F4. Effects of MDMA on an active avoidance paradigm in mice

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Previous studies have shown both biochemical and cognitive alterations following MDMA administration. The aim of this study was to evaluate the effects of MDMA on the acquisition and expression of an active avoidance task. In the first experiment, animals were treated once daily for four consecutive days with MDMA (1.1, 3.3 and 10 mg/kg, i.p.), amphetamine (1.1 and 3.3 mg/kg, i.p.) or saline, and they were trained everyday. On days 5 and 12 all animals received saline. MDMA significantly increased acquisition at the dose of 3.3 and 10 mg/kg on day 1 with respect to saline. On days 2, 3 and 4, only the dose of 3.3 mg/kg increased this response. However, on day 5 there was no significant difference between groups. Amphetamine also increased learning at the dose of 3.3 mg/kg on days 3, 4 and 12. In a second experiment, animals received saline for four consecutive days before daily sessions. On days 5 to 8, animals received MDMA (1.1, 3.3, and 10.0 mg/kg) or saline, and the expression of the task was tested every day. On day 9 all animals received saline. Results showed that MDMA (10 mg/kg) significantly impaired the expression of a previously learned active avoidance task on days 5, 7 and 8 as compared to saline. However, on day 9 when animals received saline, no significant differences were observed between groups. Together, these results indicate that MDMA may enhance acquisition of an active avoidance response in an amphetamine-like manner, while it impairs expression of a previously learned response.

F5. Apomorphine and amphetamine induce differential activity patterns in Roman high- and low-avoidance rats

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The Roman RHA/Verh and RLA/Verh rats are selectively bred for the acquisition or non-acquisition of a two-way active avoidance response. The RHA represent high novelty seeker and behaviour impulsive stereotypy. Previous studies showed that these two lines differ in their dopaminergic function suggesting RHA/Verh rats as an animal model for the symptoms of human psychosis. In the current experiments the behavioural stimulation of dopaminergic system was investigated in RHA/Verh rats as compared to their genetic counterparts, the RLA/Verh rats and the standard Sprague-Dawley (SD) rats. Thus, the dose-response curves for locomotor activity and stereotyped behaviour were determined for apomorphine (APO, 0.0067-3 mg/kg, s.c.) and amphetamine (AMPH, 0.5-2 mg/kg, s.c.). The results showed that, as compared to both RLA/Verh and SD rats, the RHA/Verh exhibited: 1) an increased spontaneous activity; 2) a marked APO-induced stereotyped behaviour (higher intensity) 3) a more long-lasting stereotyped behaviour induced by the highest dose of AMPH (2 mg/kg).

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F6. The role of brain catalase on the locomotion and sensitization induced by ethanol

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Several laboratories have suggested that the central formation of acetaldehyde through ethanol metabolism by catalase, can play an important role on the psychopharmacological effects observed after ethanol administration. In this regard, the most characterized behavior has been locomotion. In studies from our laboratory it has been shown that reductions in brain catalase activity after administration of a wide range of compounds were accompanied by significant reductions in acute ethanol-induced locomotion. This result agrees with data from genetically acatalasemic mice, which also have blunted response in locomotion after ethanol administration. Conversely, increases in brain catalase activity following several manipulations led to increases in acute ethanol-induced locomotion. Thus, all these studies have been consistently demonstrated that pharmacological treatments that modify brain catalase activity are able to produce a locomotor output that is directly related to the final activity of the enzyme. On the other hand, a role for catalase on the sensitization of locomotion observed in mice after repeated ethanol administration has also been suggested. Thus, it has been reported that the induction and expression of locomotor sensitization to ethanol in outbreed mice has been blocked by systemic pre-treatment with catalase inhibitors. Moreover, mice with genetic differences in catalase activity show different sensitivity to repeated ethanol-induced sensitization, suggesting that an inborn deficiency on brain catalase activity results in a prevention to develop ethanol-induced locomotor sensitization. All these data support the hypothesis that catalase is related to the behavioral effects of ethanol and thus acetaldehyde produced in the CNS through ethanol oxidation metabolism may be responsible of some of the behavioral actions of ethanol.

F7. Reinforcing properties of "con-specifics" on isolated male mice treated with U-50488, a selective kappa opioid receptor agonist

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Recent studies have shown that administration of U-50488, a selective kappa opioid agonist, reduces flight responses and risk assessment performances in isolated male mice. Likewise, this compound markedly increases social investigation behaviors, whereas isolated control animals show extensive repertory of aggressive behaviour and limited non-aggressive social interactions. It has been suggested that this increase of aggressive behaviour is a territoriality strengthening provoked by isolation, although it also has been pointed out that male mice may exhibit "herd instinct". This study was designed to examine the reinforcing properties of "con-specifics" and the effects of acute administration of U-50488 (4 and 8 mg/kg, i.p.) on isolated male mice tested in the conditioned place preference test. Results showed that the cohabitation with an animal of the same species and sex was a reinforcement for the isolated male mice and that the U-50488 did not reduce this effect. Likewise, this reinforcing action directly correlated with investigation social time and inversely correlated with aggression time (8 mg/kg, $P<0.05$). Overall, these results suggest that the high sociability observed in agonistic interactions after U-50488 administration could be caused by reinforcing properties of animals of the same species.

F8. A role for taurine in cognitive development?

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Although taurine, a sulphur amino acid, is found in high concentrations in the neonatal brain, little is known about its role in cognitive development. A cohort of preterm infants, showing differences in plasma taurine in the post-natal period due to dietary intervention, demonstrated a relationship between minimum plasma taurine concentration and scores on a measure of numeracy at 7.5 years. In a subgroup of 22 children, studied at a mean age of 15 years and 8 months, we showed a persisting relationship between infant minimum taurine values and measures of numeracy (but not literacy). Voxel-based morphometry studies were conducted on 3D MRI datasets collected at adolescence. Because children with a severe deficit in calculation ability have been shown to have reduced grey matter in the left intraparietal sulcus, we hypothesized that early taurine status influences numeracy as a result of its impact on the development of regions in the parietal lobe subserving this ability. Comparing adolescents with minimum taurine values above and below the group median showed that intraparietal sulcal regions bilaterally had significant decreases (P<0.02) in grey matter. There was a significant relationship between minimum taurine and grey matter density in the right intraparietal sulcus. These results are consistent with our hypothesis.

F9. Influence of learning and anxiety by substance P in the globus pallidus and amygdala

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Substance P (SP) facilitates learning, it has positive reinforcing and anxiolytic effects. By means of immunohistochemical methods it has been revealed that the globus pallidus (GP) and the central amygdala (ACE) are rich in SP immunoreactive elements. Learning deficits develop after lesions of the GP. Amygdala plays an important role in learning, memory and anxiety. SP has high affinity for neurokinin-1 (NK1) receptors but it can also act on NK2 and NK3 receptors. High density of NK1 receptors were found in both structures. In the present experiments we studied the effects of SP on positive and negative reinforcement, memory and anxiety in the GP and ACE. Male Wistar rats were injected with 0.4 µl of 10 ng or 100 ng SP or vehicle. Passive avoidance learning was facilitated by 10 ng SP in both structures, though retention was diminished in the GP while still significant in the ACE. Significant reinforcing effects have been found in place preference test by 10 ng SP either in the GP or ACE. In elevated plus maze test 100 ng SP had anxiolytic effects in both structures. Prior treatment with NK1 receptor antagonist WIN 62.577 blocked this effect. Our results show that SP: 1) facilitates learning in both structures; 2) in the GP inhibits the formation of long-term memory; 3) has positive reinforcing effect; 4) has anxiolytic effect and these effects are mediated via NK1 receptors.

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F10. Functionality of the M1 muscarinic receptors in the lateral and medial dorsal parts of the striatum in young and aged rats

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The dorsal striatum is involved in learning and memory processes and the medial and lateral parts of this structure can be distinguished on both anatomical and functional data. As cognitive performances may also be affected by striatal cholinergic system, we assessed the effects of bilateral infusion of the M1 muscarinic antagonist pirenzepine (1 to 30 µg/µl/side) either in the medial or the lateral part of the dorsal striatum in young and aged Long-Evans female rats. Cluster analysis of water-maze reference memory performances of aged (24-month-old) rats distinguished between rats with no impairment and rats with severe impairment. The procedure in this task aimed at distinguishing working and procedural memory performances. During five days, an injection was done before the four consecutive daily trials; the position of the platform and the starting point changed daily, but were the same for the four trials. Pirenzepine infused in the dorsolateral striatum impaired procedural memory (trials 3 and 4) both in young and aged unimpaired rats, but at a lower dose in aged rats (10 µg/µl vs. 8 µg/µl). Infused in the dorsomedial striatum, pirenzepine disrupted learning performances of both young and aged rats in a same dose-dependent manner. Our results show: 1) a different functional role of the medial and the lateral parts of the dorsal striatum; and 2) that, the functionality of the M1 muscarinic receptors of the dorsolateral striatum is impaired in aged rats.

F11. Intrahippocampal nicotine and pregnenolone sulfate administration on learning acquisition in alcohol drinking rats

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The effects of intrahippocampal administration of the promnesic neurosteroid pregnenolone sulfate (PREG-S) and/or nicotine on the acquisition of the lever-press response in the Skinner box were examined in voluntary alcohol drinking rats. A free-choice drinking procedure that implies an early availability of the alcoholic solution (10% ethanol v/v, 3% glucose w/v in distilled water) was used (Alcoholism Primary Praecox procedure-APP). APP rats were deprived of food and assigned at random to four groups. Each group received two consecutive intrahippocampal (dorsal CA1 region) injections immediately after 1-hour ethanol drinking. Groups were: saline-saline; saline-PREG-S (5 ng); nicotine (10 nM) -saline; nicotine-PREG-S. Following the injections, psychomotor performance (open field and 80ş inclined screen test) and then free lever-press response shaping were tested. Results showed that nicotine impaired the acquisition of the lever-press response only in alcohol drinking rats, and this deteriorating effect was neutralised by PREG-S, as shown in nicotine-PREG-S group. PREG-S had no effects *per se* on lever-press acquisition, neither in alcohol drinking rats nor in controls. Psychomotor activity was not affected by nicotine or PREG-S in any case. These results suggest the involvement of nicotinic receptors in the effects of chronic and voluntary alcohol intake. PREG-S preserved learning abilities in alcoholic rats injected with nicotine, possibly acting on central cholinergic systems.

F12. Fish oil chronic supplementation in F1 rats causes an antidepressant effect

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Fatty acids are important compounds of neuron membranes. Lipid deficiency is associated with neurological disorders like depression and Parkinson's disease. Human population in the last 100 years increased markedly the intake of saturated and n-6 polyunsaturated fatty acids which was accompanied of chronic degenerative diseases development. The aim of this work is to evaluate the effect of chronic fish oil supplementation in F1 generation upon depressive behavior in rats using forced swimming test and upon cognitive behavior by Morris water maze. Female Wistar rats were separated into three groups and daily supplemented with 3 g/kg of fish oil (FO) or coconut fat (CF) and the control group (C) received regular diet chow. They mated and during pregnancy and weanling continue to receive the supplementation. The male offspring generated were supplemented with the same diet as their dams until 90 days old. Then they were submitted to the forced swimming test and Morris water maze test. The results of forced swimming test showed that rats chronically supplemented with fish oil had immobility time significantly lower than the other groups. However, in the Morris water maze test there was no statistical difference between the groups. Our results suggest that chronic fish oil supplementation has an antidepressant effect in rats.

F13. Beta 2 subunit-containing GABA-A receptors are not necessary for etomidate-induced anaesthesia

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Specific mechanisms underlying general anesthesia for the most part are unknown. Etomidate, an intravenous general anaesthetic, acts by potentiating GABA-A receptors, with selectivity for Beta2(B2) and Beta3(B3) subunit-containing receptors determined by a single asparagine residue. We generated a genetically modified mouse containing an etomidate-insensitive B2 subunit (B2N265S) to determine the role of B2 or B3 subunits in etomidate-induced anaesthesia. Wildtype (WT) and B2N265S mice were dosed with etomidate (20-40 mg/kg, i.p. or 5-15 mg/kg, i.v.) and duration of loss of righting reflex (LORR) recorded. Both genotypes, independent of route, showed a dose-dependent LORR. These data suggest B2-containing receptors are not necessary for induction of anaesthesia. B2N265S mice were found to be significantly more active than WT controls in a locomotor test using sub-anaesthetic doses of etomidate (0.3-12.5 mg/kg, i.p.). To measure the "hypnotic hangover" produced by etomidate the performance of WT and B2N265S mice, following etomidate administration (20-40 mg/kg, i.p. or 5-15 mg/kg, i.v.), on the rotarod was assessed. B2N265S mice performed significantly better than WT controls during recovery from anaesthesia, independent of route of administration. These data indicate that GABA-A receptors containing a B3 subunit primarily mediate anaesthesia, whereas those containing a B2 subunit primarily mediate the sedative effects of etomidate.

F14. Role of dopamine and glutamate in the extinction of cocaine-induced conditioned behavior

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Contextual stimuli associated contiguously with cocaine develop the ability over time to elicit increases in locomotor activity when presented in the absence of the drug. The purpose of these studies was to determine whether dopaminergic (DA) stimulation or blockade or glutamatergic blockade would alter the extinction of such conditioned behavior. One group of rats (paired) was injected with cocaine for five consecutive days in the context of a distinct locomotor activity chamber while the other group (unpaired) received injections of cocaine in their home cage. Following such conditioning, various groups of "paired" and "unpaired" rats were pretreated over 5 consecutive days with either SCH 23390 (D1 DA antagonist), eticlopride (D2 DA antagonist), apomorphine (DA agonist), MK 801 (glutamate antagonist), and saline and placed in the activity chamber for a 30 min extinction session. Following such extinction training, all rats were tested for expression of conditioned behavior after injections of saline and low doses of cocaine. Eticlopride pretreatment completely prevented the expression of cocaine conditioned behavior and inhibited extinction. SCH 23390 appeared to decrease the expression of conditioned behavior but had no effect on the extinction process, while apomorphine was also without effect on extinction. MK 801 also inhibited extinction. It appears that intact D2 DA and glutamate function is necessary for extinction to occur.

F15. Locomotion and emotional behavior in adolescent, young and adult rats: effects of ethanol

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The first aim of the present study was to evaluate locomotion and emotional activity in rats at different ages. We used 2 months-old male rats as adolescents, 4 months-old males as youngs, and 6 months-old males as adults. Testing included open field, spontaneous activity in the home cage, elevated plus-maze, Vogel's test and shuttle-box avoidance. Adolescent rats showed increased activity in the home cage and decreased emotional behavior in the elevated plus maze as compared with adults, as well as increased licking responses during the punished period in the Vogel's test. The young group showed the best performance in the shuttle-box.

In a second experiment we tested the effects of ethanol (1-2 g/kg, 12% v/v, p.o.; control rats receiving the same volume of tap water) in 6 months-old males. The low doses (administered either acutely 30 min before testing or chronically for 30 days) increased locomotion and shuttle-box performance, and reduced emotional behavior; whereas inconsistent effects were observed in animals treated with 2 g/kg of ethanol (either acutely or chronically). The results obtained are discussed with respect to the biphasic effects of certain doses of ethanol.

F16. Effects of a mu-opioid agonist and antagonist on PVN-VTA mediated feeding

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The paraventricular nucleus (PVN) and the ventral tegmental area (VTA) have been shown to be involved in opioid mediated feeding behavior. The present study examined whether mu-opioid signalling between the PVN and VTA affected feeding behavior.

Male Sprague-Dawley rats were cannulated with one cannula placed in the PVN and two cannulae in the VTA, which allowed for co-administration of the mu-opioid receptor agonist [D-Ala2, NMe4, Gly-ol5]-enkephalin (DAMGO) in one site and the antagonist naltrexone (NTX) in the other site. Bilateral administration of DAMGO (1.2, 2.4 and 4.9 nmol) into the VTA stimulated feeding dose dependently at 2.4 and 4.9 nmol ($P<0.05$). The DAMGO (2.4 nmol)-induced increase of food intake following injection into the PVN was blocked by bilateral injection of NTX (13.2 and 26.5 nmol) into the VTA ($P<0.05$). In the reverse situation, the DAMGO (2.4 nmol)-induced increase of food intake following injection into the VTA was blocked by injection of NTX (13.2 and 26.5 nmol) into the PVN ($P<0.05$). The present study suggests that a bi-directional mu opioid-opioid signalling pathway exists between the PVN and the VTA which influences feeding.

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F17. Effects of coadministration of ondansetron with flumazenil on cholinergic function in rats

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Drug-induced increase in actylcholine (ACh) levels is considered a rational mechanism to mediate cognition enhancement. We have studied the effects of a combined treatment with the 5-HT3 receptor antagonist ondansetron, 0.1 mg/kg, and the GABAA receptor antagonist flumazenil, 10 mg/kg. on the Morris water maze (MWM) spatial learning test, and ACh release *in vivo* both in controls and animals with a cholinergic hypofunction. In MWM, administration of either ondansetron or flumazenil partially blocked the scopolamine-induced learning deficit. A full reversion of the learning impairment was found after the combined treatment. In microdialysis experiments, the maximal effect of ondansetron on cortical ACh release was significantly enhanced by flumazenil in control rats (+260% over basal values). In rats with a selective cholinergic lesion, combined administration of ondansetron+flumazenil significantly increased ACh release (+75% approximately), to a similar extent than a depolarizing stimulus with K+, 100 mM, at both 7 and 30 days post-lesion. It is suggested that a combined ondansetron+flumazenil treatment would contribute to restore a diminished cholinergic function and may provide a basis for the use of this treatment in the therapy of cognitive disorders, such as Alzheimer's disease, associated with degeneration of the cholinergic system.

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F18. Hippocampal nicotinic receptors in alcoholic rats: a binding study

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There is strong evidence that ethanol modulates positively nicotinic acetylcholine receptors (nAChR). At concentrations compatible with alcoholic intoxication ethanol stabilizes the open-channel state and increases the affinity of the receptor for the agonists. A paradoxical up-regulation of the nAChR after continuous exposure to agonist has been reported. To test if chronic ethanol produces a similar pharmacodinamic adaptation we have investigated the effect of chronic and voluntary ethanol consumption on high affinity [3H]nicotinic binding in rat hippocampus. Non-selected Wistar rats were breeded under the APP model (Alcoholism Primary Praecox) reaching toxic blood ethanol concentrations (1.051 ± 0.114 g/l). An increase ($P=0.0006$) in the Bmax values (84.78 ± 13.17 fmol/mg protein, APP group with respect to 50.12 ± 4.98 fmol/mg protein, control group) and also an increase ($P=0.0198$) in the Kd for nicotine (13.00 ± 4.54 nM, APP group with respect to 6.62 ± 1.87 nM, control group) was observed in hippocampal membranes. These results indicate that chronic consumption of ethanol has produced an increase in the density of nAChR as well as a decrease in the affinity of the receptors for the radioligand used.

F19. GHB effects on naloxone-induced motivational and physical signs of morphine withdrawal

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Gamma-hydroxybutiric acid (GHB) has been suggested to be a neuromodulator or neurotransmitter, which can play a role in drug dependence on the basis of clinical studies. In human beings, GHB administration has been proved useful in the treatment of opiate withdrawal syndrome. The aim of the present work was to validate this beneficial effects on the physical and motivational aspects of morphine withdrawal in mice. To do this, in a first experiment animals rendered morphine dependent, developed a conditioned place aversion (CPA) to the compartment paired with naloxone administration. GHB was administered during the acquisition or the expression phase of this conditioning. This compound was capable to block CPA in both phases, being more sensible when administered during the expression of this conditioning. In the second experiment, the effect of GHB in ameliorate the intensity of the physical signs of morphine withdrawal was evaluated. GHB decrease the intensity of these physical signs near to control levels measured by the modified Gellert-Holtzman scale. In conclusion, our results support the idea that GHB is capable of ameliorated both aspects of morphine withdrawal, physical as well as motivational signs. This drug could be useful for the treatment of human heroin addicts, although in the light of reports concerning its potential risk of abuse, precautions must be taken into consideration.

F20. Acoustic startle response (ASR), prepulse inhibition (PPI) and disruption of PPI by dizocilpine in selectively bred mouse lines

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ASR was elicited in mice bred for high (HA) and for low (LA) analgesia induced by swim stress, and in unselected controls (C). Startle stimuli were 112 dB white noise bursts. Each mouse was presented with four trial types: one consisting of the startle stimulus alone, and three others of a 73, 83 or 89 dB 20-ms prepulse preceding by 100 ms the startle stimulus. ASR magnitude on startle pulse-alone trials differed between the lines in the rank order HA> C>LA, and was higher in male HA than in female HA mice, whereas no sex difference was seen in other lines. ASR decreased in prepulse + startle pulse trials. Percent scores of PPI depended on prepulse intensity, and were slightly lower in LA than in HA or C mice. Dizocilpine, a non-competitive NMDA receptor antagonist, at doses 0.15, 0.25 and 0.5 mg/kg profoundly disrupted PPI in the HA line without regard to sex, so that ASR magnitudes on prepulse + startle pulse trials became about equal to magnitudes on startle-alone trials. The effect of dizocilpine was weaker in the C line. In the LA line, due to marked elevation of baseline ASR, the effect of the compound in PPI was not confirmed statistically. PPI disruption by dizocilpine in the HA line is a convenient model of sensorimotor gating deficits in schizophrenia, and can be used for screening atypical antipsychotics, not effective upon PPI disruption by dopamine agonists.

F21. Inhibition of NO synthesis and schizophrenic-like symptoms

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Alterations in neuronal integrity and functionality are frequently associated to schizophrenia. The gaseous neuromodulator nitric oxide (NO) is involved in brain development and in adult brain function, thus the inhibition of NO synthesis could be useful to induce schizophrenic-like symptoms. The aim of the present work was to study the effects of the NO inhibition in postnatal and adult age in Wistar rats. Fifteen females and thirty-one males were treated with the non-selective nitric oxide synthase inhibitor N-nitro-L-arginine (L-NAME) (30 mg/kg s.c.) or saline at P8-P11 and P90-P93. Thus, four groups according to the experimental schedule were obtained (L- NAME/L-NAME, L- NAME/Saline, Saline/L-NAME, Saline/Saline). One month after, the subjects were evaluated for the following behavioural characteristics: anhedonia (preference for a sweet solution), habituation to an open field, anxiety (social interaction test) and learning (two way active avoidance task). The effects of L-NAME administration to induce schizophrenic-like symptoms are discussed. The shaping of structural and functional alterations resulting from the NO inhibition could constitute a more accurate method than massive lesions otherwise used.

