each study, EEG activity from F3, F4, C3, C4, P3, P4, O1, and O2 (8) was Fourier-analyzed, and features based on estimates of spectral intensity in the  $\theta$  (4 to 7 Hz),  $\alpha$  (8 to 13 Hz), and  $\beta$  (14 to 20 Hz) bands were computed. Measurement vectors from each subject and each pair of tasks to be discriminated were converted to standard scores ( $\mu = 0$ ,  $\sigma = 1$ ) (9).

Two-stage, nonlinear multivariate pattern recognition analysis was used to derive EEG spectral signatures that could correctly classify an unknown EEG sample as coming from one or the other of a pair of tasks. This analysis requires the formation of an optimal linear combination of several discriminant functions, each of which may be in a linear or quad-

Table 1. Classification of the tasks in experiment 1 (complex tasks) by means of the EEG. Each entry is the percentage of correct test-set classifications of the two indicated tasks. For example, Koh's block design was distinguished from visual fixation with 94 percent accuracy. Except for the entry marked by an asterisk, all classifications were significant ( $P < .01$ ) if one assumes a moderate degree of intrasubject correlation of different trials of the same task (12).

Task	Koh's block design	Reading	Writing from memory
Visual fixation	94	82	89
Mental paper folding	75	81	
Writing from memory	85		
Scribbling			65*
Koh's block design		85	
Block manipulation	75		
Reading			84

\*Not significant.

ratic form (10). Decision rules were derived from known training samples from pairs of tasks and validated on separate test data (11). Spectral features important in the decision rules were listed according to their anatomic distribution. Multivariate pattern recognition was used in the search for EEG differences and was mainly sensitive to the consistency of the differences, and univariate descriptive statistics were used to obtain information about the average (over all subjects) size of the intertask EEG differences.

With the exception of the discrimination between writing from memory and

scribbling, the pattern recognition analysis significantly classified EEG test samples from all of the task pairs of experiment 1 (Table 1) (12). For example, 85 percent of the samples of test data were correctly classified ( $P < .01$ ) as either Koh's block design or writing from memory. The most important EEG features for discriminating these tasks were primarily higher  $\theta$ - and lower  $\beta$ -band spectral intensity in most scalp locations. Asymmetry ratios were not important in the discrimination. Thus, complex scalp distributions of EEG features generally differentiated the tasks, but it was difficult to relate individual elements of the discriminating patterns to the sensory, motor, and cognitive aspects of these complex tasks.

The results in Fig. 1 (13) show that  $\theta$ -band spectral intensity is associated with Koh's block design at all scalp locations, and is slightly higher at left-sided (odd-numbered) electrode placements than at right-sided ones. For writing from memory,  $\theta$ -band intensity is higher than in visual fixation only over the occipital (O1 and O2) region. In both tasks,  $\alpha$ - and  $\beta$ -band intensity is lower than in visual fixation (except for  $\beta$  intensity over the occipital region during writing from memory, which may represent contamination from electromyographic activity arising in neck and shoulder muscles). Other than at the right frontal placement (F4), there is no difference in the  $\alpha$  band between Koh's block design and writing from memory at right-sided (even-numbered) electrode placements. On the left side there is a slightly greater decrease of

