

Magical Ideation, Handedness, and Hemispheric Semantic Activation

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It has been suggested that people diagnosed schizophrenic show a lesser degree of functional and anatomical asymmetry, with schizophrenic symptoms reflecting a ‘dominance failure for language’ (Crow, 1997, *TINS*, 20, 339-343). Magical ideation (defined as “the belief in forms of causation that by convention are invalid” (Eckblad & Chapman, 1983, *Journal of Consulting and Clinical Psychology*, 51, 215-225) has also been suggested as an indicator of proneness to psychosis. It is possible therefore that, in general, the degree of hemispheric dominance may be inversely related to proneness to magical ideation. In this study, 250 psychology students completed a questionnaire measure of magical ideation and a handedness inventory. Questionnaire data showed an increase in magical ideation scores as a laterality quotient approached zero - or the point of ‘hemispheric indecision’. This suggests an increased presence of mixed or ambiguous handedness in persons prone to a high number of paranormal thoughts. This finding strongly supports previous suggestions of an association between reductions in normal cerebral asymmetry and schizotypal thought processes. The neurological basis of magical thinking may involve a decrease in the asymmetry of linguistic functions, characterized by an increase in bilateral language processes and mixed handedness.

Spatial Stroop, Stimulus-Response Compatibility and Disorganisation in Schizophrenia: Evidence for Compromised Response Selection

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The relationship between selective attention deficits and schizophrenic symptomatology remains equivocal. Studies using Stroop tasks indicate an inability to inhibit prepotent responses, particularly perhaps, in patients with symptoms of disorganisation. Twelve patients with schizophrenia performed five reaction time (RT) tasks, increasing in complexity: simple RT, choice RT, spatial Stroop, spatial stimulus-response compatibility (SRC), and a combination of spatial Stroop and SRC. The Positive and Negative Syndrome Scale (PANSS) was used to assess symptomatology and dimensional scores were calculated on the basis of these data. The patients with schizophrenia performed each of the SRT, CRT and spatial Stroop tasks in a comparable fashion to controls, and there were no significant correlations with the symptom dimensions. Patients and controls differed significantly on the spatial SRC task alone, and the combined spatial Stroop and SRC task. Impaired performance on these tasks was associated with the Disorganisation dimension. The results suggest that response selection mechanisms operate adequately in schizophrenia under lower demands for controlled processing (spatial Stroop), but break down, particularly in disorganisation, under higher demands (spatial SRC, and spatial SRC plus Stroop).

Misorientation with Gravity Creates Upside-Down Vision

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A fascinating, although rare, condition occurs when patients suffer from inverted vision, in which they report that their visual world has turned completely upside-down (Solms, Kaplan-Solms, Saling & Miller, 1988). An explanation involving neural routes from the retina would be unlikely. Instead, there is suspected malfunctioning integration between oculomotor control and the sense of gravity (graviception) which is informed by the semi-circular canals of the inner ear. Damage to the insular cortex sometimes causes such rotational vertigo. The posterior part of the insula (vestibular cortex) is a multisensory integration centre for spatial orientation and self-motion perception. The anterior part of the insula is involved in generation and control of spatially-oriented eye movements. If vestibular gravity sense were to mistakenly invert relative to eye muscle proprioception, one might perceive the world as turned upside-down relative to one's body orientation. This is paradoxical because neither one's body nor the topology of retinotopic maps would have actually turned upside-down. Both of Turnbull, Beschin, and della Sala's (1997) patients were particularly prone to misperceiving upside-down visual scenes as upright. I propose that vestibular information had degraded more within each type of canal than between them. Vertical eye motions or head tilting activates vertical canals while horizontal motions alter horizontal canals. Mild damage to the insular cortex degrades (but doesn't destroy) connections between direction of gaze and knowledge of specific directions related to body-parts and graviception. Such patients could still sense familiarity behind horizontal and vertical eye motions while scanning an upside-down picture.

Visual Evoked Potentials to Equiluminant Stimuli

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The visual evoked potential (VEP) has a characteristic morphology comprised of three peaks, the P1, N1, and P2. When stimuli are presented left or right of fixation the P1 is distributed over occipital electrodes contralateral to the field of stimulation, consistent with the mapping of the visual fields from the retina to the contralateral hemisphere. In contrast, the N1 and P2 show bilateral distributions indicative of interhemispheric transfer of the visual information. Source estimations of these peaks also suggest that the P1 is generated contralateral to the field of stimulation whereas the N1 and P2 have bilateral occipital generators. The VEP collected from a mature female acallosic showed the normal bilateral distribution of the N1 and P2, suggesting that the interhemispheric connections are not via the corpus callosum. VEPs to equiluminant hemifield-checkerboards collected from neurologically normal adults produced an N1 contralateral to the field of stimulation rather than a bilateral distribution. These findings suggest that the bilateral distribution of the N1 is a result of communication between visual cortex via the superior colliculus.

Age-Related Changes in AMPA and KA Receptor Pharmacology

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The neurotoxin domoic acid (DOM) is a potent agonist of 2-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and kainic acid (KA)-sensitive glutamate receptors. In a serious case of human DOM poisoning in Canada in 1987 a number of people were hospitalised, and within this group those suffering the greatest neurological effects were elderly, suggesting that aged CNS neurons are more vulnerable to excitotoxic insults. In the present study hippocampi, frontal and temporal cortices were obtained from young (2-3 month) and aged (24-27 month) male Sprague-Dawley rats, and competitive radioligand binding was employed to assess affinity of AMPA and KA receptors to DOM and the receptor-specific agonists S-fluorowillardine and KA. KA receptors from aged frontal cortex exhibited a lower affinity for KA ($K_i = 7.26 \pm 0.66$ nM vs. 3.62 ± 0.29 nM in young; $p < 0.001$) with no change in hippocampus or temporal cortex. In contrast, aged hippocampal KA receptors exhibited higher affinity for DOM ($K_i = 0.78 \pm 0.02$ nM vs. 1.51 ± 0.17 nM in young; $p < 0.005$), while aged temporal cortex exhibited a decreased affinity for DOM ($K_i = 2.65 \pm 0.64$ nM vs. 0.44 ± 0.07 nM in young; $p < 0.006$) with no change in frontal cortex. No age-related change in AMPA receptor affinity for S-fluorowillardine was apparent in any of the brain regions, but AMPA receptor affinity for DOM was significantly decreased in aged hippocampus ($K_i = 101 \pm 17$ nM vs. 56 ± 6 nM in young; $p < 0.02$). Our findings indicate that the vulnerability of aged humans to neurological damage following domoic acid relates to increased sensitivity of hippocampal KA receptors in the aged.

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Localization of 42 kDa Glutamate-Sensitive Protein in Retina

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Glutamate is one of the retinal neurotransmitters. Treatment with glutamate at 10 μ moles/eye or higher, resulted in abnormal eye growth and disappearance of many retinal proteins. Forty-two kDa protein (p42) is the most sensitive one, suggesting that p42 may be involved in the control of eye growth (Sattayasai N, Puchongkavarin H, Sattayasai J., 1996, Glutamate-sensitive protein in chick retina. *Proc 14th International Australasian Winter Conference on Brain Research*, Queenstown, New Zealand). In this study, p42 was found to be a biotin-coupled protein. Antibodies against p42 were produced for localization of this protein using immunological methods. The antibodies could bind to both native and denatured form of p42 with high sensitivity and specificity. Using immunohistochemistry, p42 was localized at the outer part of the inner nuclear layer and bacillary layer of photoreceptor in retina section. From immunocytochemistry, it was found on the cell membrane of non-permeabilized retina cell cultures indicating that it may have an associated function to the glutamate receptor. Using Western immunoblotting, p42 was also found in some other organs such as liver, cardiac muscle, spleen and adipose tissue but not as a biotin-coupled protein. It is possible that p42-related proteins are present in many tissues, and this protein family may have different functions in different tissues.

A Model of Neuronal Cell Death

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The survival of a neuron depends on at least three factors. During early development a glial-derived factor is present; later survival depends on neurotrophins transported retrogradely via axons that connect to other neurons, and on a growth factor activated by extracellular calcium entering via terminals on the neurons. A mathematical model, based on a three-layer network of cells, has been constructed. The basic assumption is that the neurons in the central layer survive only if the total growth factor, equal to the sum of the above individual factors, remains above a certain threshold level. The model also incorporates a previously formulated mechanism for synapse growth and elimination (Bennett & Robinson, 1989, *Proc. Roy. Soc. Lond. B* 235, 299-320; Bennett, 1999, *Prog. in Neurobiol.*, 57, 225-287) based on a competition between nerve terminals for certain formation molecules. The model is used to examine the conditions under which cell survival is possible. It is shown that some cells in the central layer remain if the glial-derived factor plus one of the other growth factors (calcium or neurotrophin) is present, but all three are necessary for realistic levels of survival.

Localisation of GABA_C Receptor mRNA in Rat and Human Brain

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GABA_C receptors are homo-oligomeric receptors, composed of $\rho 1$, $\rho 2$ or $\rho 3$ subunits. Although these subunits have been cloned from retina and studied extensively in the retina, few researchers have investigated the distribution of the GABA_C receptor subunits in the brain. No studies have been published to date which examine the presence of GABA_C receptors *in situ* in human brain. The aim of the present study was to investigate GABA_C receptor subunit mRNAs in rat and human brain using radioactive *in situ* hybridisation. Human and rat tissue was sectioned at 12 μ m and pretreated before use. Oligodeoxyribonucleotide probes labelled with [³⁵S]-dATP were hybridised to the tissue. Sections were washed and dried then apposed to autoradiographic film for 3 weeks. Subsequent autoradiograms were scanned on a densitometer and analysed. The level of mRNA in the tissue was evidenced by increased grey density on the film. In rat brain, GABA_C receptor $\rho 2$ subunit mRNA was detected above background in discrete areas, including regions of the cortex, thalamus, hippocampus, caudate/putamen and cerebellar cortex. In human brain, $\rho 1$ subunit mRNA was detected above background at very low levels in the cerebellum, primary visual cortex, polar temporal cortex and hippocampus. $\rho 2$ subunit mRNA was detected in the cerebellum. These novel findings provide *in situ* evidence of the recently described GABA_C receptors in rat and human brain. Localisation of the GABA_C receptors may facilitate our understanding of the role of these receptors in the brain.

Habituation, Theta and Evoked Responses in the Hippocampus: The Effect of High-Frequency Pulsed Stimulation to the Vestibular Nerve of the Awake Guinea Pig

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Vestibular and optokinetic stimulation are the primary sensory events during spatial navigation. Lesion studies have shown the relative importance of cortical and subcortical connections to the hippocampus for spatial navigation. Stimulation of the vestibular system can be used to explore the hippocampal response to discrete sensory pulses. We have implanted bipolar stimulating electrodes on the nerve leaving the vestibular end organs. By delivering brief pulsed electrical stimulation, the vestibular system is activated causing the eyes and head to move away from the stimulated side. In the recovered behaving animal we monitored hippocampal activity during discrete vestibular activation. Evoked responses were observed, at variable latencies along the rostral-caudal axis of the hippocampus. Following this, theta oscillations were present for up to 2 seconds, and the theta epoch length appeared proportional to the stimulus intensity. Interestingly, vestibular evoked hippocampal activity does not appear to habituate like other sensory modalities. Rapidly habituating evoked responses and theta to sensory events have been explored extensively, leading to an understanding of theta as a sensory filter, one which inhibits irrelevant sensory input from activating the hippocampal-cortical memory system. However, vestibular activity provides information about the animal's position and velocity, and hence is always relevant. Vestibular stimulation may therefore provide clues to the mechanisms of hippocampal habituation and lead to ways to manipulate the salience of a sensory event.

Interhemispheric Transfer in Callosal Agenesis: Extracallosal Pathways or Ipsilateral Motor Control?

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The difference in reaction times between crossed and uncrossed hand-visual field combinations (the crossed-uncrossed difference, or CUD) in subjects with callosal agenesis has been attributed to either slow extracallosal transfer of information from the hemisphere receiving the stimulus information to the hemisphere controlling the motor response, or slow responding via less efficient ipsilateral motor pathways. To date this question has not been tested using electrophysiological methods. This study collected both behavioural and EEG data from 16 control subjects and 3 subjects with complete callosal agenesis. The task was a simple reaction time task in which visual stimuli were presented either singly in one or the other visual field, or in both visual fields simultaneously. Consistent with previous findings, CUDs were lengthened in the acallosal subjects. The visual ERPs of the 3 acallosal subjects were different from controls and from each other. Analysis of the pre-motor negativity suggested normal contralateral control of the responding finger in all but 1 of the acallosal subjects. This subject showed ipsilateral control of the right-hand response in the crossed stimuli condition. While EEG data allows for good temporal resolution, its spatial resolution is less accurate. Source localization was performed to more accurately assess lateralization of response. These data were then modelled onto a 3D image of the subject's head that was digitally constructed from MRI slices.