F22. Neurobehavioural effects of ethanol in GluR-A and GluR-C knockout mice

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The excitatory amino-acid glutamate plays a major role on ethanol actions in the CNS In this respect, the blockade of both NMDA or AMPA glutamate receptors can result in a reduction of ethanol behavioural effects. Most of this research has explored the interaction between ethanol and NMDA receptor, but far less is known of the role of the AMPA glutamate receptor on ethanol effects. The ionotropic AMPA receptor is an heterodimer which can be formed by 4 different protein subunits, named A, B, C and D, respectively. Because of the absence of selective pharmacological tools, very few is known about the functional significance of AMPA receptor subunits. Therefore, we have studied acute and chronic alcohol effects in mice genetically modified to lack either the GluR-A or GluR-C AMPA subunit. All animals were first tested in some spontaneous behaviours and later on ethanol consumption. Compared to their littermate controls, GluR-A and GluR-C mice showed an enhanced/decreased locomotion in a novel environment respectively but they did not differ from wild type mice at any time point. Therefore, the results of the present study revealed that AMPA receptor subunit composition can result in behavioural differences but regarding voluntary ethanol consumption, the absence of GluR-A or GluR-C subunits in the AMPA receptor composition does not seem to produce any functional consequence.

F23. β-endorphin mechanisms in ethanol effects: the role of the hypothalamic arcuate nucleus (ArcN)

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The pro-opiomelanotropinergic projection (POMC), arising from the ventrolateral part of the ArcN, projects extensively to the VTA and the NAC. This opioidergic projection is able to maintain tonic activation of basal dopamine release and, thereby, balanced basal ganglia output. Confirming that the POMC projections have a functional role on the effects of ethanol, mu opioid receptor antagonists prevented ethanol-dependent activation of dopamine neurones in the VTA and substantia nigra. Besides, they blocked acute stimulating response and development of ethanol-induced locomotor sensitization. Thus, there were strong reasons for us to expect that removing the POMC projection from mesencephalic dopamine neurones by means of a lesion of the ArcN would affect the effects of ethanol. In the same way, we expected that exposing mice to chronic naltrexone, which induce up-regulation of mu opioid receptor, the locomotion produced by ethanol would increase. In the present report we demonstrated that lesions of the ArcN by monosodium glutamate (MSG), goldthioglucose and estradiol valerate treatments prevented the acute stimulating effect of ethanol in mice. Moreover, mice with MSG-induced lesions did not develop locomotor sensitization to ethanol, but sensitization to amphetamine was spared. The present results also revealed that acute naltrexone administration reduced specifically ethanol-induced locomotion. Conversely, after repeated naltrexone injections, a transient boost of ethanol induced locomotor activity was observed. Therefore, the effects of these naltrexone pretreatments on ethanol-induced locomotion paralleled the changes on mu opioid receptor activity described by other authors. Our data confirmed an important role for the beta-endorphinic projections stemming from the ArcN in the behavioural effects produced by ethanol.

F24. Brain penetration is necessary for the antiemetic activity of NK1 receptor antagonists

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Tachykinin neurokinin 1 receptor antagonists (NK1RA) inhibit emesis induced by a diverse range of peripherally and centrally acting emetogens in many species including ferrets and man. Preclinical studies indicate that this broad profile is due to their central site of action in the brainstem. It has been suggested that chemotherapeutic agents such as cisplatin evoke substance P-mediated inflammation in the GI tract and this may contribute particularly to the delayed phase of emesis that occurs >24 h after cisplatin administration. To test this, the ability of a non-brain penetrant NK1RA L-743310 to inhibit delayed emesis induced by cisplatin was studied. Ferrets were dosed with L-743310 (3 or 10 mg/kg s.c.) 2 h before and 24 and 48 h after cisplatin (5 mg/kg i.p.). A separate group of ferrets were dosed with L-743310 once only at 24 h after cisplatin, when the acute phase of emesis had already occurred. Ferrets were monitored continuously by trained observers for 72 h after the cisplatin administration and retching and vomiting recorded. L-743310 did not attenuate acute or delayed emetic responses to cisplatin. This result contrasts with the effects of the brain penetrant NK1RA, MK-0869 (aprepitant; EMEND®) that inhibits both acute and delayed emesis in ferrets and humans. Thus inhibition of peripheral inflammation with a NK1RA that does not penetrate into the brain is alone insufficient to prevent emesis in a ferret model with predictive value for the clinic.

F25. Modafinil: effects on attention and sleep in the rat

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In man, modafinil enhances alertness in sleep-deprived subjects and improves executive functioning and planning ability in healthy awake volunteers. The present study used radiotelemetry to assess the effects of modafinil on EEG and sleep, and the 5-choice serial reaction time test (5-CSRT) to examine its effects on attentional processes in the rat. Modafinil at doses of 64-128 mpk, but not 32 mpk, caused a significant increase in the latency to sleep and a concurrent decrease in both REM and SWS for up to 2 hours after administration (CT2.5). Conversely, there was no effect on SWS or REM bout duration or the number of awakenings, suggesting that whilst Modafinil enhanced wakefulness by delaying the time to sleep, sleep architecture per se was unaffected. In the 5-CSRT under standard test conditions, modafinil was without significant effect on performance. Subsequently, the attentional load of the task was increased by (i) reducing the stimulus duration and stimulus intensity together; rSDSI, and (ii) reducing the stimulus duration alone; rSD. However, whilst both manipulations disrupted percentile of correct responding in vehicle treated rats, modafinil failed to improve accuracy against either manipulation. Similarly, modafinil had no effect in reversing a scopolamine-induced performance deficit, unlike physostigmine. In conclusion, these data suggest that whilst modafinil can enhance wakefulness in both rodents and sleep-deprived human subjects, attentional processes in normal awake rats remain unaltered, as measured using the 5-CRST.

F26. Adenosine receptors in nociception, inflammation and hyperalgesia: a role for the A2B adenosine receptor

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We examined the effects of novel specific adenosine receptors in pain sensation and inflammation using subtype-selective antagonists. Several A2B-selective compounds showed antinociceptive effects in the hot-plate test. In contrast, A1- and A2A- selective compounds did not alter pain thresholds, and an A3 adenosine receptor antagonist produced thermal hyperalgesia. A further testing of these antagonists in an animal model for tonic inflammatory pain, the formalin test, also showed analgesic efficacy for A2B subtype-selective antagonists only. These compounds also reduced the size of formalin- or carrageenan-induced hind-paw oedemas, thus indicating anti-inflammatory activity. A single administration of A2B antagonists prior to carrageenan injection completely prevented the development of thermal hyperalgesia. Evaluation of psychostimulant effects of these compounds in the open field showed only small effects of some antagonists at high doses. Co-administration of low, sub-effective doses of A2B-selective antagonists with a low dose of morphine enhanced the efficacy of morphine. Our results indicate that analgesic effects of caffeine are mediated – at least in part – by A2B adenosine receptors.

F27. Anti-impulsive effects of caffeine and d-amphetamine: interaction with basal levels of impulsive choice behaviour in rats

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Numerous data have shown that the effects of d-amphetamine (d-AMP) on locomotor activity and operant conditioning in partial reinforcement schedules are rate dependent. The present work aimed to determine if the effects of d-AMP on impulsive choice are rate dependent and compared those effects with that of an other dopaminergic-acting drug, caffeine (CAF). Impulsive choice was assessed in 47 male Long-Evans rats in a delayed reinforcement task. Rats must choose between a lever-press response followed by the immediate delivery of 1 pellet and a lever-press response on a second lever followed by the delayed delivery of a larger reinforcer (5 pellets); the waiting period was signaled by a light remaining on until food delivery. At the end of training, rats were allocated into 5 groups according to their basal level of impulsivity. At the highest dose used, both CAF (0.3, 1, 3 and 10 mg/kg) and d-AMP (0.25, 0.5 and 1 mg/kg) significantly increased the choice for the large reinforcer. Nevertheless, only d-AMP effects were dependent on group's basal level of impulsivity, even at a low dose (0.5 mg/kg). These results:1) extend the rate-dependent effects of d-AMP on impulsive choice; 2) demonstrate that CAF may decrease this behavior; and 3) suggest that the reduction of impulsive choice induced by d-AMP and CAF may be supported by different mechanisms.

F28. Influence of duration of the abstinence smoking period in performance of the Stroop task

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Nicotine has been found to enhance performance in tasks of selective attention, although results are inconsistent. In order to better understand the effects of tobacco smoking on the Stroop color-naming test, a classical selective attention task, we evaluated the performance in this task in two groups of regular smokers (at least 15 cigarettes/day) after smoking a cigarette both in a minimal abstinence (30 min) condition ($n = 38$, 17 male and 21 female) and after overnight abstinence ($n = 32$, 16 male and 16 female). The procedure was similar for both experiments. Blood pressure, heart rate and CO levels were tested for all subjects. During experimental sessions half of the subjects smoked a cigarette in the first session, and half in the second one. Results indicate that smoking under a minimal abstinence did not improve the performance of the Stroop task. A more prolonged abstinence (abstain from smoking the night prior to the arrival at the laboratory) induced a specific facilitation of the incongruent color naming ($P<0.01$), although this improvement was not observed in the Stroop effect. These findings suggest that smoking a cigarette has different effects on selective attention depending on the abstinence period.

F29. Effect of melatonin on delay of reward in rats

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The capacity to wait for food reward, has been proposed as an approach to impulsive-related behaviour in animals. Serotoninergic (5-HT) neurones are claimed to represent a crucial, though non exclusive, substratum subserving impulse control. Accordingly, antidepressant drugs, which facilitate 5-HT neurotransmission, have been shown to improve tolerance to delay in rats. Since melatonin interacts with 5-HT systems and exhibits antidepressant-like effects in the forced swimming test or the chronic mild stress procedure of depression in animals, the present study investigated whether this neurohormone could induce variations in rats' waiting capacities. Fasting rats were given the choice, in a T-maze, between lager (10 food pellets) but 25-s delayed reward and smaller (2 pellets) immediate reward. After training, vehicle-injected rats selected the large-but-delayed reward in less than 40% of the trials, and a variety of antidepressants enhanced rats' preference for the delayed reward (Ref). Melatonin (3 and 10 mg/kg, but not 1 mg/kg, i.p.) significantly increased the number of choices of the large-but-delayed reward, but has no influence of rats' strategy when no delay was imposed before access to the 10 pellets. These results indicate that melatonin enhanced the waiting capacities of rats, suggesting that it might have beneficial effect in subjects exhibiting poor impulse control.

F30. Modulation of [35S]TBPS binding to GABAA receptors in mouse brain

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GABAA receptors are pentameric GABA-gated ion channels formed from a combination of alpha 1-6, beta 1-3, gamma 1-3, delta, theta, pi and epsilon subunits. The radioligand, [35S]TBPS (t-butylbicyclophosphorothionate) binds to a site located in the GABAA receptor channel pore. [35S]TBPS binding can be modulated *in vitro* by a variety of compounds acting at the GABAA receptor. The aim of this study was to determine if [35S]TBPS binding could be modulated in mouse brain *in vivo* by compounds acting at allosteric sites on the GABAA receptor using an *in vivo* binding receptor occupancy assay (Atack et al. 1999). Maximal [35S]TBPS binding was observed 1 min after i.v. administration in a time course experiment. Dose dependent inhibition of [35S]TBPS binding by etomidate was demonstrated with significant decreases in [35S]TBPS binding between vehicle and 3 and 30 mg/kg etomidate ($48 \pm 6\%$ and $82 \pm 9\%$ respectively, $P<0.01$; $n = 5$). Compounds acting at various sites on the GABAA receptor were investigated such as a full agonist (diazepam), partial agonist (bretazenil) and antagonist (Ro15-1788) of the benzodiazepine site. The in vivo inhibition of [35S]TBPS binding by diazepam, bretazenil and Ro15-1788 correlated well with their in vitro efficacy profiles. Loreclezole, the convulsant pentylenetetrazole and the GABA reuptake inhibitor NO-711 were also investigated. The results demonstrate that [35S]TBPS binding at the GABAA receptor can be modulated *in vivo*. (Atack et al. (1999) Neuropsychopharm 20: 255-262).

L1. Bilateral hippocampal damage spares the familiarity component of recognition memory: a single case study

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Patient (KN), a 44 year old man, suffered 50% bilateral shrinkage of the hippocampus and amygdala following meningitis. In contrast to his preserved IQ (WAIS PIQ 116, VIQ 136) he shows a severe, persistent loss of episodic memory. This is demonstrated by his failure to recall prose passages, word lists, and complex figures, so that on the WMSr he has an Attention Concentration Index of 123, yet a General Memory Index of 88, and Delayed Recall Index of 50 (at floor). Likewise, on the recall components of the Doors and People Test he performs extremely poorly (name recall 1percentile, shape recall 5 percentile). In contrast, KN appears more normal on tests of recognition memory (e.g., Warrington Recognition Memory test, words 48/50, 75 percentile; Doors and People Test, name recognition 25 percentile). Consistent with this he performs at normal levels on the Calev recognition task (20/24) but is very impaired on the Calev recall task (7/24). Performance scores on these tasks are expected to be comparable. Evidence from two different sources indicates that KN is able to perform recognition memory tasks on the basis of familiarity. First, while scalp-recorded event-related potentials (ERPs) differentiated correctly identified old and new test items, the ERP signature of recollection did not form part of this differentiation. Second, estimates of familiarity and recollection derived from an ROC analysis reveal a strong bias toward using familiarity. These findings accord with dual-process models of recognition memory in which familiarity and recollection are independent components. The former may depend on the parahippocampal region while the latter depends on the hippocampus.

L2. Brain substrates of "eyeblink" classical conditioning in goldfish

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Classical conditioning (CC) of the eyeblink response has been used extensively to study the neurobiology of associative learning and memory. These studies have revealed that the essential neural circuitry for acquisition and performance of this simple, learned motor response resides in the cerebellum and related brain stem structures. Although the study of the neural basis of CC has been carried out exclusively in mammals, the cerebellum of every vertebrate show similar anatomical organization and physiological properties. The objective of this study was to identify the neural substrate of the CC in fishes. We have developed a classical conditioning procedure for discrete motor responses in teleost fish, analogous to the eyeblink model employed with mammals. We studied the effects of telencephalon and cerebellum lesions in the acquisition of the CRs. Preliminary experiments were conducted to disregard pseudo-conditioning biases, or any other non-associative mechanism in the performance of goldfish during CC training sessions. Lesion experiments showed an important deficit in the cerebellum ablated goldfish. Whereas the performance of sham and telencephalon ablated fish improved along training, the cerebellum ablated goldfish showed no increase in the percentage of CRs along training. These results show that the cerebellum cortex is involved in the CC of a simple motor reflex of goldfish, in a similar way to that observed in mammals trained in similar conditions.

L3. Effects of dorsal mammillary body region lesions on spatial working memory

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The mammillary body region is involved in learning and memory processes and has been implicated in cognitive deficits in human Korsakoff´s psychosis and other diseases. The aim of the present study was to investigate the precise contribution of the dorsal mammillary body region (dMBR), where is located the supramamillary nucleus (SuM), to spatial working memory. This relationship was studied in rats by using electrolytic lesions of the dMBR and the learning of a working memory task. The rats had to learn a delayed matching to place (DMTP) rule. This task involves two different trials. During the first trial, the rats had to learn to locate a rewarded place (acquisition trial). Thirty seconds later, the rats had to remember the location of previously rewarded place (retention trial). The animals were tested before and after surgery, using a multiple-trials procedure during three days. Our results showed that dMBR lesioned rats, increased the number of errors (from 1.85 ± 0.16 to 3.71 ± 0.19) and the time spent (5.22 ± 0.40 s to 12.11 ± 0.75 s) to locate the rewarded place in the working memory task. Moreover, this working memory impairment is due to neither the increase of the proactive interference nor the impairment in general spatial processing. In this way, dMBR lesions impair the ability of the rats to use the delayed matching to place rule to solve a spatial task. The present findings suggest that dorsal mammillary body region is crucial for spatial working memory.

L4. Differential effects of a bidimentional local cue upon spatial abilities in male and female rats

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Sex differences in spatial abilities remain equivocal. This ambiguity could mainly depend on the attentional demand of task environments in presence of highly diverse uncontrolled cues. Males are known to rely on fewer cues than do females and they prefer distant visual information. Thus, it is possible that different task environments promote different sexually biased spatial strategies. In this study, adult male and female hooded rats were trained in a controlled environment. The distal cue was an arrangement of geometric patterns spaced around the curtain surrounding the pool. A local cue was a black triangle on the wall of the pool behind the hidden platform. Following acquisition, in the absence of the local wall cue and platform, male memory performance was not affected by the training conditions. In comparison, the local cue training reduced the expression of spatial bias in the females. Following continuation of training on a new location, male memory was affected by the removal of the local cue when its expression was not changed in females. The probe trial in the presence of the local cue following a non-spatial task showed that females were more attracted by this cue than males. This suggests a difference in discrimination and reactivity to visual cues. It also raises the question of a possible *a priori* dimorphic strategy selection used to solve spatial tasks that could be modified by familiarization with the task and changes in the experimental situation.

L5. Ionic mechanism underlying learning-induced enhancement in neuronal excitability

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We have previously shown that learning-induced enhancement in neuronal excitability is mediated by reduction in one or more of the calcium-dependent potassium currents that control neuronal frequency adaptation. The purpose of the present research was to identify the specific current that is affected. Rats were trained in an olfactory discrimination task to distinguish between pairs of odors until demonstration of rule learning. Two days after training completion, intracellular recordings were made from pyramidal neurons in layer II of piriform cortex brain slices. As previously shown, AHP amplitude was significantly smaller in neurons from trained rats, compared with neurons from pseudo trained and naive rats (-4.98 ± 0.30, $n = 32$ trained; -6.79 ± 0.38, $n = 23$ pseudo trained; -6.76 ± 0.37, $n = 24$ naive). In the presence of specific IAHP blocker apanim (50 nM), AHP amplitude remained significantly smaller in neurons from trained rats (-2.76 ± 0.41, $n = 20$ trained; -4.67 ± 0.59, $n = 16$ pseudo trained; -4.73 ± , naive). Exposure to acute stress blocks the induction of long-term potentiation of the amygdala-prefrontal cortex pathway *in vivo*.

L6. Role of neocortical sites in the consolidation of fear conditioning

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The distinct roles of three neocortical sites, the prefrontal (PFC), frontal (FC) and parietal (PAC) cortices, during memory consolidation of conditioned freezing to acoustic conditioned stimulus (CS) and context were investigated. Male Wistar rats (aged 60 days) were employed. During the single acquisition trial, to the rats placed inside the conditioning apparatus (context) were administered 7 footshocks (1 mA, 1 s) at 30 s intervals, paired with the acoustic CS. Under general anesthesia tetrodotoxin (10 ng in 1 µl) was bilaterally injected into PFC, FC or PAC at increasing post-acquisition delays (0.25, 24 or 96 h) in distinct groups of rats. Retention testing was performed 72 h after the reversible inactivation in order to avoid any possible influence on the retrieval process. None of the three sites appears to be involved in context freezing consolidation, but FC and PAC appear to be differentially involved in acoustic CS memory consolidation. FC inactivation was followed by retention impairment only when performed both immediately and at the 24 h delay but not at the 96 h one. PFC inactivation was never followed by amnesia. Thus FC and PAC are involved in fear conditioning to acoustic CS at least during the initial phases of consolidation.

L7. Negative results and the synaptotagmin I heterozygous knockout mice: behavioral analysis

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To further explore the role of pre-synaptic mechanisms in learning and memory, we have analyzed Synaptotagmin I knockout heterozygous mice in a variety of behavioral tests. Synaptotagmin I (Syt I) is thought to act as the calcium sensor in fast-evoked neurotransmitter release, and is of vital importance to the organism, as homozygous knockouts are lethal within the first 48 hours of life. Syt I +/- and wild type littermates were tested on the Rotorod for motor performance, and in an Open Field for assessment of generalized anxiety. Both genotypes performed at equivalent levels in the Open Field, but in the Rotorod Syt I +/- mutants were found to be impaired in motor performance. In behavioral tests with a hippocampal component, such as the hidden platform version of the Morris Water Maze and contextual Fear Conditioning, no significant differences were found between mutants and controls. Both groups learned the water maze task, retained the memory for platform location, and adjusted search strategy to reflect a new platform location. In context conditioning, the freezing response was equivalent for both genotypes. In a non-hippocampal dependent component of Fear Conditioning – conditioned freezing to a tone – Syt I +/- mutants displayed an increased response to tone that stabilized to the levels exhibited by their wild type littermates.

L8. Reversible inactivation of the hippocampal CA3 network: effect on contextual fear conditioning in C57BL/6J mice

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Contextual fear conditioning has been widely acknowledged as a useful model to study episodic-like memory in rodents, because animals can express "where" and "when" the aversive event occurred. The hippocampus plays an important role in learning and memory, namely its CA3 area that presents all the attributes for supporting an episodic memory framework. We compared the effects of lidocaine reversible inactivations of the hippocampal CA3 area on the acquisition, consolidation and recall of contextual fear conditioning, with those of inactivations of the CA1 area. Results showed first, that inactivations made prior to training lead to significant impairments of contextual fear acquisition for both infusion sites. Secondly, inactivations made immediately after training in the CA1 area disrupted episodic memory consolidation whereas they had no effect in the CA3 area. Third, inactivations performed just prior retention testing, had no effect on contextual fear recall for both infusion sites. Fourth, in no case, infusions of lidocaine impaired elementary tone conditioning. Lastly, even those mice that showed contextual fear deficits, still increased freezing reactions at the time when the shock occurred during the training session, demonstrating expectation of the event. Our findings indicate that the hippocampus plays an important role in the acquisition and consolidation of contextual fear conditioning, whereas it is not necessary to memory recall.

L9. Distinct roles of the different ionotropic glutamate receptors within the nucleus accumbens in passive-avoidance learning and memory in mice

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Research on the nucleus accumbens (Nac) has mainly focused on its role in conditioning to appetitive stimuli. Data on the role of Nac in aversive conditioning, on the contrary, are few and contradictory. Moreover, little evidence is available on the role of Nac in different steps (acquisition, consolidation and retrieval) of aversive learning. The purpose of this study was, therefore, to investigate the effects of a blockade of AMPA and NMDA receptors, which have been suggested to mediate the transmission of limbic information to the Nac, in the one-trial step through inhibitory avoidance task. For this purpose, we injected in mice AMPA (DNQX) and NMDA (AP-5) receptors antagonists within the Nac immediately after training, before training and before testing. AP-5 (37.5, 75, and 150 ng/side) impaired animal performance only if injected immediately after training but not before training or testing. Conversely, DNQX (0.5, 1.0, and 5.0 ng/side) reduced the step through latencies only when administered before training and testing. These results suggest that NMDA receptors within the Nac are selectively involved in memory consolidation of inhibitory avoidance response. AMPA receptor, instead, are necessary for the acquisition and the expression.

