Motor control of regenerated arm of the octopus
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The octopus arm lacks any rigid skeleton and has virtually
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Bifunctional compounds eliciting non-steroidal anti-inflammatory and cholinergic up-regulation as treatment for CNS inflammation

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It was previously noted that vagus nerve activation could suppress significantly the release of macrophage pro-inflammatory agents attenuating systemic inflammatory processes. This 'cholinergic anti-inflammatory pathway' is meditated by the alpha7 nicotinic ACh receptor in macrophages. Therefore, we examined the in vivo anti-neuroinflammatory efficacy of bifunctional compounds containing the NSAID ibuprofen (IBU) or diclofenac (DICLO) and the 3D inhibitor Pd pestdogystine Octyl (PO) or Decyl (PD)). IBU-PO caused a significant reduction in rat paw and brain edema induced by carrageenan. IBU-PO, IBU-PD, DICLO-PO or DICLO-PD 4-5 hours before soman challenge (2,2-2.3 LD50) combined with antidotal treatment (atropine and 2-PAM-C), afforded higher survival rate than with PYRID. DICLO-PD displayed 70% survival at 24h compared to 17% with PYRID. IBU-PO and IBU-PD were used in experimental autoimmune encephalomyelitis (EAE), a model used for studying human Multiple Sclerosis. These compounds ameliorated by 40-50% the neurological score (1 and 0 mg/kg, i.p.) of syngeneic and non-syngeneic animals respectively derived from C57-Bl6 mice. Animals displayed decreased reactivity in response to the myelin oligodendrocyte glycoprotein (MOG) and also to the mitogen PHA, indicating reduced activity of MOG-specific T-cells. In addition, IBU-PO at macromolar levels down regulated LPS-induced nitric oxide (NO) and PGE2 production in rat brain astrocytes. T-cell proliferation, NO and PGE2 production in astrocytes was mildly inhibited by IBU and none by PO alone, but was significantly reduced by IBU-PO. In addition, human T-cells proliferation was significantly reduced by IBU-Oetyl-Cytisine (1-Smub) that consists of NSAID and a nicotinic agonist. Our data indicate that molecular combination of NSAID with cholinergic up-regulation may be a novel approach for the treatment of CNS inflammation and demyelinating disorders.

Clinical and immunological amelioration of chronic experimental autoimmune myasthenia gravis by antinose oligonucleotide treatment

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Myasthenia gravis is an antibody-mediated, autoimmune neuromuscular disease in which the nicotinic acetylcholine receptor (AChR) is the major autoantigen. The typical neuromuscular junction symptoms can be transiently alleviated by acetylcholinesterase (AChE) inhibitors (such as pyridostigmine). Previously we found that long-term treatment of experimental autoimmune myasthenia gravis (EAMG) rats with antinose oligonucleotides suppressing AChE biosynthesis (EN101), improved muscle activity as well as clinical symptoms of the disease. In the present study we focused on the effect of EN101 treatment on the typical immunological processes occurring in EAMG. Repeated oral administration of EN101 for a month reduced the ant-rat AChR antibody level by 50%. In addition, incubation of T-cells with EN101 resulted in reduction in the proliferation rate and induction of apoptosis. EN101 also lowered total IgG antibody production by spleen cells. Our results show the beneficial effect of oral EN101 treatment on EAMG immunological parameters and highlight the potential advantage of gene-targeted drug therapy.

Ligand-induced activation of G-proteins is differentially regulated by leucine of the CB1 helix 8 domain

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The majority of physiological actions of marijuana in the CNS are mediated by activation of G-protein coupled CB1 receptors located on neurons. Modeling studies have identified the 404-414 segment of CB1 to be an intracellular helical extension of the TM7 domain, called helix8 (Hx8) domain. The peptide of CB1 401-417 can directly activated Gnaq/Gna3, but not Gna1/2 proteins. We tested the hypothesis that activation of CB1 releases Hx8 such that it can interact with G proteins, and that differences in this association may contribute to constitutive activity. We hypothesized that replacing the L7.60 to the bulkier Ile residue will make the Hx8 more mobile whereas the aromatic Phe will make the Hx8 less mobile than the wild-type human CB1 receptor (WT hCB1) thus constitutive activity will be increased or decreased, respectively. HEK293 cells were transfected with WT hCB1, L7.60I and L7.60F mutant receptors. Saturation binding analysis with [3H]CP-55,940 and [3H]SR141617A showed that ligand affinity and receptor levels of the mutant receptors were similar to that of the WT hCB1. [35S]GTPS binding analysis was performed with structurally different cannabinoids and cannabinoids. The results did not alter the basal stimulation levels but reduced the maximal stimulation (Emax). The L7.60I mutation significantly reduced the Emax. The CP-55,940-WN55,212-2-HU-210. In addition, the L7.60I mutation completely abolished [35S]GTPS binding with SR141617A. These results suggest that Leu residue of the Hx8 domain does not significantly contribute to the constitutive activity of the hCB1 receptor in this model system but is important for activation of specific G-proteins. The differential stimulation obtained with different ligands suggests that although SR141716A and CP-55,940 binding pockets are not related these ligands exclusively activate Gnaq/Gna3 through Hx8 whereas HU-210 and WIN55212-2 can still activate the hCB1 probably by docking the II3 domain to Gai1/Gai2.

Dopamine modulates the intrinsic properties of layer II stellate cells in entorhinal cortex

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In entorhinal cortex, axons of the Layer II spiny stellate cells travel in the perforant path to terminate directly on dentate granule and CA1 pyramidal cells. These cells, which are essential elements in cortex-hippocampus interaction, have distinctive electrophysiological properties, including very prominent, hyperpolarization-activated cation current (IH) and TTX-sensitive persistent sodium current (INaP). Because neuromodulation of these currents must affect the neurons' integration properties, we studied the effects of dopamine on INaP and IH using patch clamp whole-cell recordings in rat EC horizontal slices. INaP was manifest as a TTX-sensitive current elicited by a slow depolarizing voltage ramp (40 mV/s) in the presence of Ca²⁺, 4-AP, TEA, and Cd²⁺. Bath application of dopamine (.02-1 mM) induced a significant shift to the instantaneous I-V curve, and a concurrent decrease in the peak of the current. The D2 dopamine receptor agonist SKF 81297 (.005-0.25 mM), but not the D2 receptor agonist quinpirole (.025 mM), mimicked these effects. Dopamine receptor agonists are positively coupled to adenyl cyclase and the production of cAMP and protein kinase. As expected, the membrane-permeant cAMP analog, 8-Bromo-cAMP (1 mM), mimicked the response of dopamine. Moreover, a specific blocker of cAMP, 8-Br-cAMP (1 mM), inhibited the modulation. IH was manifest in current clamp recordings as a prominent, time-dependent depolarizing sag during hyperpolarizing current pulses. Dopamine reversibly led to a significant decrease in the amplitude of the sag. These effects of dopamine on the intrinsic properties of such pivotal neurons in the
parahippocampal circuitry may underlie, in part, the role of dopamine in neurological and psychiatric syndromes which involve deficits in this circuitry, such as epilepsy and schizophrenia.

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*Virtual histology* of human white matter by diffusion MR imaging

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Neuroscience in general and neuroimaging in particular has evolved tremendously since the introduction of dynamic functional brain mapping. Despite the ability to follow task related brain activity, the structural network connecting these regions was only hypothesized from histological databases. Few years ago, the concept of diffusion tensor imaging (DTI) based fiber-tracking was introduced. This method is based on the anisotropic nature of water diffusion in white matter. Parallel to the fibers the diffusion appears to be 'free' while perpendicular to them it appears disturbed. This quantity of white matter diffusion enables 3D mapping of large homogeneous fiber bundles. However, DTI suffers from artifacts in areas of heterogeneous white matter (crossing white matter bundles) and white matter fanning into gray matter. Recently we developed an experimental and theoretical framework to describe white matter diffusion even in areas of complicated white matter structures. The composite hindered and restricted model of diffusion (CHARMED) enables extraction of physical components of neuronal structure based on their diffusion characteristics. CHARMED assumes that the diffusion within the neuronal fibers is restricted while it is otherwise only hindered. With the distinction between restricted and hindered water diffusion it is possible to examine the microstructure of neuronal white matter tissue. For example, parameters such as axonal volume fraction, extra-axonal volume fraction, extra-axonal diffusivity and axonal diameter distribution can be extracted with CHARMED. Moreover CHARMED enables separation between heterogeneous white matter systems where more than one fiber-bundle passes and hence may enhance the fiber-tracking abilities. CHARMED based parameters help to obtain microstructural information that limits virtual histology and provide a new tool to follow neuronal degeneration as well as white matter connectivity and integrity.

The Insulin-like growth factor mRNA binding-protein IMP-1 and the Ras-regulatory protein G3BP associate with tau mRNA and HuD protein in differentiated P19 neuronal cells

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Tau mRNA is axonally localized mRNA that is found in developing neurons and targeted by an axonal localization signal (ALS) that is located in the 3'UTR of the message. The tau mRNA is linked to an RNA-protein complex (RNP) from the neuronal cell body to the distal parts of the axon, reaching as far as the growth cone. This movement is mucosal observed as granules that contain tau mRNA and additional proteins. A major protein contained in the granule is HuD, an Elav protein family member, which has an identified mRNA binding site on the tau 3'UTR and stabilizes the tau message and several axonally targeted mRNAs. Using GST-HuD fusion protein as bait, we have identified four proteins contained within the tau RNP in differentiated cells. In this work, we studied two of the identified proteins i.e. IGF-II mRNA binding protein 1 (IMP-1), the orthologue of chick B-protamine protein (BP) in the testis, and G3BP-1, a G3BP-SH3 domain binding protein (G3BP). We show that IMP-1 associates with HuD and G3BP-1 proteins in an RNA-dependent manner and binds directly to tau mRNA. We also show a RNA-dependent association between G3BP-1 and HuD proteins. These associations are investigated in relation to the neuronal differentiation of P19 cells.

Dual effect of CD4+CD25+ regulatory T cells in neurodegeneration: Pro- and anti inflammatory cytokines determine microglial activity

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Autoimmune T+ cells can mediate the ability to withstand neurodegenerative conditions. Here we show that the ability to spontaneously manifest a T cell-dependent protective response is restricted by naturally occurring CD4+CD25+ regulatory T cells (Treg); depletion of Treg was beneficial in two mouse strains (C57BL/6) and BALB/c/Ola) differing in their spontaneous T cell dependent ability to withstand the consequences of optic nerve injury. Passive transfer of exogenous Treg was destructive in BALB/c/Ola mice (which can spontaneously manifest a T cell dependent protective anti-self response to injury) but beneficial in C57BL/6j mice (which have only limited ability to manifest such a response). This dichotomy was resolved by the finding that, in severe combined immunodeficient mice, a beneficial effect is obtained by passive transfer of either Treg-free CD4+ T cells (Teff) or Treg alone, indicating that neuroprotection can be achieved by either Treg or Teff in the absence of the other. We attribute these disparate effects of Treg to their differential interaction (in part via IL-10) with local innate immune cells (microglia) in the presence and in the absence of effector T cells. Activation of microglia by pro- and anti-inflammatory cytokines in suitably controlled amounts might trigger different signal transduction pathways, each of which induces a neuroprotective or microglial phenotype. Inhibitors of this process suggest that, under neurodegenerative conditions, the effects of Treg, and possibly also of other regulatory T cells, might not be uniform, and that their expression in different individuals might be genetically determined. Therefore, therapeutic intervention based on induction of regulatory T cells might have limitations.

A Spiking Neural Network Model with High Memory Capacity

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A balanced network leads to contradictory constraints on memory models, as exemplified in previous work on accommodation of synfire chains. Here we show that these constraints can be overcome by introducing a 'shadow' inhibitory pattern for each excitatory pattern of the model. This is interpreted as a double-balance principle, whereby there exists both inter-level balance between excitatory and inhibitory currents and local balance between the currents carrying coherent activity at any given time frame. This principle can be applied to networks with Hebbian cell assemblies, leading to a high capacity of the associative memory. The number of possible patterns is limited by a combinatorial constraint that turns out to be P<0.5N11 within the specific model that we employ. This limit is reached by the Hebbian cell assembly network. To the best of our knowledge this is the first time that such high memory capacities are demonstrated in the asynchronous state of models of spiking neurons.

Autoimmune T cells play a role in short- and long-term plasticity

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Considering the previously observed role of mature T cells in neuronal survival and repair, we hypothesized that a similar function can be attributed to such T cells in the context of neural plasticity. We examined this hypothesis in the brain and in striatum following the CA1 region (in-vivo) of transgenic mice congenic to wild-type (WT) leading to the phenotype of absence of mature T cells (mature T-) mice. In our experiments, the reactivity to afferent stimulation had the same EPSP and population spike (PS) size in the native and WT control mice. In addition, the native mice showed enhanced paired-
pulse inhibition at 30 msec inter-stimulus-interval (ISI), which was reversed to a minor facilitation at 60 msec ISI. Short-term facilitation by long-term potentiation (LTP) was detected in the nude mice. In-vitro, the dynamic range of the EPSPs was similar in slices taken from nude mice. Moreover, both the control and the nude mice showed similar paired-pulse facilitation across 4 different ISIs. Strikingly, nude mice expressed short term but not long term potentiation of EPSP. These results suggested that the degenerative immunity is involved not only in neuronal survival but also in the maintenance of neuronal plasticity, and thus might shed light on the role of the immune system in brain learning and memory processes.

The metabotropic Glutamate receptor 1 (mGluR1) is voltage sensitive.