Brain Sources of Human Theta Oscillations in Memory Tasks

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Hippocampal theta activity (4-7 Hz) accompanies, and may be required for, exploratory spatial behaviour in rodents. Recent PET studies in humans have revealed that the right hippocampal region is activated during navigation in a virtual maze (McGuire et al., *Proc. R. Soc. Lond. B* 263, 1745-1750; 1997). Further, theta-range EEG has been recorded from subdural electrodes on human neocortex during navigation in a virtual maze (Kahana et al., *Nature* 339, 781-784; 1999). These authors have also recorded subdural theta during a working memory task (Raghavachari et al., *J. Neurosci.* 21, 3175-3183; 2001). Here, dense-array (128 channel) EEG was recorded from scalp electrodes during spatial navigation in virtual 3D mazes of varying difficulty, and during a non-spatial Sternberg working memory paradigm using character strings. Theta appeared with maximum power in frontal and right temporal derivations in the spatial navigation tasks, and at frontal and left temporal derivations in the Sternberg task. To remove spatial blurring of the EEG due to skull and scalp, inward continuation procedures (“deblurring”) were employed using a MRI-derived realistic head model. Results of this procedure suggest frontal theta is generated in the frontal and cingulate cortex and temporal theta is indeed generated in temporal cortex. It is suggested that frontal and temporal theta activity during mnemonic processing that may be coherent with hippocampal theta due to cortico-limbic interactions via the diencephalon (Kirk, *Neurosc. Biobehav. Rev.* 22, 291-302; 1998).

Changes of Vertical Posture, Walking, Short-Term Memory and Intellectual Facilities in Children with Cerebral Palsy after Treatment by using a Space Suit “Penguin”

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We used a space suit known as “Penguin” for the treatment of children with cerebral palsy (CP) of the spastic, hemiparetic, hyperkinetic and atonic-astatic forms. Before treatment all patients were separated by handedness on the basis of hand preference. Vertical posture and walking were measured by stabilography, kinematic and dynamic analysis systems. Verbal and nonverbal short-term memory and intellectual facilities were studied by standard psychological methods. The stabilography analysis showed that children with the hyperkinetic and atonic-astatic forms of CP had the lowest level of vertical stability. All of them had an asymmetry of the center weight of the body (ACWB). Biomechanical analysis of walking showed a decrease of extension and volume of movements (VMs) of the knee-joints and the ankle-joints but simultaneously an increase of VMs of the pelvic-joints, in children with the spastic form of CP. Children with the hemiparetic form of CP exhibited a decrease of VMs on the damaged side. The walking of children with atonic-astatic form of CP was like the walking of healthy children. After treatment we observed in all patients an increase of vertical stability and his visual control and an decrease of ACWB. Also there was an increase of VMs of the knee-joints and ankle-joints and simultaneously a decrease of asymmetric of movements. Short-term memory and intellectual facilities were decreased in all groups of patients. After treatment we observed an increase of the level of verbal and nonverbal short-term memory and intellectual facilities in right-handed but not find in left-handed children. The therapeutic mechanism of the space suit “Penguin” is normalization of the afferent stream from receptors of muscles, joints, and ligaments and the formation of new antigravity and locomotor reflexes. At the same time our results showed new opportunities for therapy of short-term memory and intellectual facilities in children with CP.

The Effect of Rest Duration on Maximal Voluntary Activation of Muscles: Does the Central Nervous System Care?

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The relationship between central and peripheral neuromuscular mechanisms of fatigue during performance of maximal voluntary contractions (MVCs) remains unclear. Activities like weightlifting require repeated maximal generation of force. The extent to which the length of the rest interval between lifts affects maximal force production is unknown. We examined the effect of inter-trial rest length (30, 170 and 350 seconds) on MVC, integrated electromyography (EMG), M-wave amplitude, interpolated twitch (IT) force and IT force ratio during 10, 10 second trials. Six male participants (22.3 ± 2.4 years, 79.3 ± 8.9 kg, 175.4 ± 4.9 cm), with no history of neuromuscular injury or disease, were tested. Force and surface EMG were recorded during isometric MVCs of the right knee extensors. Supra-maximal stimulation of the femoral nerve was delivered before, during and following each MVC. Interpolated twitch force prior to MVC was significantly greater for trial 2 than for trial 1 ($p=0.04$). Pre-MVC IT force was significantly greater ($p=0.001$) for the 30-second rest condition than the 170- and 350-second conditions. The rest condition effect remained across trials but pre-MVC IT force gradually diminished toward initial (trial 1) values ($p=0.001$). It appears that shorter rest intervals favour retention of cross-bridge formation resulting in greater pre-MVC IT force. The biological capabilities of the neuromuscular system to produce maximal force appear to be different than the capability to generate force by intent.

Proportionality of Duration in a Simple Human Movement

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The theory of the Generalised Motor Program (GMP) suggests that the fractional temporal contribution of individual components of an action are maintained as the overall time for the action varies. This is referred to as the Proportional Duration Model (PDM). Rapid (3 – 5 Hz), repetitive, 45 – 76 mm, unilateral movements (flexion – extension) of the forearms without visual feedback of 12 strongly right-handed subjects (20 – 27 year old females) were recorded using a Wacom™ graphic design tablet. The recorded lines were divided into reversal points, acceleration, and deceleration phases with an accuracy of ± 1 ms. The ratio of the duration of each of these components was compared between 5 arbitrary flexion-extension cycles taken from the same experimental set of lines, but displaying different linear velocities. Chi-square analysis showed remarkable consistency between these ratios for different unilateral cycles even though the overall timing of the actions was different. Although the ratios were bilaterally dissimilar for individual subjects, the proportionality was still constant. These results may indicate that the GMP for fast simple harmonic motion is immanent to the PDM. As there was no involvement of higher cognitive motor control the differences recorded may be explained by the dynamic properties of moving limb muscle systems. The temporal scheme of movement in this case may reflect the stiffness of muscles. Our results for rapid, periodic movement of the left and right upper limbs support Schmidt's GMP theory.

Locomotor Activation Produced by MDMA (Ecstasy): Acute and Chronic Effects in Rats

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Following repeated exposure to a number of psychostimulants, there is an increase in the magnitude of the behavioural and neurochemical responses. This sensitised response has been hypothesized to underlie the transition from drug use to compulsive drug use that characterizes abuse. (+/-)3,4-Methylenedioxymethamphetamine (MDMA; "Ecstasy") is becoming an increasingly popular drug of abuse in New Zealand as in the rest of the world. Like the more prototypical stimulant drug, amphetamine, MDMA has been reported to produce hyperlocomotion in laboratory rats. The present study examined the effects of repeated exposure to MDMA as well as the influence of prior exposure to amphetamine on the response to MDMA. Rats received a pre-treatment regimen consisting of 5 daily amphetamine (2.0 mg/kg/day, IP) or saline (1.0 ml/kg/day, IP) injections. Three days following the last injection, they received an acute injection of MDMA (0.0, 5.0 or 20.0 mg/kg, IP). Locomotor activation was measured for a 1 hr period following the injection. For both groups of rats, MDMA increased activity relative to the saline control group. The magnitude of the behavioural response of the group treated with 20.0 mg/kg MDMA was greater in the amphetamine-preexposed rats, suggesting that they were sensitised to this behavioural effect of MDMA. The rats received an additional 4 injections of MDMA (0.0, 5.0 or 20.0 mg/kg/day, IP) and locomotor activation was measured following this chronic treatment. There was no change in the hyperlocomotion produced by MDMA for the amphetamine-pretreated rats. However, the effect of 20.0 mg/kg MDMA was markedly increased in the saline pretreated rats, suggesting that they had become sensitised to this behavioural effect of MDMA as a result of repeated exposure. These data suggest that the effects of repeated exposure to MDMA are comparable to the effects of repeated exposure to other psychostimulants. The development of a sensitised response following repeated exposure might be a factor that contributes to the continued use of MDMA.

Use of Real-time PCR for Quantitation of mRNA Expression in Microdissected Hypothalamic Nuclei

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Analysis of gene expression in hypothalamic neurons involves measurement of mRNA in small amounts of tissue, requiring a technique that is both sensitive and quantitative. The aim of this study was to validate a new method for quantifying mRNA expression in specific populations of neurons, using microdissection followed by real-time RT-PCR. Rat brains were rapidly frozen, and thick (300 μm) coronal sections cut through the hypothalamus using a cryostat at -9°C . Specific hypothalamic nuclei were microdissected using a punch technique, and total RNA was extracted and reverse transcribed. The cDNA was then amplified using sequence specific primers, together with a dual-labeled fluorogenic hybridisation probe. Hydrolysis of the probe during amplification causes emission of a fluorescent signal that is continuously monitored (TaqMan system, ABI 7700). Fluorescence is therefore directly proportional to amount of amplified cDNA. By combining the specificity of the punch microdissection technique, with the sensitivity and accuracy of the real-time RT-PCR technique, we are able to quantify mRNA expression within anatomically defined brain regions as small as 300 μm in diameter (60 μg wet weight). Replicate measurements were extremely reliable (coefficient of variation 1.07%). Using dilution series, we have demonstrated that the assay performs in a log-linear fashion over a 1000-fold range of starting concentrations. We have utilised this approach to demonstrate 10-fold differences in the relative levels of expression of prolactin-releasing peptide mRNA in different hypothalamic nuclei, and have also quantified 3-fold changes in prolactin receptor mRNA expression in specific brain regions during pregnancy and lactation. This technique will be of value in a wide variety of Neuroscience applications.

Lateralised Linguistic Processing in Callosal Agenesis

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Behavioural laterality tasks were used to assess interhemispheric integration and specialization for linguistic stimuli in four cases of callosal agenesis (all female, ages 13, 14, 35, and 41 years). A lexical decision task was used with words and nonwords randomly presented to the left visual field (LVF), right visual field (RVF) and both visual fields together. Normal subjects show faster and more accurate lexical processing when words are presented to both hemispheres at once compared to RVF presentation alone. This “bilateral” gain, thought to be due to excitatory transcallosal connections, is not seen in the split-brain (Mohr et al., 1994 *Neuroscience Letters*, 181, 17-21), presumably because the transcallosal connections have been surgically cut. In contrast, we found that those born without a corpus callosum did show a bilateral gain on this task, suggesting extra-callosal neural integration. There was no bilateral gain for nonwords, consistent with the view that there are no interhemispheric cell assemblies representing unfamiliar stimuli. A dual-task procedure, consisting of speeded right and left finger tapping alone and during oral and silent reading, was also used. For controls, right hand tapping was more disrupted than the left during both reading conditions (consistent with left hemisphere representation). Although all of the subjects with callosal agenesis showed a similar pattern (including similar baseline rates and variability), significantly more bilateral interference was observed in the oral reading condition compared to controls, suggesting that more hemispheric processing resources were applied to the task.

Phonological Assembly in Dyslexia - A 3T fMRI Case Study

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Developmental phonological dyslexia has been characterized as a deficit in phonological assembly. At a neural level, it is possible that this deficit is represented by weak connectivity between anterior and posterior language systems in the left hemisphere. This study used 3-Tesla fMRI to investigate phonological assembly in a phonological developmental dyslexic, in comparison to a developmental surface dyslexic and a control subject. The phonological dyslexic showed increased activations in the left hemisphere of the inferior frontal gyrus (BA 44/6), and increased activations in the right hemisphere of the parietal cortex (BA 7) occipital cortex (BA 18) and in the cerebellum, in comparison to the developmental surface dyslexic and the non-impaired reader. Converging evidence suggests that the core dysfunction in phonological dyslexia resides in and around the angular gyrus of the left hemisphere. This study supports the compensatory role of posterior regions in the right hemisphere together with the left inferior frontal gyrus.

Unruptured Intracranial Aneurysm Outcome Study

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The prevalence of unruptured intracranial aneurysms (UIAs) in the general population is estimated to range between 1-2%, with an annual risk of rupture of approximately 2%. In 40-50% of cases, rupture of these aneurysms results in death or long term disability. UIAs, therefore, cannot be considered to be innocuous with many surgeons making it their policy to recommend treatment wherever possible. However evidence from a recent prestigious study by the International Study of Unruptured Intracranial Aneurysm Investigators (ISUIA) has questioned the viability of such recommendations. Research currently underway aims to further investigate outcome following UIA treatment. In the first part of this study a brief retrospective review of patients who had undergone surgery for UIAs confirmed the ISUIA finding of surprisingly high rates of morbidity following treatment. The second part of the study aims to more thoroughly investigate outcome following UIA treatment with a full battery of neuropsychological, psychosocial and functional outcome measures administered both prior to and 6 months following treatment. Preliminary results from the prospective arm of the study have cast further light on the nature of the cognitive deficits, suggesting that treatment of a UIA results in some specific localised deficits, at least for some patients. It should be noted, however, that the same degree of deficit as is noted to follow SAH has not been observed. Thus whilst elective treatment of UIAs does appear to carry some degree of risk, in most cases this risk is likely to be outweighed by the fact that treatment also removes the risk of future haemorrhage.