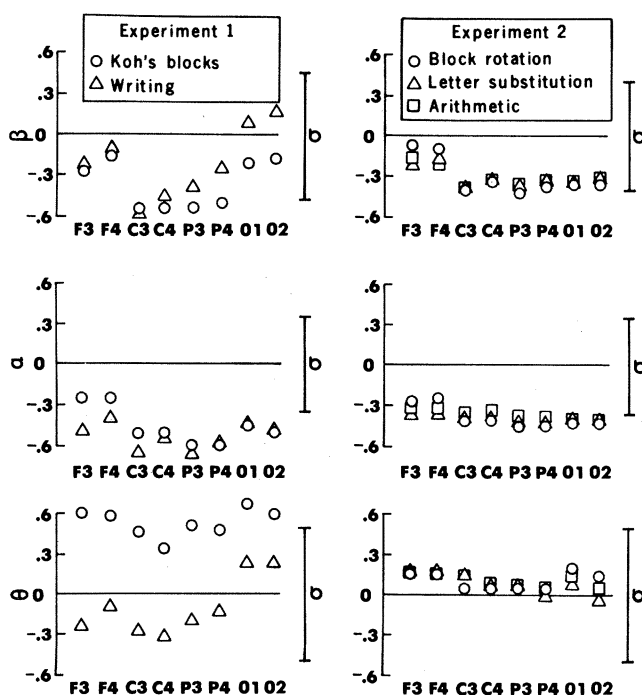


Fig. 1. Results of experiments designed to assess EEG correlates of higher cortical functions. (Left) Tasks of experiment 1 were 1 minute long and involved limb movements and uncontrolled differences in stimulus characteristics and performance-related factors. (Right) Tasks of experiment 2 were less than 15 seconds long and required no motion of the limbs; stimulus characteristics and performance-related factors were also relatively controlled. The graphs display means over all subjects of standard scores of EEG spectral intensities [expressed as changes from visual fixation values for clarity of display (13)] recorded during performance of two tasks in experiment 1 and three tasks in experiment 2. Upper, middle, and lower sets of graphs are for spectral intensities in the  $\beta$ ,  $\alpha$ , and  $\theta$  bands. The abscissa shows scalp electrode placements: F3, left frontal; F4, right frontal; C3, left central; C4, right central; P3, left parietal; P4, right parietal; O1, left occipital; and O2, right occipital. Standard deviations, which differed but slightly between electrode placements, are indicated at the right. Although there are prominent EEG differences between the uncontrolled tasks of experiment 1, EEG differences between the relatively controlled tasks of experiment 2 are lacking. Each of the controlled tasks is, however, associated with a remarkably similar bilateral reduction in  $\alpha$ - and  $\beta$ -band spectral intensity over occipital, parietal, and central regions. There is no evidence in these results that logical and spatial cognitive processes are associated with differentially lateralized EEG patterns.

$\alpha$  intensity for writing than for Koh's blocks, most evident at F3 and C3. This result appears to be associated with differences in the patterns of right-hand limb movements between the tasks. (Since it was not possible to distinguish between writing and scribbling, it is not likely that this left-sided change during writing is an indication of the left-sided localization of language functions in our right-handed subjects.) The major effects of  $\alpha$  and  $\beta$  suppression and  $\theta$  enhancement, where found, were bilateral (14).

In mental paper folding versus reading, 81 percent of the test-set observations were correctly classified ( $P < .01$ ). The EEG features selected by the pattern recognition analysis included higher frontal  $\theta$ -band intensity in paper folding than in reading, higher occipital  $\theta$ -band intensity in reading, lower parietal  $\alpha$ -band intensity in paper folding, and lower  $\beta$ -band intensity in paper folding over most placements. The EEG features sensitive to asymmetry were not used in the discrimination. Anatomic patterns of the slight differences between homologous left and right electrode placements were inconsistent.

The EEG differences found between the complex tasks in experiment 1 could not be specifically associated with the cognitive differences between the tasks. By contrast, the controlled active tasks of experiment 2 were much less strongly differentiated when subjected to the identical analytical methods (Table 2) (15). In other words, when limb movements are not required, and when stimulus characteristics and performance-related differences between tasks are relatively controlled, logical and spatial cognitive operations can be discriminated only very weakly on the basis of spectral intensity measurements of the background EEG. Furthermore, evidence of interhemispheric lateralization of these tasks was all but absent. The weak differences between active tasks found by pattern recognition in experiment 2 may be due to cognitive differences between the tasks, or to residual efferent (small eye movements) stimuli, or performance-related differences.

In terms of EEG features, the active tasks of experiment 2 were better differentiated from visual fixation than from each other (Table 2). The decision rules of experiment 2 embodied EEG differences consistent with those seen in experiment 1 (for example,  $\alpha$ - and  $\beta$ -band intensities associated with block rotation, addition, and letter substitution were lower, while  $\theta$ -band intensity was slightly higher). When we used anatomically defined subsets of features for

Table 2. Classification of tasks in experiment 2 (controlled tasks) by means of the EEG. Each entry is the percentage of correct test-set classifications of the two indicated tasks.

