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 models 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).
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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.

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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:

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DMN LESIONS IMPAIR PASSIVE AVOIDANCE LEARNING IN THE CHICK.
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Biomechanical, morphological, and electrophysiological evidence has indicated that the intermediate part of the medial hyperstriatum ventrale (DMN) plays a critical role in imprinting in the chick. Indeed, bilateral lesions to DMN prevent acquisition and impair retention of an imprinting preference (see Ross, G. Memory, Brain, and Learning, G.P., 1985). Biomechanical 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 Ross, S.P., in Brain Plasticity, Learning, and Memory, eds. P.M. Will, P. Schmitt and J.C. Delcroux-Allard, pp. 59-60, Plenum Press, 1985). In the present study we investigated whether bilateral DMN lesions affect one-trial PAL.

Young chicks will spontaneously peck at a small bright lead. If the lead has been dipped in a distasteful substance such as methyl anthranilate (MA), the chick learns not to peck a similar lead on subsequent presentations. In contrast, chicks which initially peck a water-coated lead will continue to peck a similar lead on subsequent presentations. Thus in a single trial, chicks can learn not to peck at an aversive stimulus (Chockin, A., Proc. nat. Acad. Sci. U.S.A. 81: 1094, 1984).

Chicks (approx. 12 h old) were anaesthetised by i.p. injection of Hypnorm and received bilateral lesions to DMN or to the lateral preoptic area of the anterior hypothalamus (LHA) under stereotaxic control. A smaller 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 lead (6 mm in diam.) coated with either MA 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 lead.

Significantly more (P < 0.001) sham-operated chicks trained on a MA-coated lead (77%, n = 23) avoided the test lead than did sham-operated chicks trained on a water-coated lead (54%, n = 23). Similarly, significantly more chicks with bilateral LHA lesions (P < 0.01) trained on a MA-coated lead (73%, n = 11), avoided the lead at test than did LHA-lesioned chicks trained on a water-coated lead (54%, n = 11). In contrast there was no significant difference in avoidance of the lead at test between DMN-lesioned chicks trained on either MA (27%, n = 11) or water (49%, n = 10). There was no difference in avoidance of the lead at test between sham-operated and LHA-lesioned chicks trained on either water or MA. However, the avoidance at test of DMN-lesioned chicks trained on MA differed significantly from sham-operated and LHA-lesioned chicks (P < 0.02 for both comparisons).

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

MEMORY DEVALUATION - Ivan Esquiro, Maria E. Pereira & Mieira L.V. Gavais, Centro de Memoria, Departamento de Bioquimica, Instituto de Biociencias, UFRGS, 90040 Porto Alegre, RS, Brasil

Recently acquired memories may be changed qualitatively 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 task 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.

Supported by grants from FINEP and CNPq, Brasil.

Lesions to a restricted part of the dorsomedial thalamic nucleus (DMV) impaired the acquisition and retention of filial preferences (see Horn,G. Memory, imprinting and the brain, OUP, 1985; Horn,G. Behav. Neurosci., 100: 625-637, 1986), including preferences for individual adult females (Johnson, M.H. & Horn,G., Behav. Brain Res., 23: 269-275, 1987). Do such lesions affect other behaviors 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 investigated whether female chickens which had received bilateral DMV lesions on the first day of life would be impaired in this behavior.

Thirteen female chickens received bilateral DMV lesions on the day of hatching. Fifteen other female chickens 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 2,29= 6.36, p<0.01). In contrast, the lesioned females spent equal time with all of the males (F 2,24= 0.21, n.s.).

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


The anterodorsal (AD) thalamic nucleus develops learning-related discriminative activity in response to auditory conditional stimuli (CS) during differential avoidance conditioning in rabbits (Gabriel et al., Science, 206:1050-52, 1980). The anterodorsal (AD) thalamic nucleus also demonstrates learning-induced 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 AV 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 AV nuclear activity decreased, whereas the AV nuclear activity was at its peak and many CRs occurred. Also, the activity of the AV nucleus increased significantly in response to a novel stimulus. These findings suggest that the AV 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 AV nucleus should increase AV nuclear activity and CR frequency in sessions in which novel training contingencies are experienced.

Bilateral electrolytic or chemical (isotonic acid) lesions were made in 12 male albino rabbits. Histological examination revealed bilateral damage in the AV 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 Weinard et al., accompanying abstract). As predicted, rabbits with AV nuclear lesions made significantly fewer CRs in the first acquisition session and in the first extinction session than either controls or those with hippocampal or cortical lesions (p<0.001). In the first extinction session, CS elicited activity in the AV nucleus of rabbits with the AV nuclear lesions was greater than that in control rabbits (p<0.001). No statistically significant difference was found in the first acquisition session; 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 AV nucleus (p<0.01 for both sessions). Increased activity after AV nuclear lesions also appeared in Area 24, only in the first acquisition session (p<0.05). 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 AV nucleus cooperate in the expression of AV nuclear activity and behavior in response to unexpected training contingencies. (Supported by NIH Grant 37915 to M.G.)
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.

POTENTIAL IMMUNOLOGICAL BASIS FOR SENESCENCE-RELATED COGNITIVE DEFICITS, Warrens Lal, Michael J, Forster, Kalidas Nandy, and Konrad C. Retz. Department of Pharmacology, Texas College of Osteopathic Medicine, Fort Worth, TX 76107.