L10. Intraseptal injections of 8-OH-DPAT and spatial working memory in rats

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In rats, 5-HT1A receptors are present on cholinergic neurons of the medial septum, where they might be a substrate for cognitively relevant interactions between cholinergic and serotonergic mechanisms. This experiment assessed the effects of intraseptal infusions of the 5-HT1A (and 5-HT7) receptor agonist 8-hydroxy-2-(di-n-propyl--amino)-tetralin (8-OH-DPAT; 0.5 and 4 μg). Spatial memory was assessed in a Morris water maze using a protocol placing emphasis on working-memory. The location of the hidden platform was changed every day and performance was assessed on two consecutive trials each day over 7 days. In comparison to vehicle injections, the intraseptal infusion of 4 μg (not 0.5 μg) 8-OH-DPAT impaired performance significantly: rats treated with 8-OH-DPAT swam faster and exhibited increased distances to reach the platform on Trials 1 and 2. Such effects were not observed when the platform was visible. These results are compatible with those of a previous experiment showing that intraseptal injections of 8-OH-DPAT impaired spatial reference memory. Based on the characteristics of the observed deficits, it is suggested that the 8-OH-DPAT-induced impairment, rather than being only the result of a true alteration of working memory processes, might reflect a more global cognitive deficiency in which perturbations of general memory capacities may be mixed with alterations of search strategies (on the first trial) or dysfunctions of attention and/or modifications of anxiety.

L11. Spatial learning in a partitioned water maze: distinctive capacities revealed in knockout mice lacking alpha-1B noradrenergic receptors

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In a standard water maze version, alpha-1B knockout mice have been found to perform poorly (Spreng et al. 2001). Indeed, they were unable to solve the task in stressful conditions (i.e., a large illuminated pool in the vicinity of the rats' animal room), whereas they reached at best the performance of their control littermates in neutral conditions. However, in a radial arm maze, 12 month old alpha-1B KO mice have been shown to exhibit a better working memory performance than the wild type. Recent experiments conducted with a new paradigm in the water maze have been able to assess the distinctive capacities of old alpha-1B KO mice in greater detail. This procedure used a partitioned water maze, with six symmetric compartments, and a submerged platform located in one of them. The periphery of the pool is divided with radiant partitions made of transparent Plexiglas. Thus, the animal has to cross the center of the pool to visit different compartments, but the distant visual cues are available from anywhere. Old alpha-1B KO mice tested in a partitioned water maze exhibited a good capacity to perform the task, even more so when working memory was required. In conclusion, partitioning the water maze allowed us to measure subtle changes related to the absence of alpha-1B receptors upon spatial memory performance.

L12. Molecular characterization of the orphan nuclear receptor HZF-3 in learning and memory

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HZF-3, also known as Nurr1, is an immediate-early transcription factor that is a member of the inducible orphan nuclear receptor family. hzf-3 mRNA was found by us to be upregulated in the hippocampus during spatial discrimination learning and in the amygdala during acquisition of conditioned taste aversion. Additional studies show that the hzf-3 gene is upregulated as a result of the establishment of long-term potentiation at the hippocampal mossy fiber-CA3 synapse. We are currently studying the expression of the hzf-3 gene following contextual fear conditioning and its regulation by the cAMP-Responsive Element binding protein. In addition, we are assessing the hypothesis that the protein product of the hzf-3 gene is plays a role in hippocampal-dependent plasticity. Preliminary data demonstrates that blockade of the expression of HZF-3 in the CA1 and CA3 regions of the hippocampus impairs acquisition and long-term consolidation of spatial discrimination learning. Finally, since the hzf-3 gene has been implicated in neuropsychiatric diseases we are studying the effects of diverse early life experiences on its expression in the brain. Our results so far suggest that negative experiences early in life decrease the levels of HZF-3 in discrete hippocampal regions. Results from these studies will be important for elucidating the role of a member of the orphan nuclear receptor family in cognitive processes in the rat brain.

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L13. Reward facilitates cognitive performance of mice in two spatial learning tasks

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Processing of positive (rewarding) and/or negative (aversive) stimuli enable context related behaviour and facilitate learning and memory. To study the contribution of rewarding stimuli on cognitive performance in mice, we used two memory tasks that differ in rewarding/aversive cues: water maze (WM) and circular hole board (CHB). We expect that in the WM task, aside from the strong aversive component, the additional reward will increase the effect on cognitive performance even further. Male C57Bl/6J mice (3 months) were tested. Sugar was used as reward and administered immediately after training (30 mg; 1/day); control animals received nothing. Training consisted of four trials/day in the WM and two trials/day on the CHB. Two days after training a probe trial was given to assess parameters related to learning and memory. Reward resulted in development of a more efficient strategy in solving both tasks indicated by a faster decrease in latency to the escape position. Performance was also task-dependent, as mice rewarded in the CHB improved their strategy more rapidly compared to WM trained animals. Escape strategies during the WM probe trial were more persistent compared to CHB strategies. This indicates that the effect of environmental stimuli on information processing and adaptation of behaviour is context related. Facilitation of learning and memory by reward depended on task specific demands.

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L14. Dissociated roles for the basolateral and lateral nuclei of the amygdala in contextual and elemental fear conditioning

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Although the basolateral amygdala complex (BLC) is required for both elemental and contextual conditioned associations (i.e., discrete conditioned stimulus (CS)-unconditional stimulus (US) and context-US association), anatomical and electrophysiological studies suggest a differential involvement of the lateral (LA) and basolateral (BLA) nuclei components of the BLC in these two kinds of associations. Using a classical fear conditioning paradigm, the present study investigated this hypothesis by comparing the effects of inactivation of either the BLA or the LA during training on subsequent conditioned freezing responses to the elemental (tone) CS and to the context. Results showed that inactivation of the BLA impaired conditioning to the context while sparing conditioning to the tone CS. In contrast, inactivation of the LA disrupted conditioning to the tone CS but also impaired or enhanced contextual conditioning as a function of the training protocol (CS-US unpairing vs. pairing). Therefore, these findings reveal dissociated roles for these two amygdaloid nuclei in fear conditioning. They indicate a selective involvement of the BLA in contextual conditioning and suggest that, beyond its requirement for elemental CS-US associations, the LA could modulate the processing of BLA-mediated context-US associations depending on the predictability of the discrete CS for the occurrence of the US.

L15. Chronic exposure to 2,5-hexanedione reversibly impairs learning of a conditional discrimination task in rats

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Hexane is a volatile liquid, used as a solvent in various industrial processes such as printing, car repair, shoes manufacturing, etc. A significant association between increased exposure to solvents and altered performance on some tests involving visual attention and perceptual (speed and memory) functions has been reported in workers of paint factories exposed to low levels of organic solvents. In living beings hexane is metabolized oxidatively to a number of compounds, including 2,5-hexanedione (HD), which is thought to be the ultimate neurotoxic agent. We tested whether chronic exposure to HD impairs the ability to learn a Y-maze conditional discrimination task in rats. Male Wistar rats (100-120 g) were treated with HD (1% in the drinking water) for 25 days. Rats treated with HD showed a decrease in learning ability needing more trials to reach the criterion of learning than control rats. To assess the reversibility of this effect HD was withdrawn after the 25 days of treatment and rats were maintained in tap water during 5 weeks. We carried out the same Y-maze test with animals 38-40 days after withdrawal of HD. The impairment in learning ability induced by HD was reversible. The number of trials required to learn was not significantly different in rats after withdrawal of HD than in controls.

L16. Glutamate-dopamine interactions within the nucleus accumbens on spatial memory consolidation in mice

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The functioning of the nucleus accumbens is determined by glutamatergic input from limbic structures, which in turn is modulated by the activity of the dopamine mesolimbic system. Interestingly, several evidences point to a receptor-dependent interaction between these two systems. Recently a role of nucleus accumbens in complex cognitive functions has been suggested, unfortunately, interactions between dopamine and glutamate receptors within this structure have never been thoroughly investigated from a behavioral point of view. Thus, the purpose of this study was to assess the effects of co-administration of DA and glutamate antagonists within the nucleus accumbens on the ability of mice to consolidate spatial information. The task consists in placing the animals in an open field containing five different objects; after three sessions of habituation, their reactivity to object displacement is examined 24 h later. Intra-accumbens co-administration of ineffective doses of the D2 (sulpiride 25 ng/side) and the NMDA (AP5 50 ng/side) antagonists immediately after training impaired the ability of mice to selective re-explore the spatial change. Preliminary experiments suggest that co-administration of the D1 (SCH23390 12.5 ng/side) and NMDA antagonists might also induce similar effects. These results suggest an interaction between the two neural systems in modulating memory consolidation and that the ability of DA antagonists to potentiate AP5-induced effect is not receptor dependent.

L17. Comparison between aspirative *versus* excitotoxic lesions of the lateral entorhinal cortex on conditioned odor aversion in the rat

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Converging data suggest that entorhinal cortex (EC) is involved in olfactory learning. More precisely, we showed that animals lesioned in the EC with aspirative technique showed a conditioned aversion to an odor (conditioned stimulus, CS) previously paired with a toxicosis (unconditioned stimulus, US) eventhough the interstimulus interval (ISI) between the CS and the US is too long to support conditioning in sham-lesioned rats. As the lesion technique used in this study damaged the major part of the lateral part of the EC but also partially the medial EC, the present study was aimed at determining whether lesions restricted to the part of the EC that receives most of the olfactory inputs (the lateral part) supported this above-mentioned effect. Male Long-Evans rats bilaterally lesioned in the EC using either aspirative or excitotoxic (using NMDA injections) technique received CS-US paring with a long ISI (2 h) during the acquisition of conditioned odor aversion learning (COA). Results showed that sham-operated animals did not show any COA with this ISI confirming that the memory trace of the odor is subject of rapid decay. In contrast, both type of lesioned animals displayed COA with this ISI. These data confirm that EC lesion allow odor-toxicosis association across long delays and suggest that the lateral EC may be part of the substrate involved in the control of the memory trace of the odor during COA.

L18. cAMP response element-binding protein in the hippocampal CA3-region is required for long- but not short-term spatial memory

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The transcription factor cAMP response-element binding protein (CREB) plays an important role in plasticity processes underlying learning and memory. Previous studies suggested that CREB-activated transcription is critical for long-term memory formation within the dorsal hippocampus. We investigated the role of the hippocampal CA3-region in the memory consolidation of information in the spatial version of the Morris water maze. For that, 18 hours before training, mice received an intra-hippocampal injections of a CREB antisense oligodeoxynucleotides (ODN) and control mice received PBS or sense ODN injections in the same condition. Mice were submitted to a massed training in the spatial version of the water maze and have been tested for retention immediately (short-term memory) or 24 hours (long-term memory) after the last training session. The results showed that pre-training infusions of antisense ODN directed against CREB mRNA impairs the spatial performance when the probe test was realised 24 hours after the training phase. Moreover, administration of CREB ODN antisense did not affect immediate retention performance. These finding provide the evidence that CREB-activated transcription is integral to CA3 hippocampal region-dependent memory consolidation processes.

L19. New methods for testing visual recognition memory in the rat

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Tests of recognition memory have been central to our understanding of memory systems. This poster describes three new versions of a spontaneous recognition test for rats. This task is typically carried out using trial unique 3-D junk objects in an open arena. In the sample phase rats are allowed to explore two copies of sample object A, each placed in a corner of the arena. After a delay rats are returned to the arena, in which the familiar sample object A and a novel object B are placed, for the choice phase. The extent to which the rat prefers to explore the novel object versus the familiar object during the choice session gives an indication of novelty preference, which reflects the memory of the original sample object A. In order to minimise potential spatial confounds, the first new version of the task was carried out in a spatially restricted "Y-maze" apparatus. The second version replaced the objects with trial-unique 2-D picture stimuli. This restricted the task to the visual modality. The third version used a monitor to present stimuli and a touch-screen device for automated recording of exploration (fig. 1). Rats showed a significant preference for the novel stimulus at a 15-minute delay in all three versions of the task. In conclusion, rats can be tested on versions of this task that minimise spatial confounds and that use 2-D visual stimuli. The automated version of the task may prove particularly useful due to its ease of use, precision and ability to manipulate stimulus properties systematically.

L20. Two-way active avoidance learning and perinatal disthyroidism on Wistar rats

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The active avoidance learning has been considered an animal anxiety model. Moreover, it is well known that the neurobiological mechanisms underlying this learning, such as mossy fibers and glucocorticoid receptors, are sensitive to thyroid hormone levels. Previous research carried out in our laboratory showed that perinatal disthyroidism provokes emotional changes in adult rats. The aim of this study is to analyse the effects of perinatal disthyroidism upon the two-way active avoidance learning. For this purpose, 47 Wistar rats (24 males and 23 females) were distributed in three groups according to received treatment. Disthyroidism was induced by drug administration (thyroxine or methimazole) diluted in drinking water. The treatment started on the 8th gestational day and ended at weaning, the 21st postnatal day. Behavioural test performed on 45 days old animals, included open field testing and two-way active learning. The most remarkable results were: 1) perinatal disthyroidism increased the number of subjects which reached the learning criteria; 2) among these subjects, the control group seemed to be more effective and to have an increased consolidation of learning in comparison with the treated groups; c) the methimazole-treated group showed more ambulation than the other two groups, especially among the animals which reached the learning criteria.

L21. Spaced-trained, but not massed-trained, mice show spatial learning impairment caused by zinc chelation in mossy fibers

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Zinc is localised in presynaptic terminals of hippocampal mossy fibers, from where it is coreleased with glutamate with activity. We examined the effects of zinc chelation on spatial learning using two different training procedures. C57BL/6 mice were implanted bilaterally with cannulae targeting CA3. Twenty minutes prior to each daily session, subjects were infused with 0.25 microlitre of either 200 mM diethyldithiocarbamate (DDC) or 200 mM Ca-ethylenediamine (EDTA). Mice were trained in an open-field water maze reference memory task: half of the subjects were given one session of 4 trials spaced over 4 consecutive days; the other subjects had the same amount of training massed over 2 days. For both conditions, a probe test was conducted 1 h after the last training trial. In the spaced training procedure, mice infused with DDC were impaired in acquiring the spatial reference memory task compared to the EDTA-infused mice. In the massed training protocol, DDC- and EDTA-infused mice showed a significant learning curve, with both groups attaining the same level of performance by the end of training. The probe test confirmed accurate short-term retention in all groups except in DDC-spaced trained mice. These findings confirm that synaptically released zinc contributes to spatial learning. Furthermore, we propose that increased glutamate release associated with high neuronal activity can overcome spatial learning deficits induced by synaptic zinc blockade.

L22. GABAA alpha5 receptors are involved in Pavlovian conditioning

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To clarify the roles of GABAA alpha5 receptors in behaviour, a histidine-to-arginine point mutation was introduced in position 105 of the mouse alpha5 gene. This mutation renders the receptors diazepam-insensitive, and leads to their reduction in the hippocampus. We therefore investigated possible alterations in hippocampal-mediated learning using Pavlovian trace (0 s or 20 s trace) conditioning with aversive (shock) or appetitive (food) unconditioned stimulus (US). In the aversive paradigm, we observed a weaker conditioning in the wild-type mice after introduction of a 20 s trace, but the same trace had no effect in the mutant female mice. Mutants exhibited enhanced resistance to extinction of the conditioned response. In the appetitive conditioning paradigm, mutants were impaired in CS conditioning at 0 s trace. The 20 s trace induced complete disruption of the conditioning in mutant and wild-type mice. We replicated the previously reported effect of this mutation on trace fear conditioning. In addition, we showed that the mutation is associated with increased persistence of aversive conditioning, and impaired acquisition of appetitive conditioning.

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L23. Water maze learning failure in preweanling rats impairs adult acquisition of a jumping avoidance response

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The relevance of the early learning failure in a water maze task related with early stages of hippocampal development on general adult learning abilities was studied using preweanling (P18) and postweanling (P25) Wistar rats. All the groups belonged to five different litters and were sex balanced. One group ($n = 10$) of each age was trained in a hidden platform Morris water maze task and the performance was compared with that of a control random located platform group ($n = 10$). Consistent with previous findings, twenty-five day old but not eighteen day old rats were able to learn the platform location. When they were three-months old, these animals and two added age-matched naive control groups, were trained to avoid a shock jumping in the presence of a previous tone, until they reach a three consecutive conditioned avoidance responses criterium. The group that was unable to learn the early hippocampal task at P18 performed significantly worse than the rest of the groups in the jumping avoidance task. In a second experiment, NMDA dorsal hippocampus lesions did not disrupt the acquisition or retention of the jumping avoidance response in adult rats. These results point to a general and long lasting learning deficit induced specifically by the early failure in an hippocampal task. Therefore, the fact of subjecting infant rats to a learning task before the required brain circuit has matured may have profound effects on adult learning that can not be explained by early learning failure as it was not induced in joked trained groups.

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L24. Posttraining lesions of the pedunculopontine tegmental nucleus impair two-way active avoidance under a paradigm of conditioned stimulus transfer

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While pretraining lesions of the pedunculopontine tegmental nucleus (PPTg) severely impair two-way active avoidance conditioning (perhaps as a consequence of disrupted functioning of striatal systems), posttraining lesions have no effect on the retention of this task. There are evidences that PPTg lesions also impair attentional processes, probably by disrupting the influence of this nucleus on thalamocortical activity. We tested whether posttraining PPTg lesions would impair the retention of two-way active avoidance when the attentional demands of this task are increased during the testing sessions. Two groups of rats received three sessions of two-way active avoidance conditioning (30 trials each) using a tone as the conditioned stimulus. After training, the animals received either bilateral excitotoxic (ibotenate) lesions of the PPTg, or the corresponding control procedures. After recovery, the rats were again subjected to three conditioning sessions, but the initial conditioned stimulus was replaced by a less salient visual stimulus (a light). Changing the conditioned stimulus decreased performance in both groups, but this reduction was significantly higher and long-lasting in lesioned animals. Those results support a role for the PPTg in the retention of two-way active avoidance under highly demanding conditions (such as when the attentional demand of the task is increased).

L25. Disconnection lesions of nucleus accumbens and pedunculopontine tegmental nucleus: effects on conditioned reinforcement

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Much attention has been directed to understanding the function of the nucleus accumbens (NAcc) core and shell in conditioned reinforcement (CR). Connections between NAcc and the pedunculopontine tegmental nucleus (PPTg) are thought to be important in this: bilateral PPTg lesions attenuate CR responding. We investigated the effects on CR acquisition of bilateral lesions of core or shell; unilateral core or shell plus ipsilateral PPTg; unilateral core or shell plus contralateral PPTg. In phase 1, a 5 s light conditioned stimulus (CS) predicted food pellet delivery; food hopper entries were recorded. This phase proceeded until all rats reached performance criterion. In phase 2, CR lever responses produced a CS, NCR responses did not; no pellets were delivered. Control rats responded significantly more on CR than NCR in all sessions; as did core-ipsilateral PPTg, and shell-ipsilateral PPTg and bilateral shell lesioned rats. Bilateral core lesioned rats showed no difference in responding on CR and NCR levers; neither did shell-contralateral PPTg lesioned rats. Contralateral PPTg-core lesioned rats responded significantly more on the CR than NCR lever on sessions 1-3 but not sessions 4-6. These data suggest that the role of NAcc shell in CR is secondary to that of the PPTg.

L26. Manipulations of NMDA/nNOS pathway impairs olfactory memory in different ways

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Several behavioural tasks taxing the olfactory memory of mice in different situations have been developed. Two tasks investigating learning and memory to biological odours: 1) A habituation/dishabituation paradigm with a 24-hour discrimination test; 2) The social transmission of food preference (STFP) task. In addition an olfactory conditioning task, using non-biological odours has been developed. MK801 (0.05 mg/kg) impaired olfactory memory in all 3 tasks. Mice with a targeted mutation of the nNOS gene (nNOS-/- mice) demonstrated deficits in social recognition, an effect that was repeated in NOS inhibitor (L-NARG, 25 mg/kg) treated mice and rescued in nNOS-/- mice by the NO donor, molsidomine (10 mg/kg). nNOS-/- mice showed no deficits in STFP whereas L-NARG treated mice were impaired. L-NARG treated mice were also impaired in the olfactory conditioning task, whereas nNOS-/- mice showed no deficits. However nNOS-/- mice displayed enhanced reversal learning as compared to wildtype controls. Thus whilst all three olfactory memory tasks described are dependent on both NMDA and nitric oxide signalling those involving STFP and conditional learning paradigms were not impaired in nNOS -/- mice. This suggests additional involvement of other NOS isoforms and possibly of the hippocampus where NMDA-evoked NO release can still be seen in nNOS-/- mice.

L27. Spatial learning-related changes in the hippocampal cortex of lizards

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Synaptic plasticity in the hippocampus may occur after spatial learning in mammals. Timm-staining of the mossy fibers has been successfully used to analyze spatial learning-related synaptic changes in the hippocampus of mammals. In the present work, the Timm-staining technique was used to analyze possible spatial learning dependent plasticity changes in different telencephalic areas in iguana (*Iguana iguana*) trained in two different spatial tasks. With this aim, animals were trained in a place or cue task to locate a hidden platform in a plus water maze placed in the center of a large room. Both tasks were identical except that in the cue task the information provided by the distal cues was irrelevant to locate the goal. Then, we measured the relative size of Timm positive areas within the medial (MC) and dorsal cortex (DC) and the septal nucleus. The analysis revealed significant changes in the size of the Timm positive areas according to the task. Animals in the place group, showed a high increase in the size of the deep layer of the medial cortex and also an increase in the septal nucleus, relative to the animals in the cue task. In contrast, the animals trained in the cue task showed a significant increase in the size of the Timm positive area of the medial and caudal parts of the dorsal cortex. These results are discussed in the context of comparative data and in the light of current hypothesis concerning the evolution of forebrain and cognition in vertebrates.

L28. Olfactory learning is followed by upregulation of synaptic proteins, and cell adhesion molecules and increased spine density in the hippocampus

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Water deprived rats were trained to distinguish between pairs of odors in a 4-arm maze for a water reward, a process lasting 7-8 days. The hippocampal expression of L1, NCAM, PSA-NCAM, Synaptophysin and PSD-95 was examined on the third and fifth day of training as well as 1 day and 3 days after training completion. Significant alternations in the expression of these molecules were found at 1 day after training completion; L1 expression was 24% higher in the trained rats compared to pseudo trained ones and 16% higher than the level in naive rats. In the trained rats, PSA-NCAM expression was 10% and 7% higher compared to pseudo trained and naive rats, respectively. PSD-95 was also significantly increased in trained rats (18% compared to pseudotrained and naive rats). Hippocampal levels of NCAM and Synaptophysin were not different among the three experimental groups at any of the time points examined. We then examined whether the upregulation of L1, PSA-NCAM and PSD-95 is accompanied by a change in spine density of pyramidal CA1 neurons apical dendrites. We found that 3 days after training completion, spine density is 20% higher in trained rats compared to pseudotrained and naive rats. We suggest that learning induced upregulation of synaptic proteins and cell adhesion molecules in the hippocampus precedes morphological modifications.

