females by odour exposure in the presence of a prolonged infusion of a metabotropic receptor agonist (mGluR2) into the AOB. Whereas the GABA antagonist releases all mitral cells from feedback inhibition causing a widespread discharge, the metabotropic glutamate agonist facilitates the action of only those mitral cells that respond to odour. This memory faithfully mimics the memory formed at mating and is dependent on co-activation of AMPA-kainate receptors, but not NMDA receptors, in the sub-population of granule cells activated by glutamate release from mitral cells that code for an individual's odours. Whereas experimental findings on formation of the olfactory recognition memory place emphasis on changes in mitral cell activity, the blocking of memory formation implicate postsynaptic events on the granule cells, involving both kainate-AMPA and NMDA receptors, a finding further supported by electrophysiological recordings. In so much as these presynaptic and postsynaptic events are tightly coupled through reciprocal dendrodendritic synapses, each is important in the chain of events leading to changes in the burst firing of the mitral cells as predicted from mathematical modelling of the system. Since neuroendocrine neurons are frequency coded, then a change in burst firing frequency of mitral cells would interfere with the efficacy of the olfactory signal which produces the neuroendocrine response leading to pregnancy block.

Symposium 2: Retrieval and reactivation of the memory trace
Organized by C. Bucherelli

Symp 2/1
CONSOLIDATION AND RETRIEVAL IN THE RAT: HOW THESE PHASES CAN BE INFLUENCED
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In experimental animals, the neurophysiology of memory has identified the neural correlates, both cortical and subcortical, of mnemonic processing. Distinct informations are available. There are those indicating where these processes take place, which were and are obtained using the permanent lesion techniques. More recently, by employing the reversible inactivation techniques, it has become possible to punctually ascertain and define not only where the mnemonic processing takes place, but also when and for how long a given neural structure is involved. In other words, from the topography, even detailed, there has been a progress towards the precise chronology of mnemonic processing. One important advantage of these reversible inactivation techniques derives from the knowledge of the temporal limits of the putative phases of engram formation (acquisition, consolidation, storage/retrieval) which allows to study any of these phases separately and without interference with the other ones. In our experiment, by using in the rat the passive avoidance response paradigm coupled with TTX reversible activations, it has been possible to define temporally the role played by quite a number of subcortical and cortical sites

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during consolidation and/or during retrieval. For what concerns the factors that may act on memorization and its subsequent phases, it is well known that in the rat, as in other animal species, age sex, strain may exert powerful influences especially affecting the temporal dimension. Apart from these, there are other factors which are quite crucial and not related to those recalled above. These are (i) the US (unconditioned stimulus) intensity (weight of reinforcement); (ii) the arousal level of the experimental subject during consolidation and retrieval. For instance, the duration for the memory trace formation becomes shorter if these two factors increase. Moreover, the life or permanence of the engram is positively related to the dimension of these two factors, and retrieval capacity or ability is positively related to arousal level.