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/B1NJ, BXSB/MpJ, NBL/MpJ-1pr) 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 12-20 months of age. The heterochronous 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 AG10823, AGED182, ES-129624, and RR05579, and research funds of Veteran Administration.
MULTIVARIATE ANALYSIS OF AN OPERANT MODEL AND THE PARAMETERS THAT
BEST PREDICT LEARNING AND MEMORY. A. Osorio, A. Manees and V. Alén-
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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 pa-
rameters like latencies and lever pressings, they neither offer a
complete description of the behavioral manifestations occurring du-
ring (and of important for) acquisition, nor they predict its de-
gree or percentage of learning involvement. The present model,
attends to analyze alternate but correlated parameters of an auto-
shaped lever press 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 precede the delivery of
a 85 mg food pellet (unconditioned stimulus, UCS). Besides the
active control group (AC) and those animals reached the maximal ac-
quivalence level, they were divided in five groups (N=6). Rats from
one group were sacrificed immediately after acquisition, other
were re-run 96 hr after the last session and sacrificed, this group
allow us to determine the retention level after this time. Three
other groups that were extinguished at different times (48, 72 and
96 hr). Responses during the CS presentation was the Criterion Y;
contacts to the pellet through during the CS were the X2 predictor
and contacts in the absence of CS was the X2 predictor, we there-
fore can equate \[ Y = X1 + X2 + X_{3} + e \]. In the second training session, re-
results obtained with this equation yields a R2 value of 0.5 (R2-means,
that X1 and X2 combined accounts for almost 100% of the variance of
Y) when X1 is about 80% of its maximal value. Therefore, X1 de-
crease to reach a minimum of 10% in the 5th session when R2 value
is now close to 1.0. During extinction a gradual decrease of R2
values reach a minimum of 0.4 in the third extinction session. At
the third acquisition session a crossing over between X1 and Y was
observed and this seem 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 press-
ing during the CS increases, the number of pellet through contacts
during the CS decreases. Thus Y values seem to satisfy predict
Learning since there is a gain in the precision of when and where
no match through control 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 experi-
mentally analyzed.

HIPPOCAMPAL DERENEADE FACILITATES OLFACTORY
LEARNING-SET FORMATION AND DOES NOT IMPAIR MEMORY
IN A SUCCESSIVE-CUE GO, NO-GO TASK. T.A. Otto,
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In an olfactory discrimination task using simultaneous odor presen-
tation, hippocampal denervation by lesions of the entorhinal cortex
produced an 'anterograde amnesia' syndrome in rats which is characte-
ized by unimpaired acquisition of new discriminations (given short
intertrial intervals) but deficits in retention of these discriminations
when tested 1 hour later (Stanbli et al., Proc. Natl. Acad. Sci. 81:5982,
1984). Elchenger 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 hippocam-
pal denervation on two aspects of olfactory learning using sequential
odor presentation: 1) the formation of learning sets, and 2) the reten-
tion 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 injected 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 16
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 ses-
sions. 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 AN INTERFERENCE BY POST-TRIAL TREATMENTS.
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Habitation 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., 1974; Carbone et al., 1984).

Three different approaches were used in order to validate it as a model to study learning and memory processes:
1) The interference revealed by post-trial intervals was modulated by agents which are known to interfere with the hypothesized “consolidation process(es)” (McGough, 1976) in associative learning paradigms. The interference index indicated that the 24 hour activity decrement in a novel environment, operationally defined as long-term behavioral habitation (LTH), requires polysynaptic activation, protein synthesis, a function ing mossy fiber and a balance between paracell/short 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 GABA-DA lesions of dorsal noradrenergic bundles, whereas it is facilitated by lesion of septohippocampal fibers (Sadile et al., 1974; Carbone et al., 1984).

2) Correlative studies were made a) with the entorhinal afferents to the entorhinal area, by a 24 hr's rest before a mid-septal septal lesion (RPM) which produced better LTH and significant correlation with the entorhinal input and with the infra- and infra-pyramidal mossy fibers (Lipp et al., 1967); b) with hippocampal +/− corticosterone maximal binding (H5B), which showed that LTH co-varies with H5B; c) with immunoreactive vasopressin (HR-NV) in the septum and in the hippocampus, which showed significant correlation between LTH and H5B; d) with an interference with fast turnover, which showed correlation 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 1-20 days), either during the light or dark phases of the circadian cycle, with a transversal design. The animals used were adult, random-bred Sprague-Dawley rats, and rats of the Naples High- (NHP) and Low-Scarcity (LSR) strains, selectively bred for divergent reactivity in a novelty situation (Sadile et al., 1985). A H5B/PDA gave significant effects for strain, inter-exposure interval and for post-exposure sleep or wakefulness, whereas the analysis of the temporal pattern 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. R.W. Skelton, Department of Psychology, University of Victoria, Victoria, B.C., Canada, V8W 2Y2.

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 daily sessions of 100 trials in which a 300 msec tone-CS was paired with a 100 msec peripheral electric shock US, which 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 asymptomatic 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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MEIOTIC DORSAL 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) thalamic 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 box was 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 avoiding 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 intact animals, they altered 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. P.J. van der Steay and W.G.M. Reaijmakers, 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 analyze 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 80 trials. Reference and working memory performances (MN resp WM) were differentially affected by age: no differences between groups were found in initial level of MN but the 25- and 30-month-old rats were impaired in rate of MN-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 analyzed 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 strategy 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 (MN) after 50 trials. It is therefore highly probable that differences in cognitive ability are causing the differences in performance.

The cone field was developed as an alternative to the holeboard having different response requirements. The cone field 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 MN in the old rats compared with the young ones. These results suggest that the differential effects of aging on spatial WM and MN are task independent.