L29. Neuronal activity in the rat's medial frontal cortex during odor learning task

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To study the processes of memory consolidation we use a foraging task where rats quickly associate one of three odors with a reward. Significant c-FOS increase after the learning session suggested that the medial prelimbic cortex (mFC) was activated when the rat performed the task. To examine the dynamics of its activation we run the experiment on the group of rats with chronic microelectrodes implanted into mFC. Over 75% of the cell recorded in mFC changed their firing rate: around 30% was tonically excited during whole session; some cells responded with excitation (14%) or inhibition (14%) when the rat was placed into in the experimental box and around 20% increased their firing in the start-box during inter-trial intervals. The effects can be related to many aspects of changing environment yet we suppose that the activation observed specifically during inter trial intervals could be involved in processes of memorization of experiences from preceding trial. Indeed, significant increase of cells' firing rate during this period was followed by shortening of the latency of rat's behavioral response. Such an activation was no longer observed after the rat achieved asymptotic performance. Our preliminary results confirmed that cells in prelimbic area of the medial frontal cortex are involved in complex mechanisms of underlying memorization of odor-reward association.

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L30. Cortical and medial nuclei of the amygdala are both involved in lamb odour memory formation by parturient mothers in sheep

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Maternal behaviour in sheep is characterized by the rapid formation of a selective bond with the lamb. Within 1 hour after parturition, mothers learn to recognize the individual olfactory signature of their own lambs and subsequently allow them to suck while rejecting any alien young (maternal selectivity). The aim of this study was to investigate the implication of the cortical and medial nuclei of the amygdala in this learning using pharmacological reversible inactivation through lidocaine perfusion. Just before parturition, ewes were perfused for 8h either with lidocaine (4%, 10 µl/h) or artificial cerebrospinal fluid (aCSF, control) either in the cortical, medial or basolateral nuclei of the amygdala. At 2 h, the proportion of selective mothers was lower in the cortical and medial groups (2/9 and 2/8, respectively) than in the basolateral (5/6, $P<0.05$) or in the aCSF group (9/11, $P<0.05$). This lack of selectivity still persists at 4 and 8 h although some degree of recovering was observed. Moreover, inactivation of these nuclei 2 days later, once the mothers were selective, has no effect on lamb recognition. Therefore both medial and cortical nuclei of the amygdala are involved in formation but not in retrieval of lamb olfactory memory. Our results emphasizes recent data indicating that the amygdala could be a keystone in the memory circuitry of socially relevant olfactory recognition.

L31. Involvement of NCAM polysialylation in the storage of strong fear conditioning

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Polysialic acid (PSA) attachment on the neural cell adhesion molecule (NCAM) reduces cell-adhesion and plays a key role in the regulation of cell surface interactions and synaptogenesis, synaptic plasticity and long-term memory storage. Increases in the hippocampal expression of PSA were shown to be associated with structural modifications following training in a variety of tasks. However, using the contextual fear conditioning paradigm, we recently found that whereas training rats under moderately aversive conditions (0.4 mA shock) leads to increased PSA expression in the dentate gyrus, training under highly aversive conditions (1 mA shock) is followed by a reduction on PSA expression. Here, we aimed to assess whether diminishing PSA levels in animals treated under moderately aversive conditions would strengthen fear conditioning. Wistar rats were intracerebroventricularly injected with endoneuraminidase (EndoN), that removes PSA from NCAM, either before (12-24 h pretraining) or immediately after training rats in the fear conditioning task (0.4 mA shock). Whereas posttraining injections were ineffective, long-term fear conditioning was enhanced in pretraining EndoN-injected rats. Plasma corticosterone levels were lower in EndoN-injected rats. Therefore, down-regulation of PSA-NCAM following stressful experiences might be involved in the enduring establishment of highly aversive emotional memories.

L32. The effects of left and right selective amygdalohippocampectomy on episodic memory, discourse production and spatial representation

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It has long been known that episodic memory depends on the integrity of the medial temporal lobe; the critical role of the hippocampus has been extensively researched in patients following hippocampal excision for medically intractable unilateral temporal lobe epilepsy. O'Keefe and Nadel (1978) argued that the left hippocampus contains a language-based semantic map, which works with the spatial map in the right hippocampus to form the basis for long-term memory of verbal episodes and narratives. They predicted that left hippocampal damage would result in language deficits. We describe a novel way of investigating episodic memory, discourse production and spatial representation in post-operative left and right amygdalohippocampectomy (LAH, RAH) patients and normal matched controls (NC). The results show that: (1) LAH patients are significantly impaired in both the recall of personally-relevant events and the use of language in describing such events; (2) the RAH group were most impaired at landmark recognition and location; and (3) the LAH group showed the greatest deficits in route description. These findings provide the first confirmation of O'Keefe and Nadel's predictions. We posit that the left hippocampus plays a vital role both in verbally-mediated episodic memory, and also in the real-time formulation of linguistic utterances.

L33. Time of day-dependent latent inhibition of conditioned taste aversions in rats

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We have explored the ability of changes in the temporal context to modulate latent inhibition of learned saline aversions in rats. Two temporal contexts were used (9:00 h and 20:00 h). Animals were habituated to drink water twice a day for 5 consecutive days. On the first three days they drank freely for 15 min. The last two days, rats drank during the morning drinking session a maximum of 6 ml. The preexposure phase lasted two days. Latent inhibition was absent in the group receiving saline pre-exposures and conditioning in different temporal contexts, but not in the group receiving pre-exposures and conditioning at the same time of day. The results confirm a previous report showing that the temporal context can modulate taste aversion learning independently of other environmental cues. It is proposed that the features and duration of the habituation training to the temporal contexts used may be critical for time- dependent latent inhibition to appear.

L34. What is the hippocampal-dependent memory component in step-down inhibitory avoidance tasks?

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The aim of this study was to determine whether memory for an association between a stepping-down response and footshocks can be dissociated from the memory of the context in which this experience has occurred. Indeed, according to current memory theories, only this component should depend upon an intact hippocampus. Experiments were carried out using a circular arena equipped with a grid-floor throughout which electric shocks could be delivered. For acquisition, a conditioning chamber (CC) was placed in the arena. In the standard version of the task the platform was placed in the CC. Animals received a single shock (0.5 mA) as soon as they stepped down and were immediately removed from the apparatus. In the new version: i) a sliding door made of clear Plexiglas prevented the subject from stepping-down for 30 s; and ii) electric shocks were delivered for 45 s. Twenty-four hours later the step-down latency was measured with the platform placed either inside (as in acquisition) or outside the CC (i.e., in another location). Results show that both hippocampal-lesioned (HIPP) and sham mice displayed better retention test performance in the new than in the standard version of the task. No significant effect of the lesion was observed when retention was assessed with the platform inside the CC. However, when retention was assessed with the platform outside the CC, HIPP mice continued to express the inhibitory response whereas sham did not.

L35. Analysis of the oxidative metabolism in different hippocampal subregions after a spatial training

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Spatial learning in rats has been widely related with the hippocampal function. Cytochrome Oxidase (CO) is a marker of the brain metabolic capacity. Alterations in the neuronal activity induced by training in different tasks could result in changes of CO activity. The aim of this work was to evaluate changes in the oxidative metabolism in several hippocampal subregions after training in two different tasks in the water maze. The histochemical analysis was made using the cytochrome oxidase technique in three groups of rats: 1) naive; 2) reference memory task; 3) visual cued task. Animals trained in the water maze were sacrificed 1 hour after the last training trial. Eleven measures of different subdivisions were taken of the anterodorsal portion of the hippocampus. Densitometric analysis showed no statistically significant differences between groups in all measured regions. By other hand, significant differences exits in the CO activity between the different hippocampal subregions. Moreover, correlations of the CO activity across hippocampal subregions and between CO activity in hippocampus and different indexes of learning were calculated. The results suggest that changes in the CO activity of the hippocampus are not coupled with maze performance.

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L36. Effects of electrical stimulation of the nucleus basalis on two-way active avoidance acquisition, retention and retrieval

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This study assessed the role of the NBM in specific memory phases of a two-way active avoidance conditioning. We evaluated the effects of the nucleus basalis magnocellularis (NBM) electrical stimulation applied at different moments of the learning process of the task. Rats were trained in a 30-trial acquisition session, and were tested again 24 h and 48 h later. The NBM stimulation was applied at different moments of the conditioning: (1) immediately before the first training session to determine the effects on the initial stimuli association; (2) immediately after the first training session to evaluate the effects on memory consolidation; and (3) immediately before the 24-h retention session to analyze the effects on the retrieval process. The NBM stimulation significantly improved the acquisition of the task, without affecting subsequent retention sessions. Stimulation of the NBM immediately after the first training session slightly difficulted the 24-h retention session. Stimulation of the NBM immediately before the 24-h retention session did not affect either 24-h or 48-h retention sessions. Therefore, NBM may play a more important role in acquisition and memory consolidation of aversively motivated conditioning than in retrieval of aversive memories. These results are discussed in the context of cortical and amygdala activation.

L37. Individually-housed mice show a better acquisition of two-way active avoidance than group-housed mice

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A relation between emotional processes and learning has been suggested in some studies. Differences in environmental conditions and anxiety-related behavior could influence the performance of learning tasks. The aim of the present study was to evaluate the modulation of active avoidance learning by housing conditions and anxiety level in mice, also testing the effects of nicotine in this task. NMRI male mice were either group or individually-housed for 30 days and then classified according to their anxiety level, taking into account behavior displayed in the elevated plus-maze test (percentage of time spent in open arms). The behavior of selected mice was further examined in a two-way active avoidance conditioning (30 trials/day) in a shuttle-box for a period of 5 days, after being treated with nicotine (0.35 mg/kg) or vehicle. ANOVA indicated that the factor Housing reached statistical significance in number of avoidance responses, escape latency, and number of non-responses ($P<0.001$). *Post hoc* tests revealed that individually-housed mice displayed more avoidances and less escape latency and number of non-responses than group-housed mice ($P<0.05$). The factors "treatment" and "anxiety" did not reach statistical significance. We conclude that housing conditions can modulate two-way active avoidance acquisition in mice.

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L38. Prefrontal cortex neural activity correlates with parametric stimuli representation in working memory

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The discharge of memory cells (Fuster and Alexander 1971) of the monkeys' lateral prefrontal cortex has been related to parametric (Romo et al. 1999) and categorical (Freedman et al. 2001) representation of stimuli. We used a task that requires monkeys to memorize the orientation of a line, reference, followed after a delay by a comparison of the remembered orientation with the orientation of other line. The monkey has to decide if the test stimulus is oriented to one side or to the other of the reference. We use three variants of the task: continuous discrimination; fixed discrimination; and fixed discrimination without reference (Vazquez et al. 2000). We recorded the extracellular unitary activity in the prefrontal cortex, in front of the sulcus arcuatus in *Macaca mulatta* monkeys. Eye movements were recorded with the magnetic eye search coil technique. 106 neurons change their activity during the delay between the first and second stimulus. In the continuous discrimination task, the firing rate varies as a function of the orientation of the reference stimulus – method of logistic binary regression (Wald= 29.701; $P<0.001$). In the fixed discrimination task without the reference, the discharge rate is significantly greater than in the other two tasks. The most plausible hypothesis is that these neurons encode in short term memory the parameters of the reference stimuli (i.e., the orientations). When the reference is not present, and the monkey has to use an internal reference, the working memory load is greater.

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L39. Epinephrine improves long-term retention, but not acquisition, of two-way active avoidance task in rats

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In previous experiments we have found that epinephrine (EPI) can enhance long-term retention (20 and 45 days), but not 24 h retention, of a massed (one session, 20 trials) two-way active avoidance task in rats. We have also found that EPI can improve the process of acquisition of the same task in a distributed paradigm (5 sessions, 10 trials each).The aim of the present experiment was to determine whether posttraining EPI can improve both acquisition and long-term retention in rats trained in several massed (30 trials) sessions. Rats were daily trained until achieving 80% of avoidance in one session. Immediately after each training session they received an i.p. injection of 0.01 mg/kg EPI (EPI 0.01), 0.05 mg/kg EPI (0.05 EPI) or distilled water (VEH). Retention was tested 20 days after each rat achieved the learning criterion. No differences between groups were found during the acquisition process. From the last training session to the retention session VEH group decrease the level of avoidance (P=0.029) while EPI groups maintained their performance. Moreover, considering the first 10 trials of the retention session EPI groups showed a higher number of avoidances than VEH group (EPI 0.01, P=0.011; EPI 0.05, P=0.064). We conclude that posttraining EPI is related to long-term memory processes rather than to acquisition processes and that this treatment could alleviate forgetting.

L40. Regional differentiation of reactivity in the prefrontal cortex of rats engaged in a classical conditioning task

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A major question regarding basic learning processes concerns the role of prefrontal cortex (PFC) regions. To map activity in PFC regions during associative learning, c-fos immunocytochemistry (ICC) was used during various phases of a classical conditioning task. Rats were exposed to a visual stimulus (light) paired with delivery of a food pellet (n = 18; CC group). Controls included a context group, which was only exposed to the Skinner box (n = 16; CX), and a task-naive group (n = 8; TN). Rats were sacrificed for ICC after either one session (acquisition; ac) or four sessions (post-acquisition; pa) of the task. Lateral prefrontal areas showed significantly higher levels of c-fos immunopositive nuclei in group CC-ac (1717 ± 285) compared to group CC-pa (1104 ± 177). CC groups were also significantly different from their respective CX control groups (CX-ac: 1077 ± 213; CX-pa: 691 ± 245) and TN (481 ± 134). The orbital PFC showed a trend to increased fos expression in CC-ac (842 ± 203) compared to CX-ac (668 ± 170), and significant differences between these conditions in the pa groups (CC-pa: 672 ± 211; CX-pa: 419 ± 125). In the orbital PFC, no effect was seen of number of sessions in the conditioned animals. Medial prefrontal areas showed no significant differences between groups. Thus, the various PFC areas show differential task-related and time-dependent patterns in reactivity.

L41. Lateralization of electrophysiological correlates of memory

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The aim of the present study was to test whether encoding and retrieval of verbal and nonverbal information depend on which hemisphere initiates processing of that information. Event related potentials (ERPs) to unilaterally displayed stimuli (words and Kanji) were recorded from symmetrical sites over the left (LH) and the right hemisphere (RH), i.e., the hemisphere contralateral and ipsilateral to the visual field (left - LVF, right - RVF) of stimulus presentation. ERPs recordings for new and repeated stimuli were compared. Subject's task was irrelevant to electrophysiological effects of interest. Memory-related modulation of ERPs was found for frontal recording sites. That effect, however, was present in ERPs data only in case of direct stimulation of the competent hemisphere (LH for words, RH for Kanji, as confirmed by number of errors committed for the LVF and RVF presentations). In case of words, direct stimulation of the LH led to ERPs repetition effect both in the LH and in the RH whereas direct stimulation of the RH resulted in the lack of that effect in the LH and the RH. In case of Kanji, just opposite pattern of results was observed: direct stimulation of the RH led to ERPs repetition effect both in the LH and in the RH while direct stimulation of the LH resulted in the lack of that effect in either hemisphere. Our results suggest that electrophysiological correlates of memory were influenced by the hemisphere performing initial stages of encoding of information.

L42. Independent coding of connected environments by place cells

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Place cells are hippocampal neurons that have a strong location-specific firing activity in the rat's current environment. As a collective, place cells also provide a signature of the rat's environment as their ensemble activity is markedly different when they are recorded in distinct apparatuses. This phenomenon, referred to as "remapping", suggests that the identity of an environment is encoded by a unique selection of active place cells and furthermore by a unique spatial arrangement of the firing fields of the selected place cells. In this study, we sought to determine the independence of hippocampal maps. Place cells were first recorded while rats explored three separate boxes: a white plastic cylinder, a light red square-shaped plastic box and a brown wooden hexagon-shaped box. Most cells had distinctive firing patterns in each box. Then, a runway was added to connect two initially unrelated boxes. This manipulation altered the firing of some cells but the differential firing patterns in each box were still clearly distinguishable. The final manipulation consisted in changing one of the two boxes and allowing the rat to freely commute between the changed and unchanged boxes. While the firing fields were remapped in the changed box, they were most usually unaltered in the unchanged box. Thus, the hippocampus holds a set of independent maps for each box, and each specific map is activated only according to the rat's current box even when the rat is allowed to commute between the boxes.

L43. Hippocampal high-frequency (200 Hz) network synchronization is modulated by reinforcement learning

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High-frequency oscillations (200 Hz, „ripples") in the CA1 area induced by collective discharge of CA3 neurons occur on the hippocampal EEG during consummatory behaviours. Although these oscillations are believed to represent a natural LTP stimulus, ripples have not been studied in a learning paradigm. We investigated whether features of ripples get altered by changes in the timing of food reward delivery in an operant conditioning task. Following shaping in a Skinner-box rats ($n = 6$) were implanted with adjustable microelectrode arrays into the CA1 area. Then rats received sessions on a fixed 120 s reinforcement interval followed by a reduction of the interval to 60 s (FI60). Learning dynamics were estimated by a non-linear analysis of inter-response times. During FI sessions hippocampal EEG, EMG and task-related data were recorded. The probability of ripple occurrence was increasing within sessions and reduced following a schedule switch. Intraripple frequency was elevated by up to 18 Hz as reward timing was changed ($P<0.01$). This increase and the tendency to elevated ripple amplitude were consistently observed during the initial 1 to 3 sessions on FI60, independent on behavioural activity. The results suggest a higher synchronization of pyramidal cell discharge during learning of reward timing, which could act to increase the efficacy of synaptic modification in the downstream regions.

L44. Age related changes for single event or spatial memory in Long Evans rats

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Spatial memory, long term retention and distractibility were assessed through the life span in Long Evans rats (7, 15 and 24 months) trained in the Morris water maze with a procedure including cued place training, short (0 to 3 days) and long term (15 days) retention, distractibility (by moving the cue) and single event memory. This was assessed in two special probe trials. During the first trial, following a prolonged acquisition phase, a hanging cue was placed in an untrained position and the rats swam during 60 seconds with no platform at the training position. The second probe trial took place 15 days later and tested retention of the training position and of the now absent cue (phantom cue). The young adults expressed long term retention of both the training and phantom cue positions. The middle age rats were specifically impaired in single event memory (phantom cue) but showed normal 15-day retention of the training position. Escape latencies were slightly prolonged in 24-month rats, but short-term retention was not affected by age. However, the oldest group showed no retention whatsoever following 15 days (phantom cue or training position). These results reveal an early decrease of single event "episodic" memory prior to the decline of conventionally tested spatial memory.

L45. Reversible inactivation of hippocampus and dorsolateral striatum in C57BL/6 and DBA/2 mice reveals no interaction among memory systems in these genotypes

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These experiments examine the effect of temporary inactivation of the hippocampus or the dorsolateral striatum (DLS) on place and response learning in inbred mice with genetic differences in hippocampal functionality. According to the standard procedure, C57BL/6 and DBA mice with cannulae inserted bilaterally in the dorsal hippocampus or the dorsolateral striatum were released from the south arm of a cross maze and trained to find food in the east arm. Probe trials on which mice were released from the north arm were given following either short or prolonged training. Eight minutes prior to the probe trials, mice received intra-hippocampal or intra-striatal injections of lidocaine or saline. Results of control mice first confirm previous findings (Passino et al. 2002) indicating that, on each probe trial, C57BL/6 mice still run to the east arm thus showing place learning whereas DBA/2 mice did not engage any predominant system. Inactivating the hippocampus or the dorsolateral striatum in C56BL/6 mice disrupted place learning without promoting response learning. Inactivating the same brain sites in DBA/2 did not affect their behavior. These results show that, in these genotypes, inactivating the neural substrate of one memory system does not affect learning in another system. In particular, it is apparent that the sustained hippocampal function of C57BL/6 mice is detrimental to convert cognitive responding into procedures. Conversely, the absence of any strategy in DBA/2 mice subjected or not to hippocampus or DLS inactivation suggests that in the strain no area exerts a specific control on behavior.

L46. Heterogeneous hippocampal activation during a radial maze task: a detailed 2-deoxyglucose study

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The purpose of this study was to characterize the localized metabolic changes associated with neuronal activation occurring throughout the hippocampus in mice undergoing a radial maze task. Male C57BL/6J mice were trained for either 1, 3, 6 or 9 consecutive days in an eight-arm radial maze. One group was trained for 9 consecutive days and tested 5 days after the last training session while one group was not tested and served as control for metabolic assessment. Before the last session, all mice received an i.p. injection of (14C)-2-deoxyglucose. After sacrifice, mice brain were processed for autoradiography and glucose utilization determined in different subregions over the antero-posterior hippocampal axis.

An increase in performance over 9 consecutives daily sessions was observed and it remained at the same level upon recall 5 days later. In parallel, the metabolic analysis revealed an heterogeneous and evolving pattern of enhanced metabolic activity in the hippocampus along the training period and upon recall. In the early stages of training, activity was enhanced in the CA1 area from the intermediate portion to the posterior tip as well as in the CA3 area within the intermediate portion of the hippocampus. In the late stages, CA1 and CA3 activation extended over the entire hippocampal length while DG activation occurred from the anterior to the intermediate zone. Upon recall, only DG activation was observed in the same anterior to intermediate part of the hippocampus.

L47. Interacting control mechanisms during cued task switching as revealed by fMRI

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This contribution aims at reconciling apparently contradicting patterns of behavioural and brain data observed in a series of cued task switching experiments. On the behavioural level, switching between tasks implicates costs which have been proposed to comprise additive components indicating the engagement of two independent control processes. One which can be engaged in advance prior to task implementation – reconfiguration (Reco) of stimulus set (S-Set) – and another which can be engaged only after response execution – Reco of response set (R-Set). The pattern of activation suggests that control does not mean to implement switch-specific Reco of task sets but rather to engage common processes (same for switch and repeat) of accessing task set representations. This serves counteracting proactive interference that results from recent implementations of the alternative task. Furthermore, we differentiate between one abstract task set (A-Set) representation which can be activated in advance and one R-Set representation which cannot. If the A-Set is activated in advance, this implicates reduced proactive interference at the time of task implementation. Thereby, control demands are reduced in terms of access to both A-Set and R-Set representations. A model is presented which integrates switching-related effects on the level of performance and brain activation.