**Symp 2/2**

**INTERHEMISPHERIC TRANSFER DEMONSTRATES REACTIVATION OF SPATIAL MEMORY TRACES DURING RETRIEVAL OF LATERALIZED ENGRAMS**

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Retrieval of memory traces cannot be dissociated from the acquisition or extinction processes. In fact, each reinforced retrieval trial enhances the engram formed during distributed learning and each non-reinforced retrieval trial weakens the already formed engram during extinction. While the corresponding memory trace modifications are usually explained by putative changes of synaptic weight in the circuit implementing the CS-US association, there are paradigms allowing a direct demonstration of the retrieval-induced modification of the pre-retrieval state. In the interhemispheric transfer of place navigation in the Morris water maze, memory formed in rats with functional ablation of one hippocampus is confined to the intact half of the brain and does not spread to the other side when the block is over (A.A. Fenton and J. Bures, 1994, Neuroscience, 58:488-191). This indicates either that rats are not capable of internal rehearsal or that such rehearsal does not trigger transfer. On the other hand, the lateralized engram is transferred to the naive hemisphere when a few retrieval trials are performed with intact brain. In this case, the retrieval induced modification of the engram is manifested by appearance of its independently retrieval copy in the hitherto naive hemisphere. Surprisingly, such transfer is induced not only by reinforced but, also, by non-reinforced transfer trials, presumably weakening the original trace. This suggests that extinction is implemented not only by inhibition of specific connections but that it proceeds on the basis of general engram activation which probably triggers transfer across the commissural connections. Further analytic possibilities are opened by testing transfer under conditions activating only passive retrieval of the trace, e.g. when the rat is not allowed to search the escape platform in the Morris maze, but is only placed upon it in its correct or novel location. Similarly, transfer can be examined under conditions activating only the idiothetic or only the allocrotic component of the task, e.g. when the transfer trials are applied in darkness or with rotating extra maze landmarks. It is concluded that the availability of the lateralized trace which alone can support efficient
While the cognitive modelling of language or perception has largely proceeded independently from neuropsychology, in the memory field, the investigations of disorders of function has played a crucial role in theoretical development. What is commonly called “the multiple memory system” approach has capitalised on the observation of dissociated impairment in the different aspects of memory function in human pathology. This theoretical framework must be however integrated with a process approach, which considers carefully the different stages of the formation of memory traces and the process related with retrieval of information. Both approaches have been fruitfully applied to the anatomo-functional investigation of the neural correlates of memory in humans. The development of neuroimaging methods, such as PET and fMRI, has provided new impulses to the study of the neural basis of cognitive functions, and has extendend the field of inquiry from the analyses of consequences of brain lesions to the functional investigations of brain activity, either in patients with selective neuropsychological deficits or in normal subjects engaged in cognitive tasks. In neurological patients, specific patterns of hypometabolism are associated with different profiles of memory deficits. The identification of anatomo-functional networks involved in specific components of memory function in normal subjects is the aim of PET and fMRI activation studies. The results are in agreement with “neural network” models of the neural basis of memory, as complex functions subserved by multiple interconnected cortical and subcortical structures. Specific correlates have been assigned to the multiple neocortical areas associated with declarative memory tasks. There is ample evidence that the left dorsolateral frontal cortex activation is related to semantic encoding, whereas the right prefrontal cortex has been shown to be related to intentional retrieval. It is still debated whether the latter activation increases with successful retrieval, or is simply related to retrieval attempt. Several findings support a dissociation between human neural systems that participate in the encoding and later recognition of new memories. Results from neuroimaging studies are remarkable, because they have suggested important roles in memory processing for several brains tructures, which were not predicted on the basis of neuropsychological investigations in amnesic patients. While the results coming from neuropsychology and neuroimaging may be sometimes difficilt to reconcile in an integrated approach, it is now clear that PET and fMRI have more than “a confirmatory role” with respect to the results of lesion-based neuropsychological investigations.
Symp 2/4
RECONSOLIDATION OF MEMORY AFTER ITS RETRIEVAL
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“Cue-dependent” experimental amnesia was described by several authors nearly thirty years ago. It suggested that memories are not static once consolidated, but when reactivated, memories are labile and vulnerable to the same amnestic agents as newly acquired memories. Despite its theoretical importance, little attempt has been made to integrate this phenomenon into neurobiological theories of memory consolidation. We have been investigating the vulnerability of reactivated memories to pharmacological interventions known to be effective interfering with consolidation of new memories, using several behavioural paradigms, supposedly implicating different brain circuits. The role of N-Methyl-D-Aspartate receptors was tested with the agonists propanolol or timolol, since previous work in our laboratory has shown the former to be essential for the early stages of processing of new memories and the latter in the late stages. Rats were trained in a spatial reference memory task in which the rat must choose the same 3/8 baited arms on each trial. Training took place over 3 days (5 trials/day). “4 h later, rats were submitted to one trial (reactivation) and treated with MK-801 (0.05 mg/kg, i.p.) if the performance was errorless: Injections were made at varying time intervals after the reactivation and rats were tested for retention 48h later. MK-801 induced amnesia if it was injected within 1 hr after the reactivation trial. The role of b adrenergic receptors was evaluated in the same behavioural paradigm, using the antagonist propanolol. The amnesia gradient was extended to 2h, with no effect at 5h. Control experiments assured that the reactivation trial was necessary to obtain the amnesia. Icv injections allow a more precise determination of the time window of action of a drug. using this strategy, with the b antagonist timolol, amnesia after reactivation of the memory for the spatial location in the maze was obtained when the injections were made 1h after reactivation but not at 5min, 30min or 5h. Memory for rapidly acquired odour, reward association is impaired by icv injection of timolol at a time window around 2h after learning. Preliminary results suggest a similar period in which the memory can be disrupted by timolol after it has been reactivated by a single test trial. These results provide evidence for the notion that memory is reorganised each time it is retrieval in order to integrate new percepts with past memories. Remembered events are reconsolidated over time, recapitulating some of the biochemical cascades involved in long term neuronal plasticity and memory formation.
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