of mice in a similar test situation has been noted (*8*). Latencies of the saline injected groups tested 1 hour after training are significantly ($P = <.05$) (*9*) longer than both the 1-minute and the 5-minute groups. When mice that had been injected with DDC 30 minutes previously were tested 1 minute after training, there was a significant increase in latency ($P = <.01$), reflecting increased retention as compared with saline controls. The DDC group tested 5 minutes after training had latencies significantly shorter than the 1-minute group ($P = <.05$), indicating that amnesia was rapidly developing. When tested 1 hour after training, the DDC injected mice were clearly amnesic, as were groups tested at 6 and 24 hours. The latencies of these three groups that received DDC are all significantly ($P = <.001$) shorter than their comparable controls that received saline. These data indicate that DDC injected mice show an initial enhancement of memory, followed by the development of amnesia which reaches a maximum 6 hours after training and persists up to 24 hours.

In the second experiment, we examined the effect of injecting DDC at various times before and after foot shock, with subsequent testing for retention at 24 hours. Four groups were injected subcutaneously with DDC (250 mg/kg; $N=10$) or with saline ($N=10$) 30 minutes before, immediately after, 2 hours after, and 23.5 hours after training. Figure 2 shows the results of this experiment. Significant amnesia (compared with results from saline controls) also occurs when mice are injected immediately after the training trial ($P = <.01$), but not if the injection is delayed for 2 hours. This indicates that retention defects are not due to lack of initial registration of the stimuli. Amnesia is again produced if DDC is given 30 minutes before the retention test, 23.5 hours after training ($P = <.001$). This latter effect appears to be a clear instance of interference with retrieval and may have a different basis from amnesia observed when the drug is injected immediately after training.

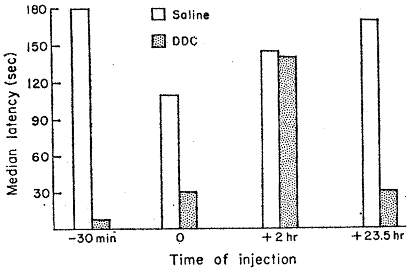

Fig. 2. Median latency to enter the large compartment on the retention test as a function of the time interval between injections of DDC and saline before and after the training trial. All groups were tested for retention 24 hours after training.

The biochemical results show that DDC, in the dose administered, effectively lowers the [^{14}C]norepinephrine biosynthesis from [^{14}C]dopa and that the endogenous norepinephrine concentrations are significantly decreased in the brains of the treated mice (Table 1). The most effective inhibition of dopamine β-hydroxylase in the brain, as measured by the conversion of [^{14}C]dopa to [^{14}C]norepinehprine, was apparent 90 minutes and 4.5 hours after administration of DDC, with partial recovery at 8.5 hours. Endogenous brain norepinehprine was decreased at 30 minutes after administration of DDC, with a further decrease observed at 1.5, 4.5, and 8.5 hours after DDC.

The enhancement of memory, tested 31 minutes after administration of DDC in this strain of mice, is associated with a decrease in brain norepinephrine. Impairment of memory at later time intervals also is associated with a decrease in the concentration of brain norepinephrine which is more marked than that observed at 30 minutes. These results may reflect the quantitative difference in concentration or early depletion of norepinephrine from storage pools with rapid turnover. The data in this preliminary report do not explain the apparent dual effects of inhibition of norepinephrine biosynthesis, which need to be investigated further. Inasmuch as DDC inhibits other enzymes, such as aldehyde dehydrogenase, which result in formation of phenolic alcohols, the possibility remains that these results on memory might be due to factors other than decreased concentration of norepinephrine in the brain. There is, however, evidence that norepinephrine is intimately involved in affective states (*10*). Common experience attests to an influence of emotion and arousal on memory. Severe dietary restriction of amino acids essential for the biosynthesis of catecholamines in man has been associated with defects in memory (*11*). The previously noted animal studies indicate that decrease of brain amines interferes with memory. Our results more directly suggest a noradrenergic compound subserving memory in mice.