L48. Memory deficits in cerebellar lesions

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The cerebellum has for a long time been considered has having only a motor function, but more recently, there have been a few studies demonstrating the importance of the cerebellum in cognitive tasks not involving any motor actions, which led Schmahmann to propose a "cerebellar cognitive affective syndrome". Thirteen patients (aged 18 to 65 years) who had a cerebellar hemisphere tumour either left (6 cases) or right (7 cases) not associated with any other cerebral lesion, were investigated before surgical removal of the tumour. Each patient had a general cognitive and neurological assessment. Memory was investigated in verbal domain with either a 15 words list or recurrent words, and in the non verbal domain with either the Rey's complex figures or faces/landscape recurrent images. Seven of 13 patients presented memory deficits, isolated or in association with executive dysfunction: in the patients with right cerebellar lesion, 1 had both verbal and non verbal memory deficits while 4 had verbal but not non verbal deficit. In the patients with left cerebellar lesion, 2 had both verbal and non verbal memory deficits. These results confirms that memory deficit can occur after cerebellar lesion alone. There seems to be a lateralisation in the right cerebellar lesions which tend to be associated with verbal memory deficit, suggesting left hemispheric dysfunction. However, left cerebellar lesions do not show a similar specialisation.

L49. Oestrus-cycle dependent effects on mouse olfactory memory and NMDA-evoked plasticity

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Ovarian hormones influence adult cognitive functions. The current study tested whether there are oestrus cycle-dependent effects on olfactory memory tasks in mice and their possible modulatory roles on NMDA receptor and nitric oxide (NO) signalling pathways in the olfactory bulb (OB) and piriform cortex (PC). Two NMDA-dependent behavioural tests with social and non-social odours were used: social transmission of food preference and a habituation-dishabituation task with a long-term retention component. In both paradigms proestrous female mice (C57Bl6/129SV) formed a robust long-term olfactory memory (24 h) whereas oestrous and dioestrous mice did not. Short-term habituation-dishabituation responses were not influenced by cycle stage. Furthermore, a NO donor rescues social recognition impairment in oestrous and dioestrous mice. *In vivo* microdialysis in anaesthetised mice showed a potentiation of neurotransmitter release as a result of repeated NMDA receptor activation in the OB. Significant enhancement of evoked glutamate, serotonin and noradrenaline release was detected in the OB of proestrous mice in response to a 3rd NMDA (250 mM) challenge 4 h after initial challenge. This was absent in dioestrous and oestrous mice. A similar enhancement in levels of glutamate, GABA and dopamine were seen downstream in the ipsilateral PC of proestrous mice and of GABA in oestrous animals. No effects were found in dioestrous animals. Results suggest a physiological role for sex hormones in facilitating NMDA-dependent plasticity changes associated with olfactory memory in the female mouse.

L50. Different involvement of AMPA receptors into the nucleus accumbens in short-term processing of information in the place or the cue versions of the water maze task: possible dissociation of learning and performance impairment

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Glutamatergic transmission within the nucleus accumbens (Nac) is considered to subserve the transfer of different types of information, and particularly of contextual information, from cortical and limbic region. However, it is still not clear which is the exact role of different classes of glutamate receptors of the Nac in such processes. In this study we investigated the effects of AMPA receptors blockade in the Nac in short-term information processing using two different versions of the water maze task, both composed by a massed training phase of 4 consecutive sessions and a probe test. In the place version mice could learn the position of the platform using visual distal cues, and in the cue version the location of the platform was indicated by a single proximal cue. Focal injections of DNQX were performed before or after the training phase, and mice were tested for retention in an immediately following probe test, in order to dissociate a possible impairment on learning or performance. The results show a more disrupting effect of DNQX injections in the cue version, compared to the spatial water maze task. This could indicate a different involvement of AMPA receptors in the Nac in performing a behavioural response which is guided by distinct learning processes.

L51. Lesions of the entorhinal cortex enhance fear conditioning in the rat: implication for latent inhibition disruption

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Lesions of the entorhinal cortex (EC) disrupt latent inhibition (LI), i.e., suppress the retarded conditioning produced by the nonreinforced preexposure (PE) to the to-be-conditioned stimulus. As the expression of LI may be dependent on a competition between the stimulus-no event association occurring during PE and the stimulus-reinforcer association occurring during conditioning, the present study was undertaken to determine whether the disruptive effect of EC lesions on LI may be the result of an increase in the stimulus-reinforcer association. To this end, a first experiment investigated the potential disruptive effect on LI of footshock intensity (0.4, 0.5 or 0.6 mA) in a conditioned suppression paradigm with a tone as the conditioned stimulus. Our results showed that PE to the tone induced LI in both 0.4 and 0.5 mA conditions but that LI was disrupted in the 0.6 mA condition. In a second experiment, rats sustaining either sham-lesions or bilateral excitotoxic EC-lesions were tested in the same paradigm using varying footshock intensities (0, 0.1, 0.2, 0.3 or 0.4 mA). Our results show that in rats with EC lesions, a conditioned response to the tone (CR) was observed with a footshock intensity for which no significant conditioning occurred in sham-lesioned rats (0.3 mA). At 0.4 mA, both groups showed a similarly strong CR. Taken together, the results of the present study suggest that the disruptive effect of EC lesions on LI could result from potentiation of conditioning.

L52. Olfactory fear conditioning induces synaptic changes in the amygdala and piriform cortex in the rat

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Current theories of the neurobiology of memory suggest that memorization of an information involves a distributed neural network including limbic as well as sensory areas and occurs *via* durable changes of synaptic efficacy at specific nodes of this network. We investigated whether synaptic changes could be detected at different levels of the olfactory pathways, following an olfactory fear conditioning learning. On 11 rats, two stimulating electrodes were implanted in the olfactory bulb (OB) and four recording electrodes respectively in the anterior piriform cortex (aPC), posterior piriform cortex (pPC), anterior cortical nucleus of the amygdala (ACO) and basolateral nucleus of the amygdala (BLA). Seven rats were then trained with six pairings of an odor (CS) with a mild footshock (US). Four rats served as control animals, only receiving the odor. On the day after training, the animals were tested for their retention of the CS. In parallel, evoked potentials (EP) induced in the four recording sites in response to electrical stimulation of the OB were collected before training (baseline) and during the retention test. The data show that learning was accompanied by a lasting increase (present before and during presentation of the CS) in EP amplitude in ACO but not in BLA. In addition, a transient increase was observed in pPC during presentation of the CS. These data suggest that in this task ACO and pPC could be involved in recognition of the learned odor.

L53. Reactivation and reconsolidation of memory for an odour-reward association: essential role of NMDA receptors

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NMDA receptors are involved in memory consolidation of a simple odor-reward association. Administration of APV (NMDA competitive antagonist) into the lateral ventricles (i.c.v.) (but not the hippocampus) immediately after training induces a profound and enduring amnesia at a retention test 48 h after training (Tronel and Sara, in press). In the present experiment, the role of the NMDA receptors in memory reconsolidation of this apparently hippocampal-independent task was studied. Rats were trained to find palatable food in a hole in a sponge impregnated with the target odor in the presence of two other sponges with nonrewarded odors. The day after learning, memory was reactivated by a 90 s exposure to the reinforced odor in the holding cage used during learning. Immediately after reactivation, rats were injected i.c.v. with the vehicle or with APV. A nonreactivated group received APV in the vivarium. Memory was tested 48 h later. Results showed that administration of APV immediately after reactivation induces amnesia, extending our previous results showing APV-induced amnesia after reactivation of an appetively motivated hippocampal-dependent memory (Przybyslawski et al. 1997). We conclude that NMDA receptors play an essential role in the early stages of memory reconsolidation processes suggesting that at least some of the cellular events that occur during the initial consolidation also take place during reconsolidation.

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L54. Noradrenergic action in prefrontal cortex in the late stage of memory consolidation

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Memory formation involves at least two phases, an early phase independent of protein synthesis and a late phase requiring new protein synthesis. The beta adrenergic receptor antagonist, timolol, can induce amnesia when injected (i.c.v.) 2 h after odour discrimination training, with no effect when administered immediately after training. This confirms a temporal dynamic of memory formation with beta adrenergic receptors specifically involved in a late stage. Studies of c-fos immunoreactivity after odour learning showed a spectacular increase in c-fos in the prelimbic area (PLC) of the prefrontal cortex in trained rats compared to yoked controls, suggesting that PLC is activated by the odour-reward training. To evaluate the PLC as a site of action of the i.c.v. timolol injection, the beta antagonist was injected *in situ* 5 min or 2 h after training. Retention test was 48 h later. Timolol at 2 h induced amnesia with no effect at 5 min after training, as seen with i.c.v. injections. Next we examined the role of beta receptors in the observed changes in c-fos expression. Rats were trained in the odour task and injected i.c.v. with timolol 2 h posttrial. One hour after injection, rats were anesthetized, perfused and brains processed for c-fos. There was a significant (20%) reduction in c-fos in PFC in trained rats receiving timolol compared to trained saline rats. The complementary pharmacological and immunocytochemical results confirm the role of both the noradrenergic system and PFC in the late phase of memory consolidation.

L55. Oscillatory activity, behaviour and memory, new approaches for LFP signal analysis

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Large neuron assemblies exhibit complex dynamic behaviours. Despite extensive investigations, the features of that behaviour that have a cognitive significance, the "neuronal code", are still poorly understood. That question can be approached experimentally by recording simultaneously the electrical activity of populations of neurons: electroencephalographic recordings and, more recently and with a much better spatial resolution, local field potential recordings. The present work focuses on the neural dynamics supporting perception and memory. Recent data have shown that learning generates clear-cut modifications of the odour-induced activity. The analysis of electrophysiological recordings is based on continuous and orthogonal wavelet transforms, aiming first at locating the occurrence of typical frequencies in the signal (in the Alpha, Beta and Gamma frequency ranges), and at studying typical sequences of frequencies, which are supposed to arise from interactions between neuronal populations implied in the cognitive tasks. We will focus on learning-induced modifications in such sequences.

L56. Involvement of perirhinal cortex in several stages of object recognition memory revealed by reversible inactivation in rats

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The perirhinal cortex (Prh) has been implicated in visual recognition memory in rats, monkeys, and humans. However, past studies have relied on findings from subjects with permanent Prh damage. The present work studied the effects of reversible Prh inactivation at different putative stages of object recognition memory – stimulus encoding, consolidation, and retrieval. In three experiments, rats were implanted bilaterally with cannulae in Prh. In Exp. 1, rats performing a spontaneous object recognition task received infusions of lidocaine (lido) or vehicle on separate days at one of three time points: 1) immediately before the sample phase (PS); 2) following the sample phase; or 3) before the test phase (PT), which occurred after a 20-min retention delay. Rats in all three groups were impaired on lido trials relative to trials in which they received vehicle infusions. In Exp. 2, the PS and PT effects of lido-induced Prh inactivation were replicated with shorter (5 min) and longer (3 h) retention delays. In Exp. 3, infusions were made during the 1-h retention delay only, at one of three time points: immediately, 20 min or 40 min post-sample. A time-dependent effect was observed, as lido infusions impaired only the immediate and 20 min groups. This result suggests that an initially labile object memory trace is consolidated over a period of 20-40 min in Prh. Together, these findings indicate a role for Prh activation in visual stimulus encoding, consolidation, and retrieval.

L57. The lateral part of the caudomedial neostriatum (NCM) receives projections from the medial nucleus of the dorsolateral thalamus (DLM) in the zebra finch brain

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Zebra finch males need to learn their song from a tutor, early in life. Exposure of adult zebra finch males to song leads to increased expression of immediate early genes (IEG) or their proteins (thought to be a reflection of neuronal activation) outside the conventional "song system", notably in the NCM and the caudomedial hyperstriatum ventrale (CMHV). IEG expression in the NCM in response to tutor song is related to the strength of song learning, suggesting that the NCM may be (part of) the neural substrate for tutor song memory. We now performed a retrograde tracing study with rhodamine B isothiocyanate (RITC) injected into the lateral part of the NCM (Stereotaxic coordinates: 0.3 mm anterior to bregma, 1.0 mm lateral from midline, 1.0 mm below dura). Injection resulted in labelling of cells in the medial nucleus of the dorsolateral thalamus (DLM). This nucleus is part of the anterior forebrain pathway (AFP), with Area X and lMAN. These nuclei are not necessary for song production but neurons in these nuclei show preferential electrophysiological responses to the bird's own song, and lMAN and Area X show increased IEG expression during singing. This is the first demonstration of a direct connection between a forebrain region (NCM) that may be involved in song memory, and a nucleus in the AFP.

L58. Behavioral characterization of terminal deoxynucleotidyl transferase (TdT) and recombination activating gene 1 (Rag-1) knockout mice

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We postulated that permanent storage of information in the brain involves a somatic DNA rearrangement mechanism similar to VDJ recombination in immune cells (Peña de Ortiz and Arshavsky 2000). To begin examining the validity of our hypothesis experimentally, we focused on two immune enzymes: terminal deoxynucleotidyl transferase (TdT) and recombination activating gene 1 (Rag 1). Recently, we reported by *in situ* hybridization that tdt mRNA levels increase in the hippocampus, cerebellum and cortex regions in rearing C57Bl/6 mice (Peña de Ortiz et al. 2003), and that tdt(-/-) mice do not improve their spatial learning after rearing in enriched environments. We are now examining the effects of enriched environment rearing on object/place recognition memory and fear conditioning in tdt and rag1 knockout mice. The preliminary data demonstrate that tdt(-/-) mice reared in an enriched environment can discriminate between the novel and familiar objects, but not between familiar or novel places. Similarly, rag1 reared in an enriched environment did not improve their learning processes, contrary to wild types.

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L59. A multiple experience paradigm induces distinct psychoemotional and behavioral phenotypes in mice

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The etiology of psychoemotional disturbances is multifactorial. We have developed a behavioral model termed the multiple experience paradigm (MEP) and we are studying its impact on cognitive, emotional, and behavioral performance in mice. We also aim to establish molecular and genetic correlates associated with MEP behavior. Male wild type weaned C57Bl/6J mice were used and divided in 3 groups: naive, MEP positive, and MEP negative. The MEP consisted of subjecting the animals to various life-experiences for 3-weeks followed by a battery of behavioral tests including locomotor activity, object recognition task, spatial discrimination learning, and fear conditioning. Our results support our hypothesis that negative life experiences early in life produce a behavioral phenotype that might associate to psychotic-like behavior. Specifically, while no differences were observed in object recognition and spatial discrimination learning and memory between the groups, the MEP negative group showed a significant impairment in contextual, but not cued fear conditioning ($P<0.05$, $n = 12$). The MEP negative group also displayed significantly more time performing stereotypic behaviors in an open field than the naive group ($P< 0.05$, $n = 12$). Moreover, our molecular analysis showed significant changes in phosphorylated CREB and in Nurr1 the hippocampus of the MEP negative group.

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L60. Mechanisms of lead-mediated long-term memory impairment in the adult rat brain

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The behavioral and cognitive dysfunctions of lead (Pb+2) are well documented in humans and other vertebrates. We characterized the effects of intrahippocampal microinfusions of low levels of Pb+2 in adult rats trained in a hippocampal-dependent holeboard task. Results obtained from learning measures showed that Pb+2 impair long-term memory (LTM) in adult animals in a retention test (performed 7 days after training). Moreover, our results demonstrated a sigmoidal dose-dependent response curve of variable slope that reaches a significant maximum effect near 1nmol dose and a plateau immediately after. We next studied the effects of intrahippocampal Pb+2 on the known (Vázquez et al. 2000) learning-induced hippocampal changes in Ca+2 and phospholipid dependent protein kinase C (PKC) activity. Our results demonstrated a significant reduction in PKC translocation index for the Pb+2 exposed rats trained on day 3 as compared with control rats. We postulate that Pb+2 interferes with cellular and molecular processes related to memory consolidation in the hippocampus and are currently working on microarrays to establish differences in gene expression between control and lead treated rats.

This work was supported by NIH (S.P.O. grants SOGGMO 8102-26S1 and a predoctoral fellowship to A.V.).

L61. Calcium/calmodulin-dependent protein kinase II (CaMKII) and memory

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A restricted region (intermediate and medial part of hyperstriatum ventrale – IMHV) of the chick brain is a memory system for the learning process of imprinting. We have studied the effect of imprinting training on the total amount of CaMKII (tCaMKII) and its level of autophosphorylation on Thr286 (apCaMKII) in membrane and cytoplasmic fractions from IMHV and from a control forebrain region, the posterior neostriatum (PN). At ~1 h after training, the amount of apCaMKII in the IMHV was significantly greater in chicks showing strong imprinting (Good Learners) than in chicks showing less learning (Intermediate Learners P=0.004, Poor Learners P=0.038) or in untrained chicks (P=0.003). The amount of apCaMKII and the percentage of autophosphorylated CaMKII in membranes, in the IMHV of Good and Intermediate Learners, were positively correlated ($P<0.02$) with preference score, a measure of the strength of learning. There was also significantly more tCaMKII in Good Learners than Intermediate Learners (P=0.004), Poor Learners (P=0.007) or untrained chicks (P=0.043) in the cytoplasmic fraction of the left IMHV. There was thus evidence of learning-specific changes in IMHV shortly after training. At 24 h, no learning-specific effects were detected in the left or right IMHV. No learning-specific effects were found at either time in the PN.

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L62. Prolonged exposure to the context impairs acquisition of fear conditioning to tone in rats

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We have studied the effect of a prolonged continuous exposition to the context on cued fear conditioning. Classical fear conditioning (four paired tone-foot shock) was tested in animals that spent 5 minutes, 10-12 hours during the day (overday) or 10-12 hours during the night (overnight) in the conditioning box previous to conditioning. An extra group of animals received only shocks without previous tone (generalization). The groups of overnight, overday and generalization showed significant lower levels of freezing during the learning test than the group of 5 minutes. No differences in leaning among the groups of overday, overnight and generalization were observed. These results suggest that a continuous over exposition to the context produces a deficit in learning that could be attributed to incapacity of integrating CS-US association with the context once the representation of the context is done. We have named this phenomenon "delayed shock deficit" (DSD). An automatic image processing system was used for unbiased counting of c-fos labelled nuclei. Histological analyses have revealed significant increased c-fos expression in CA1 in the group of 5 minutes in comparison with the rest of the groups. Hilus is also labelled in 5 minutes and overday but not in the groups of overnight and generalization. We can conclude from these results that there is a correlation between DSD and regional hippocampal activation.

L63. Olfactory information for arm selection in rats and mice: effects of age, strain, sex and cognitive impairment

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Arm selection in radial mazes can be considered as a multilevel decision process, based on an integration of different reference systems and sensory modalities. Hooded rats tend to ignore olfactory cues when patrolling an all baited illuminated radial maze (Lavenex and Schenk 1996), suggesting that vision reduces the weight of olfactory cues in arm selection. We made the hypothesis that specific olfactory cues might facilitate the discrimination of the selectively baited arms ("reference arms") based on a simple association process and that conflict situation would reveal which reference system was predominant. Rats of different ages (Long Evans and Wistar) and mice (C57Bl/6; AD-APP transgenic mice) were trained in an 8-arm radial maze with four arms baited. Visual access to the room environment was allowed through transparent Plexiglas walls and each arm was marked by a specific olfactory cue. The relative importance of olfactory or visuospatial cues was assessed when the two reference frameworks were dissociated from one another (maze rotation or arms permutation) after a 12-day acquisition phase. Adult Long Evans rats showed a rapid decrease of re-entries with slowly developing preference for the baited arms, whereas C57Bl/6 mice developed a systematic bias toward the baited arms with a high rate of re-entries throughout the acquisition phase. In cases of conflict following maze rotation, rats tended to enter spatially correct arms whereas the mice selected the olfactory correct arms. However, following tunnel permutation, only the cognitively impaired transgenic mice showed a bias for olfactory cues. As if this bias to olfactory informations in these perturbation phases might be associated to some cognitive impairment in mice (AD-APP) and rats (senescent Long Evans).

L64. Enhancement of taste aversion memory induced by glutamate infusion in the basolateral amygdala depends on NMDA receptors activation in the insular cortex

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In conditioned taste aversion (CTA), a subject learns to associate novel taste with visceral malaise. This CTA acquisition depends upon interaction between brainstem, limbic and neocortical structures, but it remains unclear which structures are involved in CTA consolidation. Here we investigate the possible interaction between the basolateral amygdala (BLA) and the insular cortex (IC) during CTA consolidation. Injection of a low dose of lithium chloride (0.075 M, i.p.) 30 min after novel taste consumption (saccharin 0.1%) induces a weak CTA. Unilateral BLA injection of glutamate (2 mg/0.5 ml) just before low lithium induces a clear CTA, as previously demonstrated (Miranda et al. (2002) PNAS 99: 11417-11422). Ipsilateral injection of an NMDA receptor antagonist (AP5, 5 mg/0.5 ml) in IC at the same time or 1 hour after the BLA injection reverses the memory-enhancing effect of glutamate. These results suggest that NMDA receptor activation in IC is necessary to maintain the CTA memory once the amygdalar glutamatergic system has conveyed visceral information. This further supports an important amygdalo-cortical interaction during CTA memory formation and a crucial role for glutamatergic system into the IC for CTA consolidation.

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L65. ERK activation is correlated with maintenance of learning-induced enhancement of synaptic transmission

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We have shown previously that olfactory learning is accompanied by enhanced neuronal excitability of piriform cortex pyramidal neurons, manifested by reduced post-burst after-hyperpolarization (AHP), and enhanced synaptic transmission between these cells, manifested by reduced paired-pulse facilitation (PPF). Extra cellular regulated kinase (ERKI/II) are thought to play major role in learning and memory as well as synaptic plasticity in cortical areas. The purpose of the present study was to determine whether ERKI/II has a role is maintaining olfactory-learning induced cellular modifications. Intracellular recordings from pyramidal neurons were performed in piriform cortex brain slices. The specific MEK inhibitor PD98059 (40 μM) caused a significant increase in PPF amplitude in neurons from trained rats only. Consequently, the difference in PPF amplitude between trained and pseudo trained rats was diminished.

