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Conference held at Irvine, California, October 14-17,1987

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FIELD	GROUP	SUB-GROUP	Neurobiology of Learning and Memory; Neuroscience; Neural Networks

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This grant provided partial support for the Third Conference on the Neurobiology of Learning and Memory which was held at Irvine, California on October 14-17, 1987. There were three symposium topics: Forms of Memory, Regulation of Cortical Function in Memory, and Representations - Beyond the Single Cell. There was a total of 24 symposium speakers, 64 poster presentations and over 300 registered participants. The primary purpose of the conference was to review and critique fact and theory derived from recent research concerning each of the topics. Particular emphasis was given to the development of neural network modals designed to accommodate experimental findings. A book based on the proceedings of the conference, Brain Organization and Memory: Cells, Systems, and Circuits (James L. McGaugh, Norman M. Weinberger, and Gary Lynch, Eds.) is in press (Oxford University Press).

This document contains the conference program.
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Technical Report

AFOSR-87-0293

This grant provided partial support for the Third Conference on the Neurobiology of Learning and Memory which was held at Irvine, California on October 14-17, 1987. There were three major symposium sessions and a poster session. There was a total of 24 symposium speakers, 64 poster presentations and over 300 registered participants. Copies of the conference program, poster abstracts and a list of registrants are attached. A book based on the proceedings of the conference, *Brain Organization and Memory: Cells, Systems, and Circuits* (James L. McGaugh, Norman M. Weinberger, and Gary Lynch, Eds.) is in press (Oxford University Press).

The primary purpose of the conference was to review and critique fact and theory derived from recent research concerning each of three topics: Forms of Memory, Regulation of Cortical Function in Memory, and Representations -Beyond the Single Cell. In each symposium, particular emphasis was given to the development of neural network models designed to accommodate experimental findings.

The first session examined forms of learning and memory seen in studies of learning and memory in animals as well as humans. Clearly, the kinds of questions addressed differed markedly. So, too, did the observations made and conclusions drawn. There was little evidence of convergence in conceptions of learning and memory. The lack of convergence in fact and theory and the lack of an acceptable taxonomy of learning and memory complicate attempts to understand the neurobiology of memory systems common to different species.

The second session examined the role of the neocortex and interactions of neocortex with subcortical systems in memory. There is increasing evidence,

from recent work, for the generally accepted (but not well substantiated) view that information is stored in the interconnections among cells in the neocortex. Subcortical systems appear, from much recent evidence, to affect memory by regulating the functioning of the neocortex.

The third session reviewed progress in the development of neural network theories of learning and memory. Such theories have, in recent years, begun to provide plausible accounts of how cognitive processes may be represented in the interactions among neurons. While such developments were given special emphasis in the third session, neural network models provided a general theme running throughout the conference. There appears to be increasing agreement that memory is based on interactions among groups of neurons. Or, at least, it seems that such an assumption aids the development of plausible neurobiological explanations of the complex phenomena of learning and memory.

Overall, the conference provided a highly effective forum for the examination of these issues by leading investigators and the proceedings will provide a useful agenda for future research.

A volume based on the presentations at the Conference will be published by Oxford University Press in late 1988 or early 1989.

The complete citation is:

McGaugh, J.L., Weinberger, N.M. and Lynch, G. *Brain Organization and Memory: Cells, Systems and Circuits*. New York: Oxford University Press, in press.

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University of California, Irvine
October 14-17, 1987

Poster Session: Thursday, October 15, 1987
6:30 - 8:30 p.m.

Center for the Neurobiology of
Learning and Memory
Bonney Center
University of California, Irvine

Posters presented by topic:

A - Behavior

B - Primate

C - Human

D - Pharmacology

E - Neurophysiological Correlates of Learning

F - Morphology

G - Long-term Potentiation

H - Neurochemistry

I - Neural Networks

Poster Session Chairs: Thomas M. McKenna, Chair
Ines B. Introini-Collison
Ursula V. Staubli
Stuart Zola-Morgan

A - BEHAVIOR

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United Kingdom

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Authors whose names are underlined are Conference participants.

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IHV LESIONS IMPAIR PASSIVE AVOIDANCE LEARNING IN THE CHICK.
D.C. DAVIES, D.A. TAYLOR AND M.H. JOHNSON*. Department of Anatomy and Cell Biology, St. Mary's Hospital Medical School, London, W2 1PG, UK. and *MRC Cognitive Development Unit, London, WC1H 0AH, UK.

Biochemical, morphological and electrophysiological evidence has indicated that the intermediate part of the medial hyperstriatum ventrale (IHV) plays a critical role in imprinting in the chick. Indeed, bilateral lesions to IHV prevent acquisition and impair retention of an imprinted preference (see Horn, G. Memory, Imprinting and the Brain, OUP., 1985). Biochemical and morphological experiments have also indicated that part of the medial hyperstriatum ventrale is involved in one-trial passive avoidance learning (PAL) in the chick (see Rose, S.P.R., in Brain Plasticity, Learning, and Memory, eds. B.E. Will, P. Schmitt and J.C. Dalrymple-Alford, pp. 39-50, Plenum Press, 1985). In the present study we investigated whether bilateral IHV lesions affect one-trial PAL.

Young chicks will spontaneously peck at a small bright bead. If the bead has been dipped in a distasteful substance such as methyl anthranilate (MeA), the chicks learn not to peck a similar bead on subsequent presentation. In contrast, chicks which initially peck a water-coated bead will continue to peck a similar bead on subsequent presentation. Thus in a single trial, chicks can learn not to peck at an aversive stimulus (Cherkin, A., Proc. nat. Acad. Sci. USA. 63: 1094, 1969).

Chicks (approx. 12 h old) were anaesthetised by i.p. injection of Equithesin and received bilateral lesions to IHV or to the lateral part of the cerebral hemisphere (LCA) under stereotaxic control. A similar number of chicks served as sham-operated controls. 15-17 h after surgery the chicks were placed individually in an illuminated arena for 5 min and were then presented with a red bead (6 mm in diam.) coated with either MeA or water. Chicks which failed to peck during training were discarded. The remainder were returned to a 'holding' incubator and all subsequent experimental procedures were performed 'blind'. Three hours later the chicks were returned to the arena and tested with an identical water-coated bead.

Significantly more ($P < 0.001$) sham-operated chicks trained on a MeA-coated bead (77%, n = 22) avoided the test bead than did sham-operated birds trained on a water-coated bead (9%, n = 23). Similarly, significantly more chicks with bilateral LCA lesions ($P < 0.01$) trained on a MeA-coated bead (73%, n = 11), avoided the bead at test than did LCA-lesioned birds trained on a water-coated bead (9%, n = 11). In contrast there was no significant difference in avoidance of the bead at test between IHV-lesioned chicks trained on either MeA (27%, n = 11) or water (0%, n = 10). There was no difference in avoidance of the bead at test between sham-operated and LCA-lesioned chicks trained on either water or MeA. However, the avoidance at test of IHV-lesioned chicks trained on MeA differed significantly from sham-operated and LCA-lesioned chicks ($P < 0.02$ for both comparisons).

Thus bilateral IHV lesions prevented the acquisition of a one-trial PAL task, but sham-operation and LCA lesions did not. This suggests that the role of IHV in learning is not restricted to imprinting.

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MEMORY DEVALUATION - Ivan Izquierdo, Maria E. Pereira & Marcia L.F. Chaves, Centro de Memoria, Departamento de Bioquimica, Instituto de Biociencias, UFRGS, 90049 Porto Alegre, RS, Brazil

Recently acquired memories may be changed quali- or quantitatively by not directly relevant information. The best studied quantitative modification is a reduction of recall, which has been explained in a variety of ways, and may be called "memory devaluation."

We have recently studied this in humans and in rats. Healthy human subjects were asked to learn a text on the 1954 World Cup of Football, and submitted to a questionnaire on specific items of the text 48 h later. Retention scores were much lower if the subjects were asked to read a non-factual derogatory comment on the general quality of the cup after the text, than if they were exposed to a favorable comment, or to no comment. Clearly, the negative comment made the previously read information less memorable. The negative comment was effective if it was presented 0 or 3, but not 6 h after the text.

Rats were trained in a shuttle avoidance task and exposed, 2 or 24 h later, either to an open field, or to a session of extinction of the avoidance task; and then tested at 48 h from training. Both treatments hindered retention test performance. The open field was effective only when presented 2 h after training, whereas, predictably, the extinction procedure was effective both at 2 and 24 h. The effect of both was cancelled by diazepam, which suggests it had to be recorded in order to be effective.

It is possible that the "memory devaluation" caused by a post-training negative comment in humans, and the "memory devaluation" caused by the open field, but not by the extinction, in rats, may be related. The time dependency of the effects suggests that the post-event information adds to the experience and influences its storage.

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LONG-LASTING EFFECTS OF IMHV LESIONS ON THE RECOGNITION OF INDIVIDUALS. M.H.Johnson, J.J.Bolhuis*, G.Horn** and P.Bateson**. MRC Cognitive Development Unit, 17 Gordon St., London WC1H 0AH, U.K.; *Zoology Dept., University of Groningen, The Netherlands. **Zoology Dept., University of Cambridge, Cambridge CB2 3EJ, U.K.

Lesions to a restricted part of the domestic chick forebrain, IMHV, impair the acquisition and retention of filial preferences (see Horn,G. Memory, imprinting and the brain, OUP., 1985; Horn,G. Behav. Neurosci., 100: 825-832, 1986), including preferences for individual adult fowl (Johnson, M.H. & Horn,G., Behav. Brain Res. , 23: 269-275, 1987). Do such lesions effect other behaviours requiring the recognition of individual birds? Animals of several species, when choosing a mate, prefer individuals that are slightly different from those that they were reared with, a phenomenon known as optimal outbreeding. In the present experiment we enquired whether female chickens which had received bilateral IMHV lesions on the first day of life would be impaired in this behaviour.

Thirteen female chicks received bilateral IMHV lesions on the day of hatching. Fifteen other female chicks served as sham-operated controls. All chicks were reared in small social groups with a single male of the same strain. When 3 months old their preferences for different males were measured in a simultaneous choice test. The sham-operated birds spent significantly more time with an unfamiliar male of the rearing strain, than with either the male with which they had been reared, or an unfamiliar male of a novel strain ($F_{2,28} = 6.36$, $p<0.01$). In contrast, the lesioned females spent equal time with all of the males ($F_{2,24} = 0.216$, n.s.).

These results indicate firstly, that intact female chickens have preferences consistent with the optimal outbreeding hypothesis, and secondly that lesions to IMHV placed early in life impair this ability. This finding is consistent with the hypothesis that the integrity of IMHV is necessary for the recognition of individuals, as well as for other conspicuous objects.

AD THALAMIC LESIONS, AV THALAMIC AND CINGULATE CORTICAL NEURONAL ACTIVITY, AND AVOIDANCE LEARNING IN RABBITS. Y. Kubota*, J. Shenker*, M. Mignard, D. Bentzinger*, and M. Gabriel. Dept. Psychol., Univ. Illinois, Champaign, IL 61820

The anteroventral (AV) thalamic nucleus develops learning-related discriminative activity in response to auditory conditional stimuli (CSs) during differential avoidance conditioning in rabbits (Gabriel et al., Science, 208:1050-52, 1980). The anterodorsal (AD) thalamic nucleus also exhibits learning-related neuronal changes which are reciprocally related to those in the AV nucleus, with respect to the stages of behavioral acquisition (Bice et al., Neurosci. Abstr., 1986). The frequency of AD nuclear neuronal firing was highest in the first training session when the activity of the AV nucleus and frequency of conditioned responses (CRs) were low. In the criterial session, however, the AD nuclear activity decreased, whereas the AV nuclear activity was at its peak and many CRs occurred. Also, the activity of the AD nucleus increased significantly in response to a novel stimulus. These findings suggest that the AD nucleus provides the source of synaptic drive that limits the activity of the AV nucleus when unexpected environmental events call for response suppression. It follows that lesions in the AD nucleus should increase AV nuclear activity and CR frequency in sessions in which novel training contingencies are experienced.

Bilateral electrolytic or chemical (ibotenic acid) lesions were made in 12 male albino rabbits. Histological examination revealed bilateral damage in the AD nucleus in 4 of these subjects. The remaining subjects had small lesions in the hippocampus or in the cortex. Rabbits were given standard conditioning, followed by extinction (procedures described in Mignard et al, accompanying abstract). As predicted, rabbits with AD nuclear lesions made significantly more CRs in the first acquisition session and in the first extinction session than either controls or those with hippocampal or cortical lesions ($p<.001$). In the first extinction session, CS elicited activity in the AV nucleus of rabbits with the AD nuclear lesions was greater than that in control rabbits ($p<.001$). No statistically significant difference was found in the first acquisition session, but there was a trend in the expected direction ($p<.12$). Neuronal activity in Area 29 showed enhanced activity in the same sessions after damage in the AD nucleus ($p<.01$ for both sessions). Increased activity after AD nuclear lesions also appeared in Area 24, only in the first acquisition session ($p<.05$). The similarity between these effects and the effects of subicular lesions (Gabriel et al., Exp. Br. Res., in press, 1987) suggests that the subiculum and the AD nucleus cooperate in the limiting of AV nuclear activity and behavior in response to unexpected training contingencies. (Supported by NIMH Grant 37915 to M.G.)

POTENTIAL IMMUNOLOGICAL BASIS FOR SENESCENCE-RELATED COGNITIVE DEFICITS.

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Increasing serum levels of brain-reactive antibodies (BRA) represent a correlate of aging in both humans and animals, Because of their potential for producing CNS pathology, BRA may be involved in the pathogenesis of senescence-related cognitive dysfunction, including Alzheimer's Disease, In order to test for a correspondence between BRA and senescence-like behavioral deficits, the age-dependent declines in active avoidance learning and memory performance by several autoimmune mouse strains (NZB/BlNJ, BXSB/MpJ, MRL/MpJ-lpr) and nonautoimmune C57BL/6 mice were compared. These autoimmune mice are known to exhibit accelerated appearance of BRA in their sera, and accordingly, it was hypothesized that they should also show accelerated learning/memory deterioration. The autoimmune mice showed a decline in their ability to acquire the learning task beginning at early ages (3-6 months), whereas C57BL/6 mice did not exhibit deterioration until 12-28 months of age, The heterochronic patterns of learning/memory deterioration closely paralleled the formation of BRA with age in each strain, A second experiment was designed to determine if an immunological manipulation which was capable of elevating serum BRA would be sufficient cause for deterioration of learning and memory, To this end, bone marrow and spleen cell suspensions were transferred from aged into young, irradiated C57BL/6 mice, Three months following the transfer, recipient mice were tested for simultaneous occurrence of BRA in serum and deficient learning of the avoidance response, Comparisons among control groups indicated no effect of irradiation or transfers of cells between age-matched mice, However, young recipients of cell suspensions from aged donors showed high BRA levels and a senescence-like learning deficit, Overall, the results of these studies support the hypothesis that BRA may be a causative mechanism in the cognitive decline associated with aging, Supported by NIH grants AG03823, AG06182, NS-129624, and RR05879, and research funds of Veteran Administration,

IMPROVEMENT OF SHUTTLE-BOX AVOIDANCE FOLLOWING POST-TRAINING TREATMENT IN PARADOXICAL SLEEP DEPRIVATION PLATFORMS IN RATS

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The effects of post-training paradoxical sleep deprivation (PSD), via the platform method, on acquisition and long-term retention (LTR) of shuttle-box avoidance were studied in Wistar rats. Animals were given a daily training session for 5 days (acquisition), following which each rat was placed for 5 h either on small platform (ø 7 cm) surrounded by water (PSD group) or on a large platform (ø 16cm) surrounded by water (Yoked control group), or was given no treatment (Dry control group). Another identical training session (LTR test) was also given to every subject 14 days after the last acquisition session. The treatment on the large platform (Yoked control animals) improved learning in successive training sessions. A similar but statistically non significant improvement was also observed in the PSD group. In the LTR test, the PSD animals tended to lose performance as compared with the conditioning level achieved in the last acquisition session. Locomotor and emotional changes produced by PSD and PSD procedures are ruled out as the cause for these findings. We suggest that arousal produced by both PSD and PSD procedures could have improved the acquisition of the conditioning, whereas PSD per se could have been detrimental for LTR of the learned response.

MULTIVARIATE ANALYSIS OF AN OPERANT MODEL AND THE PARAMETERS THAT BEST PREDICT LEARNING AND MEMORY. A. Oscós, A. Meneses and V. Alemán. Departamento de Farmacología y Toxicología y Departamento de Fisiología y Neurociencias, CINVESTAV-IPN y División de Neurociencias, Instituto Mexicano de Psiquiatría. México, D.F.

Several paradigms have been used in the study of neurobiology of learning and they involve different types of stimuli such as: food, water, sex and electrical shocks. However, traditional learning parameters like latencies and lever pressings, they neither offer a complete description of the behavioral manifestations occurring during (and of importance for) acquisition, nor they predict its degree or percentage of learning involvement. The present model, attemps to analyze alternate but correlated paramets of an autoshaped lever pressing response. Thirty 90 day-old female rats were trained to press a retroactive illuminated lever that is presented during 8 sec (conditioned stimulus, CS) and preceds the delivery of a 45 mg food pellet (unconditioned stimulus, UCS). Besides the active control group (AC) and once animals reached the maximal acquisition level, they were divided in five groups (N=6). Rats from one group were sacrified immediately after acquisition, other group was re-ran 96 hr after the last session and sacrified, this group allow us to determine the retention level after this time. Three other groups that were extinguished at different times (48, 76 and 96 hr). Responses during the CS presentation was the criterion Y, contacts to the pellet through during the CS were the X_1 predictor and contacts in the absence of CS was the X_2 predictor, we therefore can equate $Y=a_1X_1+b_2X_2+e$. In the second training session, results obtained with this equation yields a R^2 value of 0.5 (R^2 means, that X_1 and X_2 combined accounts for almost 100% of the variance of Y) when X_1 is about 80% of its maximal value. Thereafter, X_1 decrease to reach a minimum of 10% in the 6th session when R^2 value is now close to 1.0. During extinction a gradual decrease of R^2 values reach a minimun of 0.4 in the third extinction session. At the third acquisition session a crossing over between X_1 and Y was observed and this seems to be of great interest since it suggest, that at this time a long lasting change is taking place in the brain because of learning. That is, while the number of lever pressing during the CS increase, the number of pellet through contacts during the CS decrease. Thus Y values seems to satisfactory predict learning since there is a gain in the precision of when and where to make through contacts; in other words this finding indicates and predicts the degree of CS-UCS association. Also this type of analysis allow us to determine critical periods of learning when probably neurochemical events are taking place and can be experimentally analyzed.