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It is common knowledge that voltage - gated ionic channels are voltage sensors and also part of ligand - gated channels show voltage sensitivity, although much weaker. In contrast, G-protein coupled receptors (GPCRs) involved in the majority of signal transduction processes are not considered to be voltage sensitive, although they are transmembrane and could potentially be modulated by membrane voltage. In an earlier study (Ben-Chaim et al., 2003) it was shown that two GPCRs, the m2 (m2R) and the m1 (m1K) muscarinic receptors, known to modulate neurontransmitter release, are voltage sensitive; their activity toward the agonist is affected by membrane potential. Another type of GPCRs, the type 3 metabotropic glutamate receptor (mGluR3) was also shown to exhibit voltage sensitivity. Here we examine whether the type 1 metastorphic glutamate receptor (mGluR1a), member of group mGluRs, exhibit voltage sensitivity. Using Xenopus oocytes we show that the type 1a metabotropic glutamate receptor (mGluR1a), known to participate in LTP, is voltage sensitive. The mGluR1a mediated depolarized chloride channel currents were used to assay the activity of mGluR1a toward glutamate (Glu) was increased upon depolarization.

Endocannabinoids Affect Neurological and Cognitive Function in Thioacetamide-induced Hepatic Encephalopathy in Mice.

Avraham Y., Israeli E., Gabay E., Okun A., Zoltarev O., Zilberman I., Ganzburg V., Dagon Y., Pappo O., Mechodum R., Ilan Y. and Berry E.

Dept of Human Nutrition and Metabolism, Brain School of Public Health, Hadassah-Hebrew University Medical School, Jerusalem; Roux Unit, Hadassah Hospital, Jerusalem; Dept of Medicinal Chemistry and Natural Products, Jerusalem; Pathology Dept, Hadassah Hospital, Jerusalem; Background/Aims: The pathogenesis of hepatic encephalopathy involves functional changes in neurotransmitter systems. Endocannabinoids function as neurotransmitters and neuromodulators in the central nervous system via specific receptors. Recently the endocannabinoid system was found to be involved in the vasodilated state associated with cirrhosis. We hypothesized that the endocannabinoid system might also have a role in the pathogenesis of hepatic encephalopathy in an experimental model of fulminant hepatic failure. Methods: Fulminant hepatic failure in mice was induced by thioacetamide. Neurological performance was assessed by a ten point scale, by activity and by cognitive function. Levels of brain 2-arachidonoyl glycerol were analyzed by GC-MS. Results: The CNS levels of 2-arachidonoyl-glycerol were elevated in mice with thioacetamide-induced hepatic encephalopathy. Encephalopathic mice treated with the CB1 antagonist, SR141716A, demonstrated a dose-response improvement in the neurological score. Activation of the CB2 receptor with a selective agonist, HU308, caused a marked improvement in the open field motor and cognitive function also improved after administration of SR141716A or 2-AG while HU308 did not cause any effect (unpublished data). The CB1 antagonists did not affect the open field motor and cognitive function, but did not affect the CB2 antagonists. Administration of SR141716A or 2-AG showed that these compounds decreased levels of 2-arachidonoyl glycerol in the brain and splenic tissues. Conclusion: The main conclusion of our study is that endocannabinoids may have a role in the pathogenesis of hepatic encephalopathy. The role of CB1 antagonists and CB2 agonists in the treatment of hepatic encephalopathy needs to be investigated further.

Molecular mechanisms of neurorescue, neurodifferentiation and regulation of APP/Aβ peptide processing by the novel bifunctional iron chelator-monoamine oxidase inhibitor.

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Accumulation of iron at sites where neurons degenerate in Parkinson's (PD) and Alzheimer's (AD) diseases is thought to play a major role in the process of neurodegeneration. The brain permeable iron chelator, VK-28, as well as the propargylamine moiety of rasagiline, exert neuroprotective activities in cell culture models and in vivo against a variety of insults. We developed, a novel bifunctional drug, M30, possessing these components. M30 (1-10 μM) decreased apoptosis of SH-SY5Y neuroblastoma (NB) cells in a neurotoxic, serum deprivation model, via multiple protection mechanisms, including: reduction of the proapoptotic Bad and Bax; reduction of apoptosis-associated Ser139 phosphorylated H2 AX; induction of the anti-apoptotic Bel-2; inhibition of the cleavage and activation of caspase-3. Moreover, M30 promoted morphological changes resulting in axonal growth-associated protein-43 (GAP-43) implicating neuronal differentiation. VK-28 did not show any significant effect on cell differentiation. M30 markedly reduced holo- amyloid precursor protein (APP), C-terminal fragment (CTF) -β- and the amyloidogenic Aβ-6 peptides and in Chinese Hamster Ovary (CHO) cells stably transfected with APP "Swedish" mutation, the in cell media and the, in a dose dependent manner. In correlation, the non- amyloidogenic soluble APPα levels were elevated as well as the levels of CTF-alpha in cell lysate. These results complement the presence of an iron-responsive element (IRE) in the 5'- untranslated region (UTR) of the APP and the iron chelator properties of the drug. The bifunctional drug, M30 possesses neurorescue, neurodifferentiation and APP processing, resulting in a substantial reduction in Aβ- levels, might be a novel drug for the treatment of AD.

Central Control of Bone Mass

In vertebrates, bone mass is maintained constant between the end of linear skeletal growth and gonadal failure by a continuous destruction/formation process termed bone remodeling, which occurs simultaneously in multiple sites. It consists of a resorption phase of pre-existing bone by a specific cell type, the osteoclast, followed by a phase of bone formation by another bone cell type, the osteoblast. Although different foci present different phases of the cycle, the overall net effect is the balance between bone destruction and formation. The physiologic importance of bone remodeling is best illustrated in osteoporosis, the most common degenerative disease in developed countries, which results from an impaired remodeling balance that leads to bone loss and increased fracture risk. Several lines of evidence suggest that bone remodeling is centrally controlled: 1) Bones are densely innervated by the sympathetic nervous system as well as by sensory nerve fibers containing calcitonin gene-related peptide, substance P and tyrosine hydroxylase. 2) Bone cells express receptors for these and other neurotransmitters, suggesting the occurrence in bone of a non-synaptic, diffuse, and slow neurotransmitter signaling which regulates bone cell differentiation and activity. 3) Clinically, obesity protects against bone loss induced by the cessation of gonadal function. 4) Perhaps the most direct evidence for the central control of at least bone formation is the consistent finding that the open field endocrine system may have an important role in the pathogenesis of hepatic encephalopathy. 5) The immediate observation of heterotopic ossification and enhanced fracture healing in patients with traumatic brain injury. 6) Stress and depression in humans and experimental animals are associated with significant decreases in bone mass attributable to activation of the HPA-axis and perhaps other, non-sympathetic processes. It thus appears that the central control of bone remodeling is mediated by multiple pathways.
Central Interleukin-1 Receptor Signaling Regulates Bone Mass

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The pro-inflammatory cytokine IL-1α, acting via the hypothalamic IL-1 receptor type 1 (IL-1Rα), activates pathways associated with the restraint of bone formation such as the hypothalamo-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system. In addition, IL-1 has been implicated as a mediator of the bone lost induced by sex hormone depletion. To address more specifically the skeletal regulatory role of central IL-1Rα signaling, we characterized the bone phenotype of young IL-1Rα mice and mice with astrocytes-targeted overexpression of the human IL-1Rα receptor antagonist, under the control of the murine glial fibrillary acidic protein promoter (IL-1RaTG).

The genetically manipulated mice showed normal body weight and food consumption. Although a previous in vivo stereomicroscopic study reported a normal bone mass in the IL-1Rα−/− mice, a present micro-computed tomographic analysis demonstrated a lower trabecular bone density in the distal femoral metaphysis and lumbar vertebrae, as compared to their WT controls. Similar decreases were also observed in the trabecular thickness, number and connectivity.

Central Interleukin-1 Receptor Signaling Regulates Bone Mass
Bar-Am O., Tamar A., Weinreb O. and Youdim M.B.

Our recent studies have provided evidence whereby activation/regulation of protein kinase C (PKC) in association with Bcl-2 protein family promotes neuronal survival by rasagiline (N-propargyl-(IR)-aminoindan), and in relation to its pro-apoptotic role. In the present study, we further investigated the neuroprotective effects of n-propargylamine in a progressive neuronal death, induced by long term (3 days) serum deprivation in SH-SY5Y neuroblastoma cells. N-propargylamine (0.1-10 mM) dose-dependently reduced the levels of the early apoptosis-associated phosphorylation protein, H2AX (ser 139), as well as decreased the cleavage of caspase-3 and its substrate poly ADP ribose polymerase (PARP). Long-term serum withdrawal significantly down-regulated the anti-apoptotic protein, Bcl-2, as well as up regulated the pro-apoptotic protein, Bax. These effects were markedly reversed in a dose-dependent manner by N-propargylamine. Furthermore, it reduced the levels of the pro-apoptotic proteins, and finally using reverse-transcriptase PCR, we show that N-propargylamine elevated Bcl-2 and reduced Bax gene expression. In addition, serum deprivation induced an increase in protein levels of holo-APP in a consistent with pathophysiology of Alzheimer disease (AD). N-propargylamine markedly decreased holo-APP levels, accompanied by increased levels of the non-amyloidogenic g-secretase form of soluble APP (sAPPa) into the medium. Similar effects on cell survival and APP regulation/processing were demonstrated for rasagiline. These results indicate that the edaphic effects of rasagiline and N-propargylamine on APP and SAPPa levels promote a reduction in the toxic amyloidogenic pathway, involved in AD.

Do odd illusory shapes pop out? Effects of learning and expertise

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It is well documented that odd elements when embedded in a field of distractors that are similar to each other and differ categorically from the odd element in one feature, such as color, orientation, motion direction or shape. We ask whether the relevant shape needs to be defined by real edges or do illusory contours (Kanizsa, 1979) also induce a pop-out effect, though their perception is slower, and to what extent does such a pop-out depend on illusory-contour training history. Previous studies investigated the possibility of a pop-out effect when subjects search for a set of illusory-contour inducers among a field of non-inducers (Grabowsky & Tresman, ARVO, 30th: 457, 1999. Davis & Driver, Nature 31: 791, 1994). Others studied pop-out of odd shapes where subjective contours were defined by shifted gratings (Gurney et al. , Percept & Psychophys 52: 263, 1997). We explicitly tested subjects with different levels of training on a Kanizsa illusory contour task. Targets (which appeared in ½ of the trials) were illusory parallelograms and distractors were illusory triangles. Arrays contained 9, 16 or 25 illusory figures. We analyzed set-size effects and mean response time to determine if the classical tests for pop-out (relative set-size independence for odd element present trials) is relevant also for slowly induced perception. A significant difference in performance, as well as in learning rate was found between subjects with different levels of training. In contrast, a control experiment (with illusory rather than illusory) figures showed significantly less dependence on training level. These results suggest that pop-out detection of Kanizsa figures is a function of expertise. Supported by “Center of Excellence” grant #8009 from the Israel Science Foundation and the US-Israel Bi-National Science Foundation.

Quantitative analysis of Parvalbumin- and Calbindin-D28K- containing neurons in limbic brain structures and the SSC of Octodon degus after repeated early life stress

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Early adverse experience results in both physical and psychological alterations. Previous results in the trumpted-failed rat (Octodon degus) pointed out, that early life stress leads to a variety of morphological changes including region-specific changes of specific cell types. The changes of excitatory input accompanied by altered GABAergic modulation? To find answers to this question we analyzed the impact of the repeated early life stress on the development of inhibitory GABAergic neurons in the rodent hippocampus, amygdala, piriform cortex and the somatosensory cortex. The stress induced significantly lower densities of Parvalbumin- and Calbindin-D28K-immunoreactive (i)-neurons in the hippocampal subregion. Accordingly, the decreased excitatory input (lower spine densities) in the dentate granule cells appears to be compensated by increased numbers of inhibitory neurons. In the CA1 region, the increased excitatory input (enhanced spine densities) appears neither to be compensated nor amplified by altered numbers of GABAergic interneurons. Thus, an overall enhanced neuronal excitability could be predicted. The stress-induced neuronal adaptation in the basolateral amygdala again differs from that observed in the hippocampal formation. Increased cell densities of Parvalbumin- and Calbindin-D28K-immunoreactive neurons were detectable in the basolateral amygdala of early stressed degus, whereas in the central amygdaloid nucleus no differences were found. Also, the increased excitatory input (decreased spine densities) which was reported for the lateral amygdala appears to be even more downregulated by the medium spiny neurons, from which an overall dampening of neuronal excitability could be expected. These stress-induced changes of GABAAergic neurons could be more or less specific for some limbic regions, since in the piriform cortex and in the somatosensory cortex no quantitative changes were detectable.
Hippocampal sharp-wave

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Hippocampal sharp-wave ripple complexes (SPW-R) occur during slow wave sleep and behavioral immobility and are thought to represent stored information that is transferred to the cortex in a process of memory consolidation. Here we show that stimuli which induce long-term potentiation (LTP), a neurophysiological correlate of learning and memory, led to generation of SPW-R in hippocampal area CA3 that were identical to those observed spontaneously. Following repeated stratum radiatum-stimulation in area CA1 evoked SPW-R recurrently occurred in area CA3 and propagated into area CA1 and the subiculum. The induction of SPW-R was dependent on activation of NMDA receptors and involved time-dependent changes in interactions between clusters of neurons in the associative network of area CA3. Furthermore the induction of SPW-R by high frequency stimulation (HFS) could be reversed by application of low frequency stimulation (LFS) which also reversed stimulus-induced LTP in area CA3. During application of low dose acetylcholine (ACh) in presence of ACh-esterase inhibitor physostigmine a facilitation of the stimulus-induction of SPW-R was observed as well as a blockade of SPW-R activity by application of a ten fold higher dose of ACh. Our data suggest a mechanism which, by inducing SPW-R in the hippocampus, can be used to explore their role in memory consolidation, as well as the rules governing network activity in areas CA3 and CA1 and, therefore, the generation of ensemble activity in this structure. Furthermore these results suggest that, under certain cognitive states, learning-induced synaptic plasticity might result in the generation of SPW-R and the propagation of information from the hippocampus to the neocortex.