Adjuvant Chemotherapy & Neuropsychological Functioning – A Prospective Study

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Patients with cancer who receive adjuvant chemotherapy often complain of short and long-term difficulties with memory, concentration, and slowed mental agility. Despite this, few empirical studies have assessed the neuropsychological functioning of this patient group, and all used cross sectional designs. The current study uses a prospective design to document the prevalence and nature of acute and sustained cognitive impairment in breast and bowel cancer patients receiving adjuvant chemotherapy. Breast and bowel cancer patients receiving adjuvant chemotherapy completed neuropsychological assessments prior to commencing chemotherapy, four months after beginning treatment, and again nine months after completing treatment. Their performance is compared with that of an age, sex, and premorbid IQ matched sample of cancer patients who receive local treatment for cancer only. Preliminary results (n=54) indicate that four months after beginning treatment the patients receiving chemotherapy perform significantly worse than the cancer controls on tests of working memory, delayed memory, speed of information processing and verbal fluency. These performance differences are not due to the effects of anxiety or depression. The observed symptom patterns are consistent with a mild neurotoxicity syndrome. These preliminary findings suggest adjuvant chemotherapy does have at least short-term effects on cognitive functioning.

Phospholipase C Isozyme Activity in Ca²⁺-Stimulated Exocytosis from Adrenal Medullary Chromaffin Cells

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The role of specific phospholipase C (PLC) isozymes in exocytosis has been investigated using bovine adrenal medullary chromaffin cells permeabilized with digitonin. This preparation allows direct activation of the exocytosis by Ca²⁺ (bypassing receptor-mediated events) while permitting access of PLC isozyme-specific antibodies to the cell interior. Chromaffin cells, cultured on 96-well plates, were permeabilized with digitonin (20 μM for 2 mins) and then preincubated for a further 20 min in a Ca²⁺-free K⁺-glutamate buffer in the presence or absence of antibodies or inhibitors. Ca²⁺-induced exocytosis (measured by [³H]noradrenaline release) was reduced by the PLC inhibitor U73122 (10 μM). This inhibition of the Ca²⁺-response was due, in part, to an elevation in basal release (that occurring in the absence of Ca²⁺). Preincubation with PLCγ1-or PLC β3-specific antibodies (1:100) also inhibited this response, such that the addition of Ca²⁺ (5 μM) failed to elevate release above that seen in the absence of Ca²⁺. As with U73122 the inhibitory action of these antibodies was in large part due to an elevation in basal release. In contrast to the above Ca²⁺-stimulated release was still seen following preincubation with the same concentration of antibodies specific for PLCδ1, δ2, β1, β2 or β4. These data therefore suggest that PLCγ1 and PLCβ3 activity but not that of other PLC isozymes, may be important in regulating exocytosis from chromaffin cells.

The Characterisation of Tyrosine Hydroxylase Activity in Tuberoinfundibular Dopaminergic Neurons in Vitro

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Tuberoinfundibular dopaminergic (TIDA) neuron cultures from fetal rats (day18-20) have been established. These cultures have been successfully maintained for over 4 weeks in a chemically defined medium. These initial studies have focussed on tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine biosynthesis. TH-expressing cells were identified using immunocytochemistry. These TH positive cells displayed many branching processes which became more extensive with time in culture. The presence of TH in these cultures was confirmed by Western blotting and enzyme activity measurement. Western blotting revealed a single protein band with molecular weight of about 60 kDa. These cultures exhibited a measurable TH activity (determined by trapping the ¹⁴CO₂ released consequent to the decarboxylation of DOPA formed from ¹⁴C-tyrosine) under basal conditions. This TH-activity was significantly increased by prolactin (an endogenous regulator of TIDA neurons) in a time and concentration dependant (10-1000ng/ml) manner. Treatment with prolactin (1000ng/ml) significantly increased TH activity above basal after 30min, rising to approximately 120% basal after 120min. TH activity in these cultures was also increased by angiotensin II (10-100nM) but not by histamine (100mM) or 5HT (10mM). Current studies are directed at determining the differences in these two TH activation pathways.

Late Postnatal Plasticity in GABA_A Receptor Signaling in GnRH Neurons

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The gonadotropin-releasing hormone (GnRH) neurons regulate fertility through the direct regulation of gonadotropin secretion from the pituitary gland. These neurons are unusual in that they remain functionally dormant until the late postnatal period when they become activated to initiate puberty. Using molecular and cellular approaches in conventional and transgenic mouse models, we have examined the role that GABA_A receptor-mediated signaling may have in the postnatal activation of these neurons. Single cell, multiplex RT-PCR analyses revealed that the complement of GABA_A receptor subunit mRNAs expressed by GnRH neurons is reduced in adults compared with pre-pubertal mice. Whole cell, current-clamp recordings of GnRH neurons demonstrated substantial tonic and phasic GABAergic inputs mediated by the GABA_A receptor. Although adult GnRH neurons displayed increased sensitivity to exogenous GABA compared with juvenile mice, the most striking difference between the two developmental states was the marked variability in GABA responses recorded from individual juvenile GnRH neurons. Gramicidin-perforated patch recordings showed that GABA depolarized GnRH neurons in pre-pubertal mice but inhibited the firing of adult GnRH neurons. Thus, pre-pubertal GnRH neurons express multiple GABA_A receptors and display a heterogeneous sensitivity to GABA. After puberty, GABA now inhibits the firing of GnRH neurons and does so in a uniform manner. These changes are likely to be involved in the ability of GnRH cells to form a synchronized network of output neurons which initiate puberty and control fertility in the adult.

Distinct Labeling of Subcellular Compartments in Bovine Adrenal Medullary Cultures Using Different α -Synuclein Antibodies

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Alpha-synuclein (α -syn) is a protein of unknown function which is linked to Parkinson's disease. α -syn has been described in the synapses of many brain regions, and on the plasma membrane of cultured PC12 cells. We have used bovine adrenal cultures, which are neurosecretory, to study the normal function of α -syn. Immunocytochemistry and confocal microscopy showed different labelling patterns with two antibodies to α -syn. Syn-1 antibody (Transduction Labs) showed labelling reminiscent of the Golgi apparatus in chromaffin cells and other contaminating cell types. The Golgi was intensely labelled even when cells appeared to be dead. In contrast, AB5336P antibody (Chemicon) appeared to label the cell surface but not the Golgi apparatus. Chromaffin cells were labelled more strongly than other cell types. After 4 days in culture, cells had smooth surfaces and were labelled lightly. With increasing time in culture, AB5336P-positive blebs and larger bodies that resemble apoptotic bodies appeared on the surface of these cells. Our conclusions from this preliminary study are: that α -syn may have a different conformation in different parts of the cell (and thus different antibody recognition sites), in line with its putative role as a chaperonin; that it is found in the Golgi, perhaps to assist with protein folding or processing, and that it may be concentrated at points of apoptotic body formation during cell death.

Influence of Leptin on Serotonin Overflow from the Rat Hypothalamus

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Leptin is released into the blood by mature adipocytes and is known to circulate in human plasma in concentrations proportional to the amount of fat mass. Recent studies demonstrate that leptin is released from the human brain (Wiesner, G., Vaz, M., *et al. J. Clin. Endocrinol. Metab.* (1999) **84**: 2270 – 2274). Leptin receptor immunoreactivity has been reported in various regions of the hypothalamus (Håkansson, M-L, Brown, H *et al., J. Neurosci.* (1998) **18**: 559-572), while dense concentrations of serotonin (5-HT) receptors have been observed within the hypothalamus. This study investigated the relationship between leptin and brain serotonergic pathways by evaluating the effects of exogenous leptin (0.2 – 3 nM) on 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) from the rat hypothalamus using *in vitro* superfusion and HPLC with coulometric detection. Data were analysed using repeated measures ANOVA. Basal hypothalamic overflow of 5-HT and 5-HIAA averaged 2.1 ± 0.4 and 25.7 ± 3.1 pg/mg hypothalamus/10 minutes, $n = 18, 17$ respectively. Superfusion with leptin was without significant effect on basal hypothalamic 5-HT overflow but induced an increase in 5-HIAA overflow from the hypothalamus ($P < 0.05$) perhaps reflecting altered serotonergic metabolism induced by leptin. These results lend further support to the complex nature of the neurotransmitter/peptide systems involved in the control of feeding within the brain, and provides further evidence of a functional link between brain leptin and serotonin systems.

Kappa and Mu Opioid Receptor Regulation of Prolactin Secretion in Late Pregnant Rats

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Prolactin secretion is tonically inhibited by dopamine released from tuberoinfundibular dopamine neurons (TIDA) in the hypothalamus. During late pregnancy, endogenous opioid pathways (EOP) facilitate prolactin secretion by reducing TIDA neuronal activity. In this study the specific opioid receptor subtypes that mediate this suppression of TIDA neurons were investigated. Selective opioid receptor antagonists nor-binaltrophimine (kappa receptor, 15 µg/5µl), β funaltrexamine (mu receptor, 5 µg/5µl) and naltrindole (delta receptor, 15 µg/5µl) or saline were administered intracerebroventricularly at 0100 h during the *ante partum* prolactin surge on day 22 of pregnancy. Animals were sacrificed 2 hours later at 0300 h and 3,4-dihydroxyphenylacetic acid (DOPAC) content in the median eminence was measured by high-performance liquid chromatography as an index of TIDA activity. Nor-binaltrophimine and β funaltrexamine significantly increased DOPAC concentrations in the median eminence (16.85 ± 1.75 and 15.40 ± 3.89 pg/µl protein, respectively) compared to saline-treated controls (8.34 ± 0.62 pg/µl protein). Antagonist-induced increases in TIDA activity were associated with significant reductions in serum prolactin levels compared to control animals. Naltrindole had no effect on median eminence DOPAC or serum prolactin. The data suggest that EOP act at both mu and kappa opioid receptors to inhibit TIDA activity at the end of pregnancy, thereby removing the inhibitory influence on prolactin secretion and allowing the expression of the *ante partum* prolactin surge.

Secondary Epileptogenesis in Glutamate Transporter (GLAST) Knockout Mice

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Glutamate is a predominant excitatory neurotransmitter in the mammalian central nervous system. We previously reported abnormal glutamate release during seizures following kindling. GLAST and GLT-1 are astrocytic glutamate transporters, highly concentrated in the cerebellum and the telencephalon, respectively. We have investigated whether stages of amygdala kindling in knockout(KO) mice deficient in GLAST are the same as those of wild mice and whether there is secondary epileptogenesis. Method: Electrodes were implanted into the basolateral amygdala (B2.0,L3.0,H-4.5) in C57BL/6J mice and GLAST KO mice under anesthesia. Once-daily stimulation of biphasic square pulses was applied through the stimulation electrodes. Results: The behavioral changes of the kindling in mice were: 1) arrest of behavior, 2) head nodding, 3) forelimb clonus, 4) dual forelimb clonus with rearing, 5) tonic generalized convulsion with elevation of tail, falling with GTC. There was a significant difference in the development of kindling. More stimulation was required for the kindling in GLAST deficient mice. There was no difference in the duration of AD between control and GLAST KO mice until the 16th stimulations. However, the afterdischarges became slightly longer following overkindling in the control mice. The numbers of spikes at the stimulation point and secondary site in the GLAST KO mice were greater than those of control mice. These results suggest to us that the GLAST(cerebellar glutamate transporter) may have a role in secondary epileptogenesis.

Possible Linkage of Mitochondrial Benzodiazepine Receptor System with Expression of Kindled Seizures

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Recently, it has been reported that the peripheral-type benzodiazepine receptor that locates mainly on the mitochondrion (Mitochondrial Benzodiazepine Receptor, MBR), is implicated in the epileptogenesis/seizure susceptibility in the genetically prone epileptic mouse, EL. MBR exists on the mitochondrial permeability transition pore, which is constructed with several proteins including voltage dependent anion channel, pk-18, adenine nucleotide translocator etc. The mitochondrial permeability transition pore controls cell excitability and death through calcium flow and release of cytochrome-c and other apoptosis-relating proteins, respectively. At first, we examined the effects of Ro-5-4864 (5-40mg/kg) and PK-11195 (7.5-60mg/kg), which are known as an agonist and an antagonist of MBR, respectively. Unexpectedly, both agents inhibited kindled seizures in the same manner with a U-shaped profile. This suggests that the MBR has a modifying function on the kindled seizure expression. Secondly, we tested the interaction between these agents and nefiracetam, a new nootropic pyrrolidone derivative that is reported to interact with MBR. Nefiracetam itself showed potent anticonvulsant effects on the kindled seizures in a dose-dependent manner (15-90mg/kg). PK-11195 (7.5mg/kg) itself showed no remarkable effect on kindled seizures, however, it partially decreased the inhibitory effect of 30mg/kg nefiracetam and then augmented the anticonvulsant effects of 15mg/kg nefiracetam. Inexplicably, PK-11195 (15 and 30mg/kg) and Ro-5-4864 (5, 10 and 20mg/kg) did not have any effect on the anticonvulsant profile of nefiracetam (3.75-60mg/kg). These results indicate that the MBR system has cross talk with seizure expressing mechanisms in the kindled model, but further research may require to be able to explain the present results.