HIPPOCAMPAL DENERVATION FACILITATES OLFACTORY LEARNING-SET FORMATION AND DOES NOT IMPAIR MEMORY IN A SUCCESSIVE-CUE GO, NO-GO TASK. T.A. Otto, F. Schottler*, U. Staubli, and G. Lynch. Center for the Neurobiology of Learning and Memory, Univ. of California, Irvine, CA 92717.

In an olfactory discrimination task using simultaneous odor presentation, hippocampal denervation by lesions of the entorhinal cortex produces an 'anterograde amnesia' syndrome in rats which is characterized by unimpaired acquisition of new discriminations (given short intertrial intervals) but deficits in retention of those discriminations when tested 1 hour later (Staubli et al., Proc. Natl. Acad. Sci. 81:5885, 1984). Eichenbaum et al. (Behav. Neurosci. in press) have recently reported that lesions to the fornix either facilitate or impair olfactory learning-set acquisition depending on whether the olfactory cues are presented sequentially or simultaneously, respectively. In the present experiments, we investigated the effects of a more specific hippocampal denervation on two aspects of olfactory learning using sequential odor presentation: 1) the formation of learning sets, and 2) the retention of individual cues.

Ten male Sprague-Dawley rats, 250-280 g, served as subjects. Five received bilateral electrolytic lesions to the entorhinal cortex. The remaining five rats served as sham-lesion controls. During daily odor training sessions, these water-deprived rats were trained to discriminate a single pair of odors which were ejected randomly and successively into the cage by constant-flow air pressure. Nosepoke responses to the arbitrarily-designated 'positive' odor resulted in access to a 0.05 ml water reinforcer; responses to the 'negative' odor went unreinforced. Sessions were terminated when the subject reached a criterion of 18 correct responses in 20 consecutive trials, or at 400 trials maximum. Five such sessions, with session-unique odor pairs, were conducted.

Both groups exhibited olfactory learning set acquisition, evidenced by a marked decrease in the number of trials to criterion across sessions. Hippocampally denervated subjects, however, outperformed their sham-lesioned counterparts in the number of correct responses during the first 20 trials of a session ($p<.05$) and in overall accuracy within a session ($p<.01$). In contrast to the results obtained using simultaneous odor presentation, the experimental animals exhibited no deficit in subsequent tests of retention (reversal). These data are consistent with the notion that the hippocampus is not required for 'procedural' types of memory and suggest that its role in the encoding of specific cues is task, or 'strategy', dependent.

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BEHAVIORAL HABITUATION TO SPATIAL NOVELTY IN RATS: DEVELOPMENT OF AND INTERFERENCE BY POST-TRIAL TREATMENTS.

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Habituation of locomotor activity in a spatial novelty situation is a relatively simple form of behavioral plasticity, which allows to study non-associative experience-induced behavioral modifications in the freely-behaving rat (Sadile, et al., 1978; Corbone et al., 1984).

Three different approaches were used in order to validate it as a model to study learning and memory processes:

1) The inter-exposure interval was manipulated by agents which are known to interfere with the hypothesized "consolidation process(es)" (McGaugh, 1966) in associative learning paradigms. The interference approach indicated that the 24 hour activity decrement in a novel environment, operationally defined as long-term behavioral habituation (LTH), requires polysome aggregation, protein synthesis, a functioning neocortex and a balanced paradoxical/slow wave sleep ratio; it appears to be modulated by endogenously released or exogenously given vasopressin. Moreover, LTH requires an intact forebrain innervation by locus coeruleus, but is only impaired by 6-OH-DA lesion of dorsal noradrenergic bundles, whereas it is facilitated by lesion of septo-hippocampal fibers (Sadile et al., 1978; Corbone et al., 1984).

2) Correlative studies were made a) with the entorhinal afferents to CA4-regio inferior by a Timm's staining at a mid-septotemporal level, which showed that LTH is negatively correlated with the entorhinal input and with the infra- and intra-pyramidal mossy fibers (Lipp et al., 1987); b) with hippocampal ^{3}H-corticosterone maximal binding (MCB), which showed that LTH co-varies with MCB; c) with immunoreactive vasopressin (IR-AVP) in the septum and in the hippocampus, which showed significant covariation between LTH and IR-AVP; d) with a RNA fraction with fast turnover, which showed experience induced inhibition.

3) After the interference and correlative approach, the development of LTH was studied by inter-exposure intervals of different length (0.5-12 hr and 1-28 days), either during the light or the dark phase of the circadian cycle, with a transversal design. The animals used were adult, random-bred Sprague-Dawley rats, and rats of the Naples High- (NHR) and Low-Excitability (NLR) strains, selectively bred for divergent reactivity in a novelty situation (Sadile, et al., 1983). A MANOVA gave significant effects for strain, inter-exposure interval and for post-exposure sleep or wakefulness, whereas the analysis of the temporal patterns showed LTH formation to be best fitted by a non linear complex function.

In conclusion, response suppression upon re-exposure to a novel environment is a plastic phenomenon, whose underlying mechanisms appear to be multiple and which appears to be a useful model for the understanding of more complex forms of learning and memory.

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LESIONS IN THE DENTATE-INTERPOSITUS REGION OF THE CEREBELLAR DEEP NUCLEI DISRUPT CONDITIONED EYELID RESPONSES IN THE RAT.

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The dentate-interpositus (DI) region of the cerebellar deep nuclei has been shown to be essential for conditioned eyelid and leg flexion responses, but so far only in one species, the rabbit. The present study examines the effects of DI lesions on conditioned eyelid responses in a second species, the rat. The aim is to extend the cross-species generality of this phenomenon, and to demonstrate the suitability of the rat in this context.

The methods used here to condition eyelid responses in the rat were as close as possible to those used previously in the rabbit. Training in the a Pavlovian delay paradigm consisted of 3-5 daily sessions of 100 trials in which a 380 msec tone-CS was paired with a 100 msec periorbital electric shock US, which co-terminated with the CS. Integrated EMG activity was recorded from the upper eyelid during the pre-CS, CS, and Post-US trial periods, but not during the US. The use of electrical recording and stimulation made it unnecessary to restrain the rats during testing. Training continued for one complete session after criterion performance was reached (9 CRs in 10 trials). Lesions were then made under diazepam anesthesia by passing 2-3 mA anodal DC current for 10 sec through bilateral electrodes chronically implanted in the DI region.

The rat was found to be similar to the rabbit in response topography, learning rate, and cerebellar function. Conditioned eyelid responses had the same form in the rat as the rabbit, but were often contaminated by a short-latency (30-40 msec) non-associative "flinch" response. Consequently CR's were measured only in the second half of the CS-US interval. The learning rate of the rat was slower, but asymptotic levels of responding were comparable. Lesions in the DI region produced severe decrements in CR frequency, amplitude, and area in 6 rats, partial decrements in 7 rats, and no decrement in 1 rat. The UR to the eyeshock and the "flinch" response were unaffected in all rats, demonstrating that the lesion effect was not a sensory or motor deficit.

These data suggest that the role of the deep cerebellar nuclei in conditioned defensive responses may be common to many mammalian species. In addition, this study establishes that the rat is a suitable subject for investigations of the anatomical, biochemical, and electrophysiological basis of eyelid conditioning.

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MEDIODORSAL THALAMIC LESIONS AND ATTENTION TO ENVIRONMENTAL CUES IN RATS. K. A. Stokes and P. J. Best, Department of Psychology, University of Virginia, Charlottesville, VA, 22901.

Rats with mediodorsal (MD) thalamus lesions exhibit impaired post-operative performance on a number of tasks, including the radial maze (Stokes and Best, Neurosci. Abstr., 11, 833, 1985; Stokes and Best, Behav. Neurosci., in press). The radial maze deficit occurred when extramaze visual cues were diminished, leading to speculation that the performance of MD rats might improve when these visual cues are enhanced. In this experiment, a new set of MD lesioned rats were trained on the radial maze in an abundantly-cued environment. Surprisingly, performance on the maze task was still severely impaired. Thus, MD animals continued to exhibit compromised acquisition and retention despite the availability of extramaze cues.

To examine this phenomenon further, the reactivity of MD-lesioned animals to changes in environmental stimuli was tested. The task required animals simply to move from a start box to a goal box for food reward. Start and goal boxes (each 30 cm long, 15 cm wide and 15.5 cm high) contained one of three sets of cues: white walls and grid floor, black walls and smooth floor, or black and white walls and carpet floor. Animals received 5 training trials in one start box connected to an identical goal box and 5 additional trials a day in a different start box, also connected to a matching goal box. After 4 days (40 trials), stable latencies to consume the food were achieved, and the goal boxes were changed. For some animals, the two goal boxes were simply switched; for others, the novel goal box was placed at the end of both start boxes.

Intact animals exhibit awareness of the switched familiar goal boxes by arresting their behaviour and exploring the compartment. MD lesioned animals, however, do not notice this change (their latencies do not increase). MD lesioned animals were capable of attending to cue changes, though, for, like intact animals, they arrested their behaviour in response to the novel goal box change. One hypothesis to account for these and the above results may be that MD animals can pay attention to environmental cues, but do not process familiar cues in the same way intact animals do, i.e., as specific to certain contexts, and as cues for certain behavioural responses.

A FURTHER ANALYSIS OF SPATIAL DISCRIMINATION LEARNING IN AGING RATS. F.J. van der Staay and W.G.M. Raaijmakers, Neuropsychology & Psychobiology of Aging, University of Limburg Biomedical Center, P.O.Box 616, 6200 MD Maastricht, The Netherlands.

Oades (1) suggested the use of a holeboard to study spatial memory in rats. We have found this task to be sensitive to age (2). In an attempt to further analyse the influence of aging, we studied male Brown-Norway rats of 5 ages (4-,13-,19-,25- and 30-month-old). A fixed set of 4 of the 16 holes were baited with food during training (80 trials). Reference and working memory performances (RM resp WM) were differentially affected by age: no differences between groups were found in initial level of RM but the 25- and 30-month-old rats were impaired in rate of RM-acquisition, whilst the reverse was true with respect to WM: no differences between age groups in rate of learning but a decline in initial level of performance.

Two other factors that might contribute to age differences in learning the holeboard task -speed of responding and development of a response strategy- were analysed by using 'mean inter-visit-interval' (IVI) and 'trial-to-trial-correspondence in sequence of rewarded choices' as the respective measures. All age groups showed the same, rather small increase in choice correspondence making it unlikely that differences in response strategies were contributing to the differences in discrimination. IVI's differed clearly initially but within 50 trials all groups had reached the same asymptotic level, thus excluding differences in speed of responding as a cause of age differences still existing (WM) or increasing (RM) after 50 trials. It is therefore highly probable that differences in cognitive ability are causing the differences in performance.

The conefield was developed as an alternative to the holeboard having different response requirements. The conefield is a square open field with 16 cones; the rat has to lean against a cone to inspect it and collect the food. A similar task (4 cones baited) was presented to 3- and 29-month-old male Brown-Norway rats. The results were highly comparable to those of the holeboard task: an initial impairment but parallel increase for WM; no initial difference and a slower speed of acquisition for RM in the old rats compared with the young ones. These results suggest that the differential effects of aging on spatial WM and RM are task independent.

(1) Oades,R.D. & Isaacson,R.L. (1978). *Behav. Biol.*,24, 327.

(2) Van der Staay, F.J., Raaijmakers, W.G.M. & Collijn, T.H. (1986). *Adv. Behav. Biol.*,29, 603.

SPATIAL MEMORY REPRESENTATION IN PRIMATE PREFRONTAL CORTEX: EVIDENCE FOR A MNEMONIC HEMIANOPIA. S. Funahashi, C.J. Bruce, and P.S. Goldman-Rakic, Sec. of Neuroanatomy, Yale Univ. Sch. Med., New Haven, CT 06510.

The spatial delayed-response task depends on the integrity of the primate's dorsolateral prefrontal cortex (PFC), especially the cortex within and near the principal sulcus. Usually this task is administered to unrestrained monkeys under conditions which preclude precise control over visual stimulation and motor response. We used an oculomotor analog of the classical, manual delayed-response task to present target stimuli in specified locations in the visual field and to measure the monkey's relevant behavior more precisely.

Rhesus monkeys fixated on a central spot of light on a TV monitor. Visual targets were briefly presented at peripheral locations, but the monkey was required to maintain fixation of the central spot throughout the delay period. The disappearance of the central spot at the end of the delay period signaled the monkey to move its eyes to where the peripheral target had previously appeared. Target location and display varied randomly from trial to trial. We thus tested the ability to temporarily store the coordinates of visual targets and later make saccadic eye movements based on that stored information. Monkeys that exhibited near perfect performance for delays up to 6 sec were given unilateral partial lesions of PFC or were used to study single neuron activity in PFC during performance of this task.

The lesion studies showed that: (1) unilateral lesions of PFC impaired the ability to perform this task; (2) the deficit was specific for the visual field contralateral to the lesion, with performance for ipsilateral targets only mildly affected; (3) there was little effect on visually-guided saccades.

The single unit study showed that as many as 60% of PFC neurons responded in conjunction with the oculomotor version of the delayed-response task. As in analogous studies with the manual version of delayed-response, different neurons responded selectively in relation to the target presentation (16%), during the delay (39%), and at the response (36%). Among 104 delay-related neurons, 78% showed differential activity for particular target locations. The activity of half of these neurons was greater (or lesser) on trials with contralateral targets, while 17% were activated specifically with ipsilateral targets; all other delay-related neurons were activated by targets at the vertical meridian.

These studies add to the evidence that primate PFC is concerned with working spatial memory. They show that this function obtains independently of response form in that it pertains to the eyes as well as to the limbs, and that memories for targets in each visual hemifield are processed mainly by the contralateral PFC. Due to its precise temporal and spatial control of stimulus and response events, this oculomotor delayed-response paradigm holds promise for further elucidating the mechanisms of spatial memory.

REMARKABLE SIMILARITIES IN CHARACTERISTICS OF VISUAL MEMORY FOR MAN AND MACAQUES. Jeffrey D. Levine, Robert W. Doty and James L. Ringo, Center for Brain Research, University of Rochester, Rochester New York, 14642.

To determine whether the efficiency of short-term mnemonic processing is similar in man and macaque, 4 Macaca nemestrina and 4 college students were tested on identical versions of Sternberg's memory scanning task (Science, 1966). Subjects had to classify, as quickly as possible, probe images according to whether they were members of a previously defined set of 1-6 targets. In order to selectively assess visual mnemonic abilities per se, the stimuli were complex, multi-colored patterns, most of which lacked simple, unique linguistic descriptors that may provide human subjects additional mnemonic cues. Three of the macaques attained levels of performance equivalent to, or better, than 2 of the human subjects, these animals maintaining accuracies of >88% correct even when remembering 6 target images. For all subjects, the time required to correctly classify probes increased as a function of the number of relevant targets. These data are consistent with the concept that probes are evaluated against target representations via a serial exhaustive strategy. Interestingly, perhaps because they have smaller brains, the remembering of each additional target image increases the time required to classify probes by only 8 msec/target for macaques, but 21 msec/target for human subjects.

To evaluate the efficiency of "intermediate-term" mnemonic processing, 2 macaques and 6 human subjects were trained and tested on nearly identical versions of a running recognition task (RRT). Subjects viewed a sequence of images that lacked simple linguistic labels and had to classify each image as being viewed either for the first time within that experimental session, or as being identical to an image presented previously within that session. Under testing conditions when as many as 45 "distractor" images had intervened between the first and second presentations of a particular image, the abilities of the macaques to differentiate the "repeated" images from "novel" images surpassed that of one of the human subjects.

An additional macaque, also trained on the RRT, provided a unique opportunity to test "long-term" memory for briefly viewed visual stimuli. This particular animal had initially been involved in delayed-match-to-sample (DMS) experiments. During the early part of this animal's training on the RRT, some of the images that the animal had briefly (<30 sec) viewed six months previously during DMS testing were included as distractor images. On a significant proportion of trials, this animal "indicated" that these DMS images were second presentations while, in reality, they were being used for the first time with the RRT.

Although the limits of the long-term mnemonic abilities have yet to be fully defined, the above findings indicate that, despite the macaque's lack of the vast neocortical expanse characteristic of the human brain, their visual mnemonic abilities are highly developed and fully congruent with those of man.

MEDIAL TEMPORAL NEURONAL ACTIVITY RELATED TO BEHAVIOURAL RESPONSES AND MEMORY

F.A.W. Wilson, M.W. Brown & I.P. Riches, The Medical School, Department of Anatomy, University of Bristol, U.K.

Recordings of the activity of single neurones were made in the inferomedial temporal cortex (IMTC = peri- and prorhinal cortex, areas TG and TE1) and hippocampal formation (HF = hippocampus, dentate gyrus and subicular cortex). Monkeys were presented with stimuli varying in their novelty/familiarity. In a delayed matching to sample task (DMS), the monkey compared 2 successively presented stimuli on each trial. If the stimuli differed in size, the monkey pressed a panel to the left of the monitor. If the stimuli were the same size, a right press was correct. Stimuli in the DMS task were presented in blocks, typically of 8 trials, before replacement. Objects were also shown to the monkey without a behavioural response being required.

20% (26/128) of IMTC neurones responded maximally to the first presentation of stimuli which had not been seen recently, the response declining with repetition. The response was significantly reduced even after distraction caused by intervening presentations of other objects for 6/7 units so tested. For 17 (81%) of the units showing declining responses, the mean response to the first presentation of unfamiliar objects was significantly greater than that to familiar objects. Thus there is evidence that certain IMTC units may display extended memory spans. None of 268 units recorded in HF showed declining responses.

Large proportions of units in the IMTC had neuronal activity related to the stimuli (86/99 = 86%) and to the animal's panel press (82/99 = 82%) in the DMS task. Significantly fewer HF neurones had stimulus related (107/238 = 45%) and response related (99/238 = 42%) activity. Many units showed both stimulus and response related activity: 54% of the IMTC units compared to 29% of HF units. There was no significant difference between IMTC and HF in the proportion of units showing differences in activity on left compared to right trials (17% overall).

Thus the neuronal activity in the inferomedial temporal cortex appears to reflect memory for the previous occurence of stimuli as well as a possible involvement in the behavioural choices made in a short-term memory task. Neurones in the hippocampal formation were less likely to show stimulus or response related activity and no evidence could be found of an involvement in the judgement of the previous occurence of stimuli.

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PRESERVED MUSICAL SKILL IN A SEVERELY DEMENTED PATIENT.

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Patient G.W. is an 81 year old woman who has resided in a nursing home for the past 11 years because of dementia. G.W. was valedictorian of her high school class, graduated magna cum laude from college and holds a masters degree in music with a major in piano from a major midwestern university. She completed one additional year of study toward the Ph.D. After graduation G.W. taught music at the college level, gave private lessons in piano and worked as a writer. Beginning at age 61 G.W. suffered a series of bouts of agitated depression which were treated with antidepressants, neuroleptics and ECT.