Monaural and binaural fMRI activation of the brainstem auditory pathway

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Binaural processing of sound in humans is initiated within the auditory nuclei in the brainstem. An MRI study on patients with multiple sclerosis and stroke indicated that whenever hearing onset overlapped a temporal window, binaural processing was abnormal, while the monaural performance was normal. The purpose of the present study is to reveal the difference between binaural and monaural processing using functional MRI (fMRI) on healthy subjects. fMRI was performed on a 1.5 Tesla GE scanner. Axial, sagittal and coronal slices of 4 mm thickness and 0 gap were acquired. A GE-EPI sequence was used with TR based on the ECG and configured to every fourth heartbeat. Statistical analysis of the data was performed by using SPM2 software. The default bounding box of SPM was adjusted to include the brainstem. Since the brainstem auditory nuclei are relatively small structures, the analysis included removal of movement related artifacts. The analysis was performed only in the subcortical area. The auditory activation was mapped on a 3-D brainstem auditory pathway atlas. Fifteen young healthy subjects participated in the study. Subjects were stimulated by 20-30 seconds of either classical music or rock music presented binurally or monaurally. In all subjects, binaural stimulation yielded activation in at least one brainstem nucleus. Activation was identified in the cochlear nucleus, superior olivary complex, and inferior colliculus. Both right and left brainstem auditory pathways were activated only when both ears were stimulated. The right auditory pathway was primarily activated when the left ear was stimulated and vice versa. We have demonstrated that fMRI can be used to identify the brainstem auditory pathway. Further investigation is required to explore the auditory pathway with different stimuli.

Voltage Dependent Conformational Changes in Muscarinic Receptors Affect Their Coupling to Their G-proteins

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G-protein coupled receptors (GPCRs) are involved in most signal transduction processes. Although GPCRs are transmembranous and could potentially be influenced by membrane potential, they are not considered to be, by themselves, voltage sensitive. In an earlier study (Ben-Chaim et al., 2003 J. Biol. Chem. 278, 22482), we showed that two GPCRs, the m2 (m2R) and the m1 (m1R) muscarinic receptors are voltage sensitive; their affinity toward the agonist is affected by membrane potential. We hypothesized that membrane potential affects the coupling of the G-protein to the receptor and thereby determines its affinity; high affinity when coupled to the G-protein and low affinity when free. This hypothesis was tested directly by measuring the voltage dependence of the agonist's affinity of chimeric m1R and m2R in which the third intracellular loops were interchanged. We show that the voltage sensitivity of both m1R and m2R crucially relies on the loop that couples the receptor to its respective G-protein.

Weaned Rats Return to Mother After Stress

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In the progression from suckling to weaning, rat pups show a reduced preference for the mother rat in a choice situation. We report here that 31-day-old weaned rats who are exposed to 30-minutes of acute stress revert to an earlier mode of behavior reminiscent of the suckling stage—that of preferring the mother rat. Sprague-Dawley derived male rat pups (n=21) were tested for preference in a Y-maze, where one arm contained the dam while the other arm contained a female littermate. When the pup made a choice, the trial was terminated. Each animal was evaluated for choice 4-times at different postnatal ages, once as a suckling at 15-18 days and three times as a weanling at 30, 31, and 34 days. Prior to the choice test on day 31, pups were placed on small elevated platforms for a period of 30-minutes, a method commonly used to induce stress. They were then tested as usual for preference for the dam or littermate. In keeping with previous work, 70% of suckling pups (16-18 days) preferred the mother as compared with only 33% preference for the dam in weaned rats on day 30. However, immediately after the platform stress on day 31, significantly more of these weaned rats (71%) reverted back to preferring the mother much as they had done as sucklings. This stress-induced preference shift was largely reversed on the following trial on Day 34 without the stress manipulation, with only 43% of the weaned pups preferring the dam. These results suggest that stress may cause a regression to much earlier stages of socio-affective development. We speculate whether this phenomenon, observed in laboratory rats, may be related to instances of stress-induced regression or attachment reported by clinicians in humans.

Sixty-Minutes Per Day of Social Interaction Reverses Isolation-Induced Aggression and Increased-Morphine Consumption

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Laboratory rats that are housed in social isolation are more aggressive and consume more morphine solution than socially housed rats. We report here that 60-min. of social interaction per day reverses these effects of isolated housing. In one series of studies, pairs of male rats were trained in a cooperation task where both animals must coordinate their bolus intake to receive food reward. Following acquisition, subgroups were allocated to one of three housing conditions: 1) social housing (2-per cage); 2) social isolation (1-per cage); or partial social isolation (1-per cage with access to another male rat for 5-min, 60-min,
or 4-hours per day). After 21-days in these different housing conditions the animals were re-tested in the cooperation tests. For this test, all rats, regardless of housing condition, were tested for 5 min. per day of social interaction. No deficits were observed in subgroups that had at least 60-minutes of social contact per day allowing toxic syndromes attributed to neuronal death.

or 4-hours per day). After 21-days in these different social interaction tests, male rats were housed for 21-days in one of three housing conditions: 1) social housing (2-per cage); 2) social isolation (1-per cage); or 3) per cage with access to another male rat for 60-min per day). Water or 0.5 mg/0.5 ml morphine sulfate consumption were measured in one-bottle or two-bottle tests. Socially isolated animals consumed significantly more morphine but not more water than those in the social housing or partial social isolation groups. There was no difference between the social housing and the partial social isolation groups indicating that 60-minutes of social contact per day is sufficient to reverse the effects of social isolation. Taken together, these studies indicate that social isolation increases aggression, disrupts a cooperation learning task, and increases morphine intake and that a short daily period of social interaction reverses these effects of social isolation.

Activity and significance of the brain ZnR

Joseph L., Chorny U., Rimon U., Szeiler F., Hersch sustein M. Dept. of Molecular Neurobiology, Heidelberg, Germany; Charite Campus Mitte, Humboldt University of Berlin, Germany; Max-Planck Institute of Medical Research, Heidelberg, Germany. Functional NMDA receptors are made up of an NR1 and an NR2 subunit, which plays a critical role in determining the susceptibility of the receptor to Mg2+ and its single-channel conductance. Significantly, NR1/NR2A receptors have higher conductance and enhanced sensitivity to voltage-dependent Mg2+ blockade, while NR1/NR2C and NR2B receptors show lower single-channel conductance and diminished Mg2+ sensitivity, such that they are more likely to open at resting potential. Transgenic mice which express a LacZ indicator gene that is controlled by the NR2 promoter revealed that in addition to cerebellum, NR2C subunits are expressed in several forebrain regions not previously identified with in situ hybridization. One such area is layer 4 of the barrel cortex, where we also showed functional expression of NR2C-containing receptors in whole cell and single channel recording. The lack of functional expression of NR2C in superficial layers of the prefrontal cortex, which is a major source of input to the entorhinal cortex. Horizontal slices through the hippocampus were bathed in 2 mM Mg2+ and whole cell recordings were made from neurons in the superficial prefrontal cortex. Cells held at -70 mV revealed prominent, DNQX-resistant, APV-sensitive, slowly decaying spontaneous EPSCs (sEPSCs). This effect was never seen at resting potential in neurons of the deeper prefrontal layers, they were, however, prominent when the membrane was depolarized. In outside-out patches from the somas of superficial prefrontal neurons, single NMDA channel currents induced by focal glutamate application were predominantly of the low-conductance class and displayed less sensitivity to Mg2+. By contrast, only high-conductance NMDA channels with a "classical" Mg2+ sensitivity were found in deep prefrontal neurons.

It seems likely that the functional expression of NR2C subunits by neurons in this restricted region has important consequences for parahippocampal circuit function.

MRI and histological imaging of migrating bone marrow stem cells transplanted into mouse brain

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Bone marrow mesenchymal stem cells (BMSc) are multipotent cells that can be induced in vitro to differentiate into a variety of cells and replace or repair tissues in the body. In our previous studies we were able to induce differentiation of mice BMSc into neuronal-like cells. The cells changed their phenotype and expressed neuronal as well as dopaminergic markers such as tyrosine hydroxylase and dopamine. The present study was aimed to clarify whether the mouse BMSc can migrate into the lesion and differentiate into the neurons when transplanted into mice subjected to unilateral 6-OHDA lesion, an animal model of PD. BMSc obtained from transgenic mice (B5/EGFP) bearing the enhanced green fluorescent protein (EGFP) underwent differentiation during a period of 48 hours. The cells were also transplanted with iron which allowed the stem cells to be visualized on MRI scan. Iron-implanted BMSc were then injected into the right striatum of mice that were injected stereotactically with 6-OHDA, in the right hemisphere and demonstrated rotational behavior induced by amphetamine. The mice underwent an MRI scan at several time points during 45 days post transplantation. Histological studies indicated that the EGFP-BMSc, both differentiated and undifferentiated, injected into the infarcted brain (non-lesioned) hemisphere were seen to migrate to and populate the 6-OHDA lesioned hemisphere. MRI could easily image the spatial distribution of small clusters of labeled cells at high resolution within experimental times acceptable for in vivo investigations. This study demonstrates the capability of BMSc to be attracted and to migrate to lesioned areas in this animal model of PD and demonstrate the potential of high resolution MRI in vivo imaging of cells migration.

Modulation of rhythmic patterns produces in the neonatal rat spinal cord by selective activation of mu-opioid receptors in the sacrocaudal segments

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The possible involvement of sacrocaudal-afferent (SCA) pathways in activation of rhythmic motor patterns was examined in the isolated brainstem spinal cord preparation of the neonatal rat. Repetitive stimulation of SCA or the ventromedial medulla (VM) produced a locomotor-like rhythm in the thoracolumbar (TL) and an alternating left-right rhythm in the sacrocaudal (SC) segments of the spinal cord. Selective application of the mu-opioid receptor antagonist DAMGO to the SC segments blocked the locomotor and SC rhythm produced by SCA or VM stimulation. The block could be alleviated by administration of the opioid receptor antagonist naloxone to the SC cord. Both application of DAMGO to the TL
The junctional region of trained and control gracilis muscles were double-labeled with Rd-a-bungarotoxin (BTX) for synaptic acetylcholine receptors (AChRs) and with biotinylated f Fab followed by FITC-conjugated streptavidin for AChE. Quantitative analysis of confocal fluorescence images revealed that synaptic AChE in the trained muscles increased (both intensity and area) relative to the AChEs when compared with controls. Altogether, these observations suggest that the G4-AChE might become significant at the endplates of fast twitch fibers following exercise. The localization of this form at the endplates following exercise is examined.

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Model of intracortical connectivity in the primary visual cortex

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Recent voltage-sensitive dye imaging studies on anesthetized cat area 17/18 have shown that spontaneously emerging activity patterns are dynamic and are similar to those evoked by various orientations of a moving grating stimulus [Kenet et al., 2003]. This suggests that orientation maps are intrinsic preferred states of the cortical network. To assess this, we used an experimental set of 24 single condition orientation maps to construct a connectivity matrix through a modified version of the pseudo-inverse rule of the Hopfield network [Ponsonnaz et al., 1985]. This modeling suggests that long-range connections depend on the difference in orientation preference of the connected columns. Motivated by these observations, we introduce a simple connectivity rule which depends on the selectivity and orientation preference of the interconnected columns. This rule can be viewed as an extension of the "ring model" connectivity rule for orientation preference [Bienenstock et al., 1989] that accounts for non-uniform selectivity. An analytical analysis of a simple rate model with this connectivity rule shows conditions under which the network has a ring attractor that goes through the
Weaning and social isolation are critical factors for the establishment of functional neuronal networks in prefrontal cortical brain areas

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Recent studies in rodents revealed that weaning is a critical formative period for adult behaviors. Moreover, it was found that changes in social and environmental conditions interact with subsequent social environmental conditions such as social isolation, resulting in altered behavior in open-field and social-interaction tests. In the present study we wanted to clarify if the described behavioral alterations are accompanied by morphological changes in prefrontal cortical brain areas. Male Wistar rat pups were raised with their dam until 21 days of age (early weaning) or 30 days of age (late weaning) and were subsequently reared in isolation or in groups. We quantified dendritic spine frequencies and dendritic length of pyramidal neurons in the anterior cingulate cortex (ACC). We found changes of dendritic spine frequency and dendritic length specific for apical and basal dendritic branches. Two-Way ANOVA revealed an effect of weaning on apical dendritic spine frequency resulting in decreased spine frequencies in the late weaning groups. In contrast, basal dendrites did not undergo spine changes in response to weaning, however social isolation induced significantly enhanced spine frequencies. Dendritic length was affected on apical dendrites only, where we found an effect of weaning and social isolation and an interaction of these factors, resulting in decreased dendritic length after late weaning and increased length after social isolation. Our results provide the first evidence that the process of weaning in interaction with postnatal environmental conditions alters the development of neuronal connectivities in prefrontal cortical areas, which at least in part may underlie the observed behavioral alterations.