L66. Place learning deficits in rats with low glutathione during development are enhanced in ODS rats unable to synthesize ascorbic acid

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An *in vivo* animal model with chronic glutathione (GSH) deficit during brain development was set-up including non-mutant OFA rats and the mutant strain ODS, which like humans is unable to synthetize ascorbic acid. Rats were treated with L-buthionine-(S,R)--sulfoximine (BSO), an inhibitor of GSH synthesis. Phosphate buffered saline (PBS) was used for "control" rats. The effects of early treatment on visual place learning in the Morris water maze (MWM) were assessed at different ages. In a first step we compared the performance of the little known ODS strain to that of OFA juvenile (PN26) and adult rats (PN90). Both strains showed similar acquisition of place learning. Juvenile rats showed slightly prolonged escape latencies compared with the adults. ODS rats had retention scores similar to OFA during probe trial. The same protocol was used to examine the effect of an acute deficit of GSH following BSO treatment in juvenile ODS and OFA rats. At this early age, we observed a significant interaction between strain and treatment, as the BSO treated ODS could not perform the place-learning task, but the OFA treated rats suffered no deficit. However, when aged 12 months, the OFA rats showed a significant deficit in the MWM suggesting that effect of the treatment may appear at a later age only.

P1. Di-isopropylfluorophosphate (DFP) in early postnatal period impairs performance of passive avoidance in female, but not male adult mice

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ACh plays a major role in encoding, attention and regulation of cortical development. Acetylcholinesterase inhibitors (AChE-I's) are widely used as pesticides, exposing people to the risk of neurological damage. Sex differences were found for behavioral effects of AChE-I's. The present study examined the effect of chronic developmental exposure to AChEI on passive avoidance (PA). C57BL/65 mice of both sexes were injected with 1 mg/kg s.c. DFP or saline on postnatal days 4-10 or, in a second experiment, on PND 14-20. Step-down PA was conditioned at 4 months using 0.5 mA footshock for 5 s and tested after 24 h and 72 h. Females showed poorer PA than males. After treatment at PND 4-10, DFP females but not males, had shorter step down latencies at 24 h later than controls. Female mice injected with DFP on PND 14-20 showed less PA than controls at 24 h, but had significantly longer step down latencies at 72 h, suggesting latent learning of PA. No difference between male DFP and control mice was seen after 24 h, but 72 h after acquisition, step down latencies in control, but not DFP males declined significantly. The results suggest that in females DFP during development may interfere with performance of conditioning in paradigms that require behavioral inhibition, but that conditioning per se is not necessarily impaired.

P2. Unihemispheric sleep and imprinting in male chicks

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Several species of birds can sleep with only one cerebral hemisphere at time and the eye contralateral to the awake hemisphere open. We reported previously (Mascetti et al. 1999) that female chicks show age-dependent shifts in the pattern of monocular sleep which are influenced by rearing conditions. During the first week post-hatching female chicks reared soon after hatching with an imprinting object (a red plastic ball) showed relatively more right eye closure compared to chicks reared without the imprinting object. During the second week, both group showed a preference for left eye closure. When the colour of the imprinting object was suddenly changed on day 8, a striking shift towards predominant right eye closure was observed. The same occurred when the imprinting object was suddenly removed from the home-cage on day 8. Here we extended our investigation to male chicks. Contrary to the results obtained with females, there was no effect of rearing conditions during the first week; in the second week chicks reared with the imprinting object slept with the right eye closed whilst chicks reared without the imprinting object tended to sleep with the left eye closed. There were no effects of the removal of the imprinting object on day 8, whereas changing the colour of the imprinting object produced a shift toward right eye closure.

P3. Corpus callosum reduction and prematurity

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Volumetric magnetic resonance imaging (MRI) studies have showed that subjects with antecedents of prematurity (AP) have atrophy in several cerebral regions. We investigated possible regional atrophy of the corpus callosum (CC). In our study, 16 patients with antecedents of prematurity (mean age = 13.38; SD = 1.89) were compared to 16 control subjects (mean age = 15.44; SD = 2.66). Subjects were scanned on a 1.5 T Signa GE (Milwaukee, WI). We selected a medial sagittal slice in which the anterior commissure, the posterior commissure and the fornix were clearly identifiable to perform a semiautomatic analysis using the Analyze 4.0 (Biomedical Imaging Resource, Mayo Clinic) program. The callosum was partitioned in 7 parts following the method described by S. Witelson and the size of each part was corrected by the total brain size. We found between group differences for the total size of the corpus callosum and for the genu, the isthmus and the splenium. After covariating for age the same regions remained significant. In addition to the previously described atrophy of the corpus callosum in premature infants, we found that the posterior part of the CC and the rostrum are specially sensitive to the AP.

P4. Modelling of abstract acoustic regularities in the human new-born brain: an evoked potential study

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Event-related brain potentials (ERPs) were recorded to pairs of auditory stimuli in 11 human new-borns (GA: 40 weeks + 3 days; Age: 2.3 days old; Weight: 3.6 kg; Gender: 6 males). The auditory stimuli in the pairs were 40 ms pure tones (10 ms rise and fall times; 75 dB) separated by a silent gap of 50 ms. The standard pairs (P=0.875) were formed by two pure tones of ascending frequency (i.e., the second tone higher than the first one), and the deviant pairs (P=0.125) were formed by the same tones but with a descending frequency (the second tone being lower). There were seven frequency levels (1661, 1370, 1130, 932, 769, 635 and 523 Hz.) and six different physical pairs for each stimulus type. Stimuli pairs were presented with a stimulus-onset-asynchrony of 540 ms. EEG was recorded with a bandpass of 0.1-30 Hz and a sampling rate of 250 Hz from nine electrodes (F3, F4, C3, C4, CZ, T3, T4, P3, P4) with a linked reference at the two mastoids. Epochs of 540 ms were averaged including a 100 ms pre-stimulus baseline from the first stimulus of the pairs. ANOVAs including the factors stimulus type (standard vs. deviant pairs), laterality (right vs. left hemisphere) and polarity (frontal, central vs. parietal electrodes) were conducted over the mean amplitude in eight consecutive 50 ms intervals starting at the deviance onset (i.e., 90 ms). Results showed that stimulus type was significant in the 440-490 and 490-540 latency windows (i.e., starting 350 ms after the deviance onset) indicating that the new-born's brain can extract invariant relationship from acoustic variance, as the adult brain does.

P5. Expression of zif-268 in the mesocorticolimbic structures in conditions of unilateral lesion and contralateral electrical stimulation of the ventral tegmental area

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Unilateral electrolytic lesions of the ventral tegmental area (VTA) facilitate behavioral responses (feeding, exploration) induced by electrical stimulation of the contralateral VTA. In the present study we were looking for possible changes in the pattern of brain activation which may subserve this "contralateral facilitation effect". Immunohistochemical detection of protein product of the immediate-early gene zif-268 was used as a method of estimation of brain activation processes. Special attention has been paid to the efferent structures of the mesocorticolimbic system. In rats subjected to unilateral electrolytic VTA lesion and then to the 10-day electrical stimulation (for 1 h daily) of the contralateral VTA generally higher brain zif-268 expression was observed in comparison to the naive control group. Out of the mesocorticolimbic structures bilateral increase in the number of Zif-268 positive neurons was found in the nucleus accumbens both core and shell, septum both lateral and medial, basolateral and corticomedial amygdala and also in the bed nucleus of stria terminalis and the cingulate and the prefrontal cortices. Although usually zif-268 expression was higher in the stimulated hemisphere the differences between the stimulated and lesioned hemispheres were not striking. The results obtained suggest that plastic changes concomitant with "contralateral facilitation effect" involve widespread structures in both hemispheres including the target structures of the mesocorticolimbic system.

P6. Molecular mechanisms mediating the effects of "neonatal handling"

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Early experiences have long-term effects on brain function. However the precise mechanisms involved still remain elusive. In an effort to address such questions, we employed the model "neonatal handling", and determined its effects on hippocampal neurotrophin (NT-3 and BDNF) levels as well as the neurotransmitter systems through which these effects are mediated. After even one day of exposure to "neonatal handling" there was an increase in NT-3 and BDNF positive cells in the hippocampus, a brain area that is a specific target of handling. The handling-induced effects on BDNF were canceled by inhibition of NMDA, AMPA/kainate, 5-HT1A or 5HT2/1C receptors. Similarly, the effects of "handling" on NT-3 were canceled by blockade of NMDA, GABA-A, 5HT1A or 5-HT2/1C receptors. In an effort to determine the molecular mechanisms involved in neurotrophin gene regulation, we also determined the effect of "neonatal handling" on Fos and p-CREB transcription factor levels in the hippocampus. Based on our results, Fos appears to act as a negative regulator of the NT-3 gene whereas p-CREB as a positive effector of BDNF. The present work shows that the effects of "neonatal handling" are imprinted on the brain through the function of the glutamatergic, GABAergic and serotonergic systems resulting in activation of Fos and p-CREB, which effect changes in neurotrophin gene expression.

P7. fMRI pattern cerebral activation during a face-name encoding task in subjects with antecedents of prematurity

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Preterm newborns have a high-risk of cognitive impairment related to selective brain atrophy. To our knowledge there is no previous work focused on possible dysfunctions on cerebral activation. We investigated cerebral activation patterns by using functional magnetic resonance imaging (fMRI) in a declarative learning task in 10 adolescents with antecedents of prematurity (age 13.8 ± 2.4). This sample was matched to 10 controls by age (age 14.3 ± 2.5) and years of education. The activation task consisted in encoding 16 novel face-name associated pairs. Control task showed 2 repeated face-name pairs. Data acquisition was performed on a GE Signa 1.5T scanner (General Electric, Milwaukee, WI). Data analyses were carried out by SPM99 program. Contrast "activation>rest" group comparison showed that premature subjects had a significant activation in left hippocampus (P<0.005), compared to controls. In contrast, control group displayed a left predominance cortical pattern (P<0.001). The groups differed in all measures of memory, including both free recall and recognition (P<0.01). In conclusion, our results demonstrate that prematurity are associate with hippocampal hyperactivity and cortical hypoactivity.

P8. Neuroprotective effects of early neonatal handling against EAA-induced seizures in RHA/Verh-I and RLA-Verh-I rats

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Early neonatal handling has been shown to induce profound and long-lasting behavioural and neural consequences while also inducing plastic brain effects and being protective against some age-related deficits. In some of these effects glutamatergic transmission (e.g., NMDA receptors) may play a relevant role as indicated, for instance, that early neonatal handling attenuated the "glucocorticoid-glutamate-calcium" cascade (Sapolsky 1992). The present work aimed at providing behavioural evidence for neonatal handling inducing neuroprotection. We used rats of RHA/Verh-I and RLA/Verh-I strains derived from RHA/Verh and RLA/Verh lines, respectively, which have been selected and bred for their rapid (RHA) vs. extremely poor (RLA) ability to learn the two-way active (shuttle box) avoidance response. The RHA/RLA lines/strains are known to differ in many other respects, both at the behavioral and the neuroendocrine/neurochemical levels, with RLA being more emotionally reactive to stressors and pharmacological challenges than RHA. The results provide behavioural evidences of the neuroprotective effects of early neonatal handling as it was able to reduce the convulsant responses induced by a range of single doses of NMDA and the associated mortality, as much as to reach a 100% protection level (convulsant seizure and mortality induced by NMDA 60 mg/kg, i.p. in RHA/Verh rats).

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P9. Altered auditory-tactile interaction in congenitally blind humans: an event-related potential study

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It has been shown that stimuli of a task-irrelevant modality receive enhanced processing if they are presented at an attended location in space (cross-modal attention). The present study investigated the mutability of auditory-tactile interactions due to visual deprivation.

Random streams of tactile and auditory stimuli were presented at the left or right index finger of 15 congenitally blind and 15 sighted participants. They had to attend to one modality, either the auditory or tactile, and to respond to deviant stimuli of either the left or right side. In the sighted, early event-related potentials (ERPs) showed an enhanced negativity to stimuli presented at the attended position both for stimuli of the task-relevant and task-irrelevant modality (unimodal and cross-modal attention effects, respectively). By contrast, cross-modal effects were less reliable (auditory ERPs) or even absent (somatosensory ERPs) in the congenitally blind. While spatial attention effects after 200 ms were restricted to the relevant modality in the sighted, there was a cross-modal effect in the blind. However, this effect was inverted in polarity implying an active suppression of task-irrelevant stimuli at an attended location in space. The present data suggest that multisensory mechanisms of the intact modalities change when input of one sense is lacking.

P10. Modulation of frequency-dependent synaptic plasticity in area CA1 of the hippocampus by insulin

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Insulin can be synthesized and released in the brain, and insulin receptors (IRs) are abundantly expressed in several brain areas, including the hippocampus. In the present study we have characterized the effect of insulin (500 nM) on synaptic transmission and signal transduction cascades in the hippocampus. The effects on synaptic transmission were studied using sharp-electrode intracellular and field potential recordings. Our results show that: (i) insulin induces LTD only when GABAergic inhibition is blocked with Bicuculline; (ii) insulin induces LTD when the Mg2+ block of the NMDA (N-methyl-D-aspartate) receptors is reduced by lowering the extracellular Mg2+ concentration from 1.3 to 0.2 mM; (iii) the insulin-induced LTD is blocked by the NMDA receptor antagonist APV (100 μM)**;** iv) the effect of insulin depends on the stimulation frequency during the insulin application: stimulation at test frequency (0.033 Hz) results in LTD, stimulation at 1 Hz induces no change, and stimulation at 10 Hz results in LTP; v) the effects of insulin described in iv) can be blocked by a specific inhibitor of mitogen-activated protein kinase kinase (MAPKK), PD98059, and a specific inhibitor of the phosphatidylinositol 3 (PI3) kinase, LY294002.

In summary, we show that insulin induces an activity dependent shift in the frequency-response curve of synaptic plasticity and activates both the MAPK and Akt/PKB route.

P11. The effects of post-weaning enriched rearing on cognitive, emotional and motor performance in male and female C57BL/6 mice

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The mammalian brain enjoys a high degree of plasticity, with exposure to enriched rearing condition reported to improve cognitive performance in rodents. We investigated the effects of post-weaning enriched rearing, in the form of inanimate stimulation and opportunity for voluntary exercise, upon cognitive, emotional and motor aspects of behaviour in C57BL/6 mice of both genders, in comparison to control subjects reared in standard laboratory condition. Postmortem analysis confirmed the presence of anatomical alterations in the hippocampus in our enriched mice. Classical conditioning was examined using both aversive and appetitive paradigms, which yielded data suggestive of superior conditioning in enriched mice; and it was more consistently observed in the male. We went on to show that enrichment is associated with increased anxiety-like behaviour in the elevated plus maze, reduced locomotor activity in the open field, and improved motor coordination in the rotarod. It was concluded that post-weaning exposure to enriched environment can affect multiple psychological functions, and care should be taken in the interpretation of specific functional enhancement. The neural substrates underlying the behavioural effect of enriched rearing clearly warrant further characterization.

P12. Chronic exposure to glucocorticoids by subcutaneous corticosterone pellet implants in mice – effects on hippocampal neurogenesis

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Major depression is often associated with elevated glucocorticoid levels and here we describe subcutaneous implantation of corticosterone (cort) pellets in mice and the effect on neurogenesis. Male BKTO mice were anaesthetised using isofluorane and implanted with either placebo or cort pellets releasing the equivalent of 20 or 40 mg/kg per day. Mice were returned to their home cage for 14 days and on days 10-14 were injected with 50 mg/kg bromodeoxyuridine (BrdU) i.p. before being terminally anaesthetised and transcardially perfused 24 hours after the final dose. Animal experiments were carried out in accordance with the U.K. Animals (Scientific Procedures) Act 1986 and associated guidelines. Immunocytochemistry using anti-BrdU antibodies was carried out on 40 μm thick free floating sections to quantify the number of newborn cells. Results showed that at 40 mg/kg a robust 50% reduction in hippocampal neurogenesis was seen (1,808 ± 88 BrdU positive cells as compared to 3,642 ± 279 cells for placebo treated) with the 20 mg/kg group showing no effect. Using Cavalieri's Principle estimates of hippocampal volume were made and animals receiving 40 mg/kg per day of cort showed a non significant trend towards decreased hippocampal volume (-19% as compared to placebo controls) with the 20 mg/kg group showing no effect. Quantification of dentate gyrus and granular cell layer volumes is underway to determine if cort is causing cell loss or merely hippocampal atrophy.

P13. Involvement of corticosteroid receptors and BDNF in a novel paradigm of neonatal spatial learning

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Perturbations of maternal contact interact with the genetic background and determine neuronal development. We examined the effect of continuous non-reinforcement (frustration) on neonatal spatial learning by using a novel experimental paradigm. We used mother contact as a reinforcer in a T-maze in order to determine spatial learning and memory in the neonatal period (postnatal days 10-13). Continuous reinforcement (non-frustrated rats) resulted in faster acquisition and better memory performance. Immunohistochemical studies revealed that 24 h after the last training session mineralocorticoid receptors (MR) were up regulated in the septum and in the CA3 and CA2 hippocampal regions of frustrated animals. On the contrary, we observed an up-regulation of glucocorticoid receptors (GR) and BDNF in the hippocampal CA3 region of non-frustrated animals. Our results suggest that frustration of maternal contact during the neonatal period impairs acquisition and recall procedures, possibly through a mechanism that involves MR, GR and BDNF. We also determined the effect of neonatal frustration on spatial learning and memory during adulthood by using the Morris water maze. Interestingly, the effect of frustration persisted in adulthood, resulting in differences in spatial learning and memory between frustrated and non-frustrated animals.

P14. Effects of acute vs. chronic estradiol treatment on behavior and cognitive skills of the female rat

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Estrogens have been shown to have several beneficial effects on the CNS. Estradiol (E2) is considered to exert protective and trophic actions in neurons, however its involvement in the maintenance or improvement of cognitive function is still under investigation, both in humans and in animal models. In this study, we have examined the effects of estradiol treatment on cognitive function and behavior of adult female rats following long term ovariectomy (OVX), in combination with a neurotoxic insult. The insult used was a single subconvulsive dose, 7 mg/kg, of kainic acid (KA). E2 was administered either acutely, four weeks following OVX, simultaneously with KA or chronically, 1 week prior and two weeks post KA insult. The groups formed (OVX ± KA, OVX + acute E2 ± KA, OVX + chronic E2 ± KA) were examined 10 days following KA in the open field and the Morris water maze tests. Depending on the treatment duration, E2 counteracted the effects of KA on certain parameters of exploratory behavior in the open field test. No significant deficits were seen on learning ability of OVX rats following KA, however the combination of both types of E2 treatment with KA resulted in severe learning retardation. Acute, but not chronic E2 restored KA-induced deficits on memory. Our data show that the efficacy of E2 in ameliorating some of the behavioral and/or congitive deficits due to KA depends on the task and the type of treatment, suggesting the existence of distinct mechanisms in CNS estrogen actions.

P15. Prenatal nutritional deprivation increases the apoptotic cells in the olfactory bulb in rabbit pups (*Oryctolagus cuniculus*)

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In the rabbit, prenatal nutritional deprivation occurs in a natural way due to the position in the uterus during gestational period**,** and the lightest pups are those that were undernourished. This condition has adverse effects on brain structures development. In this study, we have investigated the influence of undernutrition on the development of olfactory bulb (OB) in three days old rabbit pups. For this experiment undernourished pups and control, formed by the heaviest ones**,** from 6 different litters were used. In Nissl stained sections, the parameters width, length, number of mitral and granular cells and number of apoptotic cells contained in the mitral cell layer were studied. No significant differences between groups were observed in width, length or number of granular cells. However, the number of mitral cells was significantly lower in the undernourishing pups. This decrement could have been produced by an increment in cell death of this cellular type, as the number of apoptotic cells appears significantly increased in the mitral cell layer of the undernourishing group. Our results suggest that at the age studied, undernutrition during prenatal period in the rabbit selectively affects the development of the mitral cells of the olfactory bulb.

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P16. Synaptic responses to sound in visual areas from visually deprived cats

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Cats that are visually deprived from birth show improved auditory localization (Rauschecker and Kniepert 1994). Our objective here was to determine if there is auditory and visual cross-modal reorganization in visually deprived cats and to characterize it at the cellular level. Cats were deprived of visual stimulation from birth and stimulated with sounds for 2-7 hours/day (2 and 20 KHz at 60 70 dB). Intracellular recordings were obtained from the visual cortex of anesthetized and paralyzed cats held to the stereotaxic by hollow ear-bars containing loudspeakers. The significance of spike and synaptic responses was determined with the Monte Carlo method. Sixty-nine neurons were intracellularly recorded from areas 17 and 18 in the cat visual cortex in control and visually deprived animals. All of them were tested for auditory stimulation (0.2 to 2 s pulses of 2-20 kHz or white noise). In 7 out of 24 neurons recorded in animals born in the dark we obtained significant synaptic or spike responses to sound. The latencies of these responses were 26 ± 8 ms. None of the 30 neurons that were recorded from control animals of matching ages showed any responses to sound. We conclude that, following visual deprivation from birth together with sound stimulation, the auditory-visual innervation is functionally active and induces synaptic potentials in cortical visual neurons.

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P17. Chronic dysthyroidism effects on neuronal morphology of the hippocampal trisynaptic circuit

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The hippocampus is particularly sensitive to thyroid hormones imbalances. Neonatal dysthyroidism has been shown to dramatically alter the structural development of pyramidal cells in the hippocampus. However, data about dendritic spines are contradictory. In the studies about thyroid hormone effects dysthyroidism has been usually provoked postnatally, while in rats, similarly to humans, hippocampal development is fundamentally prenatal. Therefore, the objective of this study is to analyse the effects of chronic dysthyroidism (including prenatal period) on the morphology of neurons in the trisynaptic circuit, i.e. pyramidal CA1 and CA3 and granular cells. Male Wistar rats were assigned to three experimental groups: thyroxine (n = 15), methimazole (n = 15) and control (n = 21). L-thyroxine and methimazole were administered on drinking water since 9th gestational day. The analyses reveals that pyramidal neurons, primarily CA1, but no granular cells were less developed. The distance from soma of the first dendritic branch was longer and the number of dendritic branch points was lower in hypothyroid animals than in control group.

P18 .Individual differences in normal Wistar rats: relationship to pup ultrasound vocalization and effects of transient housing in isolation

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It is known that adult rats from outbred strains can differ systematically in their behavioral responsiveness to specific testing situations. We have shown that male Wistar rats can be assigned to different sub-groups based on rearing in a novel open-field ("high"/"low responder"; HR/LR), or on open-arm avoidance in the plus-maze ("high"/"low anxiety rats"; HA/LA). These behavioural differences are probably due to separate mechanisms, since the HR/LR criteria were found to be related with brain dopamine and acetylcholine, in contrast to serotonergic mechanisms in HA/LA rats. Here, we investigated developmental factors in such rats. We asked whether ultrasound vocalization (USV), induced by separating pups (postnatal days 10-12) from their foster-mothers would predict adult open-field (HR/LR), or plus-maze behavior (HA/LA). We also asked whether transient isolation during days 22-31 would affect adult behavior, or might interfere with the possible relationship between pup USV and adult behavior. Our results show that pups with higher USV rates showed more open-arm time in the plus-maze (i.e., less anxiety) as adults. Rearing and locomotion in the open-field were not related to pup USV. Transient isolation during days 22-31 did not affect adult plus-maze behavior, but affected open-field behavior, since isolated rats showed more rearing behavior than continuously group-housed rats. These results show that adult plus-maze anxiety appears to be determined either genetically or very early during development, and that it may be less vulnerable to environmental manipulations (here transient isolation) during childhood than open-field behavior.