Extensive testing in 1986-87 revealed severe global cognitive impairment (MMSE = 10 in 10/86, 8 in 2/87) with marked anomia, receptive aphasia, severely depressed fluency, constructional and ideomotor apraxia, and impaired abstract reasoning. Although performance on WAIS Information, Vocabulary and Picture Completion scales was nominally normal, G.W. scored well below the level of age and education-matched controls on these subtests. Other measures of remote memory including Famous Faces and the Fargo Map Test revealed marked deficits and she was badly impaired in identifying the titles of common Christmas songs or well known pieces of classical music. Neurological examination at this time revealed marked dyspraxia, static tremor in the fingers of both hands, and mild cogwheel rigidity in the elbows. EEG showed diffuse slowing. MRI showed diffuse cortical atrophy without focal vascular signs.

Despite these global deficits G.W. retains considerable skill at playing the piano and some knowledge of music theory. To estimate the quality of her playing, tape recordings of G.W. and four other pianists who varied in age and training were made. Blind evaluation of these recordings by skilled musicians indicated that the overall quality of G.W.'s playing approximated that of a formerly proficient, mentally-intact 81 year old pianist whose finger mobility is compromised by arthritis. G.W. retains the ability to sight-read music and was able to play (albeit poorly) a song that was published in 1981, five years after she demented. Furthermore, she was able to sing and play on a xylophone (an unfamiliar instrument), a simple song which she played from memory on the piano. However, G.W. exhibited no improvement on the Gollin figures or pursuit rotor tasks.

Taken together, these observations suggest that this severely demented patient exhibits relatively selective preservation of skills related to musical performance rather than simply the retention of highly overlearned motor skills or the capacity for procedural learning.

C - 2

Pre- and postoperative memory testing of epileptic patients

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The assessment of memory functions is a crucial component in the diagnosis of epileptic patients considered for surgical therapy. In the present study a dichotic memory test was used to determine hemispheric memory functions in nonepileptic control subjects, and in epileptic patients before and after right (RTE) or left temporal-lobe excisions. In this test, lists of words were presented dichotically to the right or left ear with backward speech in the opposite ear, and measurements of immediate free recall (IFR), final free recall (FFR), final cued recall (FCR), serial recall (SR), and serial position effects were employed. The results from preoperative testing, early and late postoperative testing revealed (a) that both groups of patients were inferior the control group in tests tapping long-term memory functions, i.e. FFR and FCR tests and the asymptotical parts of the serial position curves, suggesting long-term memory effects rather than short-term memory effects, (b) a right-ear advantage for control subjects and RTE patients, and a left-ear advantage for LTE patients, indicating that the ear-superiority were in line with previous research and the hemispheric lesion of the two patient groups, (c) that only the LTE group showed a decrease in tests of IFR and SR from pretest to early posttest, suggesting that LTE patients were more affected by surgery compared with the RTE patients, (d) a general improvement in recall performance from early to late postoperative testing, and with a right-ear advantage for the two groups of patients in all measures. Taken together, these results indicate that the present dichotic test is a sensitive device to study hemispheric memory functions and can thus be used as a non-invasive test to complement the invasive Sodium Amytal test for diagnosis of epileptic patients.

C - 3

COGNITIVE EVOKED POTENTIALS TO VERBAL AND NON-VERBAL STIMULI IN A MEMORY SCANNING TASK.

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A modified version of the memory-scanning paradigm originally proposed by Sternberg was used to examine behavioral and evoked potential (EP) correlates of short-term memory in individuals with memory deficits, and in a group of normal controls. Memory sets consisting of 1, 3, or 5 stimuli were presented, followed by a probe item. Subjects were instructed to press one of two buttons to indicate whether the probe item was or was not a member of the memory set. Memory set items were presented sequentially at a 1/sec rate followed 2 sec later by the probe item. Memory sets and probes were grouped in blocks of 20 trials for each of the three set sizes. The stimuli used were verbal (digits) and non-verbal (musical notes). The verbal stimuli were presented acoustically (voice synthesizer) as well as visually (video display).

The scalp EEG was recorded from midline sites Fz, Cz, and Pz referenced to linked ears. For several subjects additional electrodes were used to define scalp topography. Evoked potentials were sorted and averaged from stored single trials to probes correctly identified as in the previously presented memory set. The potentials were described in terms of their scalp distribution, latency and amplitude, and were compared with behavioral descriptors of the subjects' performance, including reaction times and accuracy of performance. The effects of increasing the size of the memory set on the EPs, as well as on the behavioral measures were determined.

The potentials evoked by the probe items consisted of a positive-negative-positive sequence in the first 250 msec, followed by a later, long-lasting (approximately 500 msec) positivity. This positivity consisted of an earlier component with a frontal distribution, followed by a larger and later parietal component. In the normal subjects, the amplitude of this sustained positivity was reduced as reaction time increased. In a few of the patients this component could not be detected. The latency of the parietal component increased with memory set size in the normal subjects, with a slope that was approximately half that for reaction times to verbal stimuli, and only a third of the slope of reaction times to musical notes. In the patients, reaction times were longer overall than reaction times for the controls, and also increased with set size, as did the latency of the parietal component. Accuracy of performance was reduced in some of the patients compared to the controls, especially for the 5-item task. The results suggest that EPs are useful in complementing behavioral measures in describing memory processes.

D - 1

Effects of scopolamine on recency memory in rhesus monkeys. T.G. Aigner, R.Q. Wan, M.E. Gravelle. Lab of Neuropsychology, NIMH, Bethesda, MD 20892.

The cholinergic system is now considered to play an important role in mnemonic processes. We previously showed that scopolamine (SCOP), a muscarinic-cholinergic receptor blocker, impairs visual recognition memory in monkeys. We also reported that SCOP produced greater impairments when administered before than when administered after the acquisition trials, suggesting that this drug influences storage more than retrieval. To further characterize the actions of SCOP on memory, we administered the drug to three monkeys trained on a recency memory task (delayed nonmatching-to-sample with a small sample set) in a computer-controlled automated testing apparatus. The monkey was seated directly in front of a color video monitor onto which 5 cm squares in any one of 15 different colors could be projected. During acquisition, a square was shown in the center of the monitor and the monkey was required to touch the screen within the boundaries of the square, thereby extinguishing it. After a delay of 0, 1, 3, 10, 30, or 60 sec, the original square was presented with another one of a different color, each on a lateral portion of the screen, in a choice trial (test). The animal was rewarded with a banana pellet for touching the new symbol. In each of 200 daily trials, the colors of the squares and the delay interval were randomly selected by the computer, which also recorded the position of the touch, the symbol selected, and the reaction time to touch the screen. When performance was stable, SCOP (10.0, 17.8, or 32.0 ug/kg) was administered 20 min before the start of the session. Each dose was tested 8 times in a nonsystematic order in each monkey. Drug was administered no more than twice each week and at least 1 nondrug control session preceded sessions in which SCOP was given. During control sessions, forgetting curves were obtained in which performance was highest (90% correct choices) at short delays and lowest (less than 75% correct choices) following the longest delay. Overall performance averaged 85 percent correct across all delays. SCOP at dose of 17.8 and 32.0 ug/kg significantly reduced the overall scores to an average of 73.3 and 69.4 percent correct, respectively, but had no effect on reaction times. More importantly, SCOP produced its major effect, that is, the major divergence between drug and control curves, during the interval between 0 and 1 sec. In contrast, during the interval between 1 and 60 sec, drug and control curves were approximately parallel. These results suggest that SCOP exerts its effects at a very early stage of memory, presumably by preventing information from entering storage.

D - 2

REVERSAL OF MUSCARINIC RECEPTOR CHANGES IN SOME BRAIN AREAS DURING ACQUISITION AND EXTINCTION OF AN OPERANT TASK. V. Alemán, A. Ortega, A. Meneses and A. Oscós. Departamento de Fisiología y Neurociencias y Departamento de Farmacología y Toxicología, CINVESTAV-IPN y División de Neurociencias, Instituto Mexicano de Psiquiatría. México, D.F.

Thirty ninety day-old female rats were fasted to 85% of their body weight. Animals were divided in six groups of 6 rats each. Active control animals (AC) were placed in a similar operant conditioning chamber, the same number of times like those rats with a maximun level of acquisition (L). Another L group (R) was re-ran and immediately sacrified 96 hr after the last learning session in order to account for a retention value. Finally three other groups with maximal acquisition level were extinguished for 2, 3 and 4 days. We used and autoshaped version of an illuminated (8 sec) lever pressing (CS), paired to the delivery of a 45 mg food pellet (UCS). The intertrial interval was 60 seconds. Animals were extinguished giving them a daily session with trials in the absence of UCS. When we compared maximal binding (Bmax) of caudate fractions from L and AC groups, we observed an increment of Bmax of the L group. Bmax decrement can be seen in tempo-parietal cortex (T-Pc) from L group. Dissociation constants (Kd) seem to decrease in both septum and frontal cortex (Fc) of the L group. Similar changes in Bmax values to those just described for the L group were observed again in caudate and T-Pc of the R group, when compared to the AC group. All extinction groups were compared to the L group instead of the AC group. At 48 hr of extinction we noticed in caudate and T-Pc a decrement and an increment of Bmax values respectively. At 72 hr of extinction the Bmax value from caudate showed now an increment, on the other hand a decrement is seen at this time in amygdala. When the extinction period was 96 hr Bmax in caudate returned to the L group value. However amygdala Bmax value continued decreasing below those of the L and AC group values. The Bmax value in hippocampus at this time increased above the L and AC group values. In T-Pc Bmax also increased but only returned to the L and AC group basal values. Compared to the AC group, L group Kd values increased in septum, Fc and T-Pc. At 48 hr extinction, hippocampus Kd value tend to increase, however it returned to L group value at 96 hr of extinction. At 48 hr extinction, amygdala Kd value tend to increase, this tendency is increased at 72 hr but at 96 hr extinction the Kd value is similar to the L group value. Similar changes in Kd values were observed in T-Pc.

D - 3

DISRUPTED ACQUISITION OF CONDITIONED AVOIDANCE RESPONDING BY METOCLOPRAMIDE BUT NOT BY ATYPICAL NEUROLEPTICS. J. R. Blackburn and A. G. Phillips. Department of Psychology, University of British Columbia, Vancouver, B.C., Canada, V6T 1W5.

Neuroleptic drugs have a strong disruptive effect on the acquisition of an active avoidance response, but have relatively little impact on the performance of a previously acquired response. This effect has been shown to be due to the dopamine antagonist properties of these drugs. In the present experiments, the anti-avoidance properties of neuroleptic drugs with different profiles of action were compared. First, it was found that doses of 5.0 or 7.5 mg/kg metoclopramide completely blocked the acquisition of a one-way avoidance response over three ten-trial sessions, but did not disrupt the performance of rats that had received three drug-free training sessions. A separate experiment demonstrated that two days of pre-training was sufficient to attenuate the disruptive effect of metoclopramide on avoidance. In contrast, at doses from 10 to 30 mg/kg the atypical neuroleptic thioridazine slowed but did not prevent the acquisition of the response. Another atypical neuroleptic, clozapine, retarded acquisition of the response at doses of 1.25 to 10 mg/kg, but also disrupted performance of an acquired response, indicating non-specific effects. The different effect of metoclopramide versus the atypical neuroleptics may be due to anticholinergic properties of the atypical neuroleptics. Alternatively, the difference may be due to a preferential effect of metoclopramide on the nigrostriatal dopamine system, whereas thioridazine and clozapine have been reported to act primarily on the mesolimbic system.

D - 4

Effects of Neuroleptics on Motivation: Another Look . Geyer, Harry M. III and Fielding, Stuart. Department of Biological Research, Hoechst Roussel Pharmaceuticals Inc., Somerville, N.J. 08876.

A progressive fixed ratio (FR) schedule using nose-poke as a response was used to assess the effects of neuroleptics. It was hypothesized that this procedure would separate the motivational and motor effects of these agents. The nose-poke behavior has been shown to be relatively resistant to motor deficits which, if present, should be evident across the various FR's whereas a motivational deficit should appear as the FR's increase.

In this paradigm, a rat that has been on a restricted diet is placed in an experimental chamber which has two holes in one metal wall. The center hole contains the liquid dipper which delivers the reward of sweetened milk. The second hole has a photocell sensor which records each time the rat pokes its nose in and the milk reward is presented according to the progressive FR schedule. The effects of various drugs are evaluated by placing pretreated rats in the chambers and recording the nose-pokes over an hour test session. The performance was not reduced by doses of diazepam as high as 5 mg/kg or imipramine at 20 mg/kg. However, clozapine at 5 mg/kg significantly reduced nose-pokes as did haloperidol at 0.125 and thiordazine at 5. Chlorpromazine at 0.63 reduced responding when the FR was progressively increased to a maximum of 48, but not when maximum was limited to FR12. This indicates that the performance decrement was motivational rather than motor and is in accord with clinical reports of anhedonia induced by neuroleptic treatment. This test prodedure is being examined further as a possible measure of motivational changes induced by various pharmacological agents.

THE EFFECT OF ELECTROLYTIC LESIONS OF THE MEDIAL SEPTAL AREA ON HIPPOCAMPAL CHOLINE ACETYL-TRANSFERASE AND PERFORMANCE ON THE MORRIS WATER MAZE

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Male Lister Hooded rats weighing approximately 300 gms received 2 days of training consisting of 6 trials per day on the Morris Water Maze task. These rats were then anaesthetised with sodium pentobarbitone (Sagatal, May and Baker Ltd., UK) and placed in a stereotaxic frame. Electrolytic lesions of the medial septum were made bilaterally the co-ordinates being IB + 0.5, AP 2.3mm from Bregma, Lateral 0.3mm, Ventral, 6.1mm from the surface of the skull: 10mA ('large' lesion,n=6) 5mA ('small' lesion, n=5), 0mA ('sham' lesion, n=8) for 10 seconds. Rats were allowed to recover for 1 week and they were then retested in the water maze for their acquisition of a new island position. Each ra was given 6 training trials to a new island position, with a final 7th trial for which the island was removed. Latency to find the island, speed and percentage time spent in the island quadrant were measured. After these trials hippocampal choline acetyltransferase (CAT) activity was measured by the method of Fonnum (J.Neurochem. 24, 407-9, 1975).

The results are shown in the Table below.

The effects of septal lesions on water maze performance and hippocampal CAT levels

LESION SIZE	TRIAL 1-6 GEOMETRIC MEAN LATENCY (sec)	TRIAL 1-6 GEOMETRIC MEAN SPEED (cm/sec)	% TIME ON TRIAL 7	HIPPOCAMPAL CAT (mean dpm/mg protein)
Large	62	15.5	15	19.0 ± 2.4
Small	39	17.0	35	19.6 ± 2.1
Sham	17	24.0	43	68.6 ± 4.7

Although both large and small septal lesions produced a similar reduction in hippocampal CAT, the effects of such lesions on spatial learning are confounded by the reduction in swimming speed that these lesions also produce. In addition examination of the path plots of those rats with large lesions showed that they had an abnormal swimming pattern, spending a much greater proportion of the time at the edge of the pool compared with normal rats. Such plots also showed that the animals with small lesions tended to swim in a stereotyped circular fashion around the pool. This is similar to the behaviour seen in our laboratory when rats are treated with scopolamine and suggests that animals with small septal lesions are capable of utilising a taxon strategy.

INTRA-AMYGDALA INJECTIONS OF β-ADRENERGIC ANTAGONISTS BLOCK THE MEMORY-ENHANCING EFFECT OF PERIPHERALLY-ADMINISTERED NALOXONE.

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Recent findings have suggested that the memory-enhancing effects of naloxone are blocked by treatments interfering with central noradrenergic systems (Gallagher, 1985; Introini-Collison & Baratti, 1986; Izquierdo & Graudenz, 1980). These findings are consistent with evidence that naloxone blocks the inhibitory effect of opioid peptides on the release of norepinephrine. In view of evidence that retention can be modulated by intra-amygdala injections of norepinephrine, the present experiments were undertaken to determine whether the memory enhancing effects of naloxone are blocked by intra-amygdala administration of adrenoceptor antagonists. Sprague Dawley rats (220-250g) were bilaterally implanted with amygdala cannulae. They were then trained on an inhibitory avoidance response and then, two weeks later, on a Y-maze discrimination response. Immediately following the training on each task, they were injected (intraperitoneally, IP, and in the amygdala). Retention was tested one week following the training on each task. Naloxone administered ip (3.0 mg/kg) significantly facilitated retention of both tasks. This effect of naloxone was observed both in unoperated and cannulae-implanted control rats. The memory-enhancing effect of naloxone IP was blocked by propranolol (0.3 or 1.0 μg) injected in the amygdala, but not when this β-noradrenergic blocker (0.3 μg) was injected into either the caudate or the cortex dorsal to the amygdala. Further, when injected into the amygdala, both the β_1-adrenoceptor blocker atenolol (0.3 or 1.0 μg) and the β_2-adrenoceptor blocker zinterol (0.3 or 1.0 μg), in doses which did not affect memory when administered alone, completely blocked naloxone-induced (3.0 mg/kg; ip) enhancement of memory. In contrast, posttraining intra-amygdala administration of α-antagonists prazosin (α_1) and yohimbine (α_2) (1.0 μg) did not attenuate the memory-enhancing effects of systemically-administered naloxone.

These findings support the view that naloxone-induced memory facilitation is mediated by the activation of β- but not α-noradrenergic receptors which are located in the amygdaloid complex.

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AMYGDALA NORADRENERGIC SYSTEM, STRIA TERMINALIS AND MEMORY MODULATORY EFFECTS OF PERIPHERAL EPINEPHRINE. K.C.Liang & Tze-En Huang, Dept. of Psychol., Natl'. Taiwan Univ., Taipei, TAIWAN 10764, R.O.C.

Our previous findings indicate that pretraining intra-amygdala (Amyg) injections of 30.0 µg DSP-4, a norepinephrine (NE) depletor, attenuate the memory enhancing effect of epinephrine (E) injected peripherally. However, in view of that 30.0 µg DSP-4 by itself impairs retention and depletes 5-HT and DA as well as NE, it remains inconclusive whether the memory modulatory effect of E may depend upon specifically NE in the Amyg. The present study was designed to address this issue.