Task	Serial arithmetic	Block rotation	Letter substitution
Visual fixation	75	76	75
Block rotation	62*		
Letter substitution		61*	
Serial arithmetic			59*

\*Not significant

classification, the distribution of classification accuracies was different in block rotation versus visual fixation as compared with addition versus visual fixation. In block rotation there was higher classification accuracy over the parietal and occipital regions than over the frontal and central regions. In serial arithmetic (addition), there was higher classification accuracy over left-sided placements. This last pattern is suggestive of left-sided localization of "logical" cognitive operations, but may not be taken as evidence of same.

In experiment 2 (Fig. 1, right), there were only small differences between the means for the tasks. There was a striking uniformity in the magnitude (approximately 10 percent) and anatomic distribution of the bilateral decrease in  $\alpha$ - and  $\beta$ -band spectral intensity (except in the  $\beta$  band over F3 and F4). This pattern has previously been reported and is perhaps associated with "nonidling" of an underlying cortical region (2, 16). It is also consistent with the results of studies of regional cerebral blood flow (17).

Since the relatively controlled tasks in experiment 2 involved distinct logical and spatial cognitive operations (5), it is likely that the EEG patterns that discriminated between the tasks of experiment 1 were due to intertask differences in efferent activities, stimulus characteristics, or performance-related factors, rather than to cognitive differences. These experiments offer no support for the idea that lateralized EEG differences in different tasks reflect cognitive processes, as has previously been asserted. However, these data do strongly suggest that large, bilateral areas of cerebral cortex are involved in the performance of complex higher cortical functions.

A. S. GEVINS  
G. M. ZEITLIN, J. C. DOYLE  
C. D. YINGLING, R. E. SCHAFFER  
E. CALLAWAY, C. L. YEAGER

EEG Systems Laboratory, Langley  
Porter Institute, University of  
California School of Medicine,  
San Francisco 94143

## References and Notes

1. D. Galin and R. Ornstein, *Psychophysiology* 9 (No. 4), 412 (1972); R. Dumas and A. Morgan, *Neuropsychologia* 13, 219 (1975); S. R. Butler and A. Glass, *Electroencephalogr. Clin. Neurophysiol.* 36, 481 (1974); G. McKee, B. Humphrey, D. W. McAdam, *Psychophysiology* 10, 441 (1973); A. H. Morgan, H. Macdonald, E. R. Hilgard, *ibid.* 11, 275 (1974); D. Galin, J. Johnstone, J. Herron, *Neuropsychologia* 16, 416 (1978); S. Butler and A. Glass, in *Advances in Psychobiology*, A. M. Reisen and R. F. Thompson, Eds. (Wiley, New York, 1976), vol. 3, pp. 219-272; E. Donchin, M. Kutas, G. McCarthy, in *Lateralization in the Nervous System*, S. Harnad et al., Eds. (Academic Press, New York, 1977); A. S. Gevins and R. E. Schaffer, *CRC Crit. Rev. Bioeng.*, in press.
2. J. C. Doyle, R. Ornstein, D. Galin, *Psychophysiology* 11, 567 (1974).
3. In performing Koh's block design, subjects manipulated nine patterned blocks on a lapboard to reconstruct from memory a design presented [see J. Matarazzo, *Wechsler's Measurement and Appraisal of Adult Intelligence* (Williams & Wilkins, Baltimore, 1972), pp. 212-214]. For mental paper folding, subjects were shown a flat pattern that corresponded to a cube that had been unfolded. They were then asked to mentally fold the pattern back into the cube and determine whether or not two arrows, which were marked on the faces of the patterns, would meet when the cube was assembled [see R. Shepard and C. Feng, *Cog. Psychol.* 3, 228 (1972)]. Scribbling consisted of either repetitiously writing the sequence "abc" in longhand or scribbling small loops horizontally across the page. Subjects performed the undirected block manipulation by "randomly" manipulating blocks with their right hands.
4. Six subjects were eliminated because of poor performance [see (7)]. Five additional subjects were eliminated because of insufficient artifact-free observations.
5. Mental block rotation involved mentally rotating the top form (a picture of a string of ten cubes with three bends) and determining if it was identical to or the mirror image of the bottom form [see R. N. Shepard and J. Metzler, *Science* 171, 701 (1971)]. Letter substitution involved transposing the letters of a three-letter group one step forward (or for some subjects, backward) in the alphabet, and noting whether the new three-letter group formed an English word. For visual fixation, subjects were instructed to concentrate on their breathing while staring at a red fixation point superimposed on a dark slide. This task lasted 30 seconds and occurred randomly during the experiment.
6. Each task item was centered on the fixation point and displayed in a vertical array covering no more than 5° vertical visual angle, and a 1.5° horizontal visual angle. Subjects initiated tasks and signalled response (terminating task) by pushbutton. Initial and final 1-second data segments were discarded to avoid possible influence of sensory-evoked and premotor potentials, associated, respectively, with stimulus onset and subject response.
7. All task items were answered by pressing either a "yes" or "no" switch. (Each task contained identical numbers of "yes" and "no" response items.) Subjects verbally reported their calculated sums and trigrams to "no"-response tasks (ii) and (iii) as a double check. For responses to task (i), a criterion value of percentage correct responses was determined from the binomial probability for achieving a given accuracy rate by randomly depressing the response buttons. Six subjects whose accuracy rate was below this criterion (.01) were considered "random responders" and were eliminated from the study. The workload of each task may be increased for task (i) by increasing the rotation angle between block structures, for task (ii) by increasing the number of digits to be added, and for task (iii) by requiring backward letter transposition (rather than forward). Three "workloads" were produced for task (i) by creating sets of items with 140°, 160°, and 180° of angular rotation. For task (ii), three workloads corresponded to the addition of six, seven, or eight digits. For task (iii) there were two workloads: forward or backward. To roughly equate performance-related factors between tasks and between subjects, we chose the workload to match each subject's ability and effort. On the basis of response accuracy and average solution time for practice items, we chose for each subject a set of experimental items to which he or she could give correct responses approximately 80 percent of the time in an average of 7 seconds per trial. To test dif-