P19. Changes in the number and morphology of the dopaminergic neurons after electrical stimulation of the ventral tegmental area

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Central dopaminergic neurons respond with various neurochemical adaptations and with morphological changes to their chronic activation by opiates and psychostimulant drugs. In the present work we studied the number and morphology of cells expressing thyrosine hydroxylase (immunohistochemical staining of dopaminergic neurons) in male Wistar rats subjected to chronic electrical stimulation of the A10 dopaminergic cells (ventral tegmental area) in one hemisphere. Stimulation current intensity (at 80 Hz) was adjusted individually to evoke behavioral activation (exploration or eating). After 14-day stimulation (for 40 minutes daily) a total number of TH+ cells was significantly reduced (in comparison to the nonstimulated control group) in the A10 area both ipsi- and contralateral to the stimulation side. There were also profound changes in the morphology of TH+ cells consisting in shrinkage of cellular somata and increased variability of their size and shape. Similar effects (although less intense) were also observed in the A9 group (substantia nigra pars compacta) but not in the A12 group (hypothalamic arcuate nucleus). The results indicate adaptations in the brain structures subjected to electrical stimulation which involve changes in the morphology of the cells and expression of the neurotransmitter synthesis system.

P20. Protein synthesis immunizes hippocampal synapses against depotentiation

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Protein synthesis and transcription are necessary for expression of long-term potentiation (LTP) in hippocampal area CA1 and for the consolidation of long-term memory. The stability of LTP requires macromolecular synthesis at later stages, but a specific role for early protein synthesis has not been identified. Hippocampal LTP is sensitive to activity-induced reversal, or depotentiation (DPT), during a short time period immediately after LTP induction. In this study, we examined the molecular mechanisms that critically regulate the susceptibility of synapses to DPT. We report that synaptic immunity to DPT in mouse hippocampal slices depends on the amount of imposed synaptic stimulation. Multiple trains of high-frequency stimulation provide immediate synaptic immunity to DPT. This immunity to DPT is rapidly induced, it is input-specific, and it requires protein synthesis and transcription. Local translation, likely occurring at dendritic sites, mediates input-specific synaptic immunity against DPT. Transcription is required for heterosynaptic transfer of the immunity between adjacent synaptic pathways. Thus, the signals that are critical for establishing this synaptic immunity may originate locally at synapses, or at the soma. We propose that the cellular site of macromolecular synthesis determines whether synaptic immunity to DPT is input-specific or cell-wide. Protein synthesis and transcription may importantly regulate long-term storage of information by conferring synaptic immunity to DPT.

S1. Action impairs visual identification – fMRI correlates of action-induced blindness

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Recent behavioral studies revealed an impact of action on visual perception. If participants are engaged in a motor task they proved to be worse in identifying a visual stimulus (action-induced blindness; for an overview see: Müsseler and Wühr 2002). In the present event-related fMRI study, 16 healthy participants had to accomplish a visual identification task combined with a "go – no go" task. Three different stimulus onset asynchronies (SOAs) were used that provided different overlaps between the motor task and the visual identification task. Behavioral data revealed an impairment of visual identification in "go" trials compared to "no go" trials. This discrepancy is most pronounced in short SOAs, i.e., when the motor task and the visual identification task have the greatest overlap. Results showed a modulation of activation in brain areas concerned with visual identification, when contrasting "go" with "no go" trials. The BOLD response to visual stimuli is reduced in the area V3A in "go" trials, again more pronounced in short SOAs. Therefore, the execution of a motor response appears to modulate the activity in extrastriate visual areas.

S2. Temporal re-organization of horizontal and vertical saccades during oblique saccades

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To accomplish oblique saccades, horizontal and vertical saccades, which are controlled by the distinct generators, should be temporarily and dynamically coordinated. However, latency of visually induced horizontal saccades is typically lower than that of vertical saccades. This raises a question as to how horizontal and vertical saccades are harmonized to accomplish oblique saccades. We asked subjects to look at the center light (FP) in the head-restrained condition, and to move their eyes to one of three randomly presented target lights (T) as soon as it was presented 200 ms after disappearance of the FP. Ts were set at a 7 deg rightward, at a 7 deg downward for the FP, and at a 45 deg oblique position with 7 deg rightward and downward components. Mean latency was 148 ms for purely horizontal and 187 ms for purely downward saccades ($n = 6$). Latency of horizontal or vertical components of oblique saccades was 148 or 150 ms, respectively. The latency of the downward components was reduced by 37 ms from what it was for purely downward saccades of the same amplitude. The slope of the regression line between latencies of horizontal and vertical components was 1.018 (r=0.99), indicating vertical and horizontal components start almost simultaneously. In conclusion, oblique saccades direct the target without a temporal separation between two components in such a way that the latency of the vertical component appears earlier to synchronize with the horizontal component.

S3. Cross-modal comparisons of temporal order judgement in cochlear implant users

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A number of experimental studies has suggested that the minimum inter-stimulus-interval (ISI) between two successive stimuli necessary for correctly reporting their temporal order (TO) is about 20-80 ms. This temporal range corresponds to the processing of single units of language (phonemes). A significant prolongation of this ISI may accompany certain language problems. The aim of this study was to investigate the temporal order judgement (TOJ) in cochlear implant users. We tested 5 right-handed (aged 19-66 years) postlingually deaf monochannel implant users and 5 normal-hearing subjects. The task was to identify the TO of two (300 and 3,000 Hz) tones or of two diodes (red and green). In both tasks the duration of single stimulus was 15 ms, and the ISIs varied from 10 to 500 ms. The results showed that implant users needed longer ISI (80-150 ms) for correctly reporting the order of two stimuli than normal-hearing subjects (40-80 ms), independently of the modality. In both tasks for shorter ISIs patients achieved lower percent of correct responses than controls. This suggests difficulties in TOJ can be related to poor auditory comprehension in implant recipients. The deficits in TOJ were independent of the modality, which supports the theory postulating the presence of common central mechanism responsible for temporal ordering.

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S4. Relation of the steady state response to the spontaneous gamma activity in the auditory cortex of the cat

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Epidural surface electrodes and linear array intracortical multielectrodes were implanted into the auditory cortex of cats. Current source density (CSD) analysis was used to localize intracortical distribution of sinks and sources. Spontaneous EEG and auditory evoked responses were recorded in different behavioral situations. The changes of the spontaneous gamma oscillation and the „40 Hz" steady state response (SSR) were compared in an instrumental alimentary conditioning paradigm in which light or auditory stimulus served as CS. The amplitude of the spontaneous gamma activity increased in a modality specific way only when the animal was expecting an auditory CS. The frequency of the gamma oscillation increased during the performance of the instrumental task in a modality independent way. The SSR was induced by different frequency repetitive click stimuli. The amplitude of the SSR in the conditioning situation changed in a similar way like the spontaneous gamma activity. In the conditioning situation the stimulation eliciting the greatest amplitude SSR shifted to higher repetition rates. Intracortical CSD analysis indicated that the SSR was generated in the superficial layers of the auditory cortex as a result of sequential activation of excitatory and inhibitory synaptic processes. The conclusion was drawn that the SSR represent the activation of the auditory cortical gamma circuit driven by the repetitive auditory stimulation.

S5. Does secondary somatosensory cortex contribute to human pain localization?

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The ability to localize both touch and pain has been attributed mainly to the primary somatosensory cortex (S1), based on its fine somatotopic mapping of tactile inputs. However, recent MEG and fMRI studies also show a tactile topographic representation in the secondary somatosensory cortex (S2), suggesting that this area may also contribute to touch localization. The role of S2 in pain localization is not known, and may be quite different from touch, since nociceptive input to S2 appears to derive from direct thalamic inputs, while tactile input is mainly *via* S1. Healthy subjects underwent fMRI-scanning (1.5 Tesla, standard head coil, BOLD analysis) during painful balloon-distention of the distal esophagus and painful heat on the midline chest. For each subject, the focus of activation within S2 cortex was compared during esophageal and chest stimulation conditions. Seven of eight activation sites showed medio-lateral topography, with esophageal pain represented more laterally than cutaneous trunk pain. Wilcoxon paired comparisons revealed a clear tendency for significance (P=0.06), and a binomial distribution analysis indicated less than 5% probability of obtaining this relationship by chance. Our results suggest a medio-lateral topographic organization within human S2 for pain, similar to that reported for touch, thus implicating this region in the perceptual localization of both somatosensory modalities.

S6. Perception of rhythms in normally hearing adults and adult cochlear implant users

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A number of experiments has provided evidence for a temporal processing platform of ca. 2-3 s that reflects the existence of the temporal integration mechanism (TIM). This platform plays an important role in speech (phrase level). Here we report disorders in TIM in postlingually deaf subjects, following cochlear implantation. Subjects grouped beats generated by a metronome with different frequencies (1-5 beats/s). The task was to accentuate mentally every 2, 3 ... etc. beat, to create a subjective rhythm. Subjects reported verbally, how many beats they were able to integrate into a unit. The Integration Interval Length (IIL= number of reported beats multiplied by the time distance between two successive beats for a particular frequency) was analysed. The results showed that the upper limit of integration (IIL for the lowest frequency) was significantly shorter in patients (ca. 1.9 s) than in normally hearing individuals (ca. 2.8 s). For higher frequencies, up to 3 beats/s, IIL got systematically shorter, but in patients being always shorter than in controls. In contrast, on higher frequencies (3.5-5 beats/s) patients performed similarly to controls. This result suggests that the reorganisation of TIM accompanies the new auditory input from an implant. The specific TIM deficits may be related to deficits in auditory comprehension on the phrase level.

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S7. Auditory comprehension in mono- and multichannel cochlear implants users

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Nowadays, cochlear implantation has been recognized as a safe and effective method of treatment of patients with severe hearing loss, who have no benefit from conventional hearing aids. In the case of postlingually deafened persons two types of cochlear implants (CI) are applied: mono- and multichannel devices. Despite the more frequent usage of multichannel CI during last years, there still exists a group of monochannel CI users. The aim of this study was to compare the level of auditory comprehension (AC) in mono- and multichannel CI users. The progress of AC over the time in multichannel CI users was also evaluated. Subjects were 10 monochannel and 17 multichannel CI users. Their linguistic competencies were assessed using 6 tests: phonemic hearing, vowels, consonants, numbers, monosyllabic words and sentences. Results showed that after 2 years of linguistic rehabilitation the multichannel CI users achieved significantly higher scores in all tests, excluding numbers. Additionally, in multichannel CI users the significant improvement in AC was found during the first 6 months of rehabilitation as well as between 12 and 24 months. These results confirm the observation that the multichannel CI gives more benefits for AC than the monochannel one. Moreover, the significant progress was observed in the 2-year rehabilitation program.

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S8. Effect of eye position on the processing of auditory spatial information in human visual cortex

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While visual spatial information is based on retinal coordinates, the auditory system receives information on sound location in relation to the head. Thus, any deviation of the eyes from a central position results in a divergence between the retinal visual and the head-centered auditory coordinates. It has been suggested that this divergence is compensated by a neural coordinate transformation, using a signal of eye-in-head position. Using fMRI, we investigated which cortical areas of the human brain participate in such processes. Subjects received lateralised sound stimuli, presented with various interaural level differences, while directing their gaze to left, right, or central visual targets. When the gaze was to the left or right, we found the occipital cortex (BA 17/18/19) to be activated in both hemispheres, although fixation was correct and retinal stimulation thus constant. This occipital activation did not occur with sound lateralization *per se*, but in combination with eccentric eye position. These results suggest that the visual cortex is involved in the transformation of auditory spatial coordinates with eccentric eye position and thus may participate in the neural mechanisms performing the perceptual alignment of audition and vision with changes in gaze direction.

S9. Speed tuned cells in feline superior colliculus

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The spatial and temporal visual sensitivity of single neurons was studied in the superficial layers of the superior colliculus. Extracellular single-cell recordings were performed in halothane--anesthetized cats. Responses of neurons were recorded during stimulation with sinusoidal gratings drifting in a preferred and null direction and the spatiotemporal frequency response profiles of the neurons were mapped out. All tested neurons were responsive to very low spatial frequencies with peak sensitivity in a range of 0.05-0.15 cycles/degree. Spatiotemporal frequency response profiles revealed existence of two distinct populations of collicular cells – temporal frequency tuned and speed tuned. Temporal frequency tuned cells were sensitive to a particular temporal frequency of moving grating in a wide range of spatial frequencies tested. Speed tuned cells responded selectively to particular combination of spatial and temporal frequencies, that is, to a certain speed of stimulus movement. Regions of peak sensitivity for these cells were located along oblique lines in spatiotemporal frequency planes. Up to now the existence of speed tuned cells has been reported only in the MT of primates and in the wallaby pretectal nucleus of the optic tract and its avian homologue (Clifford and Ibbotson 2003).

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S10. Behavioral specialization in the visual system of the arthropod *Lycosa tarantula* (Araneae, Lycosidae)

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The visual system of *Lycosa tarantula* is composed of eight eyes named anterior median eyes (AMEs), anterior lateral eyes (ALEs), posterior median eyes (PMEs) and posterior lateral eyes (PLEs). Rhabdoms of the ventral region of AMEs are disposed in such a way that they can perceive polarized light. The role of eyes in two different behaviours has been studied: 1) entrainment to an LD cycle and 2) homing. In relation to the first, animals with only one functional pair of eyes and submitted to a LD phase advance or delay were studied; only AMEs were unable to entrain the rhythm. In relation to homing under natural conditions, experiments performed under different celestial conditions allowed to discover that patterns of linearly polarized light in the sky were sufficient for accurate homing. AMEs were responsible for the reception of polarized light. Homing was also studied under artificial lighting; in this case, animals did not orientate to home; they turned a fixed angle that should carry them to nest; when homing was studied at darkness most of animals turned at random. It is proposed that visual information gathered by ALEs, which have a ventral field of view, is necessary for homing under this condition. These results reveal a behavioural specialization in the visual system of *Lycosa tarantula*: AMEs are used for polarized light homing and not used for LD entrainment. The other eyes are used for LD entrainment and not used for homing. ALEs are also used for homing when no celestial cue is available.

S11. Gaze perception modulates visual extinction in right brain-damaged patients

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Brain damaged patients with extinction are fully able to detect single lateralized stimuli, but find it hard to detect a contralesional stimulus presented simultaneously with an ipsilesional one. Extinction has been classically assessed by using simple stimuli such as flashes or simple touch. Only recently, however, more complex stimuli such as schematic faces with straight and diverted eyes have been used. Others’ real gaze is a complex biological stimulus whose perception depends on the correct processing of both eyes. Since extinction patients might be expected to be unaware of the eye presented in the contralesional hemifield, their gaze perception might also be impaired. Three right-brain damaged patients with visual extinction were presented with real bilateral gaze stimuli or with bilateral but non-biological stimuli (e.g., pairs of windows in the front of a house or pairs of arrows). Moreover, single (left or right) biological or non-biological stimuli were presented. Patients were requested to report whether the experimental stimuli were unilateral (left or right) or bilateral. Patients performed better with biological stimuli their extinction being significantly lower with bilateral gaze stimuli that with non-biological stimuli. Results indicate that processing of real gaze stimuli can modulate patients’ visual extinction and reduce their attentional deficits.

S12. fMRI of delayed pointing in a patient with optic ataxia – the ventral stream is not the solitary actor

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Patients with optic ataxia show gross deviation of visually guided hand movements to peripheral visual targets after lesions of the posterior parietal cortex. Such misreaching is improved, when a delay of 5 seconds is introduced between target presentation and movement onset. This finding was interpreted such that the ventral pathway, primarily engaged in perceptual tasks, is taking part in visuomotor action when the information within the dorsal "action" pathway declines. Whereas behavioural dissociations in few stroke patients have been shown in line with this hypothesis, direct evidence for it is still lacking. Using fMRI, we investigated delayed and immediate pointing movements in a patient with bilateral parietal lesions and chronic optic ataxia. Contrasting delayed pointing with immediate target pointing we found significant differences in the right inferior frontal gyrus, bilateral premotor cortex, bilateral extrastriate occipital cortex, and the precuneus. The data show that the increase of movement accuracy due to a delay in patients with optic ataxia is not only mediated by ventral stream areas. Frontal areas previously associated with spatial working memory tasks and medial parietal areas also seem to play an important role in this process.

S13. Lateralization of response to social stimuli in tadpoles

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Tadpoles of five anuran species were tested for preferences in the use of the eyes during inspection of their own visual image in a mirror. When tested in a tank with several small mirrors, tadpoles of five different species (*Bufo bufo*, *Bufo viridis*, *Rana temporaria*, *Rana esculenta*, *Bombina variegata*) preferentially approached and positioned themselves with the mirror located on their left side, thus looking at the image with the monocular field of their left eye. Similar results were obtained with tadpoles of *Rana temporaria* tested in a task in which they had to choose approaching one or other of two mirrors located on their left and right side. Control experiment showed that the behavioural asymmetry was not due to motor preferences and that it was independent of morphological asymmetries in the positions of the spiracles. The lateral bias typically emerges some minutes after the placement of the animals in the test apparatus. We checked whether such a temporal pattern was associated with lateralisation per se or rather reflected temporal variations in social aggregation. We found that the tendency to move to make social aggregation only appears after about five minutes following placement in a novel environment and this corresponded quite well with the appearance of lateralisation, when tadpoles showed an higher probability of approaching a conspecific appearing on their left rather than on their right hemifield. These results suggests a functional visual lateralisation among juvenile amphibia before metamorphosis.

V1. Marked differences in neurogenesis and proliferation activity in the hippocampus of wild-living rodents

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Proliferation activity and neurogenesis in the subgranular layer of the hippocampus varies significantly among small wild-living rodents. Investigation in four different species with antibody Ki67 reveals that *Apodemus* sp. have more than four times as many proliferating cells per volume dentate gyrus as voles (*Clethrionomys glareolus* and *Pitymys subterraneus*). Laboratory mice of mixed genetic background show proliferation activity in-between *Apodemus* sp. and voles, being closer to voles than to Apodemus. NeuroD, a marker of young, differentiating neurons and Doublecortin, marker of young migrating neurons, reflect the findings of proliferation activity. *Apodemus* sp. have the highest number of new neurons in the dentate gyrus. In all wild species, a dramatic decrease with age in the proliferation activity and neurogenesis in the hippocampus can be observed, although the onset of the down-regulated state varies among the species. Proliferation and neurogenesis in the subventricular zone is not or is only marginally affected by age in all species. Sex differences can be seen in *Apodemus flavicollis*, but not in voles. Thus, *Apodemus* sp. could bear a key to understand the physiological role of neurogenesis.

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V2. Dynamic analysis of inter-words time intervals: a method to analyze the structure of communicative signals

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Speech analyses are usually focused on words as signifiers, ignoring inter-words time intervals (IWIs), which are related to the "form" of speech, rather than to its "content". Applying the method of power spectrum analysis to inter-vocalizations time intervals of bird singing underlying periodic processes were detected. In contrast, human IWIs revealed non-periodicity, which may be random or chaotic. To differentiate between these possibilities, the non-linear dynamic methods of unstable periodic orbits and correlation dimension were applied to show that IWIs are characterized by a low-dimensional chaotic attractor. Its correlation dimension of 3.2 SD 1.1 suggests a minimum number of four variables underlying the system. The methods developed in the present communication can be further applied: (a) for the measurement of specific alterations in the processes underlying the form of speech in human disorders, i.e., schizophrenia; (b) for the assessment of normal and pathological developmental aspects of speech processes in children; (c) for comparing communicative signals between humans and other animal species.

V3. The effect of pre-challenge learning on MK801 induced psychosis-like behavior in an animal model of schizophrenia

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This study is aimed to examine whether pre-challenge learning prevents psychosis-like behavior in an animal model of schizophrenia, and to describe the learning-related cellular mechanisms which attenuate the course of schizophrenia. By combining behavioral studies with cellular neurophysiology/morphology we explored how learning protects against the psychotomimetic effects of the NMDA receptor antagonist MK801. Rats were trained to distinguish between pairs of odors in an olfactory discrimination task. We examined whether such olfactory-learning induces protection against the effects of i.p. injections of 0.1 mg/kg MK801 in a series of behavioral tasks – the Morris water maze, prepulse inhibition and elevated plus maze. MK801 caused sensorimotor disturbances, spatial learning acquisition deficit, and swimming strategy alterations in pseudo trained and naive rats, but caused neither in trained rats. Brain slices of the hippocampus were prepared and intracellular recordings were obtained from hippocampal CA1 pyramidal neurons. Data show paired pulse facilitation is reduced in neurons from trained rats indicating enhanced synaptic transmission between CA3 and CA1 neurons. Learning-induced protection may occur due to changes that take place in synapses connecting CA3 with CA1 hippocampal neurons, as a result of strengthening of the non-NMDA mediated synaptic transmission. Thus, AMPA-receptor mediated synaptic connectivity is enhanced after learning in a manner that allows the hippocampal network to maintain its function even in the absence of NMDA-receptor mediated activity.

V4. Influence of the genetic background on the behavioural phenotype of preproenkephalin knockout mice

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Behavioural knockout phenotypes are influenced by genetic factors that may alter or even mask the genotype effect. We tested the effect of the genetic background on the manifestation of knockout phenotype. Wild type and preproenkephalin (Penk1) knockout C57BL/6J and DBA/2J mice were tested in models of anxiety and pain. Penk1-/- mice showed elevated levels of anxiety and increased pain-sensitivity. However, the knockout phenotype was highly influenced by the background genotype, increased emotionality of Penk1 knockout animals manifested only in models where the respective wild types showed low level of anxiety. The behavioural phenotype of knockouts were masked by the phenotype of wild type in tests, where the wild type mice were highly anxious probably because of the ceiling effect. The same phenomenon was observed in pain tests also with one exception: here the behavioural phenotype of the background strain dominated and did not allow the manifestation of the knockout phenotype. We concluded that the limit-effect determined in most of the cases the appearance of the knockout phenotype: the closer the background phenotype to the limit, the less probable to detect significant change in that direction. Therefore, considering the behaviour of a wild type strain makes it possible to choose an appropriate model, in which the probability of the appearance of knockout phenotype is maximal.