SPATIAL MEMORY REPRESENTATION IN PRIMATE PREFRONTAL CORTEX: EVIDENCE FOR A MNEMONIC HEMIANOPSIS. S. Prinzmetal, C. J. Ringo, 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 responses. We used an occluder motor 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 occluder motor 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 (26%), and at the response (56%). 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 varied locations.

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 persists 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 occluder motor 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 V. Doty and James L. Ringo, Center for Brain Research, University of Rochester, Rochester NY 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, the images according to whether they were members of a previously defined set of six 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 78% 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 3 sec/classify for macaques, but 21 sec/classify for human subjects.

To evaluate the efficiency of "long-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 these images were "distractors" in the RRT, the experimenter 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 images. 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 line 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 expanses 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
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Recordings of the activity of single neurones were made in the
interomodal 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% (28/139) of IMTC neurones responded maximally to the first
presentation of stimuli which had not been seen recently, the response
decaying with repetition. The response was significantly reduced even after
distraction caused by intervening presentations of other objects for 6/7
units as tested. For 17/81% of the units showing declining responses, the
mean response to the first presentation of unfamiliar objects was
significantly greater than 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 (88/99 = 89%) and to the animal's panel press (82/99 = 83%)
in the DMS task. Significantly fewer HF neurones had stimulus related
(107/233 = 46%) and response related (99/233 = 42%) activity. Many
units showed both stimulus and response related activity: 54% of the IMTC
units compared to 27% 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 interomodal temporal cortex appears
to reflect memory for the previous occurrence 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 occurrence of stimuli.

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PRESENTED MEDICAL SKILL IN A SEVERELY DEMENTED PATIENT,
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N. Parnell, & L. Fisher. Dept. of Psychology, North Dakota State
Univ., Fargo, ND 58105.

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 minor in
piano from a major midwestern university. She completed one
additional year of study toward the M.M. After graduation G.W.
taught music at the college level, played 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 16/86, 8 in 2/87) with marked amnesia,
repetitive 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. Neuropsychological 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. MR 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 used. 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 1941, five years after she deserted.
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.
COGNITIVE EVOKED POTENTIALS TO VERBAL AND NON-VERBAL STIMULI IN A MEMORY SCANNING TASK. H. Pratt (1,2), J.V. Patterson (1), H.J. Michalewski (1), and A. Starr (1). University of California, Irvine, California, V.B.A. 92617 (1) and Technion, Israel Institute of Technology, Haifa, Israel (2)

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 (sensory 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 Fz 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 sec, followed by a later, long-lasting (approximately 500 sec) 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 time to verbal stimuli, and only a third of the slope of reaction times to visual stimuli. 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.
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 in a memory task (delayed matching-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 10 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 peanut pellet for touching the correct 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 response time to touch the screen. When performance was stable, SCOP (10.0, 17.0, or 32.0 mg/kg) was administered 30 min before the start of the session. Each dose was tested 3 times in a nonreversing 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 doses of 17.0 and 32.0 mg/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 effects, 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.

REVERSION OF MUSCARINIC RECEPTOR CHANGES IN SOME BRAIN AREAS DURING ACQUISITION AND EXTINCTION OF AN OPERANT TASK. V. Alésam, A. Ortega, A. Mendezes and A. Ocaña. Departamento de Fisiología y Neurociencias y Departamento de Farmacología y Toxicología, CIMAV-IPN y División de Neurociencias, Instituto Mexicano de Psiquiatría, México, D.F.

Thirty ninety-day-old female rats were fasted to 86% 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 maximum level of acquisition (L). Another L group (R) was re-run and immediately sacrificed 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 autoscaled 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. Even decrement can be seen in tempo-pentental 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.
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.


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 pre-treated 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 3 mg/kg significantly reduced nose-pokes as did haloperidol at 0.125 and thioridazine 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 amnnesia induced by neuroleptic treatment. This test procedure 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 ACETYLTRANSFERASE AND PERFORMANCE ON THE MORRIS WATER MAZE  
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Male Lister hooded rats weighing approximately 300 g received 2  
days of training consisting of 6 trials per day on the Morris Water  
Maze task. These rats were then anaesthetised with sodium pentobarb-  
itone (Segatal, May and Baker Ltd., UK) and placed in a stereotactic  
frame. Electrolytic lesions of the medial septum were made bilaterally  
the co-ordinates being DB + 0.5, AP 2.3 mm from Bregma, Lateral 0.3 mm,  
Ventral, 6.1 mm from the surface of the skull: 10 mA ('large' lesion, n=6)  
5mA ('small' lesion, n=5), 0mA ('sham' lesion, n=9) 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 rat  
was given 6 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 Ponom (J.Neurochem. 24, 407-9, 1975).  

The results are shown in the Table below.

<table>
<thead>
<tr>
<th>LESION SIZE</th>
<th>TRIAL 1-6 LATENCY (sec)</th>
<th>on TRIAL 7 ( \beta )</th>
<th>HIPPOCAMPAL CAT (mean pmol/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>62</td>
<td>15.5</td>
<td>19.0 ± 2.4</td>
</tr>
<tr>
<td>Small</td>
<td>39</td>
<td>17.0</td>
<td>19.6 ± 2.1</td>
</tr>
<tr>
<td>Sham</td>
<td>17</td>
<td>24.0</td>
<td>68.6 ± 4.7</td>
</tr>
</tbody>
</table>

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  
bottoming seen in our laboratory when rats are treated with scopolamine and suggests that animals with small septal lesions are capable of  
utilizing a taxon strategy.