- ferences in the mean percentages of correct answers, we found the  $F$  ratios at chance level for tasks (i) and (ii):  $F_1(2, 23) = 2.6$ ;  $F_{11}(2, 23) = 3.0$ . A  $t$ -test for percentage correct differences between the two workloads of task (iii) was at chance level:  $t(24) = 0.7$ . Similarly, neither the  $F$ -test for task (ii) response times, nor the  $t$ -test for task (iii) response times was significant:  $F(2, 23) = 1.1$ ;  $t(24) = 0.2$ . Differences in average solution time between the three workloads of task (i) were marginally significant:  $F(2, 23) = 3.5$ ;  $P < .05$ . Similar calculations for differences in mean accuracy and mean response time for practice items were significant for all tasks. The lack of significant differences between workloads of the tasks for both performance measures [except as noted for task (i)] suggests that the procedures used to equalize performance-related factors across subjects and tasks were effective.
8. Recorded with a Grass model 6 electroencephalograph. Two EEG technologists independently edited and discarded data contaminated by extracortical artifacts. Reference was ipsilateral ear in experiment 1, linked ears in experiment 2. Forehead was at ground potential. The effect of reference electrode on measurements of asymmetry are discussed by A. Amochaev and A. Salamy (*Psychophysiology*, in press) who found slightly larger task-related EEG asymmetries when electrode reference was to ipsilateral ears as compared with  $C_z$ .
  9. Features used were spectral intensity averaged over the band; ratios of banded spectral intensity for the following pairs: F3-F4, C3-C4, P3-P4, O1-O2, C3-P3, P3-O1, C4-P4, P4-O2. Ratios were of form  $(a - b)/(a + b)$ . In each study, approximately 30 minutes of EEG from each task was used in the multivariate analysis. For technical details, see A. S. Gevins, C. L. Yeager, S. L. Diamond, J. P. Spire, G. M. Zeitlin, A. H. Gevins, *IEEE Proc.* **63**, 1382 (1975); A. S. Gevins, C. L. Yeager, G. M. Zeitlin, S. Ancoli, M. S. Dedon, *Electroencephalogr. Clin. Neurophysiol.* **42**, 267 (1977); A. S. Gevins, G. M. Zeitlin, S. Ancoli, C. L. Yeager, *ibid.* **43**, 31 (1977); A. S. Gevins, G. M. Zeitlin, C. D. Yingling, J. C. Doyle, M. S. Dedon, J. H. Henderson, R. E. Schaffer, J. J. Roumasset, C. L. Yeager, *ibid.*, in press; A. S. Gevins *et al.*, *ibid.*, in press.
  10. S. Viglione, in *Adaptive, Learning, and Pattern Recognition Systems*, J. Mendel and K. Fu, Eds. (Academic Press, New York, 1970), p. 115; W. B. Martin, L. C. Johnson, S. S. Viglione, P. Naitoh, R. D. Joseph, I. D. Moses, *Electroencephalogr. Clin. Neurophysiol.* **32**, 417 (1972).
  11. In experiment 1, a randomly selected trial of the two or three 1-minute trials of each task by each subject was placed in the test data set for validating the decision rule derived from the remaining trials (method 1). In another series of classifications, the test data set was composed of the observations from eight subjects randomly selected from the total group of 23, with similar results (method 2). Both methods were also used in experiment 2. For method 1, a randomly selected one-third of all trials was saved for the test set. Method 2 was used with seven of the 21 subjects comprising the test set. This was repeated for several different groups of seven subjects comprising the test set. Except for minor differences, results and conclusions were the same. Results of experiments 1 and 2 reported in Tables 1 and 2 were obtained with methods 1 and 2, respectively.
  12. Estimates of the significance of these pairwise classifications obtained from the binomial probability distribution may be positively biased by intrasubject correlation of multiple observations of a single type of task. In experiment 1, even under the most extreme assumption of intrasubject correlation, that is, that the number of independent observations of each task is equal to the number of subjects (23), each of the pairwise classifications of the tasks listed in Table 1 achieves better than  $P = .01$ . None of the classifications in experiment 2 reach this level of significance under the same stringent assumption. (Since there were 21 subjects in experiment 2, 77 percent classification accuracy was required for a  $P < .01$  significance. Based on 23 subjects, classification accuracy for experiment 1 of 74 percent or more was significant at  $P < .01$ .) Under the most lenient assumption, that