A New Psychosis Model Produced by Electrical Stimulation in the Rat Ventral Tegmental Area

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The ventral tegmental area (VTA) is a major source of the mesolimbic dopaminergic pathway. It was previously reported that repeated electrical stimulation of the VTA produced a progressive increase in abnormal behaviours in cats or rats and this could be an experimental model for paranoid psychosis (“VTA kindling”; Stevens et al, 1978, Glenthoj et al, 1993). In the present study, we made a detailed analysis of the behavioural responses induced by VTA stimulation and their interactions with methamphetamine (MAP) induced behaviours. Chronic bipolar electrodes were bilaterally implanted into the VTA of Sprague-Dawley rats. Electrical stimulation (100 Hz, 2 sec) was delivered to the VTA at various intensities (10 to 100 μ A). The behavioural responses, which consisted of forward locomotion and exploration, were increased in a stimulus intensity-dependent manner and significantly attenuated by several dopamine receptor antagonists, suggesting that VTA stimulation produces a transient hyperdopaminergic state in the rat brain. Although an acute administration of MAP did not affect these behavioural responses, chronic treatment with MAP (4mg/kg i.p. for 2 weeks; “behavioural sensitization”) caused a long-lasting reduction in the electrical threshold for the induction of the behaviours. Furthermore, in our preliminary study, MAP induced abnormal behaviours were augmented after VTA kindling. These results indicate that the VTA has an important role in the development of paranoid psychosis.

Brainstem Kindling and Its Influence on Subsequent Amygdala Kindling in Rats

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There are few studies on brainstem kindling. We found that in rats daily stimulation of the interpeduncular nucleus (IPN) at an afterdischarge-inducing threshold produced progressive afterdischarge growth and recruitment of behavioral seizures (the final form; generalized tonic-clonic seizures with or without a limbic seizure component), and that subsequent amygdala (AM) kindling resulted not only in more rapid kindling but also in tonic seizure associated with a protracted loss of postural control not observed in animals undergoing AM kindling without previous IPN kindling. We also found that in rats, the MRF can be kindled and the MRF kindling has facilitory influences on subsequent amygdala kindling. On the other hand, midline electrolytic lesioning of the midbrain, including the IPN and the medial part of the MRF, retarded the development of the primary site AM kindling and eliminated positive transfer effect at the secondary site. The results suggest that the brainstem can be kindled and that subsequent limbic kindling utilizes the proconvulsant neuroplastic changes that have been already established by brainstem kindling.

Glutamate Receptors, Kindling and Plasticity

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A number of previous studies have suggested that glutamate receptors play an important role in seizure induction and development of epileptogenesis in the kindling model of temporal lobe epilepsy. So far, three major lines of evidence have been reported: (1) repeated focal injections of glutamate produce kindling-like phenomena and interact positively with electrical kindling, (2) some types of glutamate receptor antagonists inhibit kindled seizures, and (3) extracellular concentrations of glutamate are markedly increased during kindled seizures. We have previously demonstrated that competitive and non-competitive types of NMDA receptor antagonists strongly retard kindling development, while they have only weak anticonvulsant effects on kindled seizures. It is demonstrated here that AMPA receptor antagonists (NBQX and YM90K) have potent inhibitory effects on amygdala-kindled seizures as well as on kindling development. These anticonvulsant effects are also seen when NBQX-Na is directly injected into the kindled amygdala, suggesting that the AMPA receptor subtype is involved in the seizure induction mechanism. Intra-amygdala injection of *DL*-APV does not show any effects. In contrast to NMDA receptor antagonists, AMPA receptor antagonists at the anticonvulsant dose affect neither field potentials nor long-term potentiation (LTP) in the dentate gyrus of the rat hippocampus in vivo. These results indicate clinical usefulness of AMPA receptor antagonists as an antiepileptic drug

Metabotropic Glutamate Receptors, Protein Synthesis, and Long-Term Depression in the Hippocampus

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Two mechanistically distinct forms of homosynaptic long-term depression (LTD) coexist in the hippocampus. Induction of one form depends on activation of N-methyl-D-aspartate receptors (NMDARs) and postsynaptic protein phosphatases, while induction of the other depends on activation of postsynaptic group 1 metabotropic glutamate receptors (mGluRs) and the local translation of dendritic mRNA. There is strong support for the idea that NMDAR-dependent LTD (NMDA-LTD) is a consequence of reduced synaptic expression of AMPA receptors (AMPA receptors). Less is known about expression of mGluR-dependent LTD (mGluR-LTD), although a presynaptic mechanism has been suggested. Evidence will now be presented that a consequence of mGluR activation in the hippocampus is the rapid loss of both AMPA and NMDA receptor clusters at synapses. Like mGluR-LTD, the stable expression of this postsynaptic change requires protein synthesis.

Synaptic Plasticity in the Superficial Dorsal Horn

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Long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission following high-frequency (100Hz) stimulation of dorsal roots has been reported in rat spinal dorsal horn (DH) slices. Previous studies have demonstrated a critical role of calcium influx through postsynaptic NMDA receptors in the induction of LTP and LTD. The role(s) of calcium influx through AMPA and kainate subtypes of glutamate receptors in synaptic plasticity is less well established. To test whether the GluR2, AMPAR subunit, or the GluR5 KAR subunit, play any role in the induction of LTP and LTD, we used mice in which the GluR2 or GluR5 subunit was ablated by gene targeting. EPSPs in superficial DH neurons, evoked by stimulation of A- and C-afferents, were examined by intracellular and whole-cell recordings in spinal slices. LTP, in GluR2 mutants, is increased and has a substantial NMDAR-independent component. These data strongly suggest that LTP can be mediated by Ca^{2+} influx through Ca^{2+} -permeable AMPARs. Bath-applied kainate (1-3 μ M) induces LTD of the AMPAR-mediated EPSPs evoked by A δ and/or C fiber stimulation in wild-type mice, whereas in GluR5 mutants the depressant effect is reduced. Moreover, the lack of the GluR5 subunit resulted in impairment of LTP and LTD. These results suggest that GluR5 subunits contribute to the KAR that regulates excitatory synaptic transmission and plasticity in the spinal DH. Regulating role(s) for mGluR1, NK1, and μ opioid receptors in synaptic plasticity in the DH is also supported by recent experiments in transgenic mice.

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Cooperativity Between Glutamate and Dopamine Receptors for Plasticity Induction in Rat Prelimbic Neurons

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Rodent prefrontal cortex may be involved in the construction and the utilization of selective perception-action sets, analogous to primate prefrontal cortex. We study long-term depression (LTD) and potentiation (LTP) in layer I-II to layer V pyramidal neuron glutamatergic synapses in rat prefrontal slices. Fifty Hz tetani to layer I-II fibers in the presence of bath-applied dopamine (100 μ M) induced LTD of the monosynaptic EPSP ($-22 \pm 7.6\%$, $n=14$). Tetani alone ($-0.7 \pm 1.0\%$, $n=11$) or dopamine alone ($4.7 \pm 7.0\%$, $n=5$) did not induce LTD. This LTD required at least two additional factors that cooperate with dopamine receptors (DA-Rs): postsynaptic Ca^{2+} entry from voltage-gated channels, and synaptic activation of groups I&II metabotropic glutamate receptors (mGluRs). However, agonist co-stimulation of DA-Rs and the mGluRs was sufficient to induce LTD without afferent stimuli, and this pharmacological LTD required postsynaptic converging activation of MAP kinases via these receptors. Interestingly, strong agonist sole-stimulation of group II mGluRs could also induce LTD. This group II mGluR-induced LTD depended on postsynaptic PKC, and postsynaptic IP_3 production and Ca^{2+} release. NMDA receptors participate for the group II mGluR-induced LTD, because NMDA receptor blockade blocked group II mGluR-induced LTD. Finally, we searched for conditions where dopamine facilitates LTP. Coupling tetani to dopamine application induced LTP ($19 \pm 3.6\%$, $n=8$), when the coupling was preceded (~ 30 min) by initial dopamine sole-application. DA-Rs are tonically stimulated in awake conditions. This LTP, therefore, might model a physiological plasticity induction in prefrontal neurons.

Synaptic Plasticity in Very Small Populations of Synapses Between Individual CA3 Pyramidal Neurons

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Whole cell recordings made from two individual synaptically connected pyramidal neurons in organotypic hippocampal slices provides the opportunity to study processes of synaptic plasticity in very small populations of synapses; approximately 10 per connection. These synaptic connections usually contain a mixture of active and silent synapses, but connections having all silent synapses or all active synapses are commonly found. Long-term potentiation (LTP) can be induced in all such paired recordings, except in connections having no silent synapses, supporting the hypothesis that LTP results from the activation of silent synapses. All-silent connections have no AMPAR-mediated excitatory postsynaptic current (EPSC), but do display robust NMDAR-mediated EPSCs. The induction of LTP in all-silent connections is extremely reliable (100%), and results in the addition of AMPAR-mediated responses. However, this is not accompanied by a change in the NMDAR-mediated EPSC. Comparison of the trial to trial failure rates of AMPAR and NMDAR-mediated EPSCs before and after the activation of all-silent connections rules out glutamate spillover as a mechanism to explain synapse silence. Furthermore, direct application of the agonist AMPA to synapses undergoing potentiation reveals a robust increase in postsynaptic AMPA-sensitivity. These data strongly support the idea that the activation of silent synapses and the expression of LTP are entirely postsynaptic. Synaptic plasticity of transmission between two individual neurons is also bi-directional, as they can undergo, LTP, long term-depression (LTD) and depotentiation.

Protein Synthesis in Axon Terminals Isolated from Adult Rat Cortex

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Protein synthesis in areas remote from neuronal cell bodies may in part account for the selective modification of activated synapses. Such synaptic plasticity may contribute to neural development, learning and responses to injury. Here we report evidence for presynaptic protein synthesis. Immunoblots demonstrated that purified axon terminals (synaptosomes) isolated from adult rat cortex were enriched for synapsin I, a synaptic marker, negative for histone protein, a nuclear marker and were positive for the protein synthesis factors eIF5 and eEF2. We found using RT-PCR that the synaptosomes contain β -actin, α CaMKII and elongation factor-2 mRNA but not transcription factor zif/268 mRNA. Synaptosomes were shown to undergo extramitochondrial protein synthesis by incorporation of ³⁵S-methionine into protein in the presence of chloramphenicol. Protein synthesis was constant over 60 min and inhibited by cycloheximide. These data provide new evidence for presynaptic protein synthesis in the adult rat cortex. Synaptic plasticity therefore may be regulated through the co-ordinated translation of both pre- and postsynaptic mRNA.

LTP, Learning and Immediate Early Genes

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The immediate early gene *Zif268*, encoding a zinc finger transcription factor, is activated in granule cells of the dentate gyrus by LTP-inducing trains delivered to the perforant path. Recent experiments on a mutant mouse containing a targeted inactivation of the *Zif268* gene indicate that activation of this transcription factor is necessary for the development of late LTP, but not for early LTP. Correspondingly, behavioural experiments (carried out in collaboration with Sabrina Davis and Serge Laroche, University of Paris Sud, Orsay) show that across a wide range of tasks, the *Zif268* mutant mouse scores normally in tasks which rely on short-term memory, but is impaired in tasks which require long-term memory. These results are consistent with the view that short-term memory relies on synaptic mechanisms that do not require protein synthesis, while long-term memory depends on persistent LTP that requires effector genes activated by *Zif268*.

CREB Phosphorylation-Associated Stable LTP Lasting Months in the Hippocampus

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Long-term potentiation (LTP) of synaptic efficacy is a putative memory mechanism, but an important question that remains unanswered is whether LTP can support memories lasting months or longer. Studies in the hippocampus have cast doubt on this possibility, since the longest lasting LTP reported in this structure typically decays completely over a 4-8 week period. Such findings make hippocampal LTP appear unsuitable for memory storage over extended periods of time, although they are consistent with theoretical and empirical suggestions that the hippocampus functions as only a temporary memory store. On the other hand, there is growing awareness that hippocampal damage may in some cases induce an extended retrograde amnesia. In the present experiments, we tested a variety of LTP induction protocols in the dentate gyrus region of the hippocampus to determine whether hippocampal LTP can show longevity appropriate for a mechanism underlying enduring memories. Indeed, LTP persistence in some cases was remarkably stable over periods of weeks and months. The induction of such enduring LTP was correlated with a postsynaptic increase in phosphorylation of the transcription factor cAMP-response element binding protein (CREB) in the dentate granule cells. Thus, LTP can be stably maintained across prolonged periods of time, and insofar as it is a memory mechanism, these data support the suggestion that the hippocampus can store information over very long time periods.