INTRA-AMYGDALA INJECTIONS OF \( \beta \)-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; Introviti-Collison & Baratti, 1986; Izquierdo & Graedens, 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 \( \alpha \)-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  
corresponded to both in unoperated and cannula-implanted control rats. The memory- enhancing effect of naloxone IP was blocked by  
preproenkephalin (0.3 or 1.0 \( \mu \)g) injected in the amygdala, but not when this \( \beta \)-noradrenergic blocker (0.3 \( \mu \)g) was injected into either the cuneate or the cortex dorsal to the amygdala. Further, when  
jetected into the amygdala, both the \( \beta_1 \)-adrenoceptor blocker atenolol (0.3 or 1.0 \( \mu \)g) and the \( \beta_2 \)-adrenoceptor blocker zimanol (0.3 or 1.0 \( \mu \)g), 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 \( \alpha \)-antagonists prazosin (\( \mu \)g) and yohimbine (\( \mu \)g) (1.0 \( \mu \)g) 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 \( \beta \)-but not \( \alpha \)-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., Nat'l. Taiwan Univ., Taipei, TAIWAN 707/64, R.O.C.

On male Sprague-Dawley rats with chronic cannulae implanted into the Amyg, we 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 salin or 0.01, 0.1 or 0.5 mg/kg of E. The retention performance indicated that the Veh group, 0.1 mg/kg of E improved retention (p<0.01), while 0.5 mg/kg of E impaired retention (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. NPL-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.

The effect of physostigmine on age-related deficit of spatial memory. A.L. Markowska and A. Grzela, Department of Neurophysiology, Nicola 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 U.P.S. 1986, Abstract p. 1012). In the present experiment, rats of three different ages (7 mo, 16 mo, and 26 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 5-6, 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 50-60 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 ameliorate 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, Irvine, CA 92717.

The function of acetylcholine (ACh) in auditory cortex is of particular interest because manipulations of cholinergic systems have been shown to affect 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 nM) and methacholine (MCh, 20-40 nM) 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 nM).

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.

The 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 frequency 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 ACETYLCOLINE ON SINGLE NEURON RESPONSES TO TONES IN CAT AUDITORY CORTEX. Ratu Netharatne, Jose F. Reurg, and Norman M. Weinberger. Center for the Neurobiology of Learning & Memory, Department of Psychology, 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 aresflexic by continuous infusion of barbiturate (3 mg/hr) and lactated Ringer's solution (12 ml/hr). Multibarrel glass or tungsten glass microelectrodes were inserted through a burr hole into the auditory cortex. Drug barrels contained ACh chloride (1 nM, pH 4), sodium glutamate (0.5 nM, pH 8) and sodium chloride (1 nM) for current controls. When a single neuron was initially isolated, its level of spontaneous activity was determined. The response to a single repeated tone was 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 equipped 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 on either the 2 first, 2 last or 2 median visited arms and 11 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 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.

MEMORY-ENHANCEMENT WITH INTRA-AMYGDALA POSTTRAINING OF ADMINISTRATION OF NALOXONE IS BLOCKED BY CONCURRENT ADMINISTRATION OF PROPRANOLOL. A.H. Nagahara, J.R. Intronei-Colliott and J.L. McGaugh. Center for the Neurobiology of Learning and Memory and Department of Psychobiology, University of California, Irvine, CA 92717.

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-amygdala 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 test (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 peptides in the amygdala are involved in memory modulation. Further, as we observed previously with systemic injections of naloxone, intra-amygdala injections of the β2-adrenoceptor blocking propranolol (0.3 μg) blocked the memory enhancing effects of intra-amygdala 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.

This research is supported by U.S. Public Health Service Grant MH2526 and Office of Naval Research Contract N00014-64-K-0391 to J.L. McGaugh.
MILACEMIDE, A NOVEL ANTIPEPTIC DRUG, ANTACODIZES DRUG-INDUCED MEMORY IMPAIRMENTS IN MICE. M.E. Nevin and S.M. Arnone. CNS Diseases Research, G.D. Searle & Co., Skokie, IL 60077

Milaen (2-n-pentylaminocetamide) is a glycine analog currently under clinical evaluation for anti-epileptic efficacy. In one clinical study Milacemide was found to improve attention and concentration in healthy young volunteers (Sala, B. and Gruenberger, J., Neth. J. Pharm., 19:17, 1984). In the present study, 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 arm per trial. In the absence of treatment with an amnesic 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 amnesic 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 amnesic conditions. The effects were produced by administration of either scopolamine hydrobromide (SCOP) (0.75 mg/kg i.p.), diazepam (DHN) (0.75 mg/kg i.p.) or the N-methyl-D-aspartic acid receptor antagonist 2-amino-7-phenylisoquinoline (AP7) (75 mg/kg i.p.). Milacemide was administered e. 30 min prior to administration of the amnesic agent. 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 amnesic 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, 36 and 100 mg/kg, were needed to counteract the impairment produced by DHN. The dose-response curves taken on the inverted-U shape typically seen with memory-modulating drugs. Currently used anti-epileptic 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. MA. Pelkey 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 in 14-day-old rats sacrificed 15 minutes after completing 4 sessions of training, but 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 carpeted platform in the water maze for 4 sessions (4 trials/day for 4 days). A free swim trial was interspersed with 30 min intervals. The animals were trained 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<0.02), but not when subjects were sacrificed immediately after the training session.

Pairs of young (8 pairs at 6 week) and aged (14 pairs at 23-24 week) rats were then trained in the same manner. 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 occurred 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<0.01). A proportion of the aged subjects (N=8), 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<0.02). In contrast, the aged animals that required more training than any of the younger subjects (N=6) 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 NIH MH39180, a NIA Research Service Award AG05407, and NSF R03 KO2-MH00406 to MG.
ANTAGONISM OF NMDA RECEPTORS BY APS SELECTIVELY INTERFERES WITH DIFFERENT FORMS OF MEMORY. U. Stanil, O. Talbuts, M. DiLeonardo, & G. Lynch. Bunny Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA 92717.