is, that each trial of a task constitutes an independent observation, all of the classifications in experiment 2 reach this level of significance. If one assumes moderate intrasubject correlation such that the effective number of observations of a task is half the number of trials of a task, the active task versus the visual fixation task classifications are highly significant ( $P < 10^{-5}$ ), whereas the active task versus the active task classifications fail to achieve the same level of significance ( $P = .02$  for rotation of blocks versus addition;  $P = .03$  for rotation of blocks versus letter substitution;  $P = .06$  for letter substitution versus addition).
  13. For display purposes, intensities measured for each task were grouped with those for visual fixation and transformed to standard scores. This was performed separately for each subject. The mean and standard deviation across subjects of these standard scores are shown in Fig. 1. To maximize classification performance, standardization was over the two tasks involved in each pattern recognition analysis. Descriptive statistics were computed for the unstandardized EEG feature values as well as for those standardized as described. Since only minor differences were found between the three sets of data, our conclusions are not attributable to the standardization method used.
  14. An analysis of variance by task and scalp location for  $\theta$  intensity (active tasks standardized against visual fixation) yielded significant  $F$  ratios for task [ $F(1, 352) = 126.02$ ;  $P < .001$ ] and scalp location [ $F(7, 352) = 4.23$ ;  $P < .001$ ], yet no significant interaction [ $F(7, 352) = 0.9$ ]. A similar analysis of  $\beta$  intensities yielded a marginally significant  $F$  ratio for task [ $F(1, 352) = 4.5$ ;  $P < .05$ ], a significant  $F$  ratio for scalp placement [ $F(7, 352) = 5.9$ ;  $P < .001$ ], and no significant interaction [ $F(7, 352) = 0.6$ ]. When this analysis was performed for  $\alpha$  intensities, only the scalp location was marginally significant [ $F(7, 352) = 2.58$ ;  $P < .05$ ], with task [ $F(1, 352) = 3.6$ ] and task by scalp location [ $F(7, 352) = 0.4$ ] not being significant. Correlated  $t$ -tests comparing  $\alpha$  intensities between the two tasks were significant for F3 [ $t(22) = 6.0$ ;  $P < .001$ ], and not significant for F4 [ $t(22) = 2.0$ ]. The data for Koh's block design and writing from memory were also analyzed with statistical methods identical to those applied to data collected from the same tasks from the same electrodes (P3 and P4) (2). Application of Wilcoxon matched pairs signed ranks test to the difference in right-left ratios of parietal  $\alpha$ -band spectral intensity between Koh's block design and writing confirmed previous results, that is, a positive sign for the difference was found in 18 out of 23 subjects ( $P < .01$ ). However, the results in Fig. 1, left center, show that this difference between ratio measurements is attributable to a reduction in  $\alpha$ -band intensity over the left parietal (P3) electrode, during writing.
  15. No significant differences were found in parietal  $\alpha$  ratios between block rotation and addition when Wilcoxon's test was applied as described in (14). To test the effect of having shortened the time per task in experiment 2, the Koh's blocks versus writing discrimination of experiment 1 was repeated with the first 15-second segment of data from each task. This segment was even more strongly differentiated than was the full minute (test set classification of 98 percent versus 85 percent respectively); the topographic distribution of features was essentially the same.
  16. R. Cooper, J. Osselson, J. Shaw, *EEG Technology* (Butterworths, London, ed. 2, 1974), pp. 111-114; H. Legewie, O. Simonova, O. Creutzfeldt, *Electroencephalogr. Clin. Neurophysiol.* **27**, 470 (1969); G. Dolce and H. Waldeier, *ibid.* **36**, 577 (1974).
  17. D. Ingvar and N. Lassen, Eds., *Brain Work* (Academic Press, New York, 1975); P. Roland and B. Larsen, *Arch. Neurol.* **33**, 551 (1976); J. Risberg *et al.*, *Brain* **98**, 511 (1975); B. Larsen, E. Skinhoj, N. Lassen, *ibid.* **101**, 193 (1978).
  18. Supported in part by PHS grant NS10471 and PHS biomedical research support grant RR05755. We thank J. Brody, M. Dedon, J. Henderson, H. Stuler, and R. Tannehill for technical assistance, and E. R. John, D. Galin and E. Donchin for constructive criticism.