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Prenatal stress in rats attenuates hippocampal long-term potentiation (LTP) and induces deficits in synaptic plasticity and spatial memory

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1. Dept. of Biological chemistry, Hebrew University of Jerusalem; 2. Dept. of Pharmacology, School of Pharmacy, Faculty of Medicine, Hebrew University of Jerusalem; 3. Prenatal stress (PS) in rats has been shown to reduce hippocampal neurogenesis and cause mild deficits in spatial memory in adulthood. These changes are associated with altered programming of the fetal brain by excess levels of maternal stress environmental factors. The present study investigated the effect of PS on hippocampal LTP and genes involved in its regulation, together with those implicated in synaptic plasticity. Pregnant Sprague-Dawley rats were subjected to variable maternal stress (restraint, saline injection and forced swim) on days 15-20 of gestation. Experiments were performed on male offspring aged 21 days. Field excitatory postsynaptic potentials were recorded in the CA1 region of hippocampal slices from 6 control and 6 prenatally stressed rats. The administration of low (10) to 60 minutes post-HFS) in control rats, that was significantly reduced by PS. Littermates of these rats were used for gene analysis in RNA by the Affymetrix DNA array. Hierarchical clustering showed a clear distinction between controls and PS. 3.5% of 20,000 genes represented on the array were up- or down-regulated by PS. These included several implicated in neurogenesis and synaptic plasticity that were down-regulated. Among those involved in presynaptic activity were: rab3a, synaptin 1, synapsin 1, stathmin 2 and synaptotagmin 2. Post-synaptic activity, further supporting the idea that intrinsic connectivity in this area underlies the activity in both spontaneous and evoked regimes.

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Effects of early life experience on corticosterone secretion in two animal models of depression (Wistar-Kyoto and Flinders-Sensitive Line rats)

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In light of links between prenatal depression and impaired functioning of the hypothalamic-pituitary-adrenocortical axis (HPA) in the offspring, we investigated the effect of early stress on corticosterone levels in pups. Prenatal stress (PS) is a critical formative period for adult behaviors. Moreover, it was found that this environmental factor acts in interaction with other stressors, resulting in altered behavior in open-field and social-interaction tests. In the present study we wanted to clarify if the described behavioral alterations are accompanied by morphological changes in prefrontal cortical brain areas. Male Wistar rat pups were raised with their dam until 21 days of age (early weaning) or 30 days of age (late weaning) and were subsequently reared in isolation or in groups. We quantified dendritic spine frequencies and dendritic length of pyramidal neurons in the anterior cingulate cortex (ACC). We found changes of dendritic spine frequency and dendritic length specific for apical and basal dendritic branches. Two-Way ANOVA revealed an effect of weaning on apical dendritic spine frequency resulting in decreased spine frequencies in the late weaning groups. In contrast, basal dendrites did not undergo spine changes in response to weaning, however social isolation induced significantly enhanced spine frequencies. Dendritic length was affected on apical dendrites only, where we found an effect of weaning and social isolation and an interaction of these factors, resulting in decreased dendritic length after late weaning and increased length after social isolation. Our results provide the first evidence that the process of weaning in interaction with postnatal environmental conditions alters the development of neuronal connectivities in prefrontal cortical areas, which at least in part may underlie the observed behavioral alterations.

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Transformations in Odor Percept Identity as a Function of Odor Intensity

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Anecdotal evidence suggests that a select group of odors such as indole and skatole undergo a dramatic shift in perception when sampled at high versus low concentration. This concentration-dependent transformation is thought to underlie the hedonic transformation, but also a transformation in perception identity. Here we set out to characterize these changes in odor perception, using a maximum-likelihood adaptive staircase to determine the detection threshold for the detection of indole diluted in mineral oil. The threshold was measured at 80% of the highest concentration step in the series. Each subject performed an odor quality evaluation on the sample provided using 48 descriptors from the Dravnieks Atlas of Odor Character Profiles. Following quality evaluation of this low intensity sample, each subject repeated the evaluation on a high intensity sample. Across subjects and intensities, 44 of the 48 descriptors were used at least once.
However, whereas 8 of the identity profile descriptors (almond, caramel, chocolate, dirty linen, espresso, vanilla) were used for the low, but not high concentration, no identity profile descriptors were used for the high but not low concentration. Upon collection of 30 subjects, principal components analysis will be used to characterize the odor space, and compare indole to other odorants.

A possible linkage between DA and mitochondrial complex I dysfunction: implications to schizophrenia

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Dopamine is suggested as a prominent etiological factor in several neuropsychiatric disorders including schizophrenia. In such dopamine-related diseases, mitochondrial dysfunction has been reported as well. In schizophrenia, mitochondrial complex I dysfunction was observed at the enzymatic level, as well as in the expression of mRNA and protein levels of some of its subunits both in the brain and in the peripheral blood. Notably, accumulating data show that dopamine can inhibit mitochondrial respiration both in vivo and in vitro. The purpose of the present study was to investigate the nature of the interaction between dopamine and mitochondria. When applied to human neuroblastoma SH-SY5Y cells, dopamine induced a reduction in ATP concentration, which was negatively correlated to intracellular dopamine levels. Furthermore, in disrupted mitochondria, dopamine inhibited complex I activity with no effect on complexes IV and V activities. Interestingly, complex I activity was also reduced by typical as well as atypical antipsychotic drugs. However, dopamine and haloperidol had no effect on mRNA and protein expression of three of complex I subunits (24kDa, 51kDa and 75kDa). Abnormal interaction between dopamine and mitochondrial complex I was observed in platelets of schizophrenic patients. Thus, complex I activity in disrupted mitochondria isolated from platelets of schizophrenic patients was susceptible to dopamine inhibition twice as much as that of control subjects. The results of the present study further support the existence of an interaction between dopamine and mitochondrial complex I, which can contribute to the pathology of schizophrenia, and suggests complex I as a modulation target for dopamine and antipsychotics.

Wnt1 controls the development of midbrain dopaminergic neurons in vivo
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Midbrain dopaminergic neurons play a central role in the modulation of different brain functions and are associated with important neuropsychiatric disorders. Despite the importance of these cells, the molecular mechanisms controlling their development are still poorly understood. The secreted glycoprotein Wnt1 is expressed in the midline in the floor plate, without affecting other midbrain nuclei and rostral hindbrain cell populations. Mice lacking a functional Wnt1 protein fail to develop a midbrain and part of the hindbrain. Therefore, these mutants can serve as a null model for the low, but not high concentration, no identity profile descriptors were used for the high but not low concentration. Upon collection of 30 subjects, principal components analysis will be used to characterize the odor space, and compare indole to other odorants.

The purpose of the present study was to investigate the nature of the interaction between dopamine and mitochondria. When applied to human neuroblastoma SH-SY5Y cells, dopamine induced a reduction in ATP concentration, which was negatively correlated to intracellular dopamine levels. Furthermore, in disrupted mitochondria, dopamine inhibited complex I activity with no effect on complexes IV and V activities. Interestingly, complex I activity was also reduced by typical as well as atypical antipsychotic drugs. However, dopamine and haloperidol had no effect on mRNA and protein expression of three of complex I subunits (24kDa, 51kDa and 75kDa). Abnormal interaction between dopamine and mitochondrial complex I was observed in platelets of schizophrenic patients. Thus, complex I activity in disrupted mitochondria isolated from platelets of schizophrenic patients was susceptible to dopamine inhibition twice as much as that of control subjects. The results of the present study further support the existence of an interaction between dopamine and mitochondrial complex I, which can contribute to the pathology of schizophrenia, and suggests complex I as a modulation target for dopamine and antipsychotics.

Network hippocampal activity modified by conditioning
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While neuronal plasticity is the widely accepted model of learning and memory, standard protocols, used, for example in the study of LTP involve associating postsynaptic response with a brief electrical stimulation. The failure of such studies is related to the artificial nature of the electrical stimulation. We used a conditioning procedure involving a transient enhanced activation of synaptic NMDA receptors in primary hippocampal cultures. This conditioning leads to a sustained potentiation of network activity, characterized by an increase in spontaneous activity, burst firing of many neurons in the network. Dual whole cell recordings revealed that the plasticity occurred via a decrease in inhibitory synaptic connections and an increase in excitatory synaptic connections, both of which were shown to be independent of postsynaptic intracellular calcium concentration. These changes appear to occur through a presynaptic mechanism, as they were reflected in a potentiation of synaptic release. Finally, the amplitude and frequency of mEPSCs recorded in presence of TTX was increased as a result of the NMDA induced plasticity. Our results suggest that intrinsic amplification of NMDA receptor activity leads to an overall potentiation of network activity in culture through several concomitant mechanisms.

Learning-induced enhancement of neuronal excitability is mediated by ERK-dependent reduction of the after hyperpolarization
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We studied the mechanisms that mediate learning-related long lasting reduction of the post-burst after hyperpolarization (AHP) in cortical pyramidal neurons. We previously showed that pyramidal neurons in the rat primary cortex from olfactory-discrimination trained rats have reduced post-burst AHP for three days after training completion, and that this reduction is due to decreased conductance of one or more of the PKC and calcium-dependent potassium current that mediate the medium and/or the slow AHP. In the present study we examined which potassium current is modulated by learning, and further explored the molecular mechanism that enables its long-term reduction. The small conductance (SK) channels inhibitor, apamin, reduced the AHP in neurons from trained, naive and pseudo trained rats to a similar extent, thus maintaining the difference in AHP amplitude between neurons from trained rats and controls. The protein expression level of the SK1, SK2 and SK3 channels was also similar in all groups. Noradrenalin (NE), which was shown to enhance the IAHP while suppressing the SIAHP, increased the AHP in neurons from trained rats, indicating that SIAHP conductance is reduced after training. The MEK inhibitor PD98059 increased the AHP only in neurons from trained rats, thus abolishing the differences between neurons from trained rats and controls. We suggest that learning-induced enhancement of neuronal excitability is mediated by reduction in the IAHP and that this long-term reduction is maintained by ERK1/II activation.
Cytotoxic or neuroprotective? The context-dependent activity of microglia under neuropathological conditions

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Protective autoimmunity refers to a well-controlled T cell-mediated response that helps the body resist neurodegeneration. Using an in-vitro assay of hippocampal slices to assess the cytotoxic or protective effect of microglia on neural tissue we show that interferon (IFN)-gamma and especially interleukin (IL)-4, characteristic Th1 and Th2 cytokines, respectively, endow microglia with a protective phenotype. In contrast, aggregated beta-amyloid, like bacterial cell wall-derived lipopolysaccharide (LPS), evoked a cytotoxic microglial response. Cytotoxicity was correlated with a signal-transduction pathway that down-regulated MHC-II expression through the MHC II-transactivator and the invariant chain. Protection by IL-4 regulated MHC-II expression through the MHCII-microglia in neural tissue we show that interferon (IFN)-gamma and especially interleukin (IL)-4, characteristic Th1 activity of microglia under neuropathological conditions.

Microglia activated by IL-4 support neurogenesis and oligodendrogenesis

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Cell renewal in the central nervous system (CNS) of adult mammals is limited, and is blocked in inflammatory conditions of the brain. Here we show that both neurogenesis and oligodendrogenesis from adult rat neural progenitor cells are blocked by inflammation-associated (endotoxin-activated) rat microglia. However, when activated by IL-4, a cytokine associated with helper T cells, the microglia induce and support neurogenesis and oligodendrogenesis. Blockage and support of neurogenesis were correlated with up- and down-regulation, respectively, of microglial production of TNF-alpha and interferon (IFN)-gamma. Induction of both TNF-alpha and IFN-gamma by IL-4-activated microglia could be neutralized by specific anti-IFN-1 antibodies. In vivo, hippocampal neurogenesis and cortical oligodendrogenesis were significantly boosted by IL-4-activated microglia injected into the cerebral ventricles, but were blocked by microglia activated by endotoxin. These findings suggest that immune modulation, rather than anti-inflammatory treatment, is likely to promote repair and cell renewal in the adult CNS.

Neuroimaging of Genetically-Defined Incipient CJD

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Neuroimaging of Genetically-Defined Incipient CJD

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Introduction: A new study has just been funded by the NIH to study CJD in Israel. We will use neuroimaging to elucidate early, and even premorbid, cerebral abnormalities of structure and function in a singular cluster of high incidence occurring among Libyan Jews living in Israel, caused by familial transmission of a mutated prion protein (PrP) gene. All subjects will have extensive neurological and neuropsychological examinations, as well as MRI, using both traditional structural imaging and newer neuroimaging methods: Diffusion-Weighting Imaging (DWI) and Magnetic Resonance Spectroscopy (MRS). Here we present the general logic and structure of the study, as well as results from the first seven subjects (4 patients and 3 relatives). Results: On clinical reading of the MRIs, all three controls were judged normal, and all four patients were considered abnormal. The most common findings were FLAIR and DWI hyperintensity in caudate (4/4), putamen (3/4), and cortex (4/4). Quantitative analyses showed significant loss of grey matter and higher ADC values in cortex. Focal decreases of ADC were found in the lentiform nucleus of patients. Spectroscopic imaging demonstrated reduced NAA in the patients, with the NAA/Cho ratio lowest in cingulate gyrus, where it was also correlated with a neurological severity score. Duration of disease was correlated with a decrease in the caudate nucleus and putamen. Comment: This project is the largest neuroimaging study ever conducted in CJD, and the first to observe a genetically pure JFPR sample. This study will provide data on the earliest stages of the disease, and on healthy mutation carriers before frank onset of symptomatic CJD. The large size of healthy mutation carriers, the noncarriers of similar environmental and cultural background, and rapid access to symptomatic patients, are all unprecedented features that should yield definitive data on the early stages of this devastating disease.

Do Magnets Affect our Neurons?

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Though many people started lately wearing static magnets as a therapeutic aid, the actual effects of these magnets on the nervous system is still an open issue. In order to investigate whether there is any neuroscientific basis for the claimed effects, we conducted preliminary experiments that were designed to check the impact of a relatively strong static magnetic field (SMF) on active neuronal networks. Hippocampal dissociated cultures were differentially exposed to 400mT magnets and monitored by calcium imaging (at 10Hz). We performed a combined morphological and functional comparisons of GFP transfected cells in these cultures. We checked both acute and chronic effects on network parameters such as network synchrony, burst synchrony and burst decay time and fluorescence dynamic range (DR = max amplitude- min baseline level). The acute treatment (immediate exposure to SMF while recording) showed little effect with very large variability in all parameters. The chronic treatment (11-12 days growth with the magnets) showed, on the other hand, significant effects. These cultures showed a large increase in SMF, a small decrease in maximal DR and synchronicity decline that was significant in the north magnetic pole treatment only. This unexpected asymmetry was even more pronounced in the effects on the dendritic trees morphology (Sholl analysis): south magnetic pole exposure reduced the branching at 100-150um distance from the soma, compared to the control, whereas north magnetic pole exposure increased the branching at the distances of 50-150um (both were insignificant in other distances). Overall, our results suggest that a chronic exposure to a strong SMF affects the neuronal network activity as well as cell morphology. Nevertheless, further research must be done before making any conclusions regarding the impact of these effects on the mammalian nervous system and humans in particular.

Common experimental procedures dramatically affect phosphorylation levels in Xenopus oocytes

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One of the preferred expression systems for the study of ion channels employs Xenopus oocytes. Channels mRNA is synthesized, injected to oocytes and induced ion currents are measured by the Two Electrode Voltage Clamp (TEVC) or the patch clamp techniques. To explore channel properties, oocytes are held in various membrane potentials and exposed to a variety of external conditions. Here we studied the effects of common experimental conditions on the phosphorylation levels of membrane proteins as phosphorylation/dephosphorylation events, ion channels gating and cell surface expression. Two strategies were chosen to determine relative phosphorylation levels: a direct detection with a phospho-Ser/Thr PKA substrate antibody and a functional method employing two different
leak potassium channels, as indicators. The two channels were chosen for their opposite responses to protein kinase phosphorylation: Drosophila KCNK0 channel activity is enhanced while human KCNK2 channel activity is reduced several fold following protein kinase A (PKA) activation. To eliminate possible modulation by pathways other than phosphorylation, mutants that are impaired in their PKA regulation were tested. We found that experimental conditions had a dramatic effect on the measured ionic currents: even a few minutes exposure to "physiological conditions" (4 mM KCI, -80 mV) decreased KCNK0 currents while increasing KCNK2 currents ~3 fold. Similarly, dramatic opposite current changes were observed when altering the composition, temperature, pH or osmolarity. On the contrary, mutant channels were not influenced by the same conditions. Correlating variations in phosphorylation levels were detected in un-injected oocytes by western analysis. We conclude that common experimental procedures dramatically affect phosphorylation levels in Xenopus oocytes. The use of kinases/phosphatases modulators might reduce uncontrolled effects on expressed channels.

Structure and Pathology in the Central Nervous System by q-Space Diffusion Weighted MRI

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Magnetic Resonance Imaging (MRI) is currently the most important imaging modality of the central nervous system (CNS). The main reason for the increasing non-invasiveness of the method, the many physical parameters that can be used as contrast mechanisms to construct MR images and the fact that morphological information can be coupled with biochemical information using magnetic resonance spectroscopy (MRS). Diffusion is an important contrast mechanism in the CNS. The q-space diffusion MRI in the CNS. Applications ranging from structural studies in excised spinal cord, through detection of different white matter associated pathologies of the spinal cord up to in vivo applications of this technique in MS and Dementia will be described. These examples will be used to demonstrate the potential and limitations of this technique. At the end of the lecture, if time will permit, we will highlight some new avenues of MRI in experimental neurology and neurobiology.

Autoantibodies against an extracellular peptide of the GluR3 subtype of AMPA receptors activate both homomorphic and heteromorphic AMPA receptor channels

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Autoimmunity may contribute to the pathology of some epilepsy syndromes as the sera of some epilepsy patients harbor specific autoantibodies to the GluR3 subtype of AMPA/glutamate receptor channel. Building on previous reports of a glutamatergic agonist activity of anti-GluR3 sera, we discovered here the ability of affinity-purified Abs directed against the GluR3B peptide (a.a. 372-395) to bind and activate recombinant GluR3 receptor channels expressed by Xenopus oocytes. We found that affinity-purified anti-GluR3B Abs can by themselves activate both homomeric and heteromeric GluR3-containing channels without the requirement of neuronal, glial or blood ancillary molecules. When repetitively applied, anti-GluR3B Abs didn't cause receptor desensitization. Co-applications of anti-GluR3B Abs and glutamate displayed neither inhibitory nor synergistic effects, and pre-incubation with anti-GluR3 Abs didn't affect the subsequent response to a glutamatergic agonist. We therefore conclude that anti-GluR3B Abs can activate GluR3-containing receptors, and hypothesize that if present chronically in brain fluids, these Abs may lead to a detrimental activation of GluR3-containing AMPA receptors. These findings may have important clinical relevance to epileptic patients harboring anti-GluR3B Abs.

ERK/II is essential for maintenance of olfactory-learning induced enhancement of synaptic transmission in the piriform cortex

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Previous studies have shown that olfactory-discrimination learning is accompanied by reduced paired pulse facilitation (PPF) in response to stimuli applied to the infrusinal fibers, interconnecting layer II pyramidal neurons. Extracellular regulated kinases (ERK/II) are thought to play major role in learning and memory as well as synaptic plasticity in the brain. The purpose of the present study was to determine whether ERK/II has a role in maintaining the olfactory-learning induced reduction in PPF. Intraocular recordings from pyramidal neurons were performed in piriform cortex brain slices. ERK II inhibition by application of PD98059 (38 μM) had no effect on PPF values in neurons from naive and pseudo trained rats. However, it caused a significant increase in PPF value in neurons from trained rats. Consequently, the difference in PPF values between trained and the controls was diminished (from 1.24 ± 0.04, n=19 to 1.42 ± 0.08, n=9 in trained, from 1.4 ± 0.04, n=16 to 1.51 ± 0.06, n=10 in pseudo trained, and from 1.59 ± 0.07, n=18 to 1.31 ± 0.07, n=18 in naive). In agreement with the electrophysiological analysis, Western blot analysis of symptomatical fraction, showed increased ERK/II activation (40%) in brains from trained rats (n=5) compared with control brains (naive n=7, pseudo trained n=9). We conclude that ERK/II activation is essential for maintenance of learning-induced enhanced synaptic transmission in the piriform cortex. We currently aim to identify ERK/II's pre-synaptic substrates that are mediating the learning induced synaptic plasticity.

Modeling complex receptive fields of fly interneurons

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The lobula plate tangential cells in the fly consist of a set of 60 strongly interconnected large field motion sensitive interneurons. This small network of cells has shown to exhibit a number of different computations associated with precise and unique wiring. In this study we focus on a subset of these interneurons, the vertically sensitive VS cells. VS cells were shown to have complex receptive fields extracting particular features of the optic flow that result e.g. from rotational ego-motion. Based on dual recordings from VS cells, it was suggested that neighboring VS cells are electrically coupled and distal cells inhibit each other (Haag and Borst 2004). Here, we analyze the suggested connectivity scheme using realistic compartmental modeling. Our calculations indicate that such a connectivity results in a linear decay of the signal from one cell to the other along the horizontal visual axis and can reproduce the experimental data available so far. The functional implications of this orderly arranged connectivity will be discussed.

Reference: Haag, J. & Borst, A. Nat. Neurosci. 7, 628-634 (2004).
Structure and function relationship of VIP: The importance of the N-terminus

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Accelerated neuronal death brings about cognitive as well as motor and other dysfunctions. A major neuropeptide, vasoactive intestinal peptide (VIP), has been shown to be neuroprotective (Brennemann DE and Eiden LE. Proc Natl Acad Sci 1986;83(4):1159, Gozes et al.: Proc Natl Acad Sci 1996;93(1):427). Several studies suggest that VIP could have a beneficial effect on neurological diseases such as Alzheimer’s and Parkinson’s disease. Hence, novel potent VIP analogs could be valuable for several therapeutic uses.

VIP’s effects are mediated through high affinity interaction with two receptors: VPAC1 and VPAC2. VPAC1 and VPAC2 are preferentially coupled to Gαq protein that stimulates increases in adenylyl cyclase. Currently, all the potent VIP antagonists synthesized have modifications in the N-terminal domain of the peptide. Thus, it is suggested that the N-terminal domain of VIP is responsible for the peptide’s activity. In view of the above, we examined the effect of multiplication of the N-terminal domain of the VIP ligand, on the VIP receptor (VPAC1) binding and cAMP activation. The multiplication of the VIP N-terminal was performed through extending or branching methods. We created several VIP analogs carrying multiplication of the N-terminal domain of VIP. Circular dichroism (CD) analysis revealed that these peptides maintained similar helicity to VIP in organic environment. The analog receptor binding and activation of HT29 cells expressing VPAC1 was examined. A VIP branched analog that was slightly more efficacious as compared to native VIP towards VPAC1 related cAMP production was discovered. This analog could have potential therapeutic value in neurological disorders. It is concluded that two branched N-terminal VIP sequences are superior in recognizing VPAC1 as compared to two N-terminals in tandem.

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very early frontal involvement in retrieval from working memory?

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The involvement of the frontal lobe in memory processes is long acknowledged. However, the exact role it plays is controversial. In recent years, both monkey and human studies have begun to elucidate the role of prefrontal cortex in maintenance of information across delays in working memory. As for retrieval of information however, it has been assumed that the frontal lobe is involved only in post-retrieval processes (i.e., assessing the outcome of retrieval). Following a hint from an fMRI experiment, we compared event related brain potentials during encoding and retrieval of faces in a delayed match to sample task. We asked 15 participants to remember a briefly presented face over a period of 2 seconds and then judge whether a second face is of the same person or not. The response was separated in time from the presentation of the second face. We found that the N170, a marker of face perception, recorded over parieto occipital scalp sites, is identical during the presentation of the first and second face. However, during the second presentation, when retrieval is required, a frontal scalp activity starts around 80 ms after the face is first presented. With the limitations of EEG measures to identify sources reliably, this suggests early recruitment of frontal lobe mechanisms in retrieval, consistent with a merely post-retrieval process. We propose therefore that the frontal cortex is involved with retrieval from the outset.

Encoding of Object Position in an Active-Touch System: Rat Whisker Kinematics & Somatosensory Cortex Dynamics

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Major events occurring during active vibrissal sensing, such as whisker protraction and touch, are encoded by various functional types of first-order trigeminal neurons. We examined how these events are represented in the barrel cortex, using artificial whisking in anaesthetized rats (Szwed et al., Neuron 2003). We induced whisking by direct electrical stimulation of the facial motor nerve, while positioning an object at different horizontal locations along the path of the whiskers. Whisker trajectories were monitored using high-speed video, and various parameters were extracted from the whisker motion. We investigated both whisker kinematics and cortical neuronal responses. We found that the whisker curvature encodes object position better than the angle. In addition, we recorded neurons in the rat barrel cortex and investigated the encoding of object position. Neurons were classified according to their response at steady-state into Whisking-touch (WT) units, which responded both to the whisking and to object touch, and touch (T) units, which responded only to object touch. The T units are situated predominantly near layer IV, while WT units are mostly situated in the cortical layers above and below layer IV. The two components of the WT response can be distinguished by the fact that the W component adapts within 3-4 whisk, while the T component does not adapt. Overall, our results demonstrate that the computation of object position is carried out by a dynamical process which integrates whisking and touch information at different cortical layers. Supported by The Israel Science Foundation, Israel, grant no. 377/02-1 and The Max Planck Foundation, Germany.

NAP binding to tubulin mediates cell survival

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The octapeptide NAP (NAPSVIPQ) potently protects neurons against a wide variety of insults in vivo and in vitro. NAP is the active site of the novel protein Activity-Dependent Neuroprotective Protein (ADNP), which is a VIP-responsive gene. In vivo and in vitro, NAP protected neurons from cell death induced by high glucose and oxygen deprivation. The octapeptide NAP (NAPSVIPQ) potently protects neurons against a wide variety of insults in vivo and in vitro. NAP is the active site of the novel protein Activity-Dependent Neuroprotective Protein (ADNP), which is a VIP-responsive gene. In vivo and in vitro, NAP protected neurons from cell death induced by high glucose and oxygen deprivation. NAP protects against cell death induced by high glucose and oxygen deprivation. The octapeptide NAP (NAPSVIPQ) potently protects neurons against a wide variety of insults in vivo and in vitro. NAP is the active site of the novel protein Activity-Dependent Neuroprotective Protein (ADNP), which is a VIP-responsive gene. In vivo and in vitro, NAP protected neurons from cell death induced by high glucose and oxygen deprivation. NAP protects against cell death induced by high glucose and oxygen deprivation. The octapeptide NAP (NAPSVIPQ) potently protects neurons against a wide variety of insults in vivo and in vitro. NAP is the active site of the novel protein Activity-Dependent Neuroprotective Protein (ADNP), which is a VIP-responsive gene. In vivo and in vitro, NAP protected neurons from cell death induced by high glucose and oxygen deprivation. NAP protects against cell death induced by high glucose and oxygen deprivation. The octapeptide NAP (NAPSVIPQ) potently protects neurons against a wide variety of insults in vivo and in vitro. NAP is the active site of the novel protein Activity-Dependent Neuroprotective Protein (ADNP), which is a VIP-responsive gene. In vivo and in vitro, NAP protected neurons from cell death induced by high glucose and oxygen deprivation.
Withdrawal from cocaine-seeking behavior by DHEA

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Drug addiction is a serious problem in the modern world. One of the most abused drugs is cocaine. One type of neurosteroid that seems to reduce the craving for cocaine in rats is Dehydroepiandrosterone (DHEA). Clinical trials have shown that DHEA induces a feeling of well-being. Cocaine addicts that underwent withdrawal and then relapsed to drug abuse exhibited low DHEA levels. Thus, it was hypothesized that a connection exists between mood, emotions and DHEA, and that increasing DHEA levels may assist in withdrawal from cocaine. We exposed a group of rats to cocaine using the self-administration technique. When rats achieved maintenance levels meaning they take a steady amount of drug on a daily basis, they received daily i.p injections of DHEA (2 mg/kg) for 2 weeks, 90 minutes before being placed in the self-administration chambers. We examined the possibility that DHEA treatment may have generally disrupted locomotor function in rats. Increased motor activity could itself decrease the number of lever responses. Therefore, we tested the effect of DHEA treatment on water self-administration in water-deprived rats. There were no significant differences in the number of active lever responses or the number of water reinforcements in DHEA-injected compared to untreated control rats. In conclusion, DHEA treatment induces withdrawal from cocaine-seeking behavior without causing motor deficits. Furthermore, the combination between cocaine and DHEA treatment is not rewarding. Thus, it may be a novel treatment for cocaine addiction.

GCP170 Interacts with Serine Racemase and Regulates the Synthesis of the NMDA Receptor Coagonist D-Serine.

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D-serine is an endogenous coagonist of NMDA receptors that is synthesized from L-serine by serine racemase. In order to identify new mechanisms and pathways regulating brain D-serine synthesis, we screened for protein interactors with the NH2-terminal region of serine racemase. GCP170 was first identified as a membrane associated protein present in the Golgi apparatus with unknown function. The interaction of GCP170 and serine racemase was co-immunoprecipitated from both transfected cells and brain extracts, indicating that the interaction occurs in vivo. Additionally, confocal immunofluorescence microscopy studies in HEK293 transfected cells and primary neural cultures demonstrated a high degree of colocalization in the cytosol and intracellular membranes. To evaluate the physiological role of the interaction, serine racemase was co-transfected with GCP170 in HEK293 cells and synthesis of D-serine was determined by HPLC. We found that cotransfection of GCP170 elicited a significant decrease in D-serine production by serine racemase. This indicates that GCP170 is a negative regulator of serine racemase and may physiologically modulate the production of the NMDA coagonist D-serine. Further studies may help clarify the role of D-serine in neurodegenerative and psychiatric diseases.

Circulating cholinesterase isozyme activities are altered in dystrophic-deficient mutant (mdx) mice

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Proper synaptic transmission depends on accumulation and maintenance at high concentrations of acetylcholine. Therefore, we determined the acetylcholine:receptor (AChE) concentration that is considerably greater than synaptic acetylcholinesterase (AChE) density. Previously, we demonstrated that D-serine is an endogenous modulator of neuronal function and behavior in mice, a model of Duchenne Muscular Dystrophy (DMD), and that D-serine is reduced in mdx mice. The results of this study suggest that D-serine is a potential therapeutic target for the treatment of neuromuscular and neurological disorders.

Motor Assessment within Virtual Environments: Distractor Interference Effects in Reaching Toward Visual Targets

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Background: Previous studies have demonstrated that changes in the environment may influence movement trajectory as well as reaction time and movement duration. The use of a virtual reality (VR) system provides a flexible and powerful method which allows data to be efficiently collected (e.g. in contrast to positioning real objects on each trial), and a way to examine the temporal and spatial kinematics of limb movements. We have developed a VR system, which includes a 3D tracking device for measuring limb movements. The system enables the experimenter to assess the motor performance of the subjects while interacting with virtual objects while focusing on the planning and execution of movements. The system combines a single camera, video-capture application, a 3D tracking system, and a VR environment. The main objective of this research is to investigate the interference effects caused by the presence of a distracting object while reaching towards virtual targets in 3D space, where the object's position and velocity (of both distractor and target) are manipulated. Method: The system is used to assess the motor performance of young adult healthy subjects, and focuses on the influence of the object's presence on the attentional mechanisms underlying the planning and execution of movements in 3D space. In phase 2, the system will be used to assess the motor performance of elderly healthy subjects and patients with stroke. Phase 3 will assess the usability of the system in order to demonstrate the feasibility of using such a system for rehabilitation evaluation and treatment. Conclusion: Use of the above VR system may shed light on the way in which movements are planned and executed, providing a rationale for using the current technology to lead to better diagnostic procedures for patients with neurological dysfunction.

Concept and Percept in Emotion processing: a cross-modal fMRI study

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Real-life emotion generation involves low-level perceptual processing of the physical properties of sensory information (e.g. color, form, movement etc.), and higher-level
manipulation of concepts producing emotional meaning. Isolating emotional conceptual processing is difficult since it is context dependent. Many conceptual processing of the stimuli used to elicit emotions. In order to separate the conceptual from the perceptual aspects of emotional processing, a cross-modal paradigm was applied. 12 sec video and audio clips were presented both alone and in combination (combi). Video clips, when presented alone, were rated according to the valence of the music as neutral, negative or positive (n=15, p<0.06). 12 subjects were scanned in an fMRI system while passively viewing the various clips. All clips were pseudorandomly distributed and each of the 12 subjects viewed each video clip combined with only one type of audio clip. To test for conceptual processing in emotion, we compared the combo condition to video and audio each presented alone. One day after the amygdala and the dorsolateral prefrontal cortex showed increased activity for this contrast. On the other hand, activation of high order visual areas was not augmented by the addition of video to audio irrespective of emotion. The findings of this study clearly differentiate between brain regions involved in the conceptual versus the perceptual constituents of emotional processing.

Olfactory bulb organotypic culture: an in-vitro neuronal zinc signaling model

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Zinc has long been known to play an essential role in many aspects of mammalian development and function, primarily as enzyme co-factors and as structural elements in transcription factors. In the brain, in addition to this tightly bound zinc, 'free' or loosely bound zinc ions are present in the olfactory epithelium. The function of this 'synaptic' zinc is unclear, evidence now exists for yet another pool of 'intracellular zinc' that is available to many, perhaps even all cells. We have established organotypic cultures of the olfactory epithelium and buds from 7 day old CD-1 mouse pups to study the regulation and function of zinc and zinc-homeostatic proteins. One day after establishing the cultures, basic OB architecture is intact and the vast majority of cells viable. After one week, immunohistochemical characterization of the explants included general and specific markers. Some, e.g., TH and parvalbumin, selected discrete cell populations. Expression of ZnT-1 was dramatically reduced in all layers. Periglomerular neurons that were ZnT-1 immunonegative and TH immunopositive were observed in the explants at all ages examined. This finding was not dependent upon availability of TH in medium or in the presence of zinc. Containing afferents from OE cells. MT I/II was expressed normally in astrocytes in and around the glomeruli. Connections of OE cells with their targets in the OBs glomeruli was demonstrated by DiI and immunolabeling with the synaptic vesicle protein synaptophysin. Finally, OB cultures were exposed to the nitric oxide donor (DETA/NO) to determine what if any intracellular zinc resources are maintained in these isolated slices. Explants exposed to NO for 8 hours release zinc from internal stores as seen by the zinc fluorophore, TSQ. These results demonstrate the utility of this in vitro model for the study of zinc signaling and olfaction.

Proteomic study: What is the role of ERKII in learning and neuronal plasticity?

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We are interested in the role of the extracellular regulated kinase II/III (ERKII/III) in the formation of long-term memory and plasticity. ERKII is involved in both early and late phase of LTD. We have investigated the role of ERKII in the formation of taste memory. The results of our experiments indicate that ERKII is involved in the formation of taste memory and that the activity of ERKII is necessary for the consolidation of taste memory. The data support the hypothesis that ERKII is involved in the consolidation of taste memory and that the activity of ERKII is necessary for the consolidation of taste memory.

The large cytoplasmic loop of the Na+-Ca2+ exhanger NCX1.5 protects the protein from proteolytic cleavage

Eskin-Schwartz M., Kais J., Rahamimoff H.

'Dept. of Biochemistry, Hebrew University-Hadassah Medical School, Jerusalem, Israel; 'The Na+-Ca2+ exhanger NCX1.5 is modeled to contain 9 TMS (transmembrane segments) organized in a large cytoplasmic loop between TMS 5 and 6. This loop contains the Na+ and Ca2+ regulatory sites as well as XIL and putative phosphorylation sites. Truncation of 426 amino acids from within the large cytoplasmic loop of the Na+-Ca2+ exhanger RBB-2 (NCX1.5), between I240-I666, results in expression of a mutant which exhibits about 76% of the transport activity of the parent full length protein. Western Blot analysis of amino terminal FLAG tagged wild type exhanger derived from cell extracts indicated that the protein migrates as a 120 kDa band which fits its calculated molecular mass. The cytoplasmic-loop truncated mutant however revealed multiple protein bands ranging from 25 kDa to 200 kDa including a protein of 75 kDa which corresponds to its expected molecular mass. Similar protein profile was obtained when the surface expressed mutants derived from NCX1.5 were analyzed. Addition of the proteasomal inhibitor ALLN did not alter the protein profile of either the WT protein or its loop truncated mutant, except that an overall increase in amount of the exchanger protein was detected in each protein band. 5 partially truncated mutants, each one containing different subset of regulatory sites were generated: I241deltaH479, H347deltaH513, I241deltaI395, I397deltaV667 and N490deltaR656. All the truncated mutants were surface expressed and displayed exchange activity ranging from 34 to 91 percent. Western Blot analysis of I241deltaH479 and RBB-2 mutant exchangers displayed protein bands of unexpectedly low molecular masses of approximately 50 kDa. However, I241deltaH479, having the largest loop deletion, displayed significantly reduced half life time of (1-3 h) as compared to the wild type exhanger protein (approx. 5 h). Half life time of I241deltaI395 could not be measured due to an extremely weak autoradiography signal.

Binaural Processing in Primary Auditory Cortex

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We investigated the way neurons in the primary auditory cortex (A1), which have relatively wide frequency tuning curves and thus are expected to integrate information across frequency, respond to stimuli that include interaural time differences ITD. Interaural time differences are usually considered significant only in the frequency range up to 1500Hz in humans, whereas it is much easier to physiologically record from neurons with higher best frequencies. For this reason we used a special stimulus, the transposed stimulus, for our study. Transposed stimuli are composed of a low-frequency envelope rectified and low-pass filtered to simulate stimulus, by multiplying a high frequency tone or noise carrier. To test the neural encoding of binaural disparities, the envelope consisted of a bandpass noise centered at 4 different low frequencies, and the transposed stimulus was presented to the ears at different times. The system was tuned to a 3 Hz tone. The system was tuned to a 3 Hz tone. The tone was added to the noise at both ears with the same phase,
Mechanisms of Chronic Mild Stress-Induced Depression and Bone-Loss in Mice
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In humans, major depression is often accompanied by osteoporosis. In mice, we have demonstrated that chronic mild stress (CMS), which triggers a depressive-like state, induces bone loss secondary to decreased bone formation and increased bone resorption. The present work was undertaken to uncover mechanisms that mediate the CMS-induced changes. Specifically, we explored whether stress-induced bone loss was mediated by glucocorticoids.

Results

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, induced by chronic mild stress (CMS), was associated with increased bone resorption and decreased bone formation. The increased bone resorption was mediated by elevated levels of the pro-inflammatory cytokine interleukin-1 beta (IL-1 beta), which is known to activate osteoclasts. Hyperactivity of the HPA axis also increased the expression of the glucocorticoid receptor in osteoclasts, leading to an increased sensitivity to glucocorticoids.

Conclusions

The results suggest that chronic mild stress induces bone loss in mice by activating the HPA axis and increasing the sensitivity of osteoclasts to glucocorticoids. These findings provide a potential therapeutic target for the treatment of osteoporosis in humans.
astrocyte PG production by 35%, 32% and 19% respectively. LPS increased PG synthesis in microglia and astrocytes. SS and octreotide inhibited LPS-induced microbial PG synthesis by 80% and 62% respectively but, did not change LPS-induced PG levels in astrocytes. It is suggested that the inhibition of microglial PG synthesis that is induced by inflammatory agents like LPS is significantly regulated by SS and analogues, then specific preventive and therapeutical modalities may be devised to intervene with these mechanisms.

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Biosynthesis and Degradation of D-Serine an Endogenous Coagonist of NMDA Receptor.

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Mammalian brain contains high levels of D-serine, an endogenous coagonist of N-methyl-D-aspartate type of glutamate receptors. The presence of D-serine in the brain challenges the idea that only L-amino acids will be present or play a role in mammal. We now sought to understand the mechanism of biosynthesis and degradation of brain D-serine, which will shed light on several aspects of D-serine in brain and central performance. It was synthesized by serine racemase, a brain enriched enzyme converting L- to D-serine. Degradation of D-serine is achieved by D-amino acid oxidase (DAAO), which is present in brain areas that are highly enriched in D-serine. We now report that serine racemase is a bifunctional enzyme catalyzing both the synthesis and the racemization of D-serine from L-serine, producing both D-serine and pyruvate. We found that D-serine from D-serine is from a novel mechanism for regulating intracellular D-serine levels. Robust degradation of D-serine by serine racemase was observed in both HEK293 cells and primary astrocyte cultures. In order to further investigate the role of elimination in regulating cellular D-serine, we generated several serine racemase mutants displaying selective impairment of elimination activity. As a result, levels of D-serine synthesized by the mutants are several fold higher than the wild-type both in vitro and in vivo. Extracellular D-serine is more stable toward elimination, likely due to physical separation from serine racemase and its elimination activity. Elimination provides a novel mechanism for the metabolism of D-serine in brain areas lacking D-amino acid oxidase, with implication for the regulation of NMDA receptor neurotransmission.

Cannabinoid receptors and "failure to thrive" in newborn mice

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We have previously suggested that deficiency of cannabinoid CB1 receptors may underlie the enigmatic syndrome in infants 'Non-organic failure to thrive' (NOFT). Thus we have reported that specific blockade of the CB1 receptors in one-day old mouse pups induced hypothermia, depressed ultrasonic vocalizations, prevented milk intake and resulted in death within days after birth. Similar deficiencies were found in (untreated) CB1-/-/ knockout pups. Aim: To further evaluate the validity and explore the mechanisms of neonatal CB1 receptor blockade as a model for NOFT. Procedure: We compared the effects of neonatal blockade of CB1 receptors (with SR141716) in two strains of mice (ICR and Sabra). Experiment 1: Suckling-related motivation, general motor behavior of pups were studied in pups, when exposed to an anesthetized dam. In addition, daily measurements were made of body weight, ultrasonic vocalizations and auditory responses. Experiment 2: Control and SR141716-treated pups were warmed to 300C and developmental parameters were measured as before. Results: 1. ICR mice displayed more competent suckling than Sabra's 2. The rate of mortality induced by CB1 receptor blockade is strain-dependent 3. General motor and cerebral behaviour were suppressed in SR141716-treated pups but motivation to suckle was not impaired. 4. Increasing environmental temperature prevented hypothermia in the experimental pups, but did not prevent the sucking impairment and mortality induced by CB1 receptor blockade. Conclusions: CB1 receptors play a critical role in the ability of newborn mice to suckle milk, but genetic differences determine the rate of vulnerability of the pup to blockade of the CB1 receptor. Although CB1 receptor antagonism causes hypothermia, this does not explain the inability to nurse. CB1 receptors are involved in motor functions required for the sucking apparatus, but not in the motivation to suck.

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Central and peripheral cannabinoid receptors

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Conclusive evidence for the existence of a specific receptor for delta-9-tetrahydrocannabinol (THC), the major psychoactive constituent of marijuana, was obtained in 1988. Since then this receptor has been cloned and detected in widespread areas in the brain, highly concentrated in the neostriatum, hippocampus, cerebral cortex and cerebellum. A second receptor was cloned in 1993 in peripheral tissue, and found notably on immune cells, but also in embryonal cells, osteoblasts and osteoclasts. The centrally located receptor is designated CB1, and the peripheral one CB2.

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Endogenous Coagonist of NMDA Receptor.

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Central and peripheral cannabinoid receptors Fride E.1,2, Arshavsky N.1, Ezra D.1,2, Fride E.1,2, Arshavsky N.1, Ezra D.1,2, Fride E.1,2, Arshavsky N.1, Ezra D.1,2.

The existence of additional CB receptors which await definitive identification. Research of the "Endocannabinoid-CB-Receptor System" has greatly accelerated over the last decade. Observations ensuing from these efforts will contribute to our understanding of this newly discovered, highly important biological system.

Variability of the mesolimbic neuronal activity in a rat model of depression.

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The Fidler Sensitive Line of rats is a widely accepted and validated model of depression. These rats demonstrate abnormalities in limbic locomotor system, suggesting disturbed neuronal activity in the ventral tegmental area. Interspike interval time-series were recorded from the ventral tegmental area of control Sprague-Dawley and Fidler sensitive line rats. These data were analyzed for the variance of interspike interval for each group of animals. We found that TSL rats show a significant decrease of the variance of interspike intervals of the length 0.2-0.6 sec. We suggest that the interspike intervals of this range have an important role in the information encoding in the mesolimbic dopaminergic system. Impaired variance of the interspike interval length in this area can correspond to the pathophysiologic of depression and can be a possible method for the analysis of the efficiency of antidepressant treatment.
Investigating the roles of DOC2 in calcium-activated exocytosis

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Ca(2+)-dependent exocytosis involves vesicle docking, priming, and release. This process is performed and regulated by a vast number of synaptic proteins and depends on proper protein-protein interactions and protein-lipid interactions. DOC2 are protein family that contains 3 isoforms that was found when screening DNA libraries with a C2 probe. DOC2 has 3 special domains: the Nid domain that interact with Munich, a priming factor localized to the presynaptic membrane and two tandem C2 (designated C2A and C2B) separated by a short polypeptide linker. C2 domains participate in Ca(2+) dependent associations with phospholipids. These observations suggest that DOC2 might be involved in one of the final stages of the synaptic vesicle cycle such as priming. To investigate the role of DOC2, we overexpressed DOC2B in adrenergic-chromaffin cells using lentiviral vectors.

In all 3 kinetic components of the exocytosis response, in the first and second flash. These results suggest that DOC2 is a positive regulator of exocytosis and influence exocytosis via time-dependent interaction with another priming protein.

Identification of regulatory mutations in the MECP2 gene associated with Rett Syndrome by means of quantitative RNA expression assays in peripheral blood.

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Danek Gartner Institute of Human Genetics, Sheba Medical Center, Tel Hashomer, Israel; 2 Child Neurology Dept., Sheba Medical Center, Tel Hashomer, Israel; 3 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; Rett syndrome (RTT) is an X-linked progressive neurodevelopmental disorder that primarily affects females. Disease-causing mutations have been identified in 90% of RTT cases, predominantly in the methyl-CpG-binding protein 2 (MECP2) coding region at the CpG hot-spots. Although the majority of affected patients have been found to harbor minor or major deletions involving MECP2, in attempt to verify the role of MECP2 as a single underlying cause of RTT, we pursued the detection of additional mutations in regulatory elements of MECP2 in clinically definite RTT cases. To this end, we employed quantitative RNA expression assays in the peripheral blood lymphocytes including TinMan probes for both known MECP2 transcripts and RNaseP and ODC1 reference genes. Within this framework, we identified several patients with lower blood MECP2 expression levels that had no previous indications of MECP2 mutation presence. By means of denatured-high-performance-liquid-chromatography (DHPLC) and direct sequencing of the non-coding MECP2 regions, we identified a novel splice site mutation in the first exon-intron junction of MECP2 that potentially leads to two MECP2 transcripts. We also detected several potentially meaningful elements in the intron adjacent to the alternatively spliced exon 2 of MECP2 and in the 5' UTR. These elements were highly conserved across species and were associated with RNA splicing or RNA transcription machinery in other genes. We also obtained preliminary indication of overexpression of both MECP2 in patients with missense mutations, which overlaps with recent findings in a controlled mouse animal model that traced overexpression of MECP2 to a neurodevelopmental delay phenotype reminiscent of RTT.

Novel Bifunctional Drugs with Iron- Chelating and Monoamine-Oxidase Inhibitory Activities for the Treatment of Neurodegenerative Diseases

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One of the defining characteristics of neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease and amyotrophic lateral sclerosis, is the abnormal accumulation of iron in the affected brain areas, which together with monoamine oxidase (MAO) contribute to the onset of oxidative stress via generation of reactive hydroxyl radical. We have developed several bifunctional iron chelators from the brain permeable iron chelator VK-28, possessing the neuroprotective propargyl-MAO inhibitory moiety of rasagiline. The bifunctional drug, M30, has been shown to be a potent iron chelator, with an IC50 value (9.21 μM) comparable to that of the prototype iron chelator, deferasil. It is also a potent inhibitor of brain mitochondrial MAO-A and B in vitro (IC50A= 0.04 μM, IC50B= 0.05 μM). In vivo, M30 markedly inhibits brain (striatum, hippocampus and cerebellum) MAO-A and B activities, with a greater selectivity (20-30%) for the latter at the doses (1, 2.5, 5 mg/kg) examined. It has very little effect on the liver and small intestine enzymes. These results indicate that M30 has the ability to penetrate the blood brain barrier, and suggest that similar to, l-dostigim would not induce the "cheese reaction" in response to tyramine. Importantly, M30 attenuates striatal dopamine depletion induced by the parkinsonian neurotoxin 6-N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in vivo, as well as the striatal dopamine level, serotonin and norepinephrine. M30's potential as a neuroprotective drug as compared to its individual components, since, recent studies have indicated that a combination of two drugs were more effective in preventing neurodegeneration.
Depression: Novel genetic model

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Depression is among the most prevalent forms of mental illness, but the neurobiological basis of depressive behavior is poorly understood. Many of the rodent models for depression are based on the assumption that depression is a response to acute or chronic stress. Other models are based on assumption of a certain biochemical dysfunction that underlies depression, while there is no consensus on the biochemical basis of depression. The diagnostic criteria for depression include several symptoms and it has also become clear that the risk for depression is partially genetic. We were therefore encouraged to investigate genetic factors of depressive behavior by establishing a novel animal model for depression based on selective breeding for a depressive phenotype. The selective breeding is based on tests that cover the core symptoms: loss of interest or lack of motivation (using a modified swimming test), anhedonia (using the sucrose preference test) and reduced energy/fatigue by chronically screening locomotor activity (Infrared system). Additionally, we have developed a novel scoring method of the swimming test, that allow continues monitoring of different levels of the animal’s activity using a joystick. This novel method shows a Gaussian distribution of scores (which is not observed in the standard scoring method) and is necessary for reliable selection of extreme cases for the purpose of our selective breeding. We found already at the second generation of descendants a significant differences between "depressed" and “motivated“ rats in the swimming test, in the basal locomotor activity at young ages and in offspring quantity. At this point we find no correlation between the different tests. We expect this model to allow the study of the contribution to depressive and motivated behavior and the neurochemical characterization of these behaviors.

Two discrete inactivation states with distinct pore properties coexist in a LQT1 mutant of KCNQ1 K+ channels

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The KCNQ potassium channels whose mutations cause cardiovascular and neurological disorders are members of the superfamily of voltage-gated K+ channels. The pore-forming subunit can interact with various KCNE subunits to form K+ channels with very different gating behaviors. Inactivation gating is a property of KCNQ1 that is susceptible to modulation. KCNQ1 inactivation is impossible macroscopically but can be revealed by a hook of the tail current which reflects recovery from inactivation. However, KCNQ1 that can depart into a macroscopic inactivation mode. Here we show that in a long QT mutant of KCNQ1, L273F, two distinct inactivation states coexist, one similar to WT channels and a macroscopic inactivation whose time course and recovery are much slower compared to wild type channels. The inactivation produced by WT KCNQ1 is intrinsically voltage-independent, while that elicited by L273F is highly voltage-dependent. Interestingly, the two discrete inactivation phenotypes exhibit distinct pore properties. External protons strongly depressed WT KCNQ1 inactivation but weakly affected the macroscopic inactivation of L273F mutant. Similarly, external barium ions discriminate between the two discrete inactivation states by suppressing the wild-type and barely affecting the macroscopic one. Allowing L273F channels to populate the voltage-dependent inactivation transition, produced a considerable delay in the exit of barium ions from the pore (more than 6-fold). This result suggests that during the voltage-dependent inactivation transition, the topology of the external vestibule is such that it traps barium ions inside the deep pore. A kinetic model of the LQT1 channel mutant accounts for the coexistence of two distinct inactivation states.

Clotiapin in Schizophrenia: A Controlled Study

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Clotiapin is a neuroleptic with chemical structure similar to clozapine. Probably the patients unresponsive to other neuroleptics responded to clotiapin. However after the discovery of D-2 blockade as a mechanism of neuroleptic efficacy, this claim seemed to lack logical theoretical basis. The success of clozapine in patients unresponsive to other dopamine blockers raised hopes for the discovery of new antipsychotic drugs with new mechanisms of action. Thus the authors became interested in the fact that 40 patients in our 454 bed hospital were being treated with clotiapin and the treating physicians felt that this drug has unique antipsychotic properties in neuroleptic non-responsive patients. The Lokshin et al study (1998) suggested that clotiapin may indeed have unique properties. Clotiapin affects multiple receptors like clozapine and olanzapine. It blocks 5HT3 receptors and down-regulates cortical 5HT2 receptors like clozapine. The ratio of D2 to 5HT2 blockade by clozapine is similar to that of clotiapin. Clotiapin and clozapine share high affinity for the 5HT-6 receptor. Clotiapin shows little blockade of D2 receptors and in the rat retinal model seems to possess D-4 blockade like clozapine, although D-4 blockade by clotiapin has not to our knowledge been evaluated directly. We are conducting a study of severe chronic active psychotic hospitalized patients with a history of non-response to at least 3 neuroleptics. The design is double-blind crossover of clotiapin vs. chlorpromazine (CPZ) as monotherapy. No washout is necessary from previous neuroleptic treatment, and flexible overlap over 2 weeks with the study medication is individualized for each patient. Patients are treated with 12 weeks of clozapine and 12 weeks with CPZ, in random order. Medication is supplied in identical capsules of 100 mg CPZ or 40 mg of clotiapin. PANSS and Nurse’s Observation Scale are rated every 2 weeks. 38 patients have completed the trial. Initial results are presented.
Conducting STDP in dendrites.

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Spike timing dependent plasticity (STDP) is a synaptic learning rule operating in many neuron types. When the pre-synaptic neuron fires after the post-synaptic neuron the synapse is depressed whereas the synapse is potentiated when the pre-synaptic neuron fires before the post-synaptic neuron. The time window for this plasticity rule spans over tens of milliseconds and its dynamics varies according to neuron type. We applied STDP learning rule in a dendritic neuron model, using NEURON simulation environment. Random asynchronous synaptic inputs impinged onto the model neuron with initially uniform peak conductance for all synapses. After running the STDP rule, a bimodal synaptic conductance distribution was attained at the steady state. Some of the synapses obtained the maximal conductance change whereas the conductance of the other synapses was close to zero. The proximal synapses were the strong ones and the distal synapses were near “extinction”. Indeed, STDP imposes competition among synapses over the course of the post-synaptic spike. Thus, a positive feedback loop ensues and proximal synapses, which tend to evoke larger somatic EPSPs have a better chance at gaining enough conductance and become progressively stronger. The opposite is true for distal synapses, which generate smaller somatic EPSPs. We propose several solutions for “saving” distal dendritic synapses from extinction. First, we show that a multiplicative (rather than linear) learning rule can equalize the local conductance for all dendritic synapses. Second, we apply anti-STDP rule (Rumsey and Abbott, 2004). The maximal conductance possible for each synapse. Consequently, the distribution of synaptic strengths at the soma is identical for all synapses, independent on their dendritic location. We also explore the effect of active dendrites on “saving” distal synapses from extinction. Finally, we consider STDP rule in different dendrites morphologies.

Visuospatial attention: How to measure effects of infrequent, unattended events in a blocked stimulus design

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This fMRI study investigates the differences between a blocked and event-related design in a current detection task, the so-called Posner paradigm, using a hybrid design. Validly and invalidly cued trials were presented in different blocks containing 50, 75, or 100 percent valid trials. Four analyses were conducted: i) An event-related analysis comparing invalid and valid trials, ii) a blocked analysis comparing blocks with 50 percent valid and invalid trials to blocks with 100 percent valid trials, iii) a blocked analysis detecting differences between block models when modelled as epochs or chains of events and iv) a blocked analysis that modelled blocks as chains of events to scale regressors equally to the event-related analysis. Irrespective of the type of analysis (blocked or event-related), a significant activation of the right intraparietal sulcus was observed. A larger cluster size was evident in the blocked analysis which can be attributed to higher efficiency. In addition to this common right parietal activation, the event-related analysis revealed activations in right superior parietal cortex and left intraparietal sulcus. In contrast, the blocked analysis yielded additional activity in the right occipito-parietal junction. No influences of the block model (epoch versus chain of events) were found in regions activated in the blocked or event-related analyses, respectively. In summary, using a hybrid design and both event-related and blocked analysis techniques we show both sustained and transient neural processes underlying reorienting of visuospatial attention.

Agmatine – a naturally occurring, highly efficacious neuroprotective compound

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Agmatine [(NH2(CH2)4NH2C=)NH2] is a naturally occurring guanido compound found in abundance in plants and bacteria, and recently identified in mammalian tissues. Agmatine is formed by decarboxylation of arginine, and is metabolized principally into urea and putrescine, the diamine precursor of polyamine synthesis. The compound is present in the brain and spinal cord where its synthesis, which is normally very low, is greatly increased during development and after injury. Agmatine was postulated to exert neuroprotective effects by modulating several relevant molecular targets, including modulation of several neurotransmitter receptors and receptor ionophores (e.g., nicotine, NMDA, imidazoline, and 2-adrenoceptors), blockade of key ionic channels (e.g., ATP-sensitive K+ channels and voltage-gated Ca2+ channels), inhibition of nitric oxide (NO) synthase, inhibition of ADP-ribosylation of proteins, and inhibition of advanced glycosylation end (AGE)-product formation. Treatment with agmatine results in increased insulin release, but in reduced catecholamine release. While agmatine is a cytotoxic compound, preventing proliferation of certain cell lines, endothelial cells and astrocytes, it is not cytotoxic. In several animal models of acute neurotrauma and ischemia, agmatine proved efficacious in preventing nerve cell death and in reducing neurological deficit. Additionally, our preliminary report that agmatine treatment can enhance the regeneration of cut facial nerve, a purely motor cranial nerve in rats. The cumulative evidence indicates that agmatine acts at multiple molecular targets to enhance nerve cell survival, thus fulfilling the concept of "one drug – multiple sites of action". This concept is very advantageous for neuroprotective drug development strategy.

Effect of selected antidepressants on inflammatory processes associated with model of experimental autoimmune encephalomyelitis (EAE) in mice

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Multiple sclerosis (MS) is a chronic autoimmune neurological disorder targeting the white matter of the CNS. MS symptoms result from inflammatory damage to the myelin sheath, activation of TH1 cytokines, and pro-inflammatory cytokine. Our aim was to determine the immunomodulatory effect of some antidepressants on developed motor deficits in the experimental autoimmune encephalitis (EAE) model in mice and on the secretion of TH1 cytokines from activated splenocytes in-vitro. EAE was induced in C57BL mice by immunization with rat myelin oligodendrocyte glycoprotein (MOG). Animals were divided into 4 groups (10/each) receiving saline/MOG alone or MOG and the antidepressants paroxetine, fluoxetine and clomipramine (15mg/kg x3/week i.p). Animals were followed for 24 days and manifestations of EAE were scored (scale of 1-6). MOG animals developed paralysis reaching the mean score of 1.65, all 3 antidepressants significantly protected against the induced neurological symptoms (score 0.35, 0.6 and 0.72 respectively for paroxetine, clomipramine and fluoxetine). In a 2nd experiment 4 groups of animals were treated with saline/MOG alone and MOG and paroxetine or sertraline at lower dose (5mg/kg x3/week, i.p.) or dexamethasone (1mg/kg x3/week). Results showed that after 22 days of therapy dexamethasone completely inhibited the manifestations of neurological symptoms (0 compared to 0.9 of MOG alone). Sertraline induced a delay in paralysis manifestation appearances as well as inhibition of the total score (0.45 vs 0.9), while paroxetine did not protect the animals (total score of 0.81). In-vitro all antidepressants caused a marked inhibition of Con-A or MOG-induced splenocyte proliferation. Moreover, the antidepressants significantly suppressed the production of proinflammatory cytokines IL2, INFg and TNFα resembling the effect of dexamethasone. Conclusions: We suggest that some antidepressants could be of value for the treatment of MS mainly during initial stages.
Sharp (sub-exemplar) tuning for faces revealed in human face related areas

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Although human face recognition is extremely selective, it is still unclear how this selectivity is implemented at the neuronal level in human face related cortical areas. In order to answer this question, we used the paradigm of functional magnetic resonance adaptation (fMR-A). Our stimuli consisted of colored face photographs (neutral expression, male, Caucasian) which were parametrically morphed to produce various degrees of facial similarity. The face stimuli were divided into four groups: (a) identical images (no variability); (b) different face images (maximum variability); (c) 1/3 morph faces, i.e., images morphed at 1/3 of the morphing distance from the full individual-to-distance (low variability), and (d) 2/3 morph - same procedure but morphed at 2/3 of the morphing distance (intermediate-to-high variability). Twelve subjects participated in a short block-design fMR-adaptation experiment and were scanned in a GE 1.5 T magnet. In order to balance task difficulty between the identical and 1/3/morph conditions, a 1-back memory task was used. Examination of the activation levels of the face selective fusiform gyrus (FFA) revealed that even small facial variability (created by a slight morphing level of individual faces, 1/3/morph condition) was sufficient to induce full recovery from adaptation (1/3/morph activation vs. identical-face activation (p<3*10^-4), but 1/3/morph activation vs. different-face activation (p>0.07)). Our results demonstrate that face-selective regions are tightly tuned even to subtle shape changes at the sub-exemplar level. Such sharp tuning can provide the necessary neuronal sensitivity to allow highly selective face recognition.

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Prenatal "ultramild stress" protects against stress and schizophrenia and reduces cannabinoid activity in the offspring

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Prenatal stress (PS) has long-term consequences for emotional development of the offspring. The nature of PS-induced alterations vary with stress schedule and timing. Although the newly discovered cannabinoid receptors and their ligands ("endocannabinoids") have been implicated in the stress responses and in schizophrenia, their possible role as substrates for PS is unknown. Here, we studied effects of daily prenatal "ultramild stress" on the stress response, sensorimotor gating as an indication for schizophrenia, and on cannabinoid CB1 receptor functionality. Methods: Pregnant Sabra mice were exposed daily to 2 mild stressors (incl. tilted cage, confinement, social stress). At adulthood, offspring were divided into 3 groups: a. undisturbed, b. swim stress (2 daily 9 min exposures to a water tank) or c. one 0.1 mg/kg injection of the CB1 receptor antagonist HU210. Offspring were studied for the stress response (acoustic startle response, ASR, anxiety ("plus maze") and "schizophrenia" (pre-pulse inhibition, PPI). Results: In male offspring, PS reduced anxiety and ASR, suggesting a greater severity of adult stress. Adult swim stress increased ASR in controls and PS mice, indicating enhanced anxiety. Adult stress, but not PS, reduced PPI, suggesting a greater sensitivity to stress. Adult stress did not affect PPI in PS mice, suggesting that PS protected against the deleterious effects of the adult stress. HU210 reduced ASR and PPI in controls, but not in PS males, suggesting that PS induced subsensitivity of CB1 receptors. In females, PS reduced anxiety and ASR especially after adult stress. Conclusions: 1. Prenatal daily, ultramild stress protects against PS and enhances robustness to schizophrenia in later life. 2. Stress during adulthood impairs the stress response and 3. PS seems to decrease CB1 receptor sensitivity. Assessments of endocannabinoids and CB1 receptors after PS, are currently performed.

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History Dependent Multiple Time Scales Dynamics in a Single Neuron Model

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History dependent time scales are a ubiquitous feature of neuronal systems at all levels of organization. It is not clear, however, how multiple time-scale dynamics rise from one level to the next higher one. This study approaches this question by looking at the interaction between the rich channeldynamics and the dynamics of neuronal activity; we construct a single neuron model in the spirit of single channels models. The model neuron describes its activity in response to an external stimulus. The activity is a coarse grained time-averaged representative of firing and temporal details at the resolution of action potentials are intentionally neglected. Novelty, our model input/output function is nonlinear, parametrically depending on the neural excitability. Changes of this function on long time scales has been observed experimentally, but has been neglected in other neuron models. The model neuron is composed of an ensemble of ion channels that can wander in a large pool of inactive states, and their distribution registers the history of activity. The concept of neuronal excitability is used to bridge the gap between dynamics of the channels and that of the neuron: channel kinetics modulates neuronal excitability, thus affecting the neural activity, activity in turn, enhances channel inactivation. Thus, the neural activity is both affected by excitability and determines the changes. 1/3/morph activation vs. different-face activation (p>0.07). Our results demonstrate that face-selective regions are tightly tuned even to subtle shape changes at the sub-exemplar level. Such sharp tuning can provide the necessary neuronal sensitivity to allow highly selective face recognition.

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Radial Correlation Contrast – A functional connectivity MRI contrast to map changes in local neuronal communication

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A functional connectivity MRI method that groups neighboring voxels in relation to their degree of temporal cross-correlation between their time courses is presented. This grouping generates a vector field, which is assumed to provide insights into the local organization of neuronal activity. Application with high spatial resolution fMRI rat data subjected to electric forepaw sensory stimulation (156m x 156m x 1000000m) shows a significant localized increase of the vector field amplitude in cortical layers 4 and 2/3 of the primary sensory cortex and in layer 2/3 of the primary motor cortex, suggesting a strong correlation with local neuronal communication. Vector field phases exhibit a transition with neuronal activation from random-like orientations during rest to clusters of common orientations. Cluster size is shown to be weakly dependent on the radii of the neighboring voxels with which the vector field is calculated, and shuffling voxel position within clusters generates a random-like vector orientation instead. This suggests that changes in vector orientations upon activation represent changes in the internal correlation between voxels that is interpreted as a change in the internal neuronal communication.
Perinatal enhancement of the gabaergic system impairs learning and memory - suggested mechanism.

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Antiepileptic drugs (AEDs) acting through the potentiation of GABA-ergic pathways have harmful effects on brain development. Increased risk of impaired intellectual development was reported in children born to women treated with AEDs during pregnancy. We established an animal model for the study of the damage induced by the new AED - vigabatrin (VGV) during postnatal days 4-14, which parallel the 3rd trimester of human embryo brain development. Delayed development of sensory and motor reflexes, reduced mobility in the open field, impaired object recognition and deficient spatial learning and memory were observed. A morphological study indicates only transient changes in the hippocampus (PI) and significantly lower cell density in most layers of the M2 cerebral cortex of VGV adult mice compared to the controls (P<0.01).

The possibility that perinatal VGV treatment impaired learning and memory in the adult mice by modifications in hippocampal synaptogenesis was examined in 16 weeks old mice by immunohistochemistry of synaptic vesicle proteins and were identical to the postnataction (fEPSP) recording from hippocampal slices in CA1 region. We found that perinatal VGV induced long-term enhancement of Synapsin I (184.9% of control, P<0.01) and VAMP II (196.2%, P<0.01) in the CA1 region. Overexpression of these proteins in the VGV group was associated with a significant reduction in the fEPSP efficacy, as measured by fEPSP response to stimulation at various intensities (P<0.05).

In addition, perinatal VGV treatment induced modification in the fEPSP response to a series of 