The present work shows 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-2-amino-5-phosphonovaleric 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 (Demaneghan 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 effectors learning, since high levels of NMDA receptors are reported in primary and secondary effectors projection sites (e.g., outer layer of piriform cortex, anterior olfactory nuclei, olfactory tubercle, and hippocampus (Demaneghan et al., 1984)).

Therefore, we tested the effect of AP5, administered chronically into the lateral ventricles via an osmotic pump (60nmol AP5: 0.1ul/hr), on acquisition and retention of (1) specific odor cues presented during a discrimination task, and (2) active avoidance learning. Animals of AP5 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 (ITI): It disappeared when strong odors or short ITIs (30 sec) were used. Retention of odors learned before AP5 administration was also impaired. 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. Meta-estrophic structures which contain very low density of NMDA receptor sites (Demaneghan et al., 1985) have been implicated in this form of learning (e.g., Whitting, 1979). These results are consistent with the hypothesis that different olfactory processes subserved different forms of memory.

GLUCOSE REGULATION OF MEMORY STORAGE: NOVEL CNS ACTIONS OF MILD HYPERGLYCEMIA. W.S. Stone, K.L. Cottrell, and P.R. 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, epileptiform enhancement of memory storage is correlated with the extent of hyperglycemia produced. Since plasmatic glucose is largely excluded from the CNS, these findings suggest that circulating GLU levels may represent an intermediate step between EI PI 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 (stimulatory effects, 0.05 mg/kg, GLU (maximal effects, 100-300 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 3 year-old rats, several indices of paradoxical sleep function were significantly enhanced in the direction of values typically seen in young rats.

(GLU) interaction with cholinergic systems: The effects of EPI and GLU on age-related cognitive deficits, combined with evidence that circulating GLU can regulate ACh synthesis (Gilman and Nehrlich, 1975), led us to examine interactions of EPI and GLU with cholinergic functions. 1) Avoidance 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 was significantly attenuated in those animals which received either EPI or GLU, but not scopolamine. Posttraining injections of EPI and GLU did not attenuate the amnesia. 2) Hippocampus 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) Thymus 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, hyperactivity and tremors related to cholinergic functions, and on paradoxical sleep in aged rats. Thus, the findings add support to the view 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 51141) and the American Diabetes Association.]
Stimulation of Basal Forebrain Induces Long Term Changes in Excitability of Cells in the Somatosensory Cortex of the Cat. E. Tremblay, E. Warren, and N. B. Rawson. Department of Neurology, McGill University, Montreal, Quebec, Canada.

Acetylcholine administered during neuronal activity induced by somatic stimuli produced long term changes in somatosensory cortical neurons. This effect could be blocked by atropine (Mather et al., 1987). The presence of cholinergic cells in the basal forebrain is well established and the location of efferent 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 stereotaxic device, and a craniotomy was performed over the parietal cortex. Two bipolar electrodes were introduced into the basal forebrain following stereotaxic coordinates. A multiharilal iontophoretic electrode glued to a glass recording pipette was introduced into the forelimb region of primary somatosensory cortex. Single cells with continuous 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 was injected, 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 FRQ of Quebec and MEC of Canada).


Norway rat pups learn to prefer odors paired with stimulation that mimics maternal contact. This learned odor preference is associated with an enhanced olfactory bulb metabolic response (14C-2-deoxyglucose uptake) (Coopersmith & Leon, 1964; 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., 1986; 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 terminate in the olfactory bulb (Shipley et al., 1985), 3) tactile stimulation modifies LC activity in the mature (Foote et al., 1983) and immature rat (Kimura & Nakamura, 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 15, and consisted of either: 1) peppermint odor and vigorous stroking of the pup's body with a brush (Pep-Stroked), 2) peppermint odor only, 3) stroking only, 4) neither stimulus. Within each training condition, pups were injected with either isoproterenol (NE B-receptor agonist), or saline. On day 15, different groups of pups were: 1) given a two odor choice test (peppermint vs. a familiar pine odor), 2) injected with 14C-I-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 isoproterenol produced a learned behavioral preference, enhanced focial 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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SHORT DURATION MEMORY REGISTERS AND COGNITIVE PROCESSING. J.P. Denquett and W. Smith, LENA, La Salpetriere Paris 75051 France.

The assumptions behind this experiment were: 1. One, almost trivial, that information integrated over a long time span (such as interiris 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 perceptual memory. 2. That these registers can be tested by Event Related Potentials (ERPs) which have recently been found to reflect short-duration neurophysiological correlates (e.g., specific model of post-stimulus 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-no go 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-presses to target tones. ERP's were recorded by 6 midline monopolar electrodes from Fz to Cz.

PROBABILITY EVALUATION: -Fz, a late positive parietal component indexed accurately and almost on-line both prior (global) and local probability. -F3a, an earlier frontal positive component, reacted to local probability (5 stimuli on the two sessions 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 F3a-F4a complex (reacting to the stimulus category and indexing stimulus probability) presented little change in the short-term practice, but emerged parallel to the physical features of the stimuli. In conclusion, the above results suggest that: -1 The Fz and F3a systems play two interdependent 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.

RHYTHMICITY OF HIPPOCAMPAL NEURAL RESPONSES DURING CLASSICAL JAY MOVEMENT CONDITIONING IN RABBITS. S.D. Berry, R.A. Swain and C.G. O'Flaherty, 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 eliciting membrane and rhythmic jaw movement (JN) responses. In each case, the general topography of the neural poststimulus histogram is similar to that of the transduced behavioral responses. In the case of JN 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 JN training trials.