CLARK T. RANDT
DAVID QUARTERMAIN
Department of Neurology, School of Medicine, New York University, New York 10016

MENEK GOLDSTEIN
BERTA ANAGNOSTE
Department of Psychiatry, School of Medicine, New York University

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Language Production: Electroencephalographic Localization in the Normal Human Brain

Abstract. *Slow negative potentials, which are at a maximum over Broca's area in the left hemisphere, were recorded when normal subjects spontaneously produced polysyllabic words. Bilaterally symmetrical potentials were seen with analogous, nonspeech control gestures. These potentials began up to 1 second before word or gesture articulation. These results are the first demonstration of localization of language production in normal human brain.*

In man's cerebral cortex the foot of the third frontal convolution in the left hemisphere is called Broca's area, named after Paul Broca who first suggested that it plays a major role in the expression of speech (*1*). Current neurological theory on the organization of language in the brain (*2*) is in basic agreement with the proposal that Broca's area has prime responsibility for the coding of language into articulatory commands (3). Proposals for models of the language system in the brain have been based upon a variety of experimental techniques. One study (4) of occipital lobe averaged evoked potentials to visually presented verbal and nonverbal stimuli indicated left-right occipital lobe asymmetries. There is a large body of indirect data obtained from visual and auditory perceptual asymmetry studies, in which the dichotic listening and tachistoscopic presentation techniques were used, most of which supports the view that the language system is lateralized in the left hemisphere (5). Hypotheses concerning language production, as noted by Geschwind (2), have relied exclusively on data obtained under abnormal conditions: brain damage, surgical or pharmacological intervention, and electrical stimulation during neurosurgery (6). There is some methodological criticism of using lesion evidence to infer normal function; a lesion in cortical area A that results in loss of function B does not necessarily permit the inference that cortical area A has function B when it is normal (7). A number of alternative hypotheses may be entertained; for instance, the lesion may block access to the area that has the function or may so imbalance the neural system as to produce the impaired function. Consequently, direct physiological evidence for localized language functions obtained from normally functioning brains is of considerable interest and importance; insofar as this evidence supports lesion-based models, it assumes even greater importance.

A slow negative potential over motor cortex that begins up to 1 second prior to a voluntary movement has been described (8). This readiness potential has been shown to be at a maximum over contralateral motor areas when unilateral movements are made. When the movements involve bilaterally symmetrical motor output, the potential tends also to be bilaterally symmetrical in its distribution (9). Attempts have been made to apply this methodology to the localization of speech function, but these attempts were apparently unsuccessful; unfortunately, no descriptions of the methodologies applied are available (10). Since these potentials have been shown to be enhanced by increased subjective involvement in the motor act (11), it was felt that maximizing this aspect of speech production might lead to positive results.

Subjects were eight right-handed women with normal speech enrolled in an introductory psychology course. Recording electrodes (Beckman miniature biopotential electrodes) were placed symmetrically left and right over the precentral gyri (9 cm down from vertex and 2 cm anterior to the interaural line) and over inferior frontal areas (11 cm down from vertex and 4 cm anterior to the interaural line). Recordings from these four sites were referred to linked electrodes over left and right mastoids. A seventh electrode on the forehead served as a ground.

Signals were amplified by means of Grass chopper-stabilized preamplifiers and attendant driver amplifiers in a Grass polygraph. The signals, in addition to being written out on paper, were taken to the input and record head of a Precision Instrument 6208 magnetic tape recorder. The output from the reproduce head of the recorder was fed to the input of a Nuclear-Chicago DRC signal averager. Activation of a voice trigger by the subject's verbalizations started a 2-second sweep by the averager. The distance between record and reproduce heads of the tape recorder and the time it took for tape to travel that distance allowed us to make an on-line analysis of activity occurring for approximately 1.5 seconds before the verbalization, along with 0.5 second of activity during verbalization. Samples of 30 of each of the responses were taken for analysis.