V5. Physiological evidence for a topographical projection from the subiculum to the lateral entorhinal cortex

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The possibility of a direct and topographical projection from the proximal subiculum to the lateral entorhinal cortex (LEC) has been suggested on the basis of anatomical evidence. Here we present electrophysiological evidence for the existence of this projection. Following stimulation in the proximal, medial or distal subiculum we demonstrate a negative-going deflection followed by a positive-going deflection in the evoked synaptic response in both the rostral and caudal LEC. Mean evoked-response amplitude (for both the negative and positive deflections) in both rostral and caudal LEC decreased as the electrodes were moved from proximal to distal subiculum. The mean slope between the negative and positive deflections also decreased as the stimulating electrode was positioned more distally. We further observe that the mean amplitude for both peaks was higher when recording in the caudal LEC than in the rostral LEC, whereas the latencies of the responses were slower as we moved towards caudal LEC. These results confirm anatomical evidence that suggest that the proximal subiculum projects strongly to the lateral LEC.

V6. Structural anomalies associated with IQ drop in children born preterm

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IQ scores in preterm children are lower than in age-matched, normal birthweight children, but it is not known whether their IQ scores remain stable over time as has been reported for the normal population. We compared IQ scores obtained at age 7 and again at adolescence in 91 preterm children. Significant positive correlations of scores at the two time points indicated that children maintained their position within the group over time. However, t-tests revealed that the absolute values of both VIQ and PIQ scores decreased significantly; IQ scores decreased in approximately 60% of children. Perinatal factors such as birthweight and days of ventilation were not associated with IQ change scores. Voxel-Based Morphometry studies were conducted using Statistical Parametric Mapping (SPM) software in order to explore relationships between grey and white matter composition and IQ decline. Both unilateral and bilateral analyses were conducted separately for VIQ and PIQ scores, and for grey and white matter. Children with a small decline in IQ scores over time had brains that differed in certain aspects compared to those whose IQ scores decreased more substantially. Areas in the frontal and temporal lobes were associated with VIQ decline, while PIQ drop was related to the hippocampus and the temporal stem. These are consistent with the literature on the brain and IQ.

V7. Effects of environmental enrichment in object recognition and social discrimination in male and female rats

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Male and female Sprague-Dawley rats were housed in groups of 9-12 in enrichment environment (EE) cages during 8 weeks. Control animals were housed 2-3 per cage in standard laboratory cages. When the treatment finished, enriched and control rats were isolated in individual cages and tested for object recognition (experiment 1) and social discrimination (experiments 2-3). Each experiment included two sessions; in the first one the subject was introduced in the testing box with a sample object (exp. 1), juvenile male (exp. 2) or juvenile female (exp. 3). The second session was performed 30 min later. The subject was confronted with the sample and a new object in exp. 1, with 2 juvenile males in exp. 2 (the same juvenile male of the first session and a new juvenile one), and with 2 juvenile females in exp. 3 (the same juvenile female and a new one). Enriched females showed a tendency to increase object exploration in the object recognition test (EExsex interaction: $F(1,36)=3.376$, $P=0.075$). Enriched males increased social interaction with the new juvenile in the second session of the social discrimination test (EExsex in exp. 2: $F(1,38)=4.026$, $P=0.053$; EExsex in exp. 3: $F(1,40)=5.49$, $P=0.024$). The results are discussed in relation to other data indicating sex differential effects of EE.

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V8. Stereological quantification of adult rat hippocampus and prefrontal cortex after subchronic treatment with gamma-hydroxybutiric acid (GHB)

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Gamma-hydroxybutyrate (GHB) is a new drug with abuse potential popularly known as "liquid ecstasy". It is an endogenous compound of the mammalian brain, synthesized from GABA, which can traverse the blood-brain barrier. The existence of brain receptor sites as well as brain mechanisms for synthesis, release, and uptake provides suggests that GHB may act as a neuromodulator on specific neuronal populations. Recent studies indicate that working memory may be significantly altered in GHB-treated rats, suggesting that this substance might affect memory by altering the structure and/or function of specific brain regions such as prefrontal medial cortex (1). This study was designed to examine the effects of subchronic administration of GHB (10 and 100 mg/kg, i.p.) during 12 consecutive days on the number of neurons and glia of adult male rats hippocampus (CA1) and prefrontal cortex using unbiased stereological techniques. Results showed that GHB produced a marked reduction in the number of neurons in hippocampus (10 mg/kg, $P<0.005$; 100 mg/kg, $P<0.04$) and prefrontal cortex (10 mg/kg, $P<0.1$), as well as a significant increase of glia in prefrontal cortex (10 mg/kg, $P<0.005$; 100 mg/kg, $P<0.02$), as compared with the control group. Overall, these results suggest that GHB could exhibit a neurotoxic activity in male rats.

(1) García FB, Pedraza C, Luna, G, Dávila G, Martín M, Navarro JF. (2002). European Neuropsychopharmacology, 12 (0): 389.

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V9. Neural networks involved in acquisition and consolidation of the lamb odour by parturient ewes

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Maternal behaviour in sheep is characterized by the formation of a selective bond with the lamb. Within 1 hour post-partum, mothers learn the olfactory signature of their lambs and allow them to suckle, while rejecting any alien lamb. Moreover, ewes form a long-term memory of this recognition. Neural networks activated during learning and consolidation of the olfactory identity of the lamb were mapped using immunohistochemistry of the Fos protein. During the learning phase, we compared activations between intact ewes and anosmic ewes, who are not able to discriminate their lamb from an alien at suckling. In intact ewes, a strong activation was found especially in olfactory structures (olfactory bulb, piriform cortex, frontal cortex, cortical amygdala) whereas it was not the case for anosmic mothers. This suggest that olfactory amygdala and/or piriform-frontal cortex pathways could be involved during learning of the odour of the lamb. Concerning consolidation, we compared brain activations during recognition of the lamb at the end of a separation period (3 h) performed either after short (4 h) or long (7 days) contact durations. The piriform cortex is similarly activated by recognition of the young after both contact durations with the lamb, whereas a significantly activation of the frontal cortex appears after long contact duration. This suggest that brain circuitry is different between the first stages of learning and later, once the memory is consolidated.

V10. Peptide interplay and rodent sleep

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Complex use of neuropeptides might be more effective than their single administration. Theoretical search using mathematical vector analysis revealed several peptide combinations possible to exert hypnogenic effect, including the delta sleep-inducing peptide (DSIP) with neuropeptide-tyrosine (NPY). This combination was administrated just before the 12-h dark period directly to the lateral ventricle of 8 rabbits preliminary implanted (under local procain anesthesia) with intracranial electrodes for the EEG and EMG. Otherwise the same animals treated with a saline were used as controls. Paperless polygraphic recording started immediately since administration and lasted for 24 h. Smaller dose of NPY (0.7 nmol) induced a clear decrease in SWS for the entire dark period (-28 min; $0.05<P<0.1$). Higher dose of NPY (7 nmol) induced zero total effect on sleep for the entire 12-h dark period. Combined administration of NPY (7 nmol) and DSIP (30 nmol) induced significant increase in SWS percentage (+53.5 min; $P<0.05$). Administration of DSIP alone revealed only minor changes in sleep (+21 min for 12 h; NS). It is known that both DSIP and NPY can suppress the stress hormonal axis. So the results confirm the initial hypothesis and, probably, reflect secondary participation of the administrated peptides in sleep-wake control which follow their involvement into endocrine processes.

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V11. Independent component analysis tomography

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One of the most important objectives in Neuroscience is to map accurately spatio-temporal dynamics of selected regions of the brain involved in carry out a specific neural task. To tackle this problem a new approach (ICAT) is proposed using Independent Component Analysis to unmix the neural information provided by Event Related Potentials (ERP) and Low Resolution Tomography (LORETA) to obtain sources of activation of each component. We use this algorithm to study Mismatch Negativity ERP (MMN) brain dynamics. Four Independent Components have been found in temporal range of MMN. When analyzed they reveal the contribution of several major structures, well separated in time and space, involved in the detection of auditory change reflected by MMN. These components are separated by intervals of 14-22 ms, supporting the existence of a sequentially orchestrated neural computation mechanism underlying the production of MMN.

V12. Sexual steroids modulate female proceptivity but not attraction to male pheromones in mice

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In rodents, female sexual behaviour is under hormonal control. The first step in this behaviour would be an innate attraction to male-derived nonvolatile secretions (pheromones). We wonder whether this attraction is also modulated by sexual steroids. To test this possibility, 32 ovariectomized, chemically naive adult females were assigned randomly to four groups that received either oil (control), progesterone, estradiol (E) or estradiol + progesterone (E+P) injections. Females were then tested for their attraction to male-soiled bedding and, subsequently, for their sexual behaviour (proceptivity) when confronted to adult males.

Females showed attraction to male-soiled bedding irrespective of the treatment they received (ANOVA $F(3,21)=0.47$; $P=0.7$). As expected, only those females that were treated with E or E+P showed proceptive behaviour. Therefore, female mice sexual behaviour can be seen as a two-step process: 1) an innate attraction to male pheromones independent of the hormonal status of the females; and 2) after encountering the males, females show a proceptive behaviour which is only expressed in estrous, when fertilization is more likely. The attractiveness of male sexual pheromones promotes an autostimulation by the females that ensures anticipatory endocrine changes leading to ovulation by the time of sexual intercourse.

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V13. Fast oscillations during the up states of slow cortical rhythmic activity in vitro

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Rhythmic, synchronized activity in neuronal ensembles has been implicated in sensory and cognitive processes such as attention, learning, and perception. However, the mechanisms for the generation and organization of this activity are unknown. We provide evidence here that the cortical microcircuitry alone generates fast oscillatory activity in the ferret visual cortex in vitro, where slow oscillations (<1 Hz) resembling those seen during slow wave sleep are induced through the modulation of extracellular ionic concentrations (1). These oscillations are composed of short (<1 s) bouts of spiking activity (up states) occurring at 2-5 seconds intervals interspersed with periods of relative quiescence (down states). We applied rigorous spectral techniques to data from extracellular and intracellular recordings in our in vitro preparation. Results for extracellular recordings reveal spectral peaks at lower gamma/higher beta frequencies (~15 to 40 Hz), which were temporally coherent with the up states of the oscillation. This suggests that during the epoch of network activation (up-states) cortical ensembles synchronize generating an intrinsic rhythm. We report here on this finding and how it relates to the temporal structure of independently recorded neuronal spike trains and trains of synaptic inputs.

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V14. Effect of thyroxine (T4) replacement in congenitally hypothyroid rats as determined by delayed matching to sample (DMTS)

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The behaviour of six groups of congenitally hypothyroid rats (8 in each group), and one group of 8 age-matched normal rats was assessed over a series of fixed-ratio (FR) schedules and under the DMTS schedule. Congenital hypothyroidism (CH) was induced by adding methimazole (MMI) to the drinking water of pregnant dams (0.025%) from embryonic day E16 to postnatal day P25. A Total T4 assay confirmed CH status. Five of the CH groups were given thyroxine (T4) replacement injections (0.02 μg/g BW) at specific time points (P3, P7, P14, and P21). The remaining CH group received no T4 replacement injections. The control and the CH groups that received T4 replacement progressed significantly faster through the FR schedule requirements than the CH group that received no T4 replacement injections. There were also differences in behaviour as tested under DMTS. On histological examination, dendrite branching in the CH group without T4 replacement was significantly less than in the control and CH groups that did receive T4 replacement injections.

V15. Characterization of neurological and cognitive status in young and aged AD transgenic mice in the Morris navigation task: dissociation between cognitive impairments and stereotyped circling behaviour

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PD-APP mice with modified inflammatory response at different ages were tested in spatial memory tasks and assessed for the expression of spontaneous circling behaviour in different situations. Acquisition in the Morris water maze was conducted over 5 days followed by retention and reversal learning trials. The expression of stereotyped circling behaviour was quantified during task performance and in repeated screening tests. Working memory was assessed in an olfactory radial maze. In this way, we have evaluated the performance in cognitive behavioural test of transgenic and double-transgenic mice models from 50 days to 9 months on Alzheimer's disease. The impact of age and of the abundance of AB amyloid deposits have been assessed and correlated with the level of cognitive deficits and the expression of stereotyped circling in transgenic mice models. The mutant mice were significantly impaired in the Morris task from a very early age (50 days) and there was a further decrease of performance until 9 months. This evolution appears to be due to the development of circling behaviour preventing normal swim performance. Thus two complementary processes appear to contribute for the severe impairment of the aged mice and our data suggest that the development of stereotypes is related to the density of AB Amyloid whereas the specific cognitive impairments are due to earlier brain damage.

V16. Dopamine transporter expression in dopaminergic neurons of the monkey brainstem

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The dopamine transporter (DAT) terminates dopaminergic neurotransmission by re-uptaking dopamine into the DA-releasing neuron. The level of DAT affects critically time and space parameters of dopaminergic neurotransmission. We have analyzed DAT expression in dopaminergic neurons of macaque monkeys (*Macaca nemestrina* and *Macaca mulatta*) by means of immunohistochemistry for DAT and tyrosine hydroxylase (TH) in adjacent sections and double-labeling immunofluorescence for DAT and TH. Using NIH ImageJ software, we have performed a semi-quantitative estimation of DAT expression in neuronal somata by measuring the optical density of neurons immunofluorescent for DAT. The dopaminergic groups of the ventral mesencephalon and retrorubral region (A8-A10) showed robust immunoreactivity for DAT. Virtually all TH-positive neurons were also DAT-positive, but the levels of DAT varied. Intense immunoreactivity was present in the somata of the ventral tier of the substantia nigra. In the substantia nigra dorsal tier, ventral tegmental area and retrorubral region, neurons with very low levels of DAT immunofluorescence were intermingled with others intensely stained. In addition, DAT-immunopositive neurons were present in the periaqueductal gray dopaminergic group (A11), also with varying degrees of intensity. Our results suggest that heterogeneity, or perhaps specialization, with respect to DAT activity, are present in the target structures of the primate brainstem dopaminergic cell groups.

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V17. Sleep and its significance for memory consolidation

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Numerous studies suggest an important role of sleep in learning and memory consolidation (e.g., Gais et al. 2002, Maquet 2001, Stickgold et al. 2000). This project intends to test this hypothesis by using two different memory tasks, for which it was demonstrated that performance can be increased by sleep after training. Implicit procedural motor memory is tested with a mirror-tracing task and explicit declarative memory is tested with a paired-associate word list task. Participants are recorded during a screening/adaptation-night and three experimental conditions (2x polysomnography) with full 10/20-digital EEG-recordings. Participants have to participate in a learning condition in the evening (encoding) and in the morning thereafter. Our goal is to replicate that both, early slow wave sleep (SWS) and late rapid eye movement (REM) sleep are required for memory consolidation (two-step model of memory consolidation). Klimesch et al. (1999) have demonstrated that encoding and retrieval of new information is associated with theta synchronization. Respectively, episodes of enhanced theta and delta activity – reflecting memory consolidation – are expected for REM and SWS-sleep after the encoding condition. Preliminary results on: (i) event-related desynchronization and synchronization (ERD/ERS; Pfurtscheller and Aranibar 1977); and (ii) spindle density during non-REM sleep will be presented.

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V18. Functional and behavioral impact of repetitive transcranial magnetic stimulation in the brain

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Transcranial Magnetic Stimulation (rTMS) has become a widely used tool in the field of human cognitive studies. Nevertheless, not much is known about its impact on neural populations at a cellular or network level. Two adult male cats (rTMS $n = 2$) were subjected to high frequency rTMS stimulation at 20 Hz on the left Posterior Suprasylvian Cortex (pMS). Three control animals received sham rTMS (SHAM $n = 1$) on the posterior middle suprasylvian (pMS) cortex and real rTMS on the somatomotor cortex (SM $n = 2$). At 4 different intervals during the stimulation all animals were injected intravenously with 100 μCi/kg of 2-Deoxyglucose labeled with C14 (14C-2DG). The 2DG signal was quantified (in nCi/gr) in individual sections and averaged across cortical and subcortical brain structures. Repetitive TMS induced a significant decrease in the uptake of 14C-2DG on both banks of the stimulated pMS cortex (8-17%). A significant cortico-cortical "knock on" deactivation effect was observed in visual areas 19 (4-7%) and 18 (6-10%) at the marginal gyrus and in the Splenial Visual Area (6-7%). A statistically significant cortico-subcortical deactivation was found in the Superior Colliculus (6-9%) and Pulvinar nucleus in the posterior thalamus (5-8%). We conclude that high frequency rTMS decreases local neural metabolism, induces specific transsynaptic deactivation in richly interconnected brain structures and consequently impairs behavior.

V19. NK1 receptor blockade in hamsters or deletion in mice enhances the changes in locomotor activity following photic entrainment

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The master circadian clock in mammals is in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. It drives the daily variations in many physiological and behavioural processes such as sleep-wake rhythm, daily variations in body temperature and hormone secretion. Dawn and dusk entrains the circadian clock through neural pathways that connect the retina to the SCN, so that circadian rhythms do not drift from 24 h, but remain aligned with the solar day. Chronic alterations in this clock mechanism are associated with sleep disorders and poor health. There is evidence that Substance P and NK1 receptors in the SCN modulate the photic regulation of the circadian timing system in mammals. To further investigate the involvement of NK1 receptors in photic entrainment we have looked at nocturnal wheel running in hamsters treated with the substance P (NK1 receptor) antagonist (SPA) L-760735 and compared this with nocturnal locomotor activity in NK1 receptor deleted (NK1R -/-) mice. We have found that the SPA L-760735 caused enhanced hamster wheel running at the onset of darkness. Similarly NK1R -/- mice displayed enhanced locomotor activity following darkness and settled sooner than WT when lighting was restored. Our conclusion is that NK1 receptors are involved in regulating the changes in locomotor activity that occur during diurnal photic entrainment in hamsters and mice.

V20. Co-expression of Gus and Mup genes as a probable gene-net basis for pheromonally mediated social behavior in *Mus musculus*

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The physiological activity of androgen dependent pheromones in *Mus musculus* L. is strongly associated with major urinary proteins - MUPs (Keverne 1999, Novotny 2003, Sharrow et al. 2002). MUPs are coded by Mup gene(s) cluster which is located on chromosome 4 (Bishop et al. 1982). Another well developed genetic model deals with beta-glucuronidase (GUS, EC 3.2.1.31) coded by gene Gus (Chr. 5). The enzymatic activity of this protein is also connected with pheromonally mediated social behaviors (Bush and Paigen 1992, Ingersoll et al. 1982, Novikov 1993). The detailed analysis of 7 MUPs electrophoretic bands, GUS activity in the voided urine, kidney, preputial and salivary glands, and plasma testosterone level in male mice of CBA/LacY, C57BL/6JY inbred strains and their F1 hybrids revealed significant positive correlation between these parameters only in CBA/LacY genotype with high pheromone activity level. These data suggested the importance of coordinated testosterone dependent expression of Mup and Gus genes in pheromonally mediated behavior in *Mus musculus* L. The obtained results may shed lights on particular causes of interstrain differences in pheromone activity, present valuable approach for dissection of behavioral phenotypes by using the pheromones as a fine natural tool, and can trace the concrete biochemical pathways from gene(s) to behavior (Novikov 2003).

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V21. Reliability and validity of the berlin apraxia test

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Aim of the ongoing project is to create and validate a comprehensive clinical test battery for apraxia assessment. The Berlin Apraxia test contains subtests for ideomotor limb apraxia, oral (buccofacial) apraxia as well as ideational apraxia. Motor apraxia is assessed with different input modalities: verbal, imitation, and visual. The items remain the same over different input modalities, so subtest performance can be compared directly. The test also differentiates between meaningful and meaningless items. Ideational apraxia is investigated by testing tool-object and tool-action knowledge. Psychometric properties of the test are examined with a sample of 60 stroke patients (40 patients with left and 20 patients with right hemispheric stoke). The validity aspect is investigated by the assessment of associations between the test results and both clinical diagnosis of apraxia and the performance in other psychometric tests (convergent and discriminating validity). The assessment of reliability focuses on internal consistency and retest-reliability.

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V22. Distribution of NPY immunoreactivity in the central and peripheral nervous system of amphioxus

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Immunocytochemistry techniques were employed to investigate the distribution of neuropeptide Y-like-immunoreactive (NPY-ir) cells and fibers in the central and peripheral nervous system of the amphioxus (*Branchiostoma lanceolatum* Pallas). NPY-ir neurons of commissural type were abundant in the brain and present but scarcer in the spinal cord. These neurons give rise to conspicuous NPY-ir tracts that coursed along the entire length of the nerve cord. In the peripheral nervous system, small NPY-ir neurons and a large number of thin beaded NPY-ir fibers were observed in the atrial region, indicating the involvement of this substance in visceral regulation. A few NPY-ir fibers, possibly afferent to the spinal cord, coursed in the ventral branches of the spinal nerves of this region, whereas no NPY-ir fibers coursed in the preoral or velar nerves or in the dorsal branches of the other spinal nerves. These results indicate that NPY is widely used as a neuroregulator/neurotransmitter in the central and peripheral nervous system of this primitive chordate. In addition, this study demonstrates the presence of tall thin NPY-ir cells in the putative adenohypophyseal homologue, the Hatschek’s pit organ, which is located in the roof of the preoral cavity (vestibule).

V23. Decreased neuronal density in CA1 and decreased synaptic density in CA1, CA3 and the dentate gyrus of partial trisomy 16 (Ts65Dn) mice

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Ts65Dn mice are partially trisomic for the distal region of MMU16, which is homologous with the obligate segment of HSA21 triplicated in Down syndrome. Ts65Dn mice are impaired in learning tasks that require an intact hippocampus but the neural basis of these deficits is unclear. A quantitative light and electron microscope study was therefore performed to estimate the volume densities of neurons and synapses in CA1, CA3 and the dentate gyrus (DG) of Ts65Dn mice (n = 4) and diploid littermates (DL; n = 4). Neuron density was significantly (P<0.01) lower in the CA1 of Ts65Dn mice (256,883 ± 4,204) compared to DL (302,926 ± 11,925). Synapse density (mean ± SEM. x109) was significantly lower in the CA1, CA3 and DG of Ts65Dn mice (CA1, 1.01 ± 0.04, P<0.001; CA3, 0.99 ± 0.05, P<0.05; DG, 1.04 ± 0.05, P<0.001) compared to DL (CA1, 1.55 ± 0.06; CA3, 1.15 ± 0.04; DG, 1.66 ± 0.08). The mean numbers of synapses per neuron (mean ± SEM) were also significantly lower in Ts65Dn (CA1, 3,966 ± 199, P<0.001; CA3, 6,155 ± 260, P<0.01; DG, 1,615 ± 103; P<0.001) than in DL (CA1, 5,194 ± 246; CA3, 7,592 ± 388; DG, 2,710 ± 169). Therefore, the impaired synaptic connectivity in Ts65Dn mice might, at least in part, underlie their cognitive impairment.