The subjects were 8 New Zealand White rabbits that had been implanted with chronic stainless steel electrodes under Ketamine anesthesia (Ketamine 30 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 256 sec, 65 dB, 1KHz tone as the CS and a 100 msec, 1 cc, 7222% escharin solution delivered through a micro in the right cheek as the UCS. The interstimulus interval was 200 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 escharin 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 spines (6:1 signal to noise ratio), which were accumulated into poststimulus histograms, averaged with a resolution of 10 msec. Slow waves were filtered from 0.5 to 35 Hz and digitized at 500 msec intervals. Statistical analyses were performed using the ANESTHET 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. Elisabeth Bestock, Robert U. Muller, and John L. Kubie, Stevens-Henkel 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 diameter, 51 cm high gray cylinder. A rectangular piece of white cardboard that covers 100° of arc is attached to the walls 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 presence of the white card. A control experiment was conducted to test the hypothesis that for 18 out of 21 place cells recorded during later exposure 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 elicited different spatial firing patterns. A Fisher's exact test of significance revealed a highly significant contingency table (p < .0015) of 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 was sustained when the white card reappeared and 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 better the notion that the differences in spatial firing patterns are a direct result of the difference in stimulus properties; if the visual differences between the black and white cards was crucial, the altered firing pattern would be expected in the black card that should have been seen immediately. We concluded 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 PEPEZ CIRCUIT DURING DIFFERENTIAL AVOIDANCE CONDITIONING IN RABBITS. N. Million, D. Bentzinger, B. Benzer, and M. Gabriel, Dept. of Psychol., Univ. of Illinois, Champaign Urbana 61820.

Rhythmic bursts of neuronal action potentials exhibiting frequencies (4 - 10 Hz) and behavioral relations similar to 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 into 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., 49:86, 1975), whereas bursts at high frequencies (8-10 Hz) during locomotion suggested Type I movement related theta. Here we report movement related and CS related theta-like bursts of action potentials in the posterior cingulate cortex (Brodmann's Area 29b), the anterior ventral (the thalamic nucleus, and the medial habenular (MH) nucleus. Neural activity in 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 NH 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., Holshheimer, 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* Ken A. Faller, Gregory McCarthy, and Charles C. Wood. Neuropsychology Lab—110B1, 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 role of these areas in declarative memory is 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 400-500 ms latency range. The present study follows two previous experiments designed to investigate ERP correlates of stem-completion priming. Sixteen adult subjects rated 200 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 300 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 recognised was 57%. The mean percentage of words completed in the priming test was 16% (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 recognised words were relatively more positive than ERPs to unrecognised 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. 24:148, 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-one-day-old chicks (Gallus Domesticus) were divided into two groups. Both groups received an I.p. injection of 0.8% ANM half an hour before training in the Cherkin (J.A.A.S., 4:1094, 1969) passive avoidance paradigm. Both groups were tested 6 hr and 12 hr 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 were similar to those collected for the test 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 for ammonia 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 postsynaptic density in 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-affected 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-DEOXYGlcOSE 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 IAC-2-deoxyglucose autoradiography (2DG) and the Fink-Heimer stain for deaggregating axons to determine the effects of an intra-ornal injection of tetrodotoxin (TX).

Male Sprague-Dawley rats were implanted bilaterally with guide cannulas terminating just above the amygdaloid complex. After recovery from surgery, the rats received an injection of TX in one amygdal and vehicle in the other, allowing for within rat comparisons of the TX effects. In the first phase of the experiment, rats received 0.1, 0.4, or 1.0 μl of a 10 mg/ml TX solution, followed five minutes later by an intravenous injection of 2DG (150 μg/kg). Forty-five minutes later, the rats were decapitated and the brain frozen in tissue. 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 3, 4, 8, and 12 hours were placed between the TX and 2DG injections. Finally, the brains of some rats receiving unilateral TX (but no 2DG) were stained for deaggregating axons by the Fink-Heimer method.

The results show that: 1) Intra-amygdal TX injections produce significant reductions in 2DG uptake in specific regions, with the largest and most consistent effects seen in the basolateral amygdal; 2) This effect was not seen with 2DG injections delayed 8 and 12 hours after TX; 3) No deaggregation is seen in areas receiving TX compared to those receiving vehicle. It is concluded that TX 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. Lyndon S. Hibbard and Melvin L. Billingsley, Departments of Radiology, Pharmacology and Center for Cell and Molecular Biology, The M.S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA 17033.

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. H-forskolin and 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, denervation, 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).
A TECHNIQUE FOR VISUALIZING THE NEURAL SYSTEMS INVOLVED IN ACTIVITY RELATED BRAIN DAMAGE. G.O. Ivy and H.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 (AHI) can be used to track neural systems that are involved in abnormally heightened levels of electrical activity. Using aditional histological and immunochemical 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 AHI (using antibodies to GFAP) or necrosis (using PAS or nissl stains).

Both localized electrolytic lesions and stab wounds produced discrete patterns of AHI which reflected known anatomical connectivity. In contrast, both KA and electrical brain stimulation produced recurrent seizure activity and induced patterns of AHI that labeled specific neural systems. Three weeks following seizure activity AHI was focused in the ventralateral forebrain, the medial thalamus and hippocampus. Within these regions specific structures were affected. In the forebrain, AHI was consistently seen in olfactory cortex, external capsule, endopiriform nucleus, the deep layers of insular cortex, and lamina V of lateral neocortex; within thalamus AHI was pronounced in the intralaminar nuclei, the rhomboid nucleus and nucleus reuniens; within hippocampus AHI 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 those regions varied with extent of seizure activity. Where 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 V 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 AHI. Further, 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 fasicus dentatee have a far greater vulnerability. It seems likely that similar patterns of degenerative changes occur in individuals afflicted with recurrent seizure disorders.