Male Sprague-Dawley rats with chronic cannulae implanted into the Amyg received bilateral intra-Amyg injections of 2.0 µg DSP-4 or vehicle (Veh). Five days later, they were trained on an inhibitory avoidance task and received immediate posttraining s.c. injections of saline or 0.01, 0.1 or 0.5 mg/kg of E. The retention performance indicated that in the Veh group, 0.1 mg/kg of E improved retention (U=2, $p<0.001$), while 0.5 mg/kg of E impaired retention (U=23, $p<0.01$]. Pre-training intra-Amyg injections of 2.0 µg DSP-4 did not affect retention, but readily attenuated both the enhancing and impairing effects of E on retention. HPLC-EC assays indicated that 2.0 µg of DSP-4 depleted 23% of NE in the Amyg but had no significant effect on DA or 5-HT.

To investigate whether other monoamines in the Amyg may also be involved in the effect, implanted rats received bilateral intra-Amyg injections of 15.0 µg 5,7-DHT following i.p. injections of desipramine (25.0 mg/kg). Five days later, they were trained on the previously described task and received immediate posttraining s.c. injections of E (0.1 mg/kg). The 24-hr retention performance indicated that E enhanced retention in both the Veh and the 5,7-DHT groups (U=13.& 4, $p<0.02$, respectively]. HPLC-EC assays showed that 15.0 µg of 5,7-DHT depleted 74% of 5-HT and 26% of DA in the Amyg, but had little effect on NE. These findings suggested that memory modulatory effects of peripheral E may be mediated specifically by the Amyg NE system.

Based on the previous findings that the stria terminalis (ST) lesions attenuated the memory enhancing effect of E, we pursued the present hypothesis further by investigating whether ST lesions also attenuated the memory enhancing effect of NE injected into the Amyg. ST lesioned (ST-) and sham operated (ST+) rats were trained on the previously described task and received immediate posttraining intra-Amyg injections of Veh or 0.2 µg of NE. The 24-hr retention performance indicated that intra-Amyg injections of NE enhanced retention in the ST+ rats (U= 31.5, $p<0.05$) but not in the ST- rats. These findings, taken together, suggest that the memory enhancing effect of intra-Amyg NE, similar to that of peripheral E, depends upon the integrity of the ST.

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THE EFFECT OF PHYSOSTIGMINE ON AGE-RELATED DEFICIT OF SPATIAL MEMORY. A.L.Markowska and D.S.Olton, Department of Neurophysiology, Nencki Institute of Experimental Biology, Warsaw, Poland, Department of Psychology, The Johns Hopkins University, Baltimore, MD 21218.

The ability to remember information decreases with aging. In a previous experiment, rats trained in a task that required spatial working memory showed an age-related decline in memory; young rats remembered longer than middle-aged rats, which in turn remembered longer than senescent rats (Markowska, A.L. In XXX Congress I.U.P.S. 1986, Abstract p. 1012). In the present experiment, rats of three different ages (7 mo, 16 mo, and 28 mo) were tested in an 8-arm radial maze with delays of different lengths (10 min. to 24 hr.) imposed pseudorandomly between choices 4 and 5. After they performed reliably, they were tested with saline (control conditions) or physostigmine sulfate (0.1 or 0.2 mg/kg) administered intraperitoneally either 15 min. before training or 15 min. before choice 5. Choice accuracy in the control condition (saline) decreased as the delay interval increased, but the slope of this function was different for the three groups of rats, with the senescent rats showing the fastest decrease. Physostigmine, 0.1 mg/kg administered before choices 5-8, improved choice accuracy in all groups of rats at the delay intervals at which the saline control rats showed deteriorating performance. This significant improvement occurred at 10 - 12 hr. for young rats, at 5 hr. for middle-aged, and at 30 - 40 min. for the senescent rats. The performance of rats was not improved, either when the drug was administered before training, or when rats were tested with delays not long enough to disrupt memory . These results support the notion that enhancement of cholinergic transmission can attenuate memory loss. However, the beneficial effect of such treatment is most apparent in situations involving memory impairment e.g. as a result of aging, poor learning, or forgetting during a long period of time. These results also imply that physostigmine improves performance because it facilitates retrieval rather than acquisition or storage.

CHOLINERGIC AGONISTS MODULATE THE RESPONSE PATTERN TO SINGLE TONES AND THE FREQUENCY RESPONSE FUNCTIONS OF AUDITORY CORTICAL NEURONS. T.M. McKenna, J.H. Ashe, and N.M. Weinberger. Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA 92717.

The function of acetylcholine (ACh) in auditory cortex is of particular interest because manipulations of cholinergic systems have been shown to effect auditory perception, and complex cognitive processes, including attention. Furthermore, physiological plasticity is rapidly induced in auditory cortex during learning (cf. Diamond & Weinberger, Behav. Neurosci., 1984,98:171-210), and cholinergic processes have been repeatedly implicated in various forms of plasticity.

The present experiment examined the effects of cholinergic agents upon responses to tone stimuli in the primary auditory cortex of the cat. Multibarrel micropipettes were used to record activity from acoustically-responsive single neurons and to apply cholinergic agents by micropressure or iontophoresis.

We observed that agonists acetylcholine (ACh, 2 M) and methacholine (MCh, 20-40 mM) could exhibit differential effects on spontaneous and tone evoked activity, and moreover, these agonists showed different effects (enhancement or suppression) on different response components (i.e. tone on, through, or off responses). These effects could be blocked by atropine (.2 M).

The effects of cholinergic agents on the frequency response function of auditory cortical neurons were also examined. In most cells these agonists produced a selective enhancement of "on" responses at the best frequencies, accompanied by suppression of responses to non-preferred frequencies and/or suppression of "through" responses over a range of frequencies.

These findings indicate that cholinergic agents modulate auditory cortical activity in a manner more selective than simple increases or decreases in discharge rate. The selective effects of these agents on the frequncy response and temporal pattern of evoked discharge suggest that cortical cholinergic mechanisms have the capacity to selectively modify the representation of acoustic information.

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THE EFFECTS OF ACETYLCHOLINE ON SINGLE NEURON RESPONSES TO TONES IN CAT AUDITORY CORTEX. Raju Metherate, Josée F. Bourg and Norman M. Weinberger. Center for the Neurobiology of Learning & Memory, Department of Psychobiology, University of California, Irvine, CA. 92717.

Cholinergic agents affect auditory perception and cognitive processes, and may do so by altering auditory sensory processing. To pursue this question, the present study examines the effects of iontophoretically administered acetylcholine (ACh) on single neuron responses to tones in the auditory cortex of barbiturate anesthetized cats. A further goal was to determine the extent to which pairing ACh with a single frequency tone would subsequently affect the cell's frequency receptive field (FRF).

Cats prepared for chronic recording sessions (performed at 1 week intervals) were initially anesthetized with sodium pentobarbital (35 mg/kg) and maintained areflexic by continuous infusion of barbiturate (1 mg/hr) and lactated Ringer's solution (12 ml/hr). Multibarrel glass or tungsten and glass microelectrodes were inserted through a burr hole into the auditory cortex. Drug barrels contained ACh chloride (1 M, pH 4), sodium glutamate (0.5 M, pH 8) and sodium chloride (1 M) for current controls. When a single neuron was initially isolated, its level of spontaneous activity and FRF were determined. The responses to a single, repeated tone were then noted before and during iontophoresis of ACh. Following this, the cell's FRF was re-determined.

ACh (5-70 nA) was applied to 51 neurons in 14 recording sessions. The spontaneous and/or tone-evoked activity of 39 cells (76%) was altered in the presence of ACh. The spontaneous rate increased in 34 cases, but never decreased during the ACh application. Responses to tones were increased by ACh in 16 cases and decreased in 11 cases. ACh often differentially affected a cell's activity, increasing, for example, the spontaneous rate while decreasing the evoked response. Six additional cells that did not respond to tones in the absence of drugs did so during ACh administration. When FRFs were determined following pairing of ACh with a single frequency tone, some cells displayed a decreased response to tones close to the paired frequency while responses to frequencies further away were less affected.

These data suggest that ACh can modify the activity of a large number of auditory cortical neurons. The differential effects on spontaneous and tone-evoked activity are consistent with previous observations from this laboratory (McKenna et al. 1986) using pressure ejection of ACh in unanesthetized cats. Finally, the observation of altered neuronal receptive fields subsequent to the ACh treatment bears significant implications for studies on auditory sensory processing.

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Memory performance in an automated radial maze in rats and mice : effects of cholinergic drugs.

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Rats and mice were tested in a delayed-non matching to place task performed in an automated 8-arm radial maze equiped with doors. The opening of the doors was controlled by a microcomputer according to both predefined sequences and behavior of the animal in the apparatus. Each test consisted of a presentation phase during which the animal was forced to enter successively one or several (up to 6) arms followed by a recognition phase on which the subject had to choose between the previously visited arm and an adjacent non visited arm (reinforced). Two paradigms were used :

- In the first one, the to be remembered arm was always the first of the serie and the series of arms visited between its presentation and subsequent recognition varied from 1 to 5 arms ;

- In the second one, the number of arms visited during the presentation phase was six (serial list) and subsequent recognition was tested i) on either the 2 first, 2 last or 2 median visited arms and ii) with (30 s) or no (0 s) delay interposed between the list and recognition.

In all experiments rats and mice exhibit (1st paradigm) a progressive decrease in recognition performance as the number of arms interposed between the target arms increases (from 85-95 %) for 1 interposed arm to 60-65 % for 5 arms).

The serial position functions markedly changed with delay ; thus with the 0 s delay memory performance was highly better for the last list items than for the either middle or first one while for the 30 s delay the inverse was observed.
Results obtained with scopolamine and physostigmine seem to indicate that these two drugs modify performance mainly through the memory component of the tasks.

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MEMORY-ENHANCEMENT WITH INTRA-AMYGDALA POSTTRAINING OF ADMINISTRATION OF NALOXONE IS BLOCKED BY CONCURRENT ADMINISTRATION OF PROPRANOLOL.

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Previous results from our laboratory indicate that the memory-enhancing effects of posttraining systemic (IP) administration of naloxone on memory are blocked by intra-amygdala injections of β-noradrenergic antagonists. If, as these findings suggest, naloxone affects memory through influences involving β-noradrenergic receptors within the amygdala, then the memory-enhancing effect of intra-amygdally administered naloxone should be blocked by concurrent administration of a β-noradrenergic antagonist. The present experiment examined this implication. Sprague Dawley rats (220-250g) were bilaterally implanted with amygdala cannulae. They were first trained on an inhibitory avoidance task (IA) and then, two weeks later, on a Y-maze discrimination task (YMD). Bilateral intra-amygdala injections (1.0 μl) were administered immediately posttraining. Retention was evaluated one week following training on each task. Naloxone (0.1, 0.3 or 1.0 μg) facilitated retention in both tasks. The most effective doses were 0.1 μg for the IA task and 0.3 μg for the YMD task. Naloxone (0.1 μg) did not affect retention when administered via cannulae implanted in either the caudate-putamen or cortex dorsal to amygdala. Thus, the effects of intra-amygdala naloxone does not appear to be due to diffusion of the drug to these brain regions. These results strongly support the view that opioid peptidergic systems in the amygdala are involved in memory modulation. Further, as we observed previously with systemic injections of naloxone, intra-amygdala injections of the $\beta_{1,2}$-adrenoceptor blocker propranolol (0.3 μg) blocked the memory enhancing effects of intra-amygdally injected naloxone (administered concurrently)(IA: 0.1 μg; YMD: 0.3 μg).

We interpret these findings as indicating that the enhancing effects of intra-amygdala naloxone are mediated by the activation of β-noradrenergic receptors within the amygdala. Such effects are presumably due to blocking of inhibitory effects of opioid peptides on the release of norepinephrine.

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MILACEMIDE, A NOVEL ANTIEPILEPTIC DRUG, ANTAGONIZES DRUG-INDUCED MEMORY IMPAIRMENTS IN MICE. M.E. Nevins and S.M. Arnolde. CNS Diseases Research, G.D. Searle & Co., Skokie, IL 60077

Milacemide (2-n-pentylaminoacetomide HCl) is a glycine prodrug currently under clinical evaluation for antiepileptic efficacy. In one clinical study Milacemide was found to improve attention and concentration in healthy young volunteers (Saletu, B. and Grunberger, J., Meth. Find. Exptl. Clin. Pharmacol., 6:317,1984). In the present studies, Milacemide was evaluated for its ability to antagonize drug-induced memory impairments in mice using the spontaneous alternation paradigm as a model of immediate memory. In this paradigm, naive male CD-1 mice are given two trials, 5 minutes apart, to explore a novel Y-maze. They may enter only one maze arm per trial. In the absence of treatment with an amnestic agent, approximately 90% of mice enter both arms, one on each trial; i.e., they spontaneously alternate entries into the two arms of the maze. Drugs that impair memory reduce the percentage of animals alternating to that which would be expected by chance (50%). Chance level alternation produced by low doses of amnestic agents can be considered a model of minimally impaired immediate memory. Conversely, drugs that counteract this impairment, increasing alternation toward 90%, may be expected to improve memory in humans with minimal memory impairments. Memory impairments were produced by administration of either scopolamine hydrobromide (SCOP) (0.75 mg/kg i.p.), diazepam (DZM) (0.75 mg/kg i.p.) or the N-methyl-D-aspartate receptor antagonist 2-amino-7-phosphonoheptanoic acid (AP7) (75 mg/kg i.p.). Milacemide was administered s.c. 30 min prior to administration of the amnestic agents. The behavioral test was conducted 30 minutes later. There were 28 mice in each dose group. Pretreatment with Milacemide was found to reverse the memory impairments produced by all three of the amnestic agents. It was most effective in counteracting the memory impairment produced by AP7, producing significant reversal at doses of 17.8 and 32 mg/kg. The 32 mg/kg dose of Milacemide also significantly reversed the effects of SCOP. Higher doses of Milacemide, 56 and 100 mg/kg, were needed to counteract the impairment produced by DZM. The dose-response curves took on the inverted-U shape typically seen with memory-modulating drugs. Currently used antiepileptic drugs such as phenytoin and valproate are suspected of impairing mental function over long periods of use. In contrast, the clinical data show that Milacemide enhances attention and concentration in healthy individuals, and the present data suggest that it may prove beneficial at enhancing memory in individuals with minimal memory impairments.

SPATIAL LEARNING IN YOUNG AND AGED RATS: RELATION TO CHOLINERGIC FUNCTION. M.A. Pelleymounter and M. Gallagher. Department of Psychology, University of North Carolina, Chapel Hill, NC 27514

When young adult rats are trained on a version of the Morris water maze task that requires the use of spatial information, i.e. place learning, a training-induced decrease in hippocampal high-affinity choline uptake is observed (Decker et al., in press, J. Neurosci.). This is not found in young rats that are either trained on a version of this task that does not require the use a spatial information, i.e. cue learning, or that are yoked to the place-trained animals for time spent swimming in the maze. The change in hippocampal HACU is found when animals are sacrificed 15 min after completing 4 sessions of training: no change was evident after a single session. Finally when young and aged rats were sacrificed at a point during training when the young subjects were more proficient at the task (4 sessions), the aged animals failed to exhibit an effect of place training on hippocampal HACU. Experiments were undertaken to characterize the effect of the training/sacrifice interval on HACU in young rats and to examine HACU in aged animals when their performance was matched to that of younger rats by training to a criterion prior to sacrifice.

Young rats were trained to locate a camouflaged, submerged platform in the water maze for 4 sessions (4 trials/day for 4 days). A free swim trial was interpolated as the last trial in the 3rd session in order to obtain measures of spatial bias as an index of learning. Each place trained animal had a control subject that was yoked to the place-trained animal's escape latency on each training trial. Separate groups of place-trained animals and their yoked controls were sacrificed either immediately, 15 min, or 3 hr after the completion of the 4th session. The three groups of place-trained animals exhibited comparable learning of the task. A significant effect of place training on HACU was found at the 15 min and 3 hr time points ($p<.02$), but not when subjects were sacrificed immediately after the training session.

Pairs of young (8 pairs at 4 mth) and aged (14 pairs at 23-24 mth) rats were then trained in the maze. One animal in each pair received place training (3 trials/day); the other animal served as a yoked control. Free swim trials (30 sec in length) were interpolated as every 6th trial throughout training. A criterion performance was achieved when an animal spent a minimum of 10 sec in the training quadrant and traversed the former training platform at least twice during a free swim. Sacrifice occured 15 min after the completion of a training session (3 trials) on the day after criterion was achieved. The aged animals required significantly more training to reach criterion ($p<.001$). A proportion of the aged subjects (N=6), however, achieved criterion within the range of trials required by the young group. These animals, like the young animals, showed a significant training-induced reduction in hippocampal HACU relative to their yoked controls ($p<.02$). In contrast, the aged animals that required more training than any of the younger subjects (N=8) did not exhibit an effect of training on HACU.

The deficient performance of a proportion of aged rats on this spatial learning task is associated with a diminished response of hippocampal HACU to training. These subjects differ not only from young rats, but also from non-impaired subjects of the same chronological age. Supported by NIMH MH39180, a NIA Research Service Award AG05407, and NIMH RSDA KO2-MH00406 to MG

ANTAGONISM OF NMDA RECEPTORS BY AP5 SELECTIVELY INTERFERES WITH DIFFERENT FORMS OF MEMORY. U. Staubli, O. Thibault, M. DiLorenzo & G. Lynch. *Bonney Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA 92717.*

Recent studies have shown that a class of glutamate receptors which are defined by their preferential activation by N-methyl-D-aspartate (NMDA) play a crucial role in the development of synaptic plasticity (Collingridge et al., 1983). Blockade of these receptors with the antagonist D,L-aminophosphonovaleric acid (AP5) has been repeatedly shown to suppress long-term potentiation both in vitro and in vivo, without affecting baseline synaptic transmission (Collingridge et al., 1983; Harris et al., 1984, Morris et al., 1986; Larson & Lynch, subm.).

Thus NMDA receptor blockers should be useful tools for analyzing the role of the potentiation effect in memory. Morris et al. (1986) found that chronic infusion of AP5 into the lateral ventricles produces an impairment in spatial learning without affecting visual discrimination. The highest density of NMDA receptor sites is found in the hippocampus (Monaghan et al., 1985), a site well known to play a crucial role in place, but not discrimination, learning. If AP5 does disrupt these forms of learning that are dependent upon NMDA enriched structures, as opposed to having effects peculiar to spatial tasks, then it should also interfere with olfactory learning, since high levels of NMDA receptors are reported in primary and secondary olfactory projection sites (e.g. outer layer of piriform cortex, anterior olfactory nuclei, olfactory tubercle, and hippocampus (Monaghan et al., 1984)).