Subjects were told about electroencephalographic and evoked potential methods and were carefully instructed about the effects of eye movements, swallowing, and gross movements of the head, limbs, and trunk. A "neutral position" was defined for each subject as a relaxed but immobile posture, eyes fixated on a dot within a circle displayed in front of the subject, lips together, and tongue resting on the floor of the mouth. Subjects were told to produce a response as rapidly and accurately as possible, beginning from this neutral position. Each subject produced four sets of responses in the following order: a spitting gesture, a set of words beginning with the phoneme "k" and having at least three syllables, a coughing gesture, and a set of words beginning with the phoneme "p" and having at least three syllables. The spitting and coughing gestures were chosen as nonspeech controls involving aspects of the vocal tract musculature analogous to the words beginning with "p" and "k." Responses were produced at a self-determined rate, with the proviso that subjects were to allow 4 to 6 seconds between responses; however, subjects were not asked to count the interval between responses but to concentrate on obtaining a neutral position before each response. For the spitting gesture, each subject was told to imagine a small piece of paper stuck on the bottom lip, and to remove it with a sharp puff of air. For the coughing gesture, each subject was told to simulate a natural cough but with a rapid, sharp onset and a single burst of air. For the two word lists, each subject was told to think of a different word each time—that is, to avoid repetition and to articulate the word rapidly and accurately. Sample lists of appropriate words were shown to each subject to facilitate these responses, but memorization of the list was discouraged and in fact did not occur. All four types of responses were carefully rehearsed before the actual experimental run, with particular attention given to minimizing preparatory movements of the articulatory muscles such as taking a breath, pursing the lips, or lowering the jaw, which might occur prior to the well-defined acoustic transient at the onset of each response.

Subjects were seated in a high-backed padded chair in a sound-deadened chamber. The microphone of a General Radio, model 1561-A precision sound level meter, which was used as the voice trigger, was placed directly in front of the subject's mouth approximately 2½ cm away. The meter was set at 80 db, with "flat" weighting and a "fast" response time.

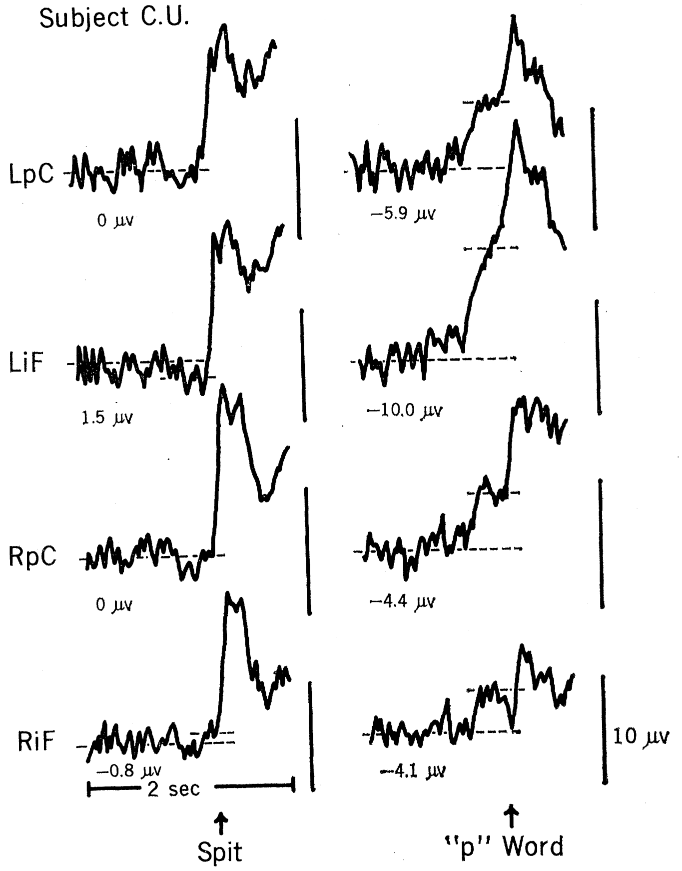
The results of three of the eight subjects were eliminated from analysis because of persistent fidgiting, blinking, or both, which caused large artifacts in the records. The records of the remaining five subjects were free of these artifacts during the 1.5-second preverbalization analysis interval.

Sample averages with their measured values are shown in Figs. 1 and 2. The tracings in Fig. 1 are the clearest demonstration from our data of a laterality difference in the inferior frontal sites with language production. Figure 2, which shows a large symmetrical positive wave about 250 msec prior to the trigger, also shows a clearly localized negativity (over the left inferior frontal area) prior to and peculiar to speech production. Most of the recordings were characterized by large, fast potentials occurring up to 500 msec prior to the voice trigger. These potentials tended to be equal in all leads and were probably movement artifacts. Prior to these large potentials, most recordings showed slower, lower-amplitude, unequal shifts; these were taken to represent the readiness potentials and were measured as average amplitude during their final 150 msec as compared with a baseline established during the initial 150 msec of the average.