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 behavioral in order to find correlations with the sizes of the MF projections. We found substantial evidence that the size of the intra- and infrapyramidal (ip) 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 facilitating 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 ip-MF terminal field and the various behaviors. In the latter tasks, information processing is obviously improved if more ip-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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HIPOCAMPAL EFFERENTS TO THE RETROSPLENIAL CORTEX IN THE RAT. Th. van Giesen and J.M. Byrne, 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 [3H] amino acids were made in the hippocampus or the subiculum. Following injections in the septal third of area CA1 the tracers were transported anterogradely to the subiculum, the postsubiculum, and the retrosplenial cortex. In the rostral retrosplenial cortex, CA1 injections lightly labeled layers III/IV, but injections 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, Fluoro gold) 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 moleculara of CA and in the portion of stratum pyramidale of CA1 contained in the fimbriae alae. In comparison, a larger number of cell bodies were labeled in the septal third of the subiculum, and a smaller 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.


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 (Kaneko and Turnbull, 1983) Byars and Langston, 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 1 weeks prior to perfusion with a mixture of paraformaldehyde (3%), lysine (0.075M) and sodium periodate (0.1M) made according to the protocol of Delean 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 thionin, (2) processed histochemically for cytochrome oxidase according to Wouters-Kiley (1979) and (3) incubated in anti-GAP antisera (a) as a single step on slices, or in a peroxidase anti-peroxidase method (Stenperger 1979). Preliminary analysis of the distribution of GAB-positive cells in normal rats showed some differences in any layer of the hindpaw representation. The same procedure in 3 deafferented rats revealed 14.3% fewer GAB-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 the positive somata in squares was made on a side under the microscope at x1000 from 3 sections of each animal confirmed this observation. Counts were made in 100 squares (200 nm square) on ipsilateral side with a mean number of 3.2 cells (S:1.5-59) per square and 93 on contralateral side with a mean of 3.4 cells (S:1.4-61). This difference averaging 14.9% was statistically significant (t-test for paired observations, t=5.01, P<0.0005).

The implication of this observation must be clarified by counts of the number of neurons; neuronal density and the ratio of GAB-positive to GABA-negative cells on both normal and partially deafferented rat cortices. Nevertheless this observation indicates an important change in GABAergic cell metabolism in layer IV following deafferentation. It may have an important role in the reorganization of somatosensory cortex. (Supported by FRSQ of Quebec to NT and RWD and MRC of Canada to RWD and RN).
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.

Artificially 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 resulted in 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. D.M. DIAMOND and G.M. ROSS, Medical Research Service, VAMC and Dept. of Pharmacology, UCHSC, Denver, CO 80262

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, Ross and Duwanddle (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 urethane anesthesia, the subjects were implanted with a stimulator in the hippocampal commissure. Contralateral to the stimulation site, a microdrive 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 (>30 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 72% (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.
The hippocampus is a brain structure particularly sensitive to ethanol (EtOH). 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 EtOH, the effects of acute EtOH on these processes remains to be adequately investigated. Accordingly, we have recently studied the effects of acute EtOH on 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 (5 trains 1/sec., 30 msec pulses at 400 Hz, 10-11). Stimuli were delivered to the angular bundle of the perforant path using an intensity adjusted to give an 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 (20-60 min. post tetanus) in a mean increase of approximately 300% in the evoked population spike compared to baseline. EtOH (2 g/kg, i.p., resulting in a mean BAC of 179 mg%) given 20 min. prior to tetanic stimulation (0-14), blocked the development of LTP (equal to < than a 60% increase in the pre-evoked population spike) assessed 20-60 min. post tetanus. Moreover, when LTP was attempted in these rats after blood EtOH levels returned to baseline (approx. 5 hrs.), normal LTP was obtained. When EtOH was given after induction of LTP, potentiation was not altered. Similar effects were seen in unrestrained, unanesthetized rats (0-2). These data suggest that long-term synaptic plasticity can be affected by low, intoxicating doses of EtOH.

The Dynamics of Free Calcium and Fully Bound Calcium/Calsenil in Dendritic Spines in Response to Repetitive Syaptic 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/calsemic complex ([Ca(CN)]) 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 magnesium also contains voltage-dependent calcium and potassium channels, two major calcium buffering systems, calsemic and calcium, 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 to a resting level of 50 nM). The calcium buffers never saturated for physiological rates of pre-synaptic 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(CN)]. While its concentration is 3.3 × 10^{-7} μM at rest, it grows to 4.5 × 10^{-6} μM following 10 spikes in 30 msec but only to 3.6 × 10^{-6} μM following 10 spikes in 200 msec. Thus, short but high-frequency bursts 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 have 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 in collaboration with Paul Adelman, we can evaluate following synaptic input 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 AMPA type of synapse.
THE NMDA ANTAGONIST APS 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-pattered 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 burst over the area of the 2-3 sec. 5-phosphorimidazole (AP5-100mM) did not significantly alter responses to moderate intensity single pulses. However, it did completely prevent LTP induction by burst stimulation (EPSP potentiation in APS: 0.4±2.0%; after washout: 35.7±6.7%).