28 June 1978; revised 11 October 1978

## Human Muscular Dystrophy: Elevation of Urinary Dimethylarginines

**Abstract.** *The amounts of the dimethylarginines  $N^G, N^G$ -dimethylarginine (DMA) and  $N^G, N^G$ -dimethylarginine (DM'A) excreted in the urine of muscular dystrophic patients were examined and compared with the amounts excreted by normal controls, patients with other types of neuromuscular diseases, and patients with disuse muscle atrophy resulting from traumatic paralysis. The patients with muscular dystrophy excreted high concentrations of DMA and this urine showed high ratios of DMA to DM'A. This finding indicates a relation between protein methylation processes and muscular dystrophy.*

Although the urinary amino acids and peptides in patients with muscular dystrophies have been examined (1-3), no consistent finding has been reported, presumably because of the lack of quantitative precision of the analytical techniques employed. Our laboratory has focused on studying the ninhydrin-positive constituents in normal human urine by means of a one-column, ion-exchange chromatographic system developed by Hamilton (4). This system, with its high sensitivity ( $1 \times 10^{-9}$  mole) and high resolution, has enabled us to establish a clear chromatographic pattern for the complex urinary amino acids and their derivatives (5). Recently, we have used the system to examine the urine of patients with muscular dystrophies and have observed that, compared to normal controls, these patients excrete larger amounts of  $N^G, N^G$ -diamethylarginine (DMA), and

their urine shows a characteristic high ratio of DMA to  $N^G, N^G$ -dimethylarginine (DM'A). The results of our study suggest that this disease may be associated with the altered metabolism of the arginine methylated proteins.

We have studied 12 patients with muscular dystrophy (ten with the Duchenne type, one with the Becker type, and one female with possible Duchenne type); five patients with other neuromuscular diseases (one with spinal muscular atrophy resulting from traumatic paralysis; and ten normal control subjects of comparable age (5 to 16 years). Urine was collected from each individual early in the morning and was stored without preservatives at  $-80^\circ\text{C}$  pending analysis. Standard DMA, DM'A, and monomethylarginine were purchased from Calbiochem.

The ion-exchange chromatographic