For purposes of statistical analysis, data from the spitting and coughing gestures were pooled, as were those from "p" and "k" words. Left-right differences were computed for the precentral and inferior frontal locations and were analyzed by means of a two-tailed t-test for difference scores. For the spitting and coughing gestures, neither of the difference distributions was significantly different from zero (precentral area: $t = .556$, mean difference $= 0.2$ μv; inferior frontal area: $t = .980$, mean difference $= 0.6$ μv).

Both of the difference distributions for the words reached statistical significance (precentral area: $t = 2.36$, $P < .05$, mean difference $= 2.6$ μv; inferior frontal area: $t = 4.14$, $P < .01$, mean difference $= 4.5$ μv. All mean differences are in the direction of greater negativity over the left hemisphere recording sites. The difference between precentral recordings was not expected and is probably due, in large part, to field effects arising from inferior frontal sites, which were a scant 3 cm distant. Analysis of the differences between left inferior frontal and left precentral areas and between right inferior frontal and right precentral areas showed that, although the mean difference on the left was in the direction of greater negativity at the inferior frontal side and the mean difference on the right was in the direction of greater negativity at the precentral site, none of these difference distributions (for either the words or the gestures) had means that differed significantly from zero. However, when left-right differences between these difference scores were computed and analyzed, a significant mean difference of 2.53 μv ($t = 1.937$, $P < .05$, one tail) was obtained for the potentials accompanying word production. The mean difference of 0.71 μv that accompanied gesture production was not significant.

The salient features of the electrical activity preceding language production may be summarized as follows. First, when electrodes are placed over the inferior frontal sites of the left hemisphere (presumably Broca's area) and of the right hemisphere, larger negative potentials are recorded from the left hemisphere. Second, inferior frontal