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Roles of Brain-Derived Neurotrophic Factor in Synaptic Plasticity in the Developing Visual Cortex

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Brain-derived neurotrophic factor (BDNF) is known to play a role in synaptic plasticity in the developing visual cortex. For example, BDNF rapidly potentiates synaptic transmission, enhances LTP and blocks LTD in the cortex of young rats (Akaneya et al., *J. Neurosci.* 17, 6707, 1997; Kinoshita et al., *J. Neurosci.* 19, 2122, 1999). Such acute actions of BDNF are suggested to be mediated mainly through presynaptic mechanisms. A chronic application of BDNF to the visual cortex of kittens is known to expand ocular dominance columns in the cortex (Hata et al., *J. Neurosci.* 20, RC57, 2000). Recently we have demonstrated that BDNF is transferred from presynaptic terminals to postsynaptic neurons in an activity-dependent manner (Kohara et al., *Science* 291, 2419, 2001), suggesting the possibility that BDNF also has chronic postsynaptic actions. To test this possibility, we used solitary neurons cultured from the visual cortex of BDNF knockout and wild type mice. BDNF was applied to one of the two groups of neurons cultured from each type of mice for 8-11 days, and then EPSCs were recorded using the whole-cell voltage-clamp technique. We found that the amplitudes of both NMDA and AMPA receptor-mediated components of evoked EPSCs recorded from neurons of the wild type were larger than those from neurons of BDNF knockout type. We also found that the degree of enhancement of NMDA receptor-mediated EPSCs by BDNF was larger than that of AMPA receptor-mediated EPSCs in either type of neurons. These results suggest that the chronic application of BDNF to cortical neurons preferentially enhances NMDA receptor-mediated responses probably through postsynaptic mechanisms.

Neural and Cellular Correlates of Associative Learning in the Honeybee

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Honeybees have small brains, but their behavioural repertoire is impressive. Reward learning in honeybees initiates a sequence of events leading to long-lasting memory passing through multiple transient memory phases. The study of memory dynamics is performed at the behavioral (both natural foraging behavior and appetitive conditioning), neural circuit and molecular levels. The transition from short to mid- and long-term forms of memory can be related to specific second messenger cascade activation (involving NOS, PKA, PKC and PKM) resembling general features of neural plasticity at the cellular level. The particular time course of the various memory traces may be adapted to the behavioral context in which they are used, here: the foraging cycle of the bee. The memory traces for even such a simple form of learning as olfactory conditioning are multiple and distributed, involving first- and second-order sensory neuropils (antennal lobe and mushroom bodies), but with distinctly different properties. Neural correlates of associative learning are traced to single neurons and specific neuropils using electro- and optophysiological recording techniques. The reinforcing property of the reward stimulus can be assigned to a single identified neuron. Changes of neural responses at the single cell and the network level indicate associative synaptic plasticities at multiple locations in the olfactory pathway. It is argued that these properties, although reflecting general characteristics of step-wise memory formation, are adapted to the species-specific adaptations in natural behavior, here to foraging at scattered and unreliable food sources.

Multiple Roles for Noradrenaline in Memory Consolidation

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Memory is labile for a period of time and fades unless an event occurs to cause it to be retained. We have shown, using young chicks and a single trial discriminated task as the model, that labile memory can be consolidated into long-term storage by the addition of noradrenaline (Gibbs & Summers, 2000, *Neuroscience*, 95, 913-922). Noradrenaline is known to be released in the central nervous system during memory formation. Our recent studies suggest that noradrenaline has its selective role in memory formation by activating up to 9 adrenoceptor (AR) subtypes that are located in different brain areas, and are activated at different times in the memory processing sequence. We have shown that β_2 - and β_3 -ARs play a role in the consolidation of memory up to 30 minutes post-training. Selective agonists for β_3 - (CL316243) or β_2 -ARs (zinterol) can enhance the consolidation of a labile memory in a dose dependent manner, when administered into the intermediate hyperstriatum ventrale (IMHV- a sensory integration area of the chick forebrain). α_2 -ARs are also important for the consolidation of labile memory but agonists that stimulate this subtype are only effective when given into the lobus parolfactorius (LPO- basal ganglia). In the same region β_1 -ARs are involved but stimulation is only effective up to 2.5 minutes after training. These studies identify specific roles for adrenoceptor subtypes in both selective regions and at specific times in the memory processing sequence. They emphasize the importance of noradrenaline in memory formation and consolidation.

CaM-Kinase as a Memory Molecule – New Insights

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Much has been learned about the autophosphorylation of CaMKII and its dephosphorylation by PSD protein phosphatase-1 (PP1). Here we show how the CaMKII/PP1 system could function as an energy-efficient, bistable switch that could be activated during LTP induction and remain active despite protein turnover. We also suggest how recently discovered binding interactions could provide a structural readout mechanism: The active state of CaMKII binds tightly to the NMDAR and forms, through CaMKII-actinin-actin-(4.1/SAP97) linkages, additional sites for anchoring AMPARs at synapses.

Learning and Synaptic Plasticity in the Corticostriatal System

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Dopamine neurons in the pars compacta of the substantia nigra show short, phasic activation after the presentation of rewards. This activity is thought to be important in reward-related learning. We hypothesise that reward signals act by facilitating synaptic modification in the main target of the nigral dopamine neurons, the striatum. We have previously shown that direct application of dopamine to neurons of the striatum *in vitro* facilitates synaptic transmission in the cortical inputs to the striatum. The aim of the present experiments was to determine the effect of rewarding electrical stimulation of the brain on synaptic transmission in these inputs. Intracranial self-stimulation (ICSS) was used as a model of reward-related learning. After behavioural testing using ICSS, *in-vivo* intracellular recording was used to measure the synaptic modification induced by ICSS-like stimulation in the same animals. Stimulation of the substantia nigra with optimal parameters for lever-pressing behaviour induced an increase in synaptic efficacy in the corticostriatal pathway ($+17.2 \pm 6.7\%$ 20 minutes after ICSS, $n=7$). This effect was blocked by the dopamine D-1 receptor antagonist, SCH 23390 ($+1.1 \pm 4.3\%$ at 20 minutes, $n=5$). These findings support the hypothesis that dopamine acts by facilitating synaptic modification in the corticostriatal pathway.

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Synaptic Modifications in Oscillatory Cell Assemblies

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Pairing electrical stimulation of the mesencephalic reticular formation (MRF) with light stimuli that elicit synchronous oscillatory responses in distributed groups of cells in the cat visual cortex induces long lasting increases in synchronisation probability. This effect can be reversed by pairing MRF stimuli with light stimuli that drive the same groups of cells but do not elicit synchronised responses. These modifications are independent of changes in discharge rates suggesting as the critical variable the degree of synchrony during conditioning. To examine this possibility we investigated in slices of the rat visual cortex the phase sensitivity of Hebbian modifications. Sustained oscillatory responses (20 Hz) of postsynaptic cells, imposed by sinusoidal current injection, were paired with EPSP trains of identical frequency that were either in phase with the peaks or the troughs of the membrane potential oscillations. In the presence of carbachol Hebbian modifications exhibited a pronounced phase sensitivity, peak pairing producing LTP and trough pairing LTD. This phase sensitivity was blocked by application of APV in which case both peak and trough pairing produced LTD, indicating that the phase sensitivity is NMDA receptor dependent. Thus, if responses are oscillatory the polarity of Hebbian modifications does not simply depend on the temporal contiguity of sustained increases in discharge rate but on the timing of individual spikes. Because the temporal windows within which coincident spikes are interpreted as related must have exactly the same duration in signal processing and learning to avoid learning of false conjunctions precise spike timing is likely to matter in neuronal processing.

Differential Mechanisms of Synaptic Processing Via Single Hippocampal Mossy Fiber Axons

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Axons of dentate gyrus granule cells, the so-called “mossy fibers”, innervate inhibitory interneuron and pyramidal neuron targets via both anatomically and functionally specialized synapses. Whole cell patch clamp recordings from visually identified cells in hippocampal slices (P17 – 23) revealed that mossy fiber synapses onto inhibitory interneurons were comprised of either calcium-impermeable (Type I synapses) or calcium-permeable (Type II synapses) AMPA receptors, while only Type I synapses existed at CA3 principal neurons. Despite innervation by common axonal input, mechanisms of both short- and long-term plasticity were distinct at all three synapse types, as was the degree of frequency dependent facilitation. Induction of LTP or iLTD at pyramidal cells and interneuron Type II synapses, respectively, altered short-term plasticity of transmission by a mechanism consistent with changes in release probability. NMDARs at Type II synapses possessed smaller amplitudes, slower decay kinetics, a higher NR2B subunit composition, but lower open probability, compared with those at Type I synapses. Consequently, activation of either synapse type by trains of afferent stimuli elicited distinct EPSP/action potential sequences. Prolonged depolarization and repetitive firing were typically observed at Type I synapses, while single or doublets of action potentials were generated by Type II synapse activity. Thus distinct patterns of activity were initiated depending on the subunit composition and the ratio of NMDA and AMPA receptors at mossy fiber-interneuron or mossy fiber– pyramidal synapses.

The Role of Kainate Acid Receptors in Controlling the Excitability of CA1 Pyramidal Cells

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Kainate is known to inhibit a slow Ca^{2+} -dependent K^+ current (I_{sAHP}) that follows brief depolarization. Bath application of kainate caused concentration-dependent inhibition of I_{sAHP} reaching a plateau of $34 \pm 11\%$ at 100 nM ($n = 6$, $\text{IC}_{50} \sim 15$ nM). This action was not accompanied by inward current and persisted in the presence of TTX/TEA ($n = 8$), suggesting a direct action. Kainate inhibition of I_{sAHP} was blocked by prior application of 20 μM CNQX ($n = 8$), but not by AMPAR-preferring antagonist GYKI52466 (100 μM , $n = 5$). Application of CNQX following kainate did not relieve the long-lasting inhibition. Thus a second messenger, rather than persistent receptor activation, is likely to underlie the inhibition. Kainate action was mimicked by 200 nM domoate ($51 \pm 6\%$ inhibition, $n = 7$) but not by fluoro-willardine (300 nM, $n = 7$) or the GluR5 subunit agonist ATPA (2 μM , $n = 5$). These data are consistent with a metabotropic action of kainate via the GluR6 receptor subtype. As reported for presynaptic effects of kainate, we found that preincubation of slices with the PKC inhibitor calphostin C (1 μM) blocked the action of kainate ($n = 10$). Subsequent application of noradrenaline (10 μM , $n = 4$) blocked I_{sAHP} , demonstrating that PKA-dependent inhibition remained intact.

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Executive Control in Frontal and Temporal Cortex

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Although it has been proposed that the prefrontal cortex plays a major role in “central executive” processes, the biological mechanisms that might underlie this putative function are currently poorly specified and understood. One possible role of prefrontal cortex is to control the switching of behavioral and/or cognitive strategies. This process could potentially be achieved via the modulation of neuronal activity in the temporal cortex brain areas where high-order representations appear to be encoded (area TE and perirhinal cortex). Prefrontal cortex could, for example, suppress certain representations and so reduce their influence on “downstream” behaviour-producing brain regions or, by selectively decreasing this inhibition, allow them to exert a greater influence. Recent electrophysiological data from our lab are generally consistent with this hypothesis. The firing of neurons in area TE and perirhinal cortex, regions was recorded in awake, freely moving rats as they performed a working memory task. We found that in animals with lesions of prefrontal cortex many more neurons (50%) fired in just one location in the environment compared to cells in control animals (5%). Our data indicate that the temporal cortex cells in lesioned animals were disinhibited and were more responsive to either the spatial position of the animal, or to cues in the environment that were observed from a particular position. It is possible that this lesion-induced change in neuronal responses may underlie the inflexible cue-driven behaviour sometimes observed after frontal damage in humans.

Is the Avian Hippocampus a Functional Homologue of the Mammalian Hippocampus?

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The effects of hippocampal lesions on the processing and retention of visual and spatial information in birds and mammals is reviewed. For both birds and mammals, damage to the hippocampus results in severe impairments on a variety of spatial tasks, such as navigation, maze learning, and the retention of spatial information. In contrast, neither birds or mammals with damage to the hippocampus are impaired on a variety of visual tasks such as delayed matching-to-sample, concurrent discrimination, or retention of a visual discrimination. In addition, both birds and mammals with hippocampal damage display impairments in acquisition of an autoshaped response as well as alterations in response suppression. These findings suggest that the avian hippocampus is a functional homologue of the mammalian hippocampus, and that in both birds and mammals the hippocampus is important for the processing and retention of spatial, rather than purely visual information.

Hebb, Pandemonium and Catastrophic Hypermnnesia: The Hippocampus as a Suppressor of Inappropriate Associations

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A bewildering number of types of memory supposedly account for dissociations between hippocampal-sensitive and hippocampal-insensitive learning. None fully captures the observed dissociations. Gray and McNaughton (*The Neuropsychology of Anxiety*, 2nd ed., 2000) propose that the hippocampus functions to resolve conflict between goals and is not specifically involved in memory. It is often minor procedural features of training or testing that control hippocampal-sensitivity of memories. This paper shows how our theory of hippocampal function allows a uniform, purely Hebbian, view of the neural representation of associative memory, via a modified “pandemonium” model of learning and consolidation. The basic idea is that all associative learning is fundamentally Hebbian and does not consist of different mechanistic types. Particular choices of stimulus type, prior learning, innate prior tendencies and paradigms can, together, increase the probability of storage of false engrams as a consequence of the attempt to store the correct engram. This will especially be true for any factor that increases stimulus interference. On our theory the hippocampus acts to suppress choice of incorrect alternatives and to decrease their associative strength in the neocortex both during a task and during consolidation. A patient such as H.M., then, suffers from catastrophic hypermnnesia – a pandemonium of retrieved items coupled with an inability to select from them a single item to be transferred to consciousness.

The Role of the Hippocampus in Pattern Separation of Spatial and Temporal Information

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One possible role for the hippocampus in processing all forms of sensory information might be to provide for sensory markers to demarcate a spatial location or temporal event, so that the hippocampus can more efficiently mediate spatial or temporal information. That is, one of the main functions of the hippocampus might be to encode and separate spatial locations as well as temporal events from each other. This function would enhance the possibility of remembering and temporarily storing one place as separate from another place and temporally storing one event as separate from another event. It is assumed that this is accomplished via pattern separation of event information, so that spatial locations and temporal events can be separated from each other. Data will be presented to show that there appears to be subregional specificity for these functions within the hippocampus, in that the dentate gyrus is primarily involved in spatial, but not temporal, pattern separation. In contrast, the CA1 region is involved in temporal, but not spatial, pattern separation. Additional data will be presented to show that the hippocampus is not involved in pattern separation for visual objects, motor responses, and reward value information. Instead, it appears that the perirhinal cortex, caudate nucleus, and amygdala support pattern separation for visual objects, motor responses and reward value, respectively. Therefore, for pattern separation the role of the hippocampus may be limited to spatial and temporal domains.

POSTER PRESENTATIONS

POSTER 1

Involvement of the Central Noradrenergic System in Memory Impairment in Prenatally Compromised Chicks

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Four days of restricted gas exchange during incubation impairs growth and the ability of chicks to consolidate labile memory into long-term storage (Camm, Gibbs and Harding, 2000, *Proc.Aust.Neuroscience Soc.*, 11, 167). Plasma adrenaline levels one day following hatching were found to be increased in compromised chicks, suggesting that the memory impairment could be associated with a disturbance in the central noradrenergic system. We investigated whether the administration of a β_2 - or β_3 -adrenoceptor (AR) agonist, which have been shown to enhance memory consolidation (Gibbs and Summers, 2000, *Neuroscience*, 95, 913-922), would promote memory consolidation in chicks exposed to a prenatal insult. Gas exchange across the eggshell was restricted by wrapping one half of the eggshell with an impermeable membrane from day 14-18 of incubation. Chicks were trained on a one-trial bead discrimination task, and 20 min after training were given an intracranial injection of either the β_2 - or β_3 -AR agonist. Recall of the aversive bead was assessed 120 min following training. The β_3 -AR agonist enhanced memory consolidation, whereas the β_2 -AR agonist was unable to promote memory consolidation. Increased levels of circulating adrenaline during incubation and after hatching may lead to downregulation or desensitisation of the β_2 -AR. In conclusion, prenatal compromise during late incubation may stress the embryo, leading to enhanced levels of catecholamines which then alter the responsiveness of particular adrenoceptors.

Multiple Memory Systems: Contributions of Human and Animal Serial Reaction Time Tasks

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Human memory systems are divided into two broad domains, one responsible for 'declarative memory' and the other for 'non-declarative memory'. The serial reaction time task (SRT) is one sensitive test of non-declarative memory. The human literature on this task follows the conventional analysis, suggesting that damage to extrapyramidal brain systems disrupts SRT performance whereas limbic system neuropathology leaves performance intact. A meta-analysis of the SRT literature with neuropathological patients unexpectedly revealed that amnesiac patients are impaired on the SRT task, although less severely than patients with extrapyramidal damage. Patients with known or suspected frontal pathology also show an SRT impairment. Thus the finding with amnesiacs may be due to the additional frontal pathology often evident in these patients. An animal-analogue of the human-SRT task was developed to test the specific neural substrates responsible for sequence learning, using intra-cranial self-stimulation (ICSS) to promote rapid and continuous responding over a prolonged single-test session. Hippocampal lesions facilitated, whereas caudate lesions inhibited, rat-SRT performance. In contrast, rats with hippocampal lesions but not those with caudate lesions were impaired in an ICSS-adapted hole-board task. This double dissociation of task and lesion site supports the conclusion that learning in the SRT task is not dependent on the hippocampal system.

The Effect of Calcium Channel Antagonists on Reference Memory

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Recent data suggests that activation of N-Methyl-D-Aspartate receptors (NMDAR) and voltage-dependent calcium channels (VDCCs) independently lead to the induction of LTP through different mechanisms. The LTP formed through these different mechanisms seems to have different characteristics. Using the radial arm maze we have shown that animals in which VDCCs have been antagonized increase the number of reference memory errors (RMEs) made after a 7-10 day training break. Importantly, animals treated with saline or MK801 do not increase their errors. Here, we used a similar procedure except that animals were injected immediately after completing a given trial. Compared to the animals injected with MK801 or saline, animals injected with verapamil took much longer to reach criterion (saline - 23 days; MK801 - 22 days; verapamil - 34 days, verapamil & MK801 - 34 days). Furthermore, comparisons of RMEs made before and after the break in training show that only the groups injected with verapamil significantly increased their number of errors (saline: 1.07 ± 0.21 vs 1.18 ± 0.22 ; MK801: 1.22 ± 0.25 vs 1.37 ± 0.27 ; verapamil: 1.26 ± 0.20 vs 1.89 ± 0.21 ; MK801 + verapamil: 1.26 ± 0.21 vs 1.70 ± 0.24). Thus, these results suggest that activation of VDCCs is important for the learning and consolidation of information necessary to navigate the radial arm maze.

The Consequences of Beer Consumption in Rats: Acute Anxiolytic and Ataxic Effects and Withdrawal-Induced Anxiety

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Male Wistar rats were given daily sessions in which they were given 30 min access to “near-beer” (a malt beverage that looks and tastes like beer but which contains < 0.5% ethanol). Rats drank this solution avidly, with typical consumption of 25 mls in the 30 min session. On test day, for some rats, ethanol (either 2% or 4% v/v) was added to the near-beer to make it resemble standard (alcohol-containing) beer of “light” (2%) or full strength. The addition of ethanol had little effect on consumption on test day. Immediately, following consumption of near-beer, near-beer +2% ethanol, (“2% beer”) or near-beer +4% ethanol (“4% beer”) rats were tested in an anxiety battery (predatory odor avoidance, emergence test, elevated plus-maze and social interaction). The rats were then tested on an accelerating rotarod, to determine any ataxic effects of the beer. Rats drinking 4% beer approached the predatory cue significantly more than those given near-beer indicating an anxiolytic effect of beer consumption. Rats given 4% beer also displayed a clear anxiolytic effect in the elevated plus maze and emergence tests but not in a test of social interaction. Rats given 4% beer remained on the rotarod for a significantly shorter time than rats given near-beer, indicating an ataxic effect of beer consumption. Finally, when given access to near-beer on the following day, rats in the 4% beer group drank significantly less than those given near beer only the previous day, suggesting a moderate conditioned taste aversion or “hangover effect” following beer consumption. In a second paradigm, rats were given free access to either ethanol (4% v/v) or near-beer for two weeks and then 24 hour deprivation (withdrawal). During this withdrawal, rats were tested on the same anxiety battery whereby those rats exposed to ethanol withdrawal displayed an anxiogenic profile. While many studies have now shown that rats will avidly drink beer, these results are the first to our knowledge, to show that rats will consume beer at levels that produce clear effects on anxiety and on motor coordination and produce withdrawal-induced anxiety.

Do Local Modification Rules Allow Efficient Learning about Distributed Representations?

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Distributed representations permit very many distinguishable events to be coded on a set of cells, with each cell used in many events. Since synaptic modifications can only depend on local influences, there is a fundamental problem learning how often and under what conditions distributed patterns of activity may occur. Frequencies of use and the associations of individual active elements can be measured locally and pooled for active elements within an event, but overlap leads to interference that can only be compensated on an average basis, with inevitable added variance. This constrains the compactness of distributed representations if they are to operate efficiently. Gardner-Medwin & Barlow (2001, *Neural Computation* 13: 477-504) have employed counting (a form of familiarity discrimination) to explore such constraints quantitatively. Counting underlies estimation of probabilities and association, and is fundamental to learning. Though precise counts are only possible if events have direct representations, high efficiency (i.e. effective use of available data samples) is only possible with distributed representations at the cost of high redundancy. With counts based on usage of individual cells, efficiencies >50% require a number of cells (Z) at least comparable to the number of events (N). Synapses counting activity in pairs of cells can reduce this to around $Z=(6N)^{0.5}$ cells. More sophisticated use of dendritic information (e.g. modification conditions requiring combined activity in 3 cells: adjacent presynaptic terminals and a post-synaptic cell) can improve performance, but nowhere near the information theoretic limit: $Z=\log_2(N)$.

Facilitation in Nerve Terminals: A Model Incorporating a Calcium-binding Facilitation Site

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Facilitation is a form of short-term synaptic enhancement whereby subsequent impulses release more transmitter at a nerve terminal. It is mediated by calcium, but theories based on a build-up of calcium in the terminal, whether free or bound to buffers and/or to the exocytotic site, cannot account for experimental results. Here, we use a previously developed Monte Carlo method (Bennett, Farnell and Gibson, 2000, *Biophysical J.*, 78, 2201-2240) to investigate the effects of a secondary site (the facilitation site) that also binds calcium and enhances the affinity of the exocytotic site. Simulations were performed in which both the conditioning and test pulses are rectangular step potentials and a wide range of parameter values and stimulation protocols were investigated. This resulted in a set of parameter values that reproduces the corresponding experimental results for F2 facilitation at the crayfish neuromuscular junction. Calculations using these parameter values were then done for the case of a train of action potentials and were able to account for observations of facilitation under 100 Hz stimulation for this same preparation.

ATF3 Induction by High-Frequency Stimulation in Dentate Gyrus

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Activating transcription factor 3 (ATF3) is a member of the ATF/CREB family of bZIP transcription factors. The rapid induction of ATF3 by a number of physiological stress signals has led to its general designation as a stress response gene. In the CNS for example, induction of ATF3 has been observed following axotomy and seizure activity. This induction may be linked to Ca²⁺ influx, as ATF3 is induced by calcium ionophore treatment of SH-SY5Y neuroblastoma cells. Here, we describe the induction of ATF3 following LTP induction in the dentate gyrus of rat brain. ATF3 protein immunoreactivity was detected in dentate granule cells of the tetanised hemisphere 2 h (6/6 animals), but not 10 min (0/4 animals), following a robust high-frequency stimulation (HFS) protocol (400 Hz, 50 trains). ATF3 expression was also observed at 4 h (7/9 animals) and 8 h (1/2 animals) post-tetanisation. The induction of ATF3 by HFS is dependent on NMDA receptor activation, as pretreatment with the NMDA receptor antagonist CPP blocks ATF3 induction at 2 h post-tetanisation (4/4 animals). These results indicate that a stress response may be initiated in dentate granule cells as a result of HFS. The implications of this response to LTP mechanisms, and to memory processes in general, remain to be determined.

Theta Activity Facilitates Induction of Synaptic Plasticity: Functional Implications

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Previous studies have shown that stimulating with 5-15 stimuli phase-locked with theta activity can induce LTP in the hippocampus. Theta oscillations are modulations of local inhibition. These produce time windows of low inhibition during which pyramidal neurons are brought near firing threshold. These system properties have the following implications: 1. The system can be activated from a 'safe' state of inhibition to an active state without running the risk of overexcitation, since the system will be inhibited when theta enters the high-inhibition phase again. This safety- delay enables feedback projections to reduce excitation before the next excitatory phase. 2. Oscillations of inhibition focuses neuronal activity to defined time windows. The only time when noise is relayed is during the relatively short time window of low inhibition. This increases the signal-to noise ratio. 3. The focusing of neuronal activity also enable Hebbian mechanisms of synaptic plasticity, which require synchrony of input. Since neuronal activity follows a Poisson distribution, synaptic plasticity would be difficult to induce without 'focusing' by theta. 4. Such focusing also enables the system to bind neurons that collaborate on processing of information within a neuronal network. 5. In addition, it has been shown that several independent neuronal networks can co-exist in the same brain area, separated by Gamma frequency oscillation phases. This enables the system to support several attractor network states without running the risk of collapse into one.

mGluR-Induced Persistent Excitability Increase in Hippocampal CA1 Pyramidal Neurons is Independent of Phospholipase C

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Previously, we have shown that the metabotropic glutamate receptor (mGluR) agonist, (RS)-3,5-dihydroxyphenylglycine (DHPG), produces a persistent increase in excitability in hippocampal CA1 pyramidal neurons. Here we have investigated the signal transduction pathways downstream from mGluR activation and associated phospholipase C (PLC) activity, that mediate this effect. Intracellular current-clamp recordings were made from rat CA1 pyramidal neurons in acute hippocampal slices maintained *in vitro* at 32.5°C. During experiments, neurons were held at a membrane potential of -65 mV by manually adjusting the holding current. DHPG abolished the slow afterhyperpolarization (sAHP) and medium AHP (mAHP) and caused a consequent increase in the number of action potentials fired during a 0.5 nA depolarizing current pulse, as well as an increase in input resistance and membrane depolarization (inferred by a change in holding current). With the exception of the suppression of the mAHP, these effects were persistent, with the suppression of the sAHP lasting for more than 1 hour after agonist washout. Unexpectedly, blockade of the major signalling pathways activated by PLC, using chelerythrine to inhibit protein kinase C and cyclopiazonic acid to inhibit IP₃-activated Ca²⁺ stores, did not prevent the effects of DHPG. Further, inhibition of PLC itself with U-73122 did not prevent the actions of DHPG. These results demonstrate that the mGluR-induced persistent increase in excitability in CA1 pyramidal neurons is mediated by one or more PLC-independent transduction pathways.

Failure of an Enriched Environment to Induce Long-Term Potentiation in Freely Moving Rats

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Recurrent exposure to a stimulus-enriched environment (EE) induces a long-term potentiation (LTP)-like effect in the dentate gyrus (DG) region of the rat hippocampus when tested in vitro (Foster, Gagne & Massicotte, 1996, *Brain Research*, 736, 243-250). However inconsistent effects have been observed in vivo (Sharp, McNaughton & Barnes, 1985, *Behavioral Neuroscience*, 101(2), 170-178; Sharp, Barnes & McNaughton, 1987, *Brain Research*, 339, 361-365). One explanation for these differential effects is the difference in living conditions of rats during EE exposure; for example, group versus isolated housing may influence the degree to which EE exposure can alter synaptic efficacy. In the present research, adult male Sprague-Dawley rats were chronically implanted with a DG recording and perforant path stimulating and housed singly. After stable recordings of the field excitatory postsynaptic potentials (EPSPs) were established, the effect of group housing (social interaction, three rats) on evoked potentials was assessed. Group housing induced a transient increase in cell excitability and decrease in the EPSP. Both isolated and grouped rats were then exposed to an EE for one hour daily over three weeks. For both conditions a transient increase in cell excitability was observed, but no LTP-like changes were found. These results suggest that exposure to an EE does not necessarily induce LTP and that type of housing was not a factor contributing to the effects of EE exposure on synaptic efficacy in previous in vitro research.

Prefrontal Lesions Affect the Stability of Hippocampal Place Fields

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Prefrontal cortex (PFC) lesions have been shown to augment the location-related firing properties of cells in the perirhinal cortex (PRC) of rats (Zirani et al, in press). On the basis of this finding, it was predicted that PFC lesions might also enhance place-related firing in hippocampal pyramidal cells (place cells). Place cells (PCs) typically encode place fields, which are specific regions in the environment in which an otherwise quiet cell is intensely active. In the current study, rats received electrolytic (n=6) or sham (n=5) lesions of the PFC and electrodes were implanted into the CA1 layer of the hippocampus for single unit recording. PCs (n=64) were recorded as the animals foraged freely. PFC lesions significantly ($p < 0.05$) reduced the mean overall firing rate (FR), the infield FR, and outfield FR of HPC PCs, but did not affect place field size. The fields of lesion rats were, however, less stable than those of sham animals. The centre of mass of fields in lesioned animals was shown to shift a significantly greater distance compared to sham controls when both long (5 hr, n=39, $p < 0.00005$) and short (3 min., n=19, $p < 0.05$) intervals were inserted between recording sessions. Therefore, although PFC lesions did not increase place field resolution, they did reduce the stability of fields across delay intervals. This novel effect indicates that the prefrontal cortex normally modulates spatial responses in the hippocampus.

AT₄ Receptor Ligands Potentiate Spatial Learning in the Barnes Circular Maze

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Central administration of AT₄ receptor agonists enhances performance of rats in both the passive avoidance and spatial memory paradigms; however, all studies on spatial memory have used either repeated doses or chronic administration of AT₄ receptor agonists. The purpose of this study was to examine the effect of a single acute injection of the AT₄ receptor ligands, Nle1-Ang IV and LVV-hemorphin-7, on spatial learning in the Barnes circular maze. Rats were trained, in response to aversive stimuli (light and sound), using visual cues, to locate a hidden escape compartment located beneath one of 18 holes positioned around the perimeter of a large circular surface. All rats treated with a single dose of LVV-hemorphin 7 or Nle1-AIV (100 pmol) 5 min prior to the first trial on the first day, achieved learner criterion by day 5 of testing whereas the control rats given artificial CSF (aCSF) took 3 days longer. Analysis of day 1 of testing revealed that the rats treated with LVV-hemorphin 7 and Nle1-AIV made fewer errors ($p < 0.005$) and took shorter time to find the escape compartment ($p < 0.01$) than the aCSF-treated controls. Thus our data indicate that central administration of AT₄ receptor ligands results in both an immediate event, which may be associated with facilitation of synaptic transmission or enhancement of acetylcholine release and a sustained, long term effect which could be attributable to synaptic remodelling.

The Effects of NMDA Lesions Centered on the Postrhinal Cortex In Spatial Memory Tasks in the Rat

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The parahippocampal region is critical for certain types of learning and memory. Although entorhinal and perirhinal subcomponents of this region have received much attention, the function of the postrhinal cortex component in learning and memory is less clear. In the present study, we investigated the effects of postrhinal cortex lesions in a series of spatial learning and memory tasks. Rats with bilateral NMDA lesions centered on the postrhinal cortex (POR) were significantly impaired relative to SHAM controls during the initial training and reversal test in the reference memory version of the water maze task, but did not show any impairment during probe tests. The POR rats displayed a delay-independent impairment in the working memory versions of the water maze task. The POR rats also showed poorer performance relative to the sham controls in the standard working memory version and reference memory version of the radial arm maze task. Furthermore, the POR rats displayed a delay-independent impairment in a delayed non-match to place (DNMP) version of the radial arm maze task and were also impaired in a DNMP procedure conducted in the T-maze. These findings indicate that the postrhinal cortex has a delay-independent role in the processing of certain types of spatial information.

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Perirhinal Lesions Affect Firing Properties of Hippocampal Place Cells

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The hippocampal cortex (HPC) is critically involved in spatial memory processing. The neighbouring perirhinal cortex (PRC) has a role in visual recognition memory. The present study investigates what information is provided by PRC to HPC by comparing the location-related and movement-related firing of place cells in PRC lesioned and sham operated rats. Twenty-three neurones were recorded from PRC lesioned rats and 14 neurones from sham rats as they foraged freely in a square environment. The data analysis showed that there was no significant difference in HPC place fields when lesioned and sham rats were compared. There was however a significant difference in the correlation between firing rates and velocity. Few neurones (14%) showed a negative relationship between firing rate and velocity in sham rats, however, 43% of neurones showed a negative relationship in PRC lesioned rats ($p < 0.05$). These results replicated a previous finding by Muir and Bilkey (2000). In a preliminary study aimed at investigating what factors produced the firing and velocity relationship, 8 neurones were recorded from lesioned rats and 5 neurones from sham rats while they were passively moved on a linear track. There was no clear relationship between firing rate and velocity in those neurones that had a strong relationship in the open field. There was also no significant difference between lesioned and sham rats. Further work will be required to determine how the PRC and HPC interact as regards movement information.

Priming of Metabotropic Glutamate Receptors Regulates Hippocampal Long-Term Depression

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The ability of priming activation of metabotropic glutamate receptors (mGluRs) to regulate long-term depression (LTD) was studied in area CA1 of hippocampal slices taken from young adult male rats. Pharmacological activation of Group I mGluRs (20 μ M DHPG) 30-40 min prior to a strong low-frequency stimulation protocol (3 Hz, 1200 pulses) failed to affect the subsequent LTD. In order to investigate a possible ceiling-effect priming Group I mGluR still failed to affect subsequent LTD, when induced by a mild low-frequency protocol (3Hz, 600 pulses). Activation of Group II mGluRs (1 μ M DCG-IV), however, significantly inhibited the strongly induced LTD by >50%. The inhibition of LTD by activation of Group II mGluRs was even stronger when the Group II agonist was applied during the low-frequency stimulation. Even though the same signalling cascades have been implied for Group II and III mGluRs, prior activation of Group III mGluRs (500 μ M L-AP4) had no statistically significant effect on LTD. Because activation of Group II mGluRs is also known to inhibit LTP, the net effect of such stimulation is the induction of a metaplasticity that greatly restricts the effective range of stimuli that can evoke synaptic plasticity in the hippocampus.

Spatial Working Memory and the Brainstem Cholinergic Innervation to the Anteroventral Thalamus Nucleus

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Lesions of the anteroventral thalamic nucleus (AV) impair spatial memory in rats, but the role of the prominent ascending brainstem cholinergic input from the laterodorsal tegmental nucleus to the AV is unknown. Hence, infusions of scopolamine, a muscarinic antagonist, were made into the AV of rats at the start of a 10-minute delay between the sixth and seventh choices in a 12-arm radial maze task and then prior to testing in a standard (no delay) task. Bilateral infusions of scopolamine (1.00, 2.51, 6.31, 10.00 and 15.85 μg) when administered during the delay impaired performance in a dose-dependent manner with the dose of 10.00 μg producing the clearest impairments. PBS infusions also caused impairments relative to No-infusion sessions, but this impairment was shown to result from the cannulation procedure (i.e. simply inserting the internal cannulae alone). Testing in the standard task confirmed that bilateral infusions of scopolamine (10.00 μg) impaired performance over and above the effects of both PBS infusions and No-infusion conditions. PBS infusions again produced minor impairments relative to No-infusion. Choice latencies and choice strategies of the rats were unaffected following any type of infusion. This study provides the first demonstration that brainstem cholinergic innervation to the limbic thalamus influences learning and memory, which may have important implications for several disorders including dementia and schizophrenia.

The Effect of Dopamine D1/D5 Receptor Activation on Hippocampal Synaptic Plasticity: De-depression or Slow-onset Potentiation?

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The late phase of long-term potentiation (L-LTP) is the persistent and stable component of LTP which requires protein kinase A (PKA) activation and protein synthesis. In hippocampal CA1, L-LTP is dependent on the activation of dopamine D1/D5 receptors. A previous study reported that administration of D1/D5 agonists was sufficient to activate L-LTP, without an intervening early phase of LTP (Huang & Kandel, 1995, *Proceedings of the National Academy of Science*, **92**, 2446-2450), but this effect has not been observed by other investigators (Swanson-Park *et al*, 1999, *Neuroscience*, **92**, 485-497). The present study further examined the role of D1/D5 receptors in synaptic plasticity. Field excitatory postsynaptic potentials were recorded in area CA1 of hippocampal slices prepared from 6-7 wk male Sprague-Dawley rats. The D1/D5 receptor agonists 6-bromo-APB (100 μM) and SKF38393 (100 μM), either alone or under conditions of enhanced N-methyl-D-aspartate (NMDA) receptor or PKA activation, failed to produce L-LTP. We then considered whether D1/D5 receptor activation affects the persistence of long-term synaptic depression, as induced by 20 μM NMDA for 3 min ($-32.9 \pm 6.3\%$ 150 min post-NMDA). SKF38393 applied 30 min after NMDA application caused a significant reversal of the depression back to baseline levels ($-1.0 \pm 8.2\%$, $p < 0.05$ compared to controls). These findings indicate that D1/D5 receptor activation is sufficient to cause a return of synapses to their naive state from a depressed state (i.e. de-depression), but is not sufficient under our conditions to potentiate basal synaptic transmission.

Pair Recordings Reveal Heterogeneity in Synaptic Depression

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Simultaneous whole cell recordings from individual pre- and postsynaptic CA3 pyramidal cells in organotypic hippocampal slice cultures have previously shown that two neurons can be connected entirely by postsynaptically silent synapses (Montgomery et al., 2001, *Neuron* 29, 691-701). Extending the study of synaptic plasticity in this system to long-term depression (LTD) we now show that CA3 pyramidal cell pairs exhibit NMDAR-dependent synaptic depression following low frequency stimulation (LFS). Longer periods of LFS could drive some synaptic connections to a silent state, i.e., no AMPAR-mediated EPSCs were recorded following LFS. However, NMDAR-mediated EPSCs were still evident at depolarized potentials. Potentiated synaptic currents were also depotentiated following LFS. In contrast to de novo LTD, depotentiation was not NMDAR-dependent but rather was Group I/II mGluR-dependent. This may represent two functionally different pathways for synaptic depression, or a time-dependent 'switch' in the induction mechanism employed for synaptic depression. Interestingly, immediately following the unsilencing of all-silent synaptic connections, these synapses could not express significant LTD, demonstrating that these newly functional connections were somehow protected from synaptic depression. This protection was not permanent, as increasing the time period following synapse unsilencing enabled depotentiation to occur. Thus, the previous history of synaptic activity between pyramidal cells may determine both the induction mechanism of LTD and the plasticity of a synaptic connection.

Comparative Effects of Perirhinal Cortex and Anterior Thalamic Nuclei Lesions on Radial-Maze Learning, Spontaneous Object Recognition and Configural Learning

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The anterior thalamic nuclei (ATN) and the perirhinal cortex (PRC) have been implicated in independent memory systems concerned with spatial learning and familiarity-based object recognition respectively (Aggleton & Brown, 1999). A more traditional view is that these two regions sub-serve a single declarative memory system (Squire & Zola-Morgan, 1991). This study examined the comparative effects of ATN and PRC lesions in rats on three memory tasks. Neither ATN nor PRC lesions impaired spontaneous object recognition (in an open-field) even across extended sample-choice delays (80sec, 5min, 14min, 40min). Irrespective of task conditions (e.g. delay), ATN lesions severely impaired spatial memory in a 12-arm radial maze whereas rats with PRC lesions showed intact spatial memory. Using complex objects in the radial maze, however, PRC lesions produced impairments on the elemental-cue learning and configural-cue learning tasks, whereas ATN lesions did not affect performance. These findings confirm the differential involvement of the ATN and PRC in learning and memory, but provide only partial support for Aggleton & Brown's (1999) specific dual memory system hypothesis.

MDMA (“Ecstasy”) Causes Long Term Changes in Olfactory Discrimination and Object Recognition Memory in Rats

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MDMA (“Ecstasy”) is a drug that is widely used by young people around the world. There is increasing concern that the drug may have a neurotoxic effect on brain 5-HT systems that could lead to cognitive problems (e.g. memory impairment and learning deficits) in heavy MDMA users. However, there is an absence of compelling evidence on this issue. In the present study, we sought to investigate serotonergic neurotoxicity on performance in two models of memory in rats. We gave male Wistar rats either (a) a known neurotoxic dose of MDMA (4 x 5 mg/kg i.p. over four hours on each of two days), (b) a possibly neurotoxic dose of MDMA (1 x 5 mg/kg on each of two days), (c) a matched dose of d-amphetamine (4 x 1 mg/kg over four hours on each of two days), or (d) vehicle injections. The neurotoxic MDMA dose and the amphetamine treatment both produced an acute hyperactivity and hyperthermia. In experiment 1, rats, previously trained on olfactory discrimination tasks, were given olfactory memory tests 2-4 weeks following MDMA administration. In experiment 2, rats were tested 12-14 weeks later on a visual object recognition memory task. In the olfactory experiments, the neurotoxic regime of MDMA produced a strong trend towards impaired olfactory memory performance. In the object recognition task, rats given the neurotoxic MDMA dose regime showed significant impaired memory relative to all other groups. These data suggest that heavy MDMA exposure may predispose to increased memory impairment.

‘Stop Cells’ in the Rat Hippocampus

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The neurons of the rat hippocampus whose electrophysiological properties and behavioural correlates are best known are place cells and theta cells. Both can and do fire when an animal locomotes. Here, we describe neurons (‘stop cells’) that fire almost exclusively when the animal is stationary. Data were collected during a standard food-foraging task, where the rats moved freely in a circular arena while unit activity in the CA1 region of the hippocampus and their position were recorded. Forty-two out of 47 15-min. recordings contained at least one place cell. Stop cells were identified in 7 cases. While a typical place cell generated more than a hundred spikes per recording session, the stop cells’ total spike count was 52 ± 6 . Bursts of 16 ± 3 spikes (mean firing rate 12.2 ± 3.3 Hz) were generated only after the animal stopped and remained in place before setting in motion again. The stops were on average 4.2 ± 0.7 s long and the bursts occurred 1.4 ± 0.3 s after the animal halted. This event occurred once per session in four cells and twice per session in three cells, despite the fact that the animals passed through the same place (9x9 cm) 24 ± 4 times. On only one occasion did the firing occur at the same place twice. The signal stop cells respond to is unknown, however, unlike place or theta cells it does not appear to derive from place, head direction, or locomotion.

Differential Expression of PKC γ in the Mouse Hippocampus Following Training on the Barnes Maze

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The γ -subtype of protein kinase C (PKC γ) has been suggested to be a key regulatory component in learning and memory formation. Similarly, the immediate early gene, *c-fos*, has been implicated in learning and memory. In the present study, we aimed to examine the expression of PKC γ and *c-fos*, following a learning event. Mice were exposed to the hippocampal-dependent spatial learning test, the Barnes maze. Adult C57 BL/6 mice were divided into 3 groups: Naive, pseudo (familiarised with the maze but not trained), and trained (trained on the spatial version of the Barnes maze). Brains were taken 24hrs after the last trial and immunoreactivity was examined for PKC γ and *c-fos*. Results revealed that both trained and pseudo groups showed significant increases in PKC γ expression in comparison to naive controls in the CA1 region. Analysis of *c-fos* expression however revealed no major differences between naive, pseudo or trained groups. It appears that 24hrs after the last trial on the Barnes maze, there are differences in PKC γ expression between naive, and pseudo and trained animals. The major change was related to experience on the Barnes maze rather than to finding a specific hole on the maze. Thus, experience of an altered environment is enough to stimulate increased expression of PKC γ in the CA1 region.

Inhibitory as well as Excitatory Responses are Prominent in Rat Dopamine Neurons During Behaviour

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Midbrain dopamine neurons are activated by unpredicted rewards or signals predicting reward. Inhibitory responses have also been reported but little attention has been paid to them. To determine their incidence and properties we have recorded dopamine neurons (identified by apomorphine inhibition) in thirsty, free-moving rats. Neurons were recorded sequentially through several conditions including “random reward”, “signal-only” (randomly delivered sensory cue stimuli), “signalled reward” (fluid reward paired with two preceding cues), and “extinction” (blocks of signal-only). We found 4 types of response in 17 dopamine cells. Nine (53%) were excited by reward and signals associated with reward, 24% (4/17) were inhibited, 18% (3/17) showed an inhibition-excitation pattern, and 1 cell did not show any responses. Initial inhibitions thus represented 44% (7/16) of responsive cells. Apart from the sign, excitatory and inhibitory responses had similar properties. There was no significant difference in latency (80 ± 46 ms, 52 ± 9 ms respectively). Both response types were contingent upon stimulus salience, occurred to cues as well as reward, and the response to reward could be modified by the presence of predictive signals. These data suggest that *reduction* in dopamine release by particular cells following salient stimuli may be functionally important. This should be taken into account by theories of dopamine cell involvement in reward mediated learning, and when considering the effects of dopamine replacement therapy in Parkinson’s disease.

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Pharmacological Characteristics of the Ca²⁺ Propagation Within Dendrites of Hippocampal CA1 Neurons

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Spatial-temporal intracellular Ca²⁺ increases during high-frequency stimulations are key signals for the activation of mechanisms underlying long-term plasticity. Thus, we investigated if local induced Ca²⁺ rise can propagate within dendrites. Focal 100 Hz stimulation in area CA1 of hippocampus elicits an intradendritic Ca²⁺ rise, which propagates as a wave within the dendrite. Pharmacological inhibition of action potentials revealed a biphasic signal: a fast initial component due to Ca²⁺-influx and a second component which propagates as a wave within dendritic structures. Pharmacological studies with the mGluR class I receptor antagonist, 4-CPG, identified the involvement of mGluR-mediated Ca²⁺ release via G-protein mediated, metabotropic, internal sources for the generation of Ca²⁺ waves. Wash-in of AP5 diminished the biphasic signal in a threshold-like manner. However, ryanodine and cyclopiazonic acid, both drugs affecting the Ca²⁺ metabolism of internal Ca²⁺ stores, had minor effect on the Ca²⁺ signal, elevating the portion of the post-tetanic Ca²⁺ increase upon tetanization and slowing down the decay time constant of the Ca²⁺ signal. These results point to the coincidental involvement of NMDA-receptor-dependent Ca²⁺ increase and mGluR dependent Ca²⁺ release for mechanisms of the synaptically-driven slow-spreading Ca²⁺ waves.

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Hippocampal Neuron Firing Rate Correlations with Velocity, Acceleration, Angular Velocity and Angular Acceleration in Rats with Vestibular Lesions

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Previous research has shown that the average firing rate of hippocampal cells has a positive correlation with the velocity of the animal. The aim of the current study was to investigate the contribution of the vestibular system to this correlation. Sprague Dawley rats received bilateral vestibular labyrinthectomies and had microelectrodes implanted into the hippocampus (CA1) for single unit recording. Recordings were made, several months post lesion, as rats foraged in a cylindrical environment while their position was monitored using a tracking system. Velocity, acceleration, angular velocity and angular acceleration were all computed from the tracking data and correlated with firing rate. The firing rate of hippocampal neurons correlated positively with velocity and negatively to both angular velocity and angular acceleration. There was no significant difference between vestibular lesion animals and control animals in any of these measures. No correlation was observed with acceleration in control animals but there was a significant correlation in lesion animals. One possible explanation for this latter result is that acceleration information from the vestibular system and another system (eg motor efferent or sensory flow data) are subtracted to generate an error signal. Thus a non-zero signal is observed only in the absence of a vestibular signal.

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Stress and Plasticity in the Hippocampus: An Electrophysiological Study of the Effect of Stress on the Plasticity in the Mouse Hippocampal CA1 Area

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This study evaluated the effects of psychological stress (rat exposure) in adult male mice on synaptic plasticity induced subsequently in the hippocampus in vitro. The plasticity was studied by monitoring the changes of the synaptic field responses due to a primed burst stimulus (a single pulse followed 180 ms later by four pulses at 200 Hz) in order to evoke long-term potentiation (LTP). Three groups of mice were studied: (1) undisturbed mice in their home cage (naive), (2) mice placed in an experimental cage for a nocturnal stay (control), and (3) mice placed in an experimental cage for a nocturnal stay and confronted with a rat 60 min. before decapitation (stressed). All the groups were decapitated at the same time of the day. Trunk blood samples were obtained, and the hippocampal area was prepared for in vitro recordings. Only the stressed group had significantly elevated levels of corticosterone (CORT). When primed burst stimulation was delivered to the Schaffer collateral/commissural pathway, rat exposure gave a clear trend in attenuating LTP of the slope of excitatory postsynaptic potentials (EPSP) evoked in the hippocampal CA1 area, compared to the two control groups. A decrease in LTP was not observed for the population spike amplitude measurement. The preliminary findings of this study are therefore that high CORT-levels, elicited by an ethologically realistic stressor can lead to an inhibition of synaptic plasticity in the hippocampus.

Fos-tau-lacZ Transgenic Mice Show Inducible Expression of Beta-Galactosidase in Axons and Dendrites in the Brain

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We have used a transgenic approach to visualise neurons and their projections activated following functional stimuli. The transgenic mice contain a tau-lacZ fusion gene regulated by the promoter for c-fos, an immediate early gene which is rapidly induced in neurons following functional stimulation. In these animals, lacZ was expressed in cell bodies, axons and dendrites. Basal expression of lacZ was low and there was high induction following treatment with Kainic acid, a strong inducer of endogenous c-fos. The pattern of lacZ expression within the neurons changed over time following Kainic acid treatment. Early after kainate treatment, lacZ was expressed mainly in cell bodies, by 2 hr expression was found both in cell bodies and processes, and at later times expression extended further along the neuronal processes. By six hours after kainate treatment, lacZ was expressed in the entire dendritic field of the dentate gyrus in the hippocampus. The results show that expression of lacZ in the fos-tau-lacZ transgenic mice is under the same regulation as endogenous c-fos and that expression can be traced to terminal fields of the neurons. The inducible expression of lacZ in the neuronal processes in these mice may be useful in visualising and mapping projections of neurons whose functional activation involves c-fos expression.