APS produced a small depression of the response to the priming burst (8.0±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 APS and 52.7±10.7% after washout). Moreover, APS blocked the response potentiation that developed across repeated primed bursts.

In summary, APS completely blocked the short and long-term forms of synaptic potentiation produced by primed 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 inter-burst 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 GMH 800014-86-K-0333.)

SYNAPTIC CHANGES IN THE COURSE OF LONG-TERM TRACE FORMATION. H. Mathies, R. Jork, H. Ruther, W. Pohl, G. Grascha. 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 partially attributable 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 fucosac 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.

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 cytoplasmic compartment. Protein synthesis increased immediately after tetanization; its inhibition by anisomycin did not influence initiation and early maintenance (2 hrs) of LTP, but late potentiation (5-6 hrs) was abolished. The posttetanic EPSP-potentiation in dentate 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
- Anisomycin-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 during the 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 FOR 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 interpulse 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 neurones. The observed properties of cortical LTP (long time course, input specificity, additivity and cooperativity) made it possible to suggest the similarity between cortical LTP and widely distributed hippocampal LTD. The cortical LTD differed from LTP in the possibility of its appearance not only for tetanised but also for unstimulated inputs. The kind of posttetanic effect (LTP or LTD) depended on the strength of conditioning stimulation. It was found 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 LTD and LTP in neocortex might serve as evidence for assumption that some cortical synapses could be characterised by high level of plasticity. Such "modifiable" synapses provided the basis of several models for learning and memory.

Neuronal plasticity is characteristic of the dynamic adaptive processes which can now be assessed at the behavioral, biochemical, structural, and genomic level of analysis. Because glucocorticoids 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 vesica phosphoproteins P 38 and Synapain 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 μg/ml corticosterone in the drinking water for a period of 5 days (= 8 at each dose). P 38, Synapain I, NF-200 and GFAP were assayed by on-cell phase contrast microscopy. O'Callaghan, J. Neurosci. 7(931-937). Twenty and 200 μg/ml CORT produced a significant 25% increase (F(3,28)=1.2, 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. Synapain 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 μg/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 adrenalectomised, the relative abundance of P 38, Synapain I and GFAP all increased significantly while NF-200 remained unaffected. Administration of CORT in the drinking water of adrenalectomised animals restored Synapain 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 transgenic inhibitor of Synapain I and GFAP while also acting as a synthetic initiator of P 38. Collectively, these results provide a specific and detailed test of the 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. Ranner (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 enriched and impoverished experience (Ranner 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 cages). For 30 days. After this 30 day subjects were then injected with 200 mg/kg of the L-aromatic amino acid decarboxylase inhibitor NMD-1015, held 30 minutes, and sacrificed (under code numbers that did not reveal an individual's environmental history) by 800 mas of 104 W microwave irradiation to the head at 2.45 GHz. (Mitsubishi Microwave Irradiator, Mitsubishi-Japan Radio Company). Brains were then removed from the head and dissection 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 (LCCE) using a reversed phase column packed with 3 micron particles (P.P. Liu et al., J. Chromatogr. A, 563-566, 1990). Determination of 10 species of catecholamines, indoleamines, precursors and metabolites. Data for serotonin in the hippocampus (indicated by builup 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: 394 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.
Synthesis of postsynaptic membrane heparan sulfate proteoglycan is required for long-term memory in the chick.

Steven P. R. Ross, Brain Research Group, Open University, Milton Keynes, MK7 6AA, UK

Day-old chicks peck spontaneously at small bright beads; if the bead is coated with a bitter-tasting substance (methanol/ethanol, 60:40), they peck once and avoid a similar, but dry bead subsequently. This is central to Pavlovian avoidance learning. Memory formation for this task involves a sequence of biochemical, physiological and morphological changes in three forebrain nuclei: mediodorsal prefrontal (mPFC), medial septum and nucleus and locus ceruleus. Some but not all of these changes are left-hemisphere lateralized. 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 carbohydrate into membrane and especially postsynaptic 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 62,000 and 170,000 are of particular interest. Training birds on the M-bead but rendering them amnesic by transcranial electroshock abolishes the increase in heparan sulfate. The increase appears to involve post-translational modification of pre-existing proteoglycans, as it is cycloheximide-resistant. On the other hand, a specific inhibitor of glycosyltransferase, N-deacetylase, injected up to two hours prior or two hours following training, prevents long-term memory formation. Thus heparan sulfate 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 heparan sulfate, heparitinase. As we have in other experiments shown that M-training results in substantial increase in the numbers of dendritic spines and the diameter of the spines in projection neurons of the Min, one role for the glycoproteins might be in membrane modifications that such dendritic changes must involve.

Supported by grants from NHMRC and SERC. Thanks to R. K. Pease, B. Leamer, M. M. McCabe, S. Patel and M. Stewart.

Excitatory amino acids activate calpain I and structural protein breakdown in vivo. J. C. Nees E. and R. S. K. Nees E. Neuroscience Group, Medical Research Group, Medical Products Dept., The Du Pont Co., Wilmington, DE 19898.

Membrane 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 mg) or kainate (1 mg) intravenously 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 autophosphorylation upon activation. Calpains I and II were separated by SDS-PAGE and detected and quantified by immunoblotting with polyclonal antibodies to the Mr 84,000 catalytic subunit of human erythrocyte calpain I. Rats 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 84,000, calpain II Mr 76,000). 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. Concomitantly 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. Consequently, 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.
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, providing these subsets are unique, because the diviser 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.
N0VELTY DETECTION IN NEURAL NETWORKS

Yehuda Salu, Department of Physics and Astronomy, Howard University, Washington DC. 20059

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 third 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 classifies 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.
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