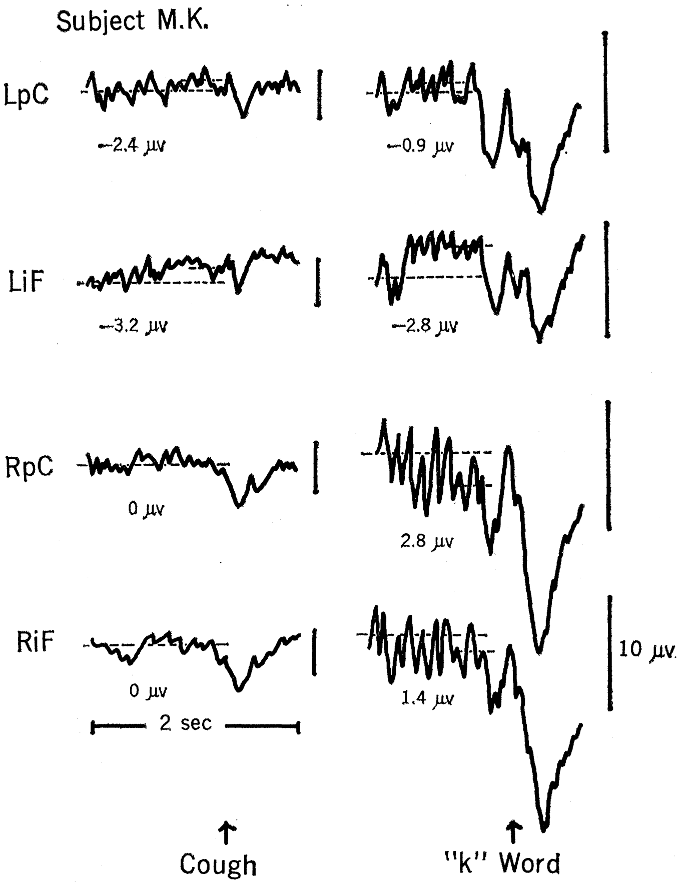


Fig. 1 (left). Average responses and their measured values from subject C.U. during production of the spitting gestures and the "p" words. A maximum negative shift is seen over the left inferior frontal area before word production. *LpC*, left precentral; *LiF*, left inferior frontal; *RpC*, right precentral; *RiF*, right inferior frontal. Fig. 2 (right). Average responses and their measured values from subject M.K. during production of the coughing gestures and the "k" words. Prior to the large symmetrical positive potential that occurs before the voice trigger (arrow), a maximum negative shift is seen over the left inferior frontal area prior to word production. *LpC*, left precentral; *LiF*, left inferior frontal; *RpC*, right precentral; *RiF*, right inferior frontal.

and precentral potentials show significant differences between hemispheres, which is suggestive evidence for within-hemispheric localization. These data provide the first direct physiological evidence for localization of language production functions in the intact, normal human brain.

DALE W. MCADAM
HARRY A. WHITAKER
Departments of Psychology, Languages and Linguistics, and Neurology, University of Rochester, Rochester, New York 14627

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Neural Events and Psychophysical Law

A verbal report of the intensity of a tone entails considerable processing of sense organ input by the brain. With this come the wide variety of perceptual effects as well as the great individual differences in subjective effect which Stevens has recognized (*1*) but barely alludes to in "Neural events and the psychophysical law" (*2*). Nowhere is this more evident than in data from average evoked responses (AER), which many studies have linked to perceptual and attentional processing. Far from being a reflection of the operation of a power law mechanism governing subjective magnitude in the central nervous system, as Stevens suggests, AER data on stimulus intensity seem more to reflect the operation of a complex system of interpretation and modulation.

We, and others, have found that the amplitude of an individual's AER components (especially after 100 msec) may increase, remain the same, or even decrease with increasing stimulus intensity (*3*). Davis (*4*) found that a single mathematical relationship between amplitude and intensity "may be useful as a first approximation to predict an average trend, but it does not predict usefully for all individuals."

We find that these individual differences in amplitude-intensity functions are fairly reliable across time, and appear to reflect neither trivial physiological artifacts nor purely saturation phenomena.

The changes of an individual's AER amplitude with increasing stimulus intensity may be related to behavior on other perceptual tasks, drug treatment, or even psychiatric diagnosis. In recent studies at the National Institute of Mental Health, for example, manic patients showed AER's which increased strongly (augmented) with increasing stimulus intensity, whereas depressed patients showed less strongly increasing or actually decreasing amplitudes (reducing) with increasing stimulus intensity (*5*). When normal college students were tested on the same AER procedure, those who scored high on the Zuckerman stimulus-seeking questionnaire (*6*) tended to be augmenters, and those who scored low tended to be reducers. Similarly, Hall *et al.* (*7*) report that aggressive, exploratory, stimulus-seeking cats augmented, whereas retiring, timid cats reduced.

Stevens has developed elegant methodologies and a wide body of psychophysical data. The "turbulence of electrophysiology" to which he alludes may reveal the crucial role of individual differences in the study of perception.

MONTE BUCHSBAUM
Unit on Psychophysiology, National Institute of Mental Health, Bethesda, Maryland 20014

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22 December 1970

Buchsbaum is indeed correct. It took a century to discover how to elicit and process a subject's "verbal reports" in a way that could disclose the operating characteristics of the various sensory systems. Averaged evoked responses may prove almost as labile, and how to interrogate them effectively may call for ingenuity and a lot of good fortune. An electrode on the skull may or may not be able to reflect the operation of the sensory transducer in a meaningful way. The full answer to that question remains to be discovered. Perhaps it is significant that when evoked potentials at the cortex have been shown to increase as a power function of the intensity of the stimulus, the exponents have tended to be much lower than the exponents that are now thought to characterize the transducer process. In other words, the amplitude of the potential picked up on the skull does not keep pace either with the subject's experience of intensity or with the potential that can be recorded in closer proximity to the sense organ. Much additional processing appears to have intervened.

Granted all the difficulties, I would like to believe that the knowledge that can be gleaned about sensory systems by studying evoked potentials is greater than zero, and I assume that Buchsbaum would concur.

S. S. STEVENS
Harvard University, Cambridge, Massachusetts 02138

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