Therefore, we tested the effect of AP5, administered chronically into the lateral ventricles via an osmotic pump (40mM AP5: .5ul/hr), on acquisition and retention of (1) specific odor cues presented during a discrimination task, and (2) active avoidance learning. Animals treated with AP5 (n=10) made significantly more errors than saline controls (n=10) in acquiring novel olfactory discrimination problems. The deficit in acquisition was dependent on the strength of odors and the length of intertrial intervals (ITIs): it disappeared when strong odors or short ITIs (<2min) were used. Retention of odors learned before AP5 administration was unimpaired. Animals treated with AP5 also had no difficulty in remembering odors that had been acquired with a deficit 24 hrs earlier. Active avoidance learning was not affected by chronic infusion of AP5. Non-telencephalic structures which contain very low densities of NMDA receptor sites (Monaghan et al., 1985) have been implicated in this form of learning (e.g. Whitfield, 1979). These results are consistent with the hypothesis that different cellular processes subserve different forms of memory.

GLUCOSE REGULATION OF MEMORY STORAGE: NOVEL CNS ACTIONS OF MILD HYPERGLYCEMIA. W.S. Stone, K.L. Cottrill and P.E. Gold. Department of Psychology, University of Virginia, Charlottesville, VA 22903.

Glucose (GLU) administration enhances memory in both rodents and elderly humans. In addition, blood GLU levels measured shortly after training are correlated with later retention performance under several conditions in rodents. For example, epinephrine enhancement of memory storage is correlated with the extent of hyperglycemia produced. Since plasma EPI is largely excluded from the CNS, these findings suggest that circulating GLU levels may represent an intermediate step between EPI and memory modulation. GLU is readily transported into the CNS and may therefore regulate directly the neuronal mechanisms underlying memory storage, a possibility supported by findings that intraventricular GLU injections enhance memory storage. Because of the potential significance of GLU to memory storage, we are currently evaluating GLU effects on a variety of CNS functions. We report here that GLU injections have effects on both sleep and cholinergic systems; the effects in each case are inverted-U dose-response curves comparable to those observed in previous studies of EPI (maximal effects, 0.05 mg/kg), GLU (maximal effects, 100-500 mg/kg) and memory.

GLU effects on sleep: Sleep deficits have been related to memory impairment during aging in many species. In particular, the extent of disruption of paradoxical sleep is correlated with the decline in memory performance in individual old rats (Stone et al., Sleep Res., 1985). When GLU was administered to 2-yr-old rats, several indices of paradoxical sleep function were significantly enhanced in the direction of values typically seen in young animals.

GLU interactions with cholinergic systems: The effects of EPI and GLU on age-related cognitive deficits, combined with evidence that circulating GLU can regulate ACh synthesis (Gibson and Blass, *J. Neurochem.*, 1975), led us to examine interactions of EPI and GLU with cholinergic functions: *1) Amnesia with cholinergic antagonists:* Mice were treated with scopolamine (3 mg/kg) 30 min prior to training in a one-trial inhibitory avoidance task. Immediately after training, the animals received an injection of EPI, GLU, or a cholinergic agonist, arecoline. On retention tests 48 hrs later, scopolamine-induced amnesia was significantly attenuated in those animals which received either EPI or GLU, but not arecoline; delayed posttraining injections of EPI and GLU did not attenuate the amnesia. *2) Hyperactivity with cholinergic antagonists:* Scopolamine (3 mg/kg) increases in locomotor activity in young mice were reversed by additional treatment with GLU or EPI. In addition, physostigmine (0.2 mg/kg), but not arecoline (1-10 mg/kg), also attenuated the hyperactivity, and combined injections of physostigmine and GLU were more effective than either one alone. *3) Tremors with cholinergic agonists:* Physostigmine (0.4 mg/kg) was used to elicit tremors in mice. Animals which received GLU injections prior to physostigmine treatment exhibited accelerated onset of physostigmine-induced tremors.

These studies demonstrate several CNS actions of circulating EPI and GLU, including effects on memory, on hyperactivity and tremors related to cholinergic functions, and on paradoxical sleep in aged rats. Thus, the findings add support to the views that circulating GLU has potent effects in regulating brain functions including memory and that EPI may affect memory and other behaviors through the resultant hyperglycemia. [Supported by ONR (N00014-85-K0472), NIMH (MH 31141) and the American Diabetes Association.]

Stimulation of Basal Forebrain Induces Long Term Changes in Excitability of Cells in the Somatosensory Cortex of the Cat. M.Tremblay, R.Warren, R.W.Dykes. Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada.

Acetylcholine administered during neuronal activity induced by somatic stimuli produced long term changes in excitability of somatosensory cortical neurons. This effect could be blocked by atropine (Metherate et al., 1987). The presence of cholinergic cells in the basal forebrain is well established and the location of cholinergic cells projecting to the somatosensory cortex of the cat has been identified recently by Bear et al.,(1987). Based on these studies, we hypothesized that cortical neurons activated by somatic stimuli during stimulation of the basal forebrain would undergo long term changes in their excitability.

Cats were anesthetized with halothane, mounted in a steriotaxic device, and a craniotomy was performed over the parietal cortex. Two bipolar electrodes were introduced into the basal forebrain following steriotaxic coordinates. A multibarrel iontophoretic electrode glued to a glass recording pipette was introduced into the forelimb region of primary somatosensory cortex. Single cells with cutaneous receptive fields were isolated and their responsiveness to somatic stimuli measured following three different experimental treatments: first, the basal forebrain was stimulated in the absence of peripheral stimulation; second, receptive fields were stimulated during basal forebrain stimulation, but while atropine was administered iontophoretically, and third, after the atropine dissipated, the receptive fields were stimulated in the presence of basal forebrain stimulation without atropine.

At this point of our study, 12 cells with receptive fields have been tested. Five cells showed a long term effect after the simultaneous stimulation of the basal forebrain and skin. For these cells it was not possible to compare this effect with the same treatment in the presence of acetylcholine since the pairing had already produced a long term effect. However it was possible to increase the effect produced by the basal forebrain further by iontophoretic administration of acetylcholine. In the other 7 cases for which stimulation of the basal forebrain did not induce a long term effect, administration of acetylcholine during peripheral stimulation did not induce a long term change in excitability.

In somatosensory cortex, 60-70% of the cells are unresponsive to somatic stimuli. Stimulation of the basal forebrain during glutamate-induced depolarizations, causes some of these neurons to display long term enhancement of their responsiveness to glutamate. (Supported by FRSQ of Quebec and MRC of Canada).

NOREPINEPHRINE INFLUENCES EARLY OLFACTORY LEARNING: SINGLE-UNIT, METABOLIC AND BEHAVIORAL RESPONSES TO LEARNED ODOR CUES. D.A. Wilson, R.M. Sullivan and M. Leon, Dept. of Psychobiology, University of California at Irvine, 92717.

Norway rat pups learn to prefer odors paired with stimulation that mimicks maternal contact. This learned odor preference is associated with an enhanced olfactory bulb metabolic response (14C 2-deoxyglucose uptake) (Coopersmith & Leon, 1984; Sullivan & Leon, 1986) and modified olfactory bulb single unit response patterns to the odor in an odor-specific region of the bulb (Wilson et al., 1985; 1987). Previous work suggests that norepinephrine (NE) may be involved in the acquisition of these conditioned behavioral and neural effects: 1) NE modulates olfactory bulb responding to a conditioned odor in mature rabbits (Gray et al., 1986), 2) 40% of locus coeruleus (lc) neurons terminte in th olfactory bulb (Shipley et al., 1985), 3) tactile stimulation modifies lc activity in the mature (Foote et al., 1983) and immature rat (Kimura & Nokamura, 1985). This report examined the role of norepinephrine (NE) in the development of behavioral and neural responses associated with postnatal olfactory learning.

The olfactory training procedure lasted for 10 min/day from postnatal day 1 to 18, and consisted of either: 1) peppermint odor and vigorous stroking of the pup's body with a brush (Pepp-Stroked), 2) peppermint odor only, 3) stroking only, 4) neither stimulus. Within each training condition, pups were injected with either isoproteronol (NE B-receptor agonist), or saline. On day 19, different groups of pups were: 1) given a two odor choice test (peppermint vs. a familiar pine odor), 2) injected with 14C-2-deoxyglucose (200 uCi/kg) and given a 45 min test exposure to peppermint, or 3) tested for mitral cell single unit responses to peppermint.

The results indicated that early odor experience paired with either stroking or isoproteronol produced a learned behavioral preference, enhanced focal 2-DG uptake and modified mitral cell response patterns to that odor. These results suggest that NE is sufficient for the acquisition of learned olfactory neural and behavioral responses early in life.

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E - 1

SHORT DURATION MEMORY REGISTERS AND COGNITIVE PROCESSING. J.P. Banquet* and M. Smith*, LENA, La Salpetriere Paris 75651 France.

The assumptions behind this experiment were: 1- One, almost trivial, that information integrated over a long time span (such as interitem or contextual information) can only be handled by memory registers with sufficiently long time-constants, whereas physical information related to single items can be processed in short-duration preperceptual memory. 2- that these registers can be tested by Event Related Potentials (ERPs) which have recently been found to reflect short-duration neurophysiological correlates (engrams or neuronal models) of past stimuli and are also known to index information transactions in the brain.

Three factors, physical stimulus characteristics, local and global probability (which can be considered to require increasing amount and duration of processing respectively) were manipulated during learning of a go-nogo task. Eight subjects were submitted to Bernoulli series (events of complementary probability) of high and low-pitched tones delivered at fixed ISIs during two sessions a week apart. They responded by lever-press to target tones. ERPs were recorded by 6 midline monopolar electrodes from Fz to Cz. **PROBABILITY EVALUATION:** -P3b, a late positive parietal component indexed accurately and almost on-line both prior (global) and local probability. -P3a, an earlier frontal positive component, reacted to local probability (5 stimuli upstream) but not significantly to prior probability. -The amplitude of Mismatch Negativity (MMN), a modality-specific negative component, did not react to prior probability but to changes in the physical features of the stimuli. **LEARNING CONDITION.** -Over time, Mismatch Negativity effect in reaction to a shift in the physical characteristics of the stimuli changed in amplitude: small at the beginning of practice, it became maximal at the end of short-term practice (5 min). This learning did not last through the long-term (1 week). -The P3a-P3b complex (reacting to the stimulus category and indexing stimulus probability) presented little change in the short-term practice, but an enduring practice effect lasted throughout the second session.

In conclusion, the above results suggest that: -1 The P3b and P3a systems play two interdependant roles: a) Storage of respectively medium range (prior probability) and short-range (local probability) categorial information concerning the stimuli and b) Comparison between this information and that involving subsequent stimuli; -2 The MMN system does not react directly either to prior probability or to probability changes, but a)intervenes in the short duration storage of physical features of the previous stimuli and b)compares this information with that of the subsequent stimulus. At two different levels of complexity, these comparison processes are instances of cerebral functions usually qualified as cognitive (comparison between two or several subsequent stimuli), that in fact occur at an automatic, pre or post-perceptual level.

E - 2

RHYTHMICITY OF HIPPOCAMPAL NEURAL RESPONSES DURING CLASSICAL JAW MOVEMENT CONDITIONING IN RABBITS. S.D. Berry, R.A. Swain and C.G. Oliver. Department of Psychology, Miami University, Oxford, Ohio 45056.

Prior research has shown that conditioned unit responses in area CA1 of the rabbit hippocampus occur during classical conditioning of both the nictitating membrane and rhythmic jaw movement (JM) responses. In each case, the general topography of the neural poststimulus histograms is similar to that of the transduced behavioral response. In the case of JM conditioning, both behavioral and neural responses are rhythmic and, in addition, rhythmic hippocampal theta rhythm is triggered by the tone conditioned stimulus (CS). In order to better quantify the rhythmicity of these measures and to assess their interrelationships, we applied auto and cross correlational analyses to averaged unit, slow wave, and behavioral responses recorded during 48 paired JM training trials.

The subjects were 8 New Zealand White rabbits that had been implanted with chronic stainless steel electrodes under Ketamine anesthesia (Ketamine 50 mg/kg; Rompun 10 mg/kg). All recordings were verified to be from the pyramidal cell layer of CA1. After one week, animals were placed on a 22 Hr water deprivation schedule and adapted to the conditioning apparatus. Four of the animals were given paired training with a 350 msec, 85 dB, 1KHz tone as the CS and a 100 msec, 1 cc, .022% saccharin solution delivered through a fistula in the right cheek as the UCS. The interstimulus interval was 250 msec, and the intertrial interval was 60 sec. 48 paired trials were run in each daily session. The remaining 4 animals received 48 unpaired tone and saccharin presentations. Permanent tape records of the transduced jaw movement, neural activity and event marker pulses were recorded during each training trial. Unit activity was band pass filtered (500 - 5KHz) and put through a window discriminator to select the largest spikes (3:1 signal - to - noise ratio), which were accumulated into poststimulus histogram averages with a resolution of 10 msec. Slow waves were filtered from 0.5 to 25 Hz and digitized at 10 msec intervals. Statistical analyses were performed using the ASYSTANT+ software on an IBM PC/XT with Keithley System 570 analog to digital converter.

Poststimulus histograms of unit activity showed the development of conditioned responses to the conditioning stimuli in trained but not control animals. Slow wave averages indicated significantly larger (and shorter latency) CS and UCS evoked responses in trained animals than in controls. Auto and cross correlations demonstrated that all CA1 and behavioral responses were highly periodic, with the hippocampal activity preceding the behavioral movements. These data are consistent with a role for the hippocampus in the modulation of the amplitude time course of learned, but not reflex, movements.

THE SPATIAL FIRING PATTERNS OF PLACE CELLS CAN BE MODIFIED BY EXPERIENCE. Elizabeth Bostock, Robert U. Muller, and John L. Kubie, SUNY-Health Sciences Ctr., Brooklyn, NY 11203.

Place cells are hippocampal pyramidal neurons that fire rapidly only when a rat is in a restricted region of the space to which the animal has access; this region is called the cell's "firing field". In our laboratory, place cell recordings are most frequently done when the animal is in a 76 cm diam, 51 cm high gray cylinder. A rectangular piece of white cardboard that covers 100° of arc is attached to the wall to act as a polarizing stimulus. Before recordings are made, each rat is thoroughly pretrained to recover small food pellets that are thrown into the cylinder with the white cue card in place. During pretraining, the rat is never exposed to the alternate polarizing stimulus, a black card of the same size as the white one. In this study, we explored the effects of substituting the novel black card for the familiar card on the firing fields of individual place cells.

When a cell was well isolated on a recording electrode, a 16 min recording session was done in the presence of the white cue card. The animal was returned to its home cage, and a black card was put into the cylinder at the same position previously occupied by the white card. A second session was run, and color coded firing rate maps of the two sessions were inspected to determine if the firing fields were the same or different in the presence of the two cards. Thirty seven cells were recorded from 13 rats using this protocol.

The firing fields of 13 out of 16 place cells recorded during the first exposure to the black card appeared to be the same as the fields seen in the preceding white card session. By contrast, the spatial firing patterns for 18 out of 21 place cells recorded during later exposures to the black card appeared to be completely unpredictable from a knowledge of the firing pattern in the presence of the white card. Thus, place cells initially respond to the black card in the same fashion as to the white one. Subsequently, however, the two cards are associated with distinct spatial firing patterns. A Fisher test of exact probability revealed a highly significant contingency ($p < 0.0005$) of the similarity of the firing pattern on the number of exposures to the black card.

Five of the 16 place cells recorded during the first black card exposure were also recorded on subsequent days. Four of these cells showed the expected change in their the spatial firing pattern with repeated exposures to the black card. The time course over which the change took place was quite variable from rat to rat. Despite the altered firing in response to the black card, the firing associated with the white card remained stable for each cell. The fifth cell continued to respond the same way to the two cards over 10 days of recording. The fact that many of the same cells initially treated the two cue cards as equivalent belies the notion that the differences in spatial firing patterns are a direct result of the difference in stimulus properties; if the visual difference between the black and white cards was crucial, the altered firing associated with the black card should have been seen immediately. We conclude that the altered, time-variant spatial firing pattern to black cards reflects the operation of a plasticity mechanism whose site is unknown.

TYPE I AND II THETA-LIKE UNIT ACTIVITY IN STRUCTURES OF THE PAPEZ CIRCUIT DURING DIFFERENTIAL AVOIDANCE CONDITIONING IN RABBITS. M. Mignard, D. Bentzinger*, N. Bender*, and M. Gabriel. Dept. of Psychol., Univ. of Illinois, Champaign IL 61820.

Rhythmic bursts of neuronal action potentials exhibiting frequencies (4 - 10 Hz) and behavioral relations similar to the the hippocampal theta rhythm occur in the hippocampal formation during differential avoidance conditioning (Gabriel & Saltwick, Physiol. & Behav., 24:303, 1980). In this task, rabbits learn to avoid a shock unconditional stimulus (US) by stepping in an activity wheel in response to a positive conditional stimulus (CS+, a 1 or 8 kHz .5-sec tone) initiated 5 sec before US onset. They also learn to ignore a negative conditional stimulus, a CS-, never followed by the US. Trains of rhythmic 7-8 Hz unit bursts following CS onset were similar to type II "immobility" theta (Kramis et al., Exp. Neurol., 49:58, 1975), whereas bursts attaining 10 Hz just before CR initiation, and continuing at high frequencies (8-10 Hz) during locomotion suggested Type I "movement related" theta. Here we report movement related and/or CS related theta-like bursts of action potentials in the posterior cingulate cortex (Brodmann's Area 29b), the anterior ventral (AV) thalamic nucleus, and the medial mammillary (MM) nucleus. Neither the anterior cingulate cortex (Brodmann's Areas 24 and 32), the medial dorsal thalamic nucleus, nor the anterior dorsal (AD) nucleus exhibit such bursts. The CS related bursts were evident in a majority of the approximately 300 Area 29b records obtained since 1983. A similar high prevalence of this pattern has been noted in the dorsal magnocellular region of the AV nucleus just ventral to the AD nuclear border. In 4 MM nuclear recordings to date, each has exhibited CS related bursts. The cortical and thalamic CS related bursts, like immobility theta, were severely attenuated by systemic atropine (25 & 50 mg/Kg) and scopolamine hydrobromide (1, 2, & 4 mg/Kg), but not by scopolamine methylbromide. Clear phase differences between CS+ and CS- elicited burst trains in conditioned rabbits suggested an informational function for the bursts. We have recorded movement related bursts in Area 29b and in the AV nucleus, but at a substantially reduced prevalence relative to CS related bursts. These results implicate the entire circuit of Papez in theta processes. They also support cingulate cortical involvement in these processes (e.g., Holshiemer, Exp. Brain Res. 47:2, 1982), and they indicate that cingulate cortical theta is not volume conducted from the hippocampus as suggested in recent literature. (supported by NIMH Grant 37915 to M.G.)

BRAIN POTENTIALS PREDICTIVE OF LATER PERFORMANCE ON TESTS OF RECOGNITION AND PRIMING[1] *Ken A. Paller, Gregory McCarthy, and Charles C. Wood.* Neuropsychology Lab-116B1, VA Hospital, West Haven, CT and Departments of Neurology and Psychology, Yale University.

Recent evidence from studies of human amnesia supports a distinction between *declarative memory*, which pertains to facts and episodes subject to conscious recollection and is impaired in amnesia, and other types of memory—such as motor skills, cognitive skills, simple classical conditioning, and priming—which are intact in amnesia. Despite the link between declarative memory and the brain areas damaged in amnesia, the functional roles of these areas in declarative memory are currently unclear. For example, hypotheses regarding the specific functions of hippocampal circuitry in declarative memory are vague at best, although the anatomical connections of the hippocampus and the physiology of the trisynaptic circuit have been extensively studied. Bridging the gap between conceptions of declarative memory and of the brain areas damaged in amnesia may be aided by studying the electrical activity generated in these areas during memory tasks. Event-related potentials (ERPs) may be sensitive to such activity and can be recorded from human subjects engaged in tasks in which the distinction between declarative memory and priming can be exploited.

Previous studies have shown that ERPs are sensitive to processes correlated with encoding and/or consolidation. In these studies, ERPs elicited by words that were later remembered were compared to ERPs elicited by words that were later forgotten. Generally, an electrophysiological correlate of memory performance was found in the 400-800 ms latency range. The present study follows two previous experiments designed to investigate ERP correlates of stem-completion priming. Sixteen adult subjects rated 288 concrete nouns (critical words) as either *interesting* or *uninteresting*. Two memory tests were given, with test order balanced across subjects. The recognition test was a list of 700 words, 100 of which were critical words, which subjects were instructed to circle. The priming test was a list of 230 stems, 100 of which matched critical words. Subjects were instructed to complete each stem verbally with the first word to come to mind.

The mean percentage of words recognized was 57%. The mean percentage of words completed in the priming test was 18% (baseline completion = 11%). ERPs elicited during acquisition differed as a function of later performance in both memory tests. As in several previous experiments, ERPs to recognized words were relatively more positive than ERPs to unrecognized words. Further, the scalp distribution of ERP differences associated with recognition appeared different from that associated with priming. Preliminary results using a shorter delay interval in normal subjects and in epileptic patients with electrodes implanted in the medial temporal and other brain regions will also be presented.

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STRUCTURAL CHANGES AT THE SYNAPSE ASSOCIATED WITH STATE DEPENDENT RECALL OF A PASSIVE AVOIDANCE TASK. P.M. Bradley and K.M. Galal, Department of Anatomy, Medical School, University of Newcastle upon Tyne, U.K. and Department of Anatomy, University of Juba, Sudan.

Passive avoidance training in the chick has been shown to be associated with an increase in the size of synapses in the left medial hyperstriatum ventrale (MHV) (Bradley & Galal, Neurosci. Lett.,Suppl.24:48, 1986). Learning of this task and the concomitant synaptic changes can be abolished following a single administration of the protein synthesis inhibitor, anisomycin (ANM). If, however, chicks which have been trained following ANM injection are tested subsequent to a second administration of the drug, recall for the task can be demonstrated. The experiments reported here were designed to test whether, in chicks which showed such state-dependent recall, there were detectable synaptic changes.

Eighty 1-day old chicks (Gallus Domesticus) were divided into two groups. Both groups received an i.p. injection of 0.8mg ANM half an hour before training in the Cherkin (P.N.A.S.,4:1094, 1969) passive avoidance paradigm. Both groups were tested 6hr and 12hr later. Group 1 received an i.p. injection of ANM before Test 1. Group 2 were reinjected with the drug before Test 2. Avoidance scores showed that recall for the task was only seen in chicks which had received ANM before the test. Twelve chicks from each group were killed immediately after the second test and samples of the left and right MHV removed and processed for quantitative electron microscopy.

Group 1 which had shown recall during Test 1 and amnesia during Test 2 showed no evidence of an increase in synaptic size in the left MHV. Their synaptic parameters were similar to those measured in untrained chicks. By comparison, chicks in Group 2 which had shown amnesia in Test 1 and recall in Test 2 showed a significant increase in the length of the post-synaptic density in symmetrical synapses in the left MHV. This result was consistent with that seen in birds trained on the same task but not injected with ANM.

These results suggest that training per se, in the presence of ANM does not produce morphological changes but that recall of the task in the drug-effected state may subsequently induce synaptic modifications. The implications of this for studies in which animals are behaviourally tested immediately prior to analysis of synaptic structure or function will be discussed.

LOCAL INJECTION OF TETRODOTOXIN DECREASES METABOLIC ACTIVITY IN DISCRETE BRAIN REGIONS: A 2-DEOXYGLUCOSE AUTORADIOGRAPHY ANALYSIS

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The production of reversible brain "lesions," with local injections of drugs such as tetrodotoxin or procaine, is a powerful method of analyzing brain function. With such procedures, however, the extent and duration of the treatment is often unknown. In this study we have used 14C-2-deoxyglucose autoradiography (2DG) and the Fink-Heimer stain for degenerating axons to determine the effects of an intra-cranial injection of tetrodotoxin (TTX).

Male Sprague-Dawley rats were implanted bilaterally with guide cannulae terminating just above the amygdaloid complex. After recovery from surgery, the rats received an injection of TTX in one amygdala and vehicle in the other, allowing for within rat comparisons of the TTX effects. In the first phase of the experiment, rats received 0.1, 0.4, or 1.0 µl of a 10 ng/µl TTX solution, followed five minutes later by an intravenous injection of 2DG (150 µC/kg). Forty-five minutes later, the rats were decapitated and the brains frozen in freon. After cryostat sectioning (20 µm), the tissue was exposed for 10 days and the autoradiographs analyzed with a computer-based digital image processor. In the second phase, delays of 2, 4, 8, or 12 hours were placed between the TTX and 2DG injections. Finally, the brains of some rats receiving unilateral TTX (but no 2DG) were stained for degenerating axons by the Fink-Heimer method.

The results show that: 1) Intra-amygdala TTX injections produce significant reductions in 2DG uptake in specific regions, with the largest and most consistent effects seen in the basolateral amygdala; 2) This effect was not seen with 2DG injections delayed 8 and 12 hours after TTX; 3) No degeneration is seen in areas receiving TTX compared to those receiving vehicle. It is concluded that TTX reversibly slows metabolic activity in discrete regions following local injection, and produces no neuronal death.

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COMPUTERIZED THREE-DIMENSIONAL RECONSTRUCTION OF THE NEURAL SUBSTRATES OF LEARNING AND MEMORY.

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Computer-assisted, three-dimensional reconstruction (3D) of the brain from digital images of serial tissue sections provides a mechanism for observing biochemical changes in detail throughout the brain. At Penn State, a system of general purpose digital image processing programs has been developed and applied to 3D metabolic mapping of the brain from quantitative autoradiographs of individual brain sections (Hibbard, et al., Science 236). Using only the mathematical properties of the digitized images, this system provides objective registration of serial images using one of two methods. The first method superimposes image centroids and principal axes, while the second method superimposes the edges of high contrast features by correlation. Using a defined coordinate system, reconstructions can be combined point-by-point to yield 3D maps of averages and differences, or examined by multivariate statistical methods to determine regions of maximum variance. We have applied this system for the 3D reconstruction of immunocytochemical profiles of pre- and postsynaptic proteins and for 3D mapping of second messenger systems in brain. The hippocampus has been used for studying impulse-induced changes in synaptic activity; one assumption is that neurotransmitter activation of second messenger systems can alter the functional and/or structural state of the synapse. The hippocampus is rich in second messenger systems such as adenylate cyclase, protein kinase C and calmodulin-dependent enzymes. We are using immunocytochemistry of presynaptic markers (synaptophysin) and postsynaptic calmodulin binding proteins for reconstructing the rat hippocampus. By digitizing the immunocytochemical profile of these proteins, we will map the three-dimensional synaptic architecture of the hippocampus. ^{3}H-forskolin and ^{3}H-phorbol esters will be used to map adenylate cyclase and protein kinase C. Our goal is to map 3D topographic changes in pre- and postsynaptic hippocampal proteins and second messenger systems, and to determine whether specific 3D changes occur as a result of aging, deafferentation, repetitive stimulation, or other paradigms associated with long-term changes in synaptic transmission and efficiency. Supported by NSF-BNS 85-06479 (LSH), PHS AG-06377 (MLB), and a grant from the ILSI Research Foundation (MLB).

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A TECHNIQUE FOR VISUALIZING THE NEURAL SYSTEMS INVOLVED IN ACTIVITY RELATED BRAIN DAMAGE. G.O. Ivy and N.W. Milgram. Div. of Life Sciences, Univ. of Toronto, Scarborough, Ontario, M1C 1A4

Hypertrophy of astrocytes in the CNS is a well known marker of neural trauma. We demonstrate here that patterns of astrocyte hypertrophy (AH) can be used to trace neural systems that are involved in abnormally heightened levels of electrical activity. Using additional histological and immunocytochemical methods, the degree of specific neural damage or death in various parts of the system can then be determined.

Rats were given one of several treatments: systemic injection of kainic acid (KA), repetitive electrical brain stimulation, or localized electrolytic lesions or stab wounds to various brain regions. After various survival times, the rats were perfused and the brains processed to demonstrate AH (using antibodies to GFAP) or necrosis (using PAS or nissl stains).

Both localized electrolytic lesions and stab wounds produced discrete patterns of AH which reflected known anatomical connectivity. In contrast, both KA and electrical brain stimulation produced recurrent seizure activity and induced patterns of AH that labeled specific neural systems. Three weeks following seizure activity AH was focused in the ventrolateral forebrain, the medial thalamus and hippocampus. Within these regions specific structures were affected. In the forebrain, AH was consistently seen in olfactory cortex, external capsule, endopyriform nucleus, the deep layers of insular cortex, and lamina Va of lateral neocortex; within thalamus AH was pronounced in the intralaminar nuclei, the rhomboid nucleus and nucleus reuniens; within hippocampus AH was particularly notable in the hilus of dentate gyrus. The PAS stain revealed that these areas contained cells in various stages of necrosis, a result that could also be detected in nissl stains. The numbers of regions affected and the extent of cell damage in these regions varied with extent of seizure activity. While cell death was typically seen in the hilar region of hippocampus, it was not typical in dorsal areas CA1 and CA3. In contrast, the endopiriform nucleus, external capsule and lamina Va of temporal and parietal neocortex exhibited marked necrosis, possibly indicating much lower thresholds for damage.

Our results indicate that a variety of different treatments, all of which produce generalized seizure activity cause a common pattern of degenerative changes in the brain that is clearly reflected in patterns of AH. Futher, while fields CA1 and CA3 of hippocampus are most commonly emphasized as being vulnerable to the excitotoxic effects of seizure activity, we show that structures such as the endopiriform nucleus, specific nuclei of the medial thalamus and the hilus of fascia dentata have a far greater vulnerability. It seems likely that similar patterns of degenerative changes occur in individuals afflicted with recurrent seizure disorders.

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GENETICALLY-DETERMINED VARIATION IN HIPPOCAMPAL MORPHOLOGY AND BEHAVIORAL CORRELATES IN RODENTS.

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Large heritable differences can be found in mouse hippocampal morphology. These differences are most pronounced in the sizes of the mossy fiber terminal fields. The mossy fibers (MF) form the only connection from the dentate gyrus to the Ammon's horn. Thus, in view of the hippocampal role in learning and memory processes, variations in numbers of MF synapses should have functional consequences. We studied several behaviors in order to find correlations with the sizes of the MF projections. We found substantial evidence that the size of the intra- and infrapyramidal (iip) mossy fiber terminal field is negatively correlated with two-way avoidance learning and intertrial activity as measured in a shuttle-box. Also, negative correlations were found with activity in a water maze and locomotor activity in an open-field. Apparatus-induced activity is a fascilitating component of learning performance in the shuttle-box and, in contrast, in activity-independent behavioral paradigms (visual and tactile Y-maze discrimination, radial maze, open-field habituation) and in water-maze learning performance we found strong positive correlations between the size of the iip-MF terminal field and the various behaviors. In the latter tasks, information processing is obviously improved if more iip-MF synapses are present. In summary, negative correlations emerge, if high activity improves learning, whereas positive correlations are found in activity-independent tasks. These results are in agreement with common theories on hippocampal function and with the results of lesion studies.

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HIPPOCAMPAL EFFERENTS TO THE RETROSPLENIAL CORTEX IN THE RAT. Th. van Groen and J.M. Wyss, Department of Cell Biology and Anatomy, University of Alabama at Birmingham, Birmingham, AL 35294.

The hippocampal formation plays a prominent role in memory function, and much attention has been given to its connections with the entorhinal cortex. In contrast, the connections between the hippocampal formation and the retrosplenial cortex have received much less attention. In our ongoing investigation of the connections of the retrosplenial cortex, we recently focused on the hippocampal input to this cortex.

In order to investigate the projections of the hippocampal formation to the retrosplenial cortex, anterograde and retrograde tracing studies were conducted. Small injections (5-20 nl) of either wheat germ agglutinin conjugated horseradish peroxidase (WGA-HRP) or [^{3}H] amino acids were made in the hippocampus or the subiculum. Following injections of the septal third of area CA_1 the tracers were transported anterogradely to the subiculum, the postsubiculum, and the retrosplenial cortex. In the rostral retrosplenial cortex, CA_1 injections lightly labeled layers III/IV, but injections of the septal part of the subiculum gave rise to heavy labeling in layer III/IV and light labeling in layer I of the retrosplenial cortex. Injections in the postsubiculum labeled only layer I. To confirm the origin of these projections retrogradely transported fluorescent dye (Fast Blue, Fluorogold) injections were made in the retrosplenial cortex. Following injections in the rostral part of the retrosplenial cortex, two classes of cell bodies were labeled in the hippocampus. Cell bodies were labeled in strata oriens, radiatum and moleculare of CA and in the portion of stratum pyramidale of CA_1 contained in the fasciola cinerea. In comparison, a larger number of cell bodies were labeled in the septal third of the subiculum, and a small number of cell bodies in the postsubiculum also were labeled. Injections in the caudal third of the retrosplenial cortex labeled cell bodies in the subiculum, but a larger number of cell bodies were labeled in the postsubiculum. These results demonstrate that direct projections to the rostral retrosplenial cortex originate in pyramidal and non-pyramidal layers of CA and in the subiculum and postsubiculum. In contrast, direct projections to the caudal retrosplenial cortex originate only in the subiculum and postsubiculum, and none originate in the pyramidal layer of area CA_1.

An Anatomical Correlate of Functional Plasticity: Reduced Numbers of GAD Positive Neurons in Rat Somatosensory Cortex Following Deafferentation. R. Marran, M. Tremblay, R.W. Dykes.

Reorganization of the somatosensory cortex following deafferentation has been well documented in several species of mammals but the mechanisms underlying this phenomenon are far from being resolved. Recent studies (Rasmusson and Turnbull, 1983; Dykes and Lamour, 1987) suggest that there is a decrease of inhibition and/or an increase of excitation in somatosensory cortex during reorganization. We examined the effects of partial deafferentation on the immunoreactivity of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD) in the somatosensory cortex. The rat was chosen for this study because the representation of different body parts is easily identifiable based on the cytoarchitecture of layer IV.

Ten adult male Long Evans rats were used in this study. Five animals were normal and 5 had the sciatic nerve cut on either left or right side 2 weeks prior to perfusion with a mixture of paraformaldehyde (3%), lysine (0.075M) and sodium periodate (0.1M) made according to the protocol of McLean and Nakane (1974). Coronal sections 30 microns in thickness were cut through the somatosensory cortex on a freezing microtome. All sections were saved and processed so that adjacent sections were: (1) stained with thionine, (2) processed histochemically for cytochrome oxidase according to Wong-Riley (1979) and (3) incubated in anti-GAD antiserum (supplied by Dr. D. Schmechel) at 1:1500 and processed by the peroxidase/anti- peroxidase method (Sternberger 1979). Preliminary analysis of the distribution of GAD-positive somata in 3 normal rats showed no apparent right-left differences in any layer of the hindpaw representation. The same procedure in 3 deafferented rats revealed 14.3% fewer GAD-positive somata in layer IV of the contralateral side to nerve cut when compared to the ipsilateral side ($P<0.05$). There were no obvious differences in the other layers. Further analysis of layer IV in all 5 deafferented rats by counting GAD-positive somata in squares measuring 100 microns on a side under the microscope at x1000 from 3 sections of each animal confirmed this observation. Counts were made in 191 squares, 98 on ipsilateral side with a mean number of 4.0 cells (s.d:1.59) per square and 93 on contralateral side with a mean of 3.4 cells (s.D:1.41). This difference averaging 14.9% was statistically significant (t-test for paired observations, $t=-5.01$ $P<0.005$).

The implication of this observation must be clarified by counts of the number of neurons, neuronal density and relative proportions of GAD-positive cells in layer IV of both normal and partially deafferented rat corticies. Nevertheless this observation indicates an important change in GABAerbic cell metabolism in layer IV following deafferentation that may have an important role in the reorganization of somatosensory cortex. (Supported by FRSQ of Quebec to MT and RWD and MRC of Canada to RWD and RW).

HIPPOCAMPAL SHARP WAVES: A CANDIDATE PHYSIOLOGICAL PATTERN FOR LONG-TERM POTENTIATION

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During consummatory behaviors, immobility, and slow wave sleep, irregular sharp waves (SPW) at 0.01 to 2 Hz were recorded from all hippocampal fields. They occurred either isolated or in groups of several successive waves (40-150 msec in duration, 1 to 3.5 mV). The interwave interval within the SPW-burst varied from 50 to 200 msec. Concurrent with the SPWs a large number of pyramidal cells occasionally formed a series of "mini" population spikes at 50-200/sec in the pyramidal layer. SPWs occur synchronously in both hippocampi, thus pyramidal cells may be excited via the associational and commissural fibers in a cooperative manner.

Artifically induced population bursts in CA3 region, triggered by single pulse stimulation in the presence of bicuculline, produced LTP in the target CA1 region. In these experiments bicuculline was applied locally to the CA3 region and a series of small population spikes, similar to the "mini" population spikes during the SPW, was induced by antidromic single pulses. The potentiation outlasted the local effects of bicuculline on the CA3 cells and thus represents a true long-term synaptic change. Conversely, high frequency stimulation of the Schaffer collaterals in vivo increased the amplitude and frequency of the spontaneous SPWs for several hours.

Synchronous activation of several input fibers is required to produce LTP. We suggest that the optimal stimulation parameters for LTP to produce long-term neuronal changes, as observed empirically, are similar to the SPW-associated population bursts.

Our results thus suggest a possible physiological mechanism which might be responsible for LTP under natural conditions.

INDUCTION OF HIPPOCAMPAL LONG TERM POTENTIATION IN THE AWAKE RAT USING PHYSIOLOGICALLY PATTERNED STIMULATION.

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Long term potentiation (LTP) has been described extensively as a mnemonic model. However, in most studies the stimulation required to induce LTP exceeds normal physiological activity. Recently, Rose and Dunwiddie (Neurosci. Lett., 69:244, 1986) reported that the threshold to induce LTP was reduced when the stimulation parameters more closely mimicked hippocampal discharge activity. They incorporated two well known characteristics of physiological activity in the hippocampus into a pattern of electrical stimulation: 1) hippocampal neurons discharge in a burst of activity, and 2) rhythmic activity at approximately 6 Hz (170 msec period) is observed during exploration (theta rhythm). Using the in vitro preparation, they stimulated the commissural input to CA1 with a single pulse, followed 170 msec later by a high frequency burst of 4 pulses (primed burst, PB). This pattern of stimulation, combining the timing of the theta rhythm with the bursting activity intrinsic to hippocampal neurons, resulted in a long term increase in the amplitude of the population spike (PB-LTP). In contrast, a high frequency train of 5 pulses (unprimed burst) did not induce long lasting effects. In this report, we have extended the findings of the in vitro study by using patterned stimulation to induce PB-LTP in the awake rat.

Data were obtained from 9 rats in 26 recording sessions. Under barbiturate anesthesia, the subjects were implanted with a stimulator in the hippocampal commissure. Contralateral to the stimulation site, a microdrive base was implanted over CA1. A miniature microdrive was then attached to the base after the subject recovered from the surgery. The removable microdrive allowed for accurate localization of the recording electrode in the CA1 cell body layer. Responses were recorded in CA1 following stimulation of the commissure. Population spike amplitude was just above threshold (.5-1 mV). The subjects were either asleep or in a quiet awake state during all baseline and post-high frequency recordings. Immediately prior to patterned stimulation (1+4 pulses), the subjects were awakened. Lasting increases (>20 min) in population spike amplitude occurred in 65% (17/26) of the recordings. In 13 sessions in which an initial EPSP was evident, increases in the slope occurred in 54% (7/13) of the recordings. There were no changes (0/17) in response to a train of 5 pulses.

Studies using patterned stimulation have provided an initial understanding of the relationship between endogenous rhythms and synaptic plasticity. By replicating the earlier in vitro work, we can now apply a two-tiered approach towards understanding both the mechanisms and behavioral basis of LTP.

This work was supported by the VA Medical Research Service.

ACUTE ETHANOL BLOCKS LONG-TERM POTENTIATION (LTP) IN THE RAT DENTATE GYRUS S. Sharifkhani, and M. Tuchal, Res. Inst. Scripps Clin. La Jolla, Ca.

The hippocampus is a brain structure particularly sensitive to ethanol(E). Indeed, cognitive deficits including impairment in the consolidation of memory for recent events have been documented in human alcohol abusers. The hippocampus also demonstrates short and long-term response "plasticity" following repetitive stimulation, a complex process hypothesized to be a substrate for associative learning. Although some hippocampal evoked events are altered by chronic E, the effects of acute E on these processes remains to be adequately investigated. Accordingly, we have recently studied the effects of acute E on the the ability to evoke long-term potentiation (LTP) in the rat dentate gyrus in halothane anesthetized and freely moving rats. LTP was induced, in control subjects, using a standard paradigm (8 trains 1/sec., 20 msec pulses at 400 Hz, N=11). Stimuli were delivered to the angular bundle of the perforant path using an intensity adjusted to give one evoked population spike equal to 1/2 maximal amplitude. Evoked synaptic events were recorded from the granule cell layer of the dentate gyrus. LTP stimuli resulted (30-60 min. post tetanus) in a mean increase of approximately 200% in the evoked population spike compared to baseline. E (2 gm/kg, i.p., resulting in a mean BAL of 178 mg%) given 25 min. prior to tetanic stimulation (N=14), blocked the development of LTP (equal to < than a 50% increase in the pre-ethanol population spike) assessed 30-60 min. post tetanus. However, when LTP was attempted in these same rats after blood E levels returned to baseline (approx. 5 hrs.), normal LTP was obtained. When E was given after induction of LTP, potentiation was not altered. Similar effects were seen in unrestrained, unanesthetized rats (N=6). These data suggest that long-term synaptic plasticity can be effected by low, intoxicating doses of E.

The Dynamics of Free Calcium and Fully Bound Calcium/Calmodulin in Dendritic Spines in Response to Repetitive Synaptic Input. Christof Koch, Division of Biology 216-76, Caltech, Pasadena, CA 91125.

Increased levels of intracellular calcium ($[Ca^{2+}]_i$) and/or the fully bound calcium/calmodulin complex ($[Ca_4CM]_i$) is believed to be the critical signal initiating the sequence of events leading to short- or long-term modifications of synaptic strength. In the cortex, the majority of excitatory, postsynaptic sites are on dendritic spines. We numerically solved the appropriate electro-diffusion equations for spines, comparing the levels of evoked calcium in response to repetitive synaptic input to that expected at a typical vertebrate cell body. The input to the spine is provided by a glutamate, voltage-independent channel; the spine head membrane also contains voltage-dependent calcium and potassium channels, two major calcium buffering systems, calmodulin and calcineurin, calcium diffusion throughout the spine and into the dendrite and an ATP-driven calcium pump. As much as possible, we choose numerical values in accordance with physiology and anatomy.

If the spine receives a burst of 10 presynaptic spikes in 30 msec, the level of free, intracellular calcium in the spine neck reaches 1.44 μM, while 10 spikes in 200 msec only increases $[Ca^{2+}]_i$ to 0.31 μM (up from a resting level of 58 nM). The calcium buffers never saturated for physiological rates of presynaptic spiking activity due to loss of calcium via diffusion into the dendrite and loss due to the calcium pump. A much more dramatic effect can be observed if one considers the dynamics of $[Ca_4CM]_i$. While its concentration is 3.3×10^{-8} μM at rest, it rises to 4.5×10^{-3} μM following 10 spikes in 30 msec but only to 5.8×10^{-6} μM following 10 spikes in 200 msec. Thus, short but high-frequency burst of spikes are more effective in elevating the concentration of free calcium in dendritic spines than much longer trains of lower frequency. Furthermore, small, experimentally almost undetectable differences in the level of calcium binding proteins. These conclusions are to a large extent independent of the specific parameters chosen for our model.

Calcium summation behavior at the cell body is very different. Based on a model of the electrical behavior of type B bullfrog sympathetic ganglion cells developed by us in collaboration with Paul Adams, calcium summation following synaptic input is to a large extent independent of its firing frequency; because of the cell's large volume, levels of $[Ca^{2+}]_i$ do not depend on the timing of the synaptic activity, but only on the absolute number of inputs. We will discuss these results and contrast them with results expected at an NMDA type of synapse.

THE NMDA ANTAGONIST AP5 BLOCKS A COMPONENT OF THE POSTSYNAPTIC RESPONSE TO THETA BURST STIMULATION AND PREVENTS LTP INDUCTION. J. Larson and G. Lynch. Center for the Neurobiology of Learning and Memory, Univ. of Calif., Irvine, CA, 92717.

Short bursts of high frequency stimulation (4 pulses, 100 Hz) produce maximal long-term potentiation (LTP) at Schaffer/commissural synapses on CA1 neurons in hippocampal slices when the bursts are spaced 200 ms apart. A single burst to one set of fibers does not induce LTP but "primes" the post-synaptic neurons such that the depolarization produced by a burst to a second input 200 ms later is much larger and LTP is induced. The present experiments show that part of the response enhancement produced by priming is mediated by N-methyl-D-aspartate (NMDA) receptors and that the NMDA component is necessary for the development of synaptic potentiation.

Theta patterned burst stimulation to induce LTP consisted of pairs of bursts to the priming and test inputs separated by 200 ms; the pairs were given ten times at 5 sec. intervals. Dendritic field EPSPs were recorded in response to single-pulse stimulation of the test input; the response to a burst was quantified as the area of negativity evoked by the 4 pulses in the burst.

2-amino-5-phosphonovalerate (AP5-100uM) did not significantly alter responses to moderate intensity single pulses. However, it did completely prevent LTP induction by burst stimulation (EPSP potentiation in AP5: 0.4%+2.8%; after washout: 35.7%+6.7%).

AP5 produced a small depression of the response to the priming burst (8.8%+3.0%) but a larger and more consistent reduction of the response enhancement caused by priming (enhancement relative to an unprimed burst was 34.7%+9.2% in AP5 and 52.7% +10.7% after washout). Moreover, AP5 blocked the response potentiation that developed across repeated primed bursts.

In summary, AP5 completely blocked the short and long-term forms of synaptic potentiation produced by patterned burst stimulation. The response enhancement observed in primed bursts that induce LTP appears to have two components, one of which is mediated by NMDA receptors. The NMDA receptor is known to be voltage-sensitive; it seems likely that the non-NMDA component of the primed burst response provides sufficient depolarization to allow activation of the NMDA response and this response is then responsible for producing synaptic potentiation. Since the short bursts used in these experiments are similar to naturally occurring discharge patterns of hippocampal cells and the optimal interburst interval corresponds to the period of the theta rhythm, the results suggest links between these two aspects of hippocampal physiology and a receptor type that promotes synaptic plasticity. (Supported by AFOSR 86-0099 and ONR N00014-86-K-0333.)

SYNAPTIC CHANGES IN THE COURSE OF LONG-TERM TRACE FORMATION. M. Matthies, R. Jork, H. Ruthrich, W. Pohle, G. Grecksch. Institute of Pharmacology and Toxicology, Medical Academy Magdeburg, GDR.

Acquisition of a brightness discrimination in rats was associated with an increase of glycoprotein synthesis in hippocampal structures, which does not occur after their activation by stimulation of single inputs. This increase formation of glycoproteins seems to be particularly attributed to the synthesis of a class of fucosylglycoproteins, its inhibition results in profound amnesia. To evaluate, whether such learning-related macromolecular changes also occur in posttetanic LTP and refer to LTP-like functional alterations in defined synaptic populations, perforant path-granular cell synapses were investigated after acquisition of an active avoidance in rats with stimulation of the perforant path as CS as well as after tetanization.

Using this behavioral task, good learners exhibited a pronounced postconditioning LTP, whereas poor learners developed a long-term depression of test potentials in the dentate area. The necessary involvement of this synaptic population in the learning procedure was demonstrated by selective destruction of granular cells following microinjection of colchicine, which prevents conditioning by perforant path stimulation, but not by light and tone.

Comparing the ability of individual rats to learn the active avoidance with perforant path stimulation as CS and to develop posttetanic LTP, it was shown that good learners also show a pronounced posttetanic LTP, whereas poor learners reveal no potentiation after tetanization. These results demonstrate the occurrence of synaptic changes in a conditioning pathway similar to those obtained after tetanization and the existence of a common cellular mechanism for both kinds of synaptic long-term enhancement, thus supporting assumptions that posttetanic LTP is a mnemonic device.

However, when labeled fucose was intraventricularly injected to determine the formation of fucosylglycoproteins either after LTP-producing tetanization, after acquisition of active avoidance with perforant path stimulation as CS, or after corresponding control stimulations not inducing synaptic potentiation, only successful conditioning resulted in a significantly increased fucosylation of glycoproteins in hippocampal structures.

This result suggests that LTP-like synaptic changes represent only a component or a transient stage of memory formation, but not the complete processes underlying the formation a long-term memory trace at the molecular and cellular level.

DIFFERENT STAGES OF LTP: WHEN IS LTP A REAL "LONG-TERM" POTENTIATION? H. Matthies, K. Reymann, U. Frey, M. Krug, N. Popov, B. Lehmar. Institute of Neurobiology and Brain Research, Academy of Sciences of GDR, Magdeburg. Institute of Pharmacology and Toxicology, Medical Academy Magdeburg.

Memory formation is characterized by the occurrence of at least three consecutive stages: short-term (STM), intermediate (IM) and long-term memory (LTM). STM and IM are insensitive to inhibition of protein synthesis and posttrial ECS, whereas LTM depends on intact protein synthesis during a time window after acquisition and is associated with increased glycoprotein formation. To evaluate the significance of posttetanic LTP as a mechanism of memory, its maintenance in vivo and in vitro was examined for more than 8 hours after influencing the initiation by different procedures. Immediately after tetanization, cytosolic calmodulin was found to be translocated to membranes and subsequently redistributed in the course of the following hour to the cytosolic compartment. Protein synthesis increased immediately after tetanization; its inhibition by amisomycin did not influence initiation and early maintenance (2 hrs) of LTP, but late potentiation (5-6 hrs) was abolished. The posttetanic EPSP-potentiation in dendritic stumps, which are separated from cell bodies as main site of protein synthesis, showed the same time course as intact slices after inhibition of protein synthesis. Inhibitors of protein kinase C (PKC), which prevent phorbol ester-induced LTP, did not influence initiation of posttetanic LTP and its very early maintenance (1 hr), but depressed LTP already after 2 hours. The results suggest that posttetanic LTP exhibits subsequent stages with different underlying mechanisms:

- induction and short-term stage of LTP associated with calmodulin-dependent processes
- intermediate stage of LTP dependent on protein kinase C
- amisomycin-sensitive late stage of LTP dependent on protein synthesis.

A real posttetanic LTP only exists about 4-7 hours after tetanization. Investigations at earlier times do not completely refer to mechanisms of "long-term" potentiation, but rather to intermediate states.

Posttetanic LTP exhibits subsequent stages with similar time courses as observed during memory formation in learning experiments, thus supporting assumptions on the role of LTP as a mnemonic device.

However, the occurrence of additional processes and mechanisms completing a distributed memory trace has to be considered with regard to the increased glycoprotein synthesis only observed after acquisition of a learned behavior, but not after monosynaptic activation of principal cells.

LONG-TERM POTENTIATION AND DEPRESSION IN NEOCORTEX AS POSSIBLE MODEL FOR SEARCHING OF MECHANISMS OF LEARNING AND MEMORY.

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The present report deals with some aspects of long-lasting changes of neuronal impulse reactions in the cortex. The evoked impulse responses of single neurons in the sensorimotor and visual cortex were studied and the effects of repetitive stimulation of relay thalamic nuclei were examined. The index of monosynaptic discharge was estimated during 0,5 - 1 h before and after high frequency tetanization (4 pulses trains, 100 Hz, 0,5 - 1,5 min; the intervals between the trains corresponded with the interspike intervals in spontaneous activity of previously recorded cortical neuron, mean frequency 1,8 imp/s).

The experimental data produced some evidence for the possibility of long-term potentiation (LTP) or depression (LTD) of monosynaptic impulse reactions of cortical neurons. The observed properties of cortical LTP (long time course, input specifity, additivity and cooperativity) made it possible to suggest the similarity between cortical LTP and widely discribed hippocampal LTP. The cortical LTD differed from LTP in the possibility of its appearance not only for tetanized but also for untetanized inputs. The kind of posttetanic effect (LTP or LTD) depended on the strength of conditioning stimulation. It was founded that strong stimulation (4-5 thresholds for impulse discharge) more often resulted in LTP whereas more weak stimulation (about two thresholds for spike initiation) mostly produced LTD. Cortical LTD could be induced by delivering high frequency conditioning stimulation as distinct from hippocampal homosynaptic LTD that was usually observed after low frequency tetanization. The presented results showed that long-lasting changes of monosynaptic impulse reactions might be induced not only by high frequency trains but also by single stimuli of high strength.

It was reasonable to propose that potentiation of inhibitory process probably played some role in the genesis of LTD. The existence of LTP and LTD in neocortex might serve as evidence for assumption that some cortical synapses could be characterized by high level of plastisity. Such "modifiable" synapses provided the basis of several models for learning and memory.

REGULATION OF NEURONAL AND GLIAL PROTEINS IN THE NERVOUS SYSTEM BY GLUCORTICOIDS AND ENVIRONMENTAL CHALLENGE. R.E. Brinton [1], J.P. O'Callaghan [2], M.D. Browning [3] and B.S. McEwen [1]. Laboratories of Neuroendocrinology [1] and Molecular and Cellular Neuroscience [3], Rockefeller University, New York, NY 10021 and U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 [2].

Neural plasticity is characterized by a dynamic adaptive process which can now be assessed at the behavioral, biochemical, structural and genomic level of analysis. Because glucorticoids act to influence gene expression via nuclear DNA binding receptors we have used corticosterone (CORT) as a probe into the genomic regulation of structural proteins potentially involved in neuronal plasticity. These proteins include the synaptic vesical phosphoproteins P 38 and Synapsin I, the neurofilament triplet protein, NF-200, and the major intermediate filament protein of astrocytes, glial fibrillary acidic protein (GFAP).

Adult male rats received either 0, 2, 20, 200 ug/ml corticosterone in the drinking water for a period of 5 days (n=8 at each dose). P 38, Synapsin I, NF-200 and GFAP were assayed by solid phase RIA (Brock and O'Callaghan, J. Neurosci. 7:931, 1987). Twenty and 200 ug/ml CORT produced a significant 25% increase ($F(3,28)=6.2$, $p < .01$) in the relative abundance of P 38 in the hippocampus. This increase was specific to the hippocampus and was not expressed in the cerebral cortex. Synapsin I abundance was unchanged in response to CORT in both the hippocampus and the cerebral cortex. NF-200 was also unchanged by CORT treatment. In contrast, GFAP showed a marked and significant decrease ($F(3,28)=5.0$, $p < .01$) in relative abundance particularly at the 200 ug/ml dose of CORT. The significant suppressive effect of CORT upon GFAP was also apparent in the cerebral cortex ($F(3,28)=5.2$, $p < .01$). When animals were adrenalectomized, the relative abundance of P 38, Synapsin I and GFAP all increased significantly while NF-200 remained unaffected. Administration of CORT in the drinking water of adrenalectomized animals restored Synapsin I and GFAP levels to control values, while P 38 levels resembled those of intact animals treated with CORT. These results suggest that CORT acts as a tonic synthetic inhibitor of Synapsin I and GFAP while also acting as a synthetic initiator of P 38. Collectively, these results indicate a specific and significant influence of glucocorticoids upon neuronal and glial cell structural proteins in select cell populations. Experiments to explore the influence of stress upon these same structural proteins are currently in progress.

ENRICHED AND IMPOVERISHED ENVIRONMENTS: EFFECTS ON THE TURNOVER RATES OF MONOAMINE NEUROTRANSMITTERS. M. J. Renner (Department of Psychology, University of Wisconsin, Oshkosh, WI 54901), C. L. Blank, & K. Freeman (Department of Chemistry, University of Oklahoma, Norman, OK 73019)

Last year we reported data concerning tissue concentrations in several brain regions for monoamine transmitters and their metabolites in rats after enriched and impoverished housing experience (Renner, et al., Society for Neuroscience Abstracts, 1987, 12, 1136). Those studies are extended here by examining the effects of enriched and impoverished experience on turnover rates of these transmitters. In two replications, 27 weight-matched pairs of 70-day old Sprague-Dawley male rats were randomly assigned, one to an enriched condition (EC; group housing in a 75 x 75 x 40 cm cage, with a number of junk objects, some of which were replaced daily) and one to an impoverished condition (IC; solitary housing in a small cage without cagemates), for 30 days. After this 30 days, subjects were then injected with 200 mg/kg of the L-aromatic amino acid decarboxlyase inhibitor NSD-1015, held 30 minutes, and sacrificed (under code numbers that did not reveal an individual's environmental history) by 800 msec of 10kW microwave irradiation to the head at 2.45 GHZ (MJE-2603 Microwave Irradiator, New Japan Radio Company, Ltd.). Brains were then removed from the skull and dissected into 11 sections: four sections from the cortex (occipital, somesthetic, frontal pole, and remaining dorsal) and seven others (hippocampus and amygdala, corpus striatum, hypothalamus, cerebellum, medulla-pons, midbrain, thalamus). Samples are analyzed via liquid chromatography combined with electrochemical detection (LCEC) using a reversed phase column packed with 3 micron particles (P. Y. T. Lin., et al., J. Liquid Chromtog., 1984, 7(3), 509-538), permitting determination of 10 species of catecholamines, indoleamines, precursors and metabolites. Data for serotonin in the hippocampus (indicated by buildup of 5-HTP), show that IC significantly exceeds EC in turnover rate (IC 5-HTP: 383 ng/g (SEM = 12 ng/g), EC 5-HTP: 334 ng/g (SEM = 7 ng/g), $p = .002$). Dopamine turnover (indicated by Dopa buildup, also indirectly indicative of norepinephrine synthesis via dopamine) was marginally significantly different in one of two replications (IC Dopa: 157 ng/g (SEM = 12), EC Dopa: 129 ng/g (SEM = 7), $p = .04$), but not in the other (IC Dopa: 144 ng/g, EC Dopa: 146 ng/g, n.s.). These findings, with IC exceeding EC where differences exist, are opposite the direction of brain differences typically reported for other measures in EC-IC comparisons. No significant differences of monoamine neurotransmitter turnover were revealed in occipital cortex, the region of largest EC-IC anatomical differences. Analyses of additional brain regions are being conducted and will be fully reported.

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Synthesis of postsynaptic membrane fucoglycoprotein is required for longterm memory in the chick

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Day old chicks peck spontaneously at small bright beads; if the bead is coated with a bitter-tasting substance (methylanthranilate, M), they peck once and avoid a similar, but dry bead subsequently. This is one-trial passive avoidance learning.Memory formation for this task involves a sequence of biochemical, physiological and morphological changes in three forebrain nuclei: medial hyperstriatum ventrale (MHV), paleostriatum augmentatum and lobus parolfactorius. Some but not all of these changes are left-hemisphere lateralised. One crucial biochemical sequence for long-term memory seems to be synthesis of postsynaptic membrane glycoproteins. Training chicks on M-beads results in lasting increases in incorporation of radiolabelled fucose into synaptic membrane and especially post-synaptic density glycoproteins by comparison with the rate in control birds which peck at a water-coated bead (W). Glycoproteins of molecular weights in the range 88-120 and 170kD are of particular interest. Training birds on the M-bead but rendering them amnestic by transcranial electroshock abolishes the increase in fucosylation. The increase appears to involve post-translational modification of preexisting proteins, as it is cycloheximide-resistant. On the other hand a specific inhibitor of galactoglycoprotein fucosylation, 2-deoxygalactose, injected up to two hours prior or two hours following training, prevents long-term memory formation. Thus fucosylation of membrane glycoproteins appears to be necessary for long-term memory formation. The increase appears to be mediated by activation of one of the enzymes of fucosylation, fucokinase. As we have in other experiments shown that M-training results in substantial increases in the numbers of dendritic spines and the diameter of the spine heads in projection neurons of MHV, one role for the glycoproteins might be in the membrane modifications that such dendritic changes must involve.

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EXCITATORY AMINO ACIDS ACTIVATE CALPAIN I AND STRUCTURAL PROTEIN BREAKDOWN *IN VIVO*. J.C. Nozsek* and R. Simon, Neuroscience Group, Medical Products Dept., The DuPont Co., Wilmington, DE. 19898.

Mammalian brain contains two calcium-activated proteases, calpain I and calpain II, that are activated, respectively, at low micromolar and high micromolar calcium concentrations. Calpain activation has been hypothesized to be critically involved in structural modification of synapses, and in neuronal degeneration. It has not yet been demonstrated, however, that physiological stimuli can activate the calpains *in vivo*. We report here that administration of the excitatory amino acids kainate or N-methyl-D-aspartate (NMDA) *in vivo* causes activation of calpain I and degradation of neuronal structural proteins.

Rats were administered kainate (12 mg/kg) intraperitoneally or NMDA (80 ug) or kainate (1 ug) intraventricularly and allowed to survive for up to 24 hours. The extent of calpain activation was assessed in dorsal hippocampus, taking advantage of the property of the calpains to undergo autoproteolysis upon activation. Calpains I and II were separated by SDS-PAGE and detected and quantified by immunoblotting with polyclonal antibodies to the Mr~84kD catalytic subunit of human erythrocyte calpain I. Blots of partially purified rat brain calpain I or rat brain calpain II indicated that the antibodies detect the catalytic subunits of both proteases (rat brain calpain I Mr~84kD, calpain II Mr~76kD). Kainate and NMDA induced time-dependent decreases in calpain I but had little effect on calpain II, with calpain I levels decreasing as much as 50% by 24 hours. Concomitant with the calpain I decrease, the amino acids stimulated the degradation of brain spectrin and the microtubule protein MAP2, quantified by immunoblotting with appropriate antibodies. Spectrin proteolysis was accompanied by up to a seven-fold increase in two lower molecular weight breakdown products; these fragments are of identical size as those produced upon cleavage of purified brain spectrin by purified calpain I. In contrast to the spectrin and MAP2 polypeptides, neither kainate nor NMDA affected glial fibrillary acidic protein, an excellent calpain substrate *in vitro*, or altered levels of actin, a poor calpain substrate.

These results indicate that excitatory amino acids can provide sufficient intracellular calcium to activate the high-sensitivity protease calpain I, without apparently affecting the low-sensitivity variant, calpain II. The activation occurs in neurons, but perhaps not in glia, and leads to degradation of major neuronal structural proteins. The findings support the hypothesis that calpain I activation is an obligatory step in the neurotoxic action of excitatory amino acids. Conceivably, less pronounced stimulation of excitatory amino acid receptors than employed here could act through calpain I to produce more modest structural changes than those associated with neurotoxicity.

DERIVATION OF SYNAPTIC LEARNING RULES VIA COMBINED EXPERIMENTAL AND COMPUTATIONAL APPROACHES. G. Lynch, R. Granger, J. Larson, R. Henry. Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA 92717.

We have constructed a computational model of piriform cortex, based on its known anatomical and physiological characteristics, including sparse connectivity between bulb and layer II; EPSP and IPSP properties including excitatory feedback and long and short feedforward and feedback inhibitory currents; multiple cell firing frequencies; a two-step firing threshold; necessary conditions for LTP induction; cell-specific long afterhyperpolarization (AHP); relative duration of short EPSPs and short and longer IPSPs; and so on. Experimentation with the computer simulation has identified network-level functional properties not immediately apparent from its cellular-level physiology, as well as revealing gaps in the extant physiological data, suggesting specific physiological experiments to provide answers to these computational questions.

Larson and Lynch (1986) found that 'patterned' stimulation of CA1, consisting of short (30ms) bursts at 100Hz, separated by an interburst interval of 200ms (i.e., bursts occuring at ≈ 5Hz, the theta rhythm), produce optimal synaptic potentiation in vivo, without any artificial blocks of inhibition necessary. The same patterned stimulation, applied to the lateral olfactory tract, produces LTP in piriform cortex correlated with behavioral learning in rats performing an olfactory discrimination task (Staubli et al, 1986). An unanswered question is how the transient synaptic facilitation produced by patterned stimulation (the 'priming' effect) interacts with existing potentiation in synapses that have previously been potentiated. In network simulations it frequently occurs that previously-potentiated synapses are activated in a theta burst pattern; formalization of the rule underlying LTP induction requires specification of the function that combines stable potentiated synaptic strength values with the increment due to transient facilitation. Experimental comparisons were made of the net depolarization produced by four-pulse bursts given in the theta pattern on naive vs potentiated synapses. Early results indicate that LTP *sums* nonlinearly with priming; i.e., previously-potentiated synapses are only slightly more effective in depolarizing target dendrites than are naive synapses during theta bursting stimulation (Larson et al., unpublished data). Hypothesizing that theta bursting corresponds to learning mode in a behaving animal, these results suggest that synaptic conductance will differ in learning (theta bursting) vs. performance (non-theta burst) firing modes, in marked contrast to typical network models.

A related question is how synaptic change is affected in the presence of asynchronous stimulation of multiple pathways, which undoubtedly occurs in vivo and in any network model containing feedback. Theoretical considerations in the simulation prompted experiments on these temporal attributes of LTP using staggered bursts arriving on a primed target, such that burst 2 began halfway through burst 1, and burst 3 began halfway through burst 2. Preliminary results show retrograde facilitation, a counterintuitive result in which burst 1 generated strong LTP, while burst 3 generated only slight potentiation, indicating an inverse relation between arrival time and magnitude of induced synaptic potentiation.

These and related results indicate that computer simulation can be of value not only for interpretation of existing experimental results, but also for specification of further experiments. Our simulations have led to a series of experiments that have given rise to counterintuitive findings, with the dual benefit of advancing the body of data on the physiological mechanisms underlying LTP, and further constraining the set of biologically-valid models of cortical networks, enabling us to move closer to an understanding of the nature of such networks.

THE ROLE OF FEED-FORWARD INHIBITION IN ASSOCIATIVE RECALL AND PATTERN COMPLETION IN HIPPOCAMPAL CIRCUITS. B. L. McNaughton, Department of Psychology, University of Colorado, Boulder, CO 80309

Marr (1971) proposed that the hippocampus implemented associative memory using a simple Hebb rule to store multiple, non-orthogonal neural representations, and to recall a given representation from some fragment of the original (the completion operation). A crucial element of the model was a set of feed-forward inhibitory interneurons which sampled the density of afferent activity, and divided the resulting excitation of the principal neurons by a proportional signal. The result was that only those principal cells discharged which possessed a sufficient number of modified (enhanced) synapses in the input pattern. The principal can be illustrated by considering a simple matrix of modifiable connections between two binary input channels (binary correlation matrix) whose nodes are transformed from zero to one by Hebb type conjunction of their inputs. Selective recall from a stored set of paired input vectors can be achieved (in a single cycle) by forming the inner product of the matrix and one input vector, and then performing integer division of the result by the sum of the elements in the input. Reduced subsets of the input will also complete the appropriate output pattern, provided these subsets are unique, because the divisor will be correspondingly reduced.

Hippocampal synapses are enhanced according to a simple Hebb rule, and hippocampal principal neurons do perform pattern completion in the transmission of spatial information. There are at least five properties of hippocampal inhibitory interneurons (basket cells) which are consistent with, and predicted from Marr's simple associative net model: 1) Both principal and inhibitory cells receive input from the same excitatory pathways. 2) The inhibitory mechanism is fundamentally that of a somatic conductance shunt, thus dividing the dendritic excitation by a term proportional to how many afferents were activated. 3) The inhibitory cells respond to afferent excitation significantly faster than the principal cells, and thus the division operation is in effect when the afferent excitation arrives at the principal cell somas. 4) The inhibitory cells are far fewer in number than the principal cells (1/100 to 1/200), but have diffuse axonal trajectories. 5) Whereas the principal cells are highly spatially selective, the inhibitory cells convey little or no spatial information. This is consistent with a role in signaling not which afferents are active, but how many;.

Hippocampal principal cells carry out their pattern completion operation without any obvious period of progressive "minimization of global energy". A possible source of this capability may result from periodic global inhibition (the "theta" cycle of hippocampal EEG, to which single units are phase locked). As a result of this inhibition, new information gets presented to a silenced network. This would permit the recall operation to occur without interference from preceding states.

NOVELTY DETECTION IN NEURAL NETWORKS

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A novelty detector is a functional unit that indicates whether an incoming stimulus is familiar or novel. There are various levels of novelty detection in the CNS. In its simplest form, the detector will classify as familiar any event which is the exact repetition of a recorded event. All other events will be considered novel. Higher level novelty detectors have less definite boundaries between familiar and novel events. A five engine airplane may be classified as familiar, even though it has never been observed by that individual, while a green dog will probably be classified as novel.

Novelty detectors have to deal with three kinds of concepts. 1. Concrete concepts, which are pieces of information that appear in the external world as whole entities. 2. Abstract concepts, which are pieces of information that are subgroups of concrete concepts, and are defined by the intersection of two or more concrete concepts, e.g. the abstract concept 'blue' may be formed by the intersection of the concrete concepts 'blue sky', and 'blue sea'. The 3rd kind are the recombined concepts, which are combinations of concrete and/or abstract concepts. ('a five engine airplane', and 'a green dog' are recombined concepts.)

Novelty detectors perform two functions. They record information, and classify incoming events. The proposed models of novelty detectors assume that recording information is carried out by modifying efficacies of synaptic ties. The models assume that three factors control those modifications:1. Whether the involved cells are active or not. 2. The total activity level in each layer of the network, and 3. whether or not the cells involved have already recorded information. Two classification mechanisms are proposed. The first is a filter-like mechanism. It allows only familiar information to pass through the network. In the second mechanism, the same information is recorded independently in two compartments, and classification is accomplished by comparing invoked representations in those two compartments. The second mechanism has similarities to observed activities in the cerebral cortex.

Computer simulations have demonstrated that the bi-compartmental novelty detector classifys information in a way similar to humans.

EMERGING OPPORTUNITIES IN NEURAL NETWORK RESEARCH

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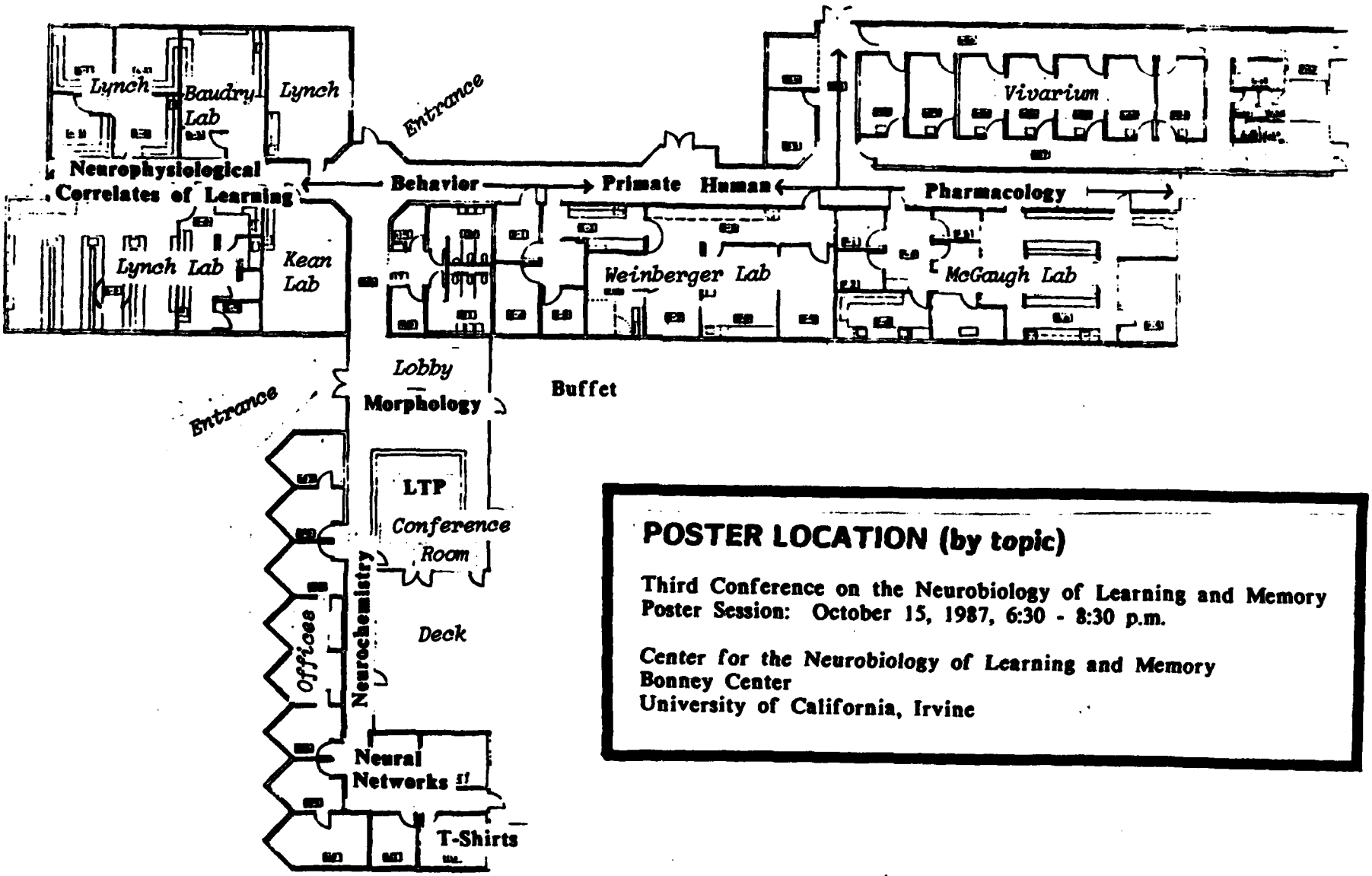
The Office of Naval Research (ONR), through its Biological Intelligence (BI) program is actively seeking to stimulate interdisciplinary research designed to extract from neural systems computational properties applicable to nonbiological electronic devices. This program incorporates the expertise of neurobiologists, computer scientists, electronic engineers, and mathematicians working in concert to fulfill the goal of providing a new generation of computational devices based upon neural-like solutions. The program is focusing upon uniquely interdisciplinary teams of researchers coupling their diverse expertise to provide new and unique approaches to investigate the powerful computational abilities of neural networks. The poster will define neural networks, indicate the types of basic computational issues of interest to ONR, provide examples of ONR-supported on-going basic network research, and highlight potential future directions.



POSTER LOCATION (by topic)

Third Conference on the Neurobiology of Learning and Memory
Poster Session: October 15, 1987, 6:30 - 8:30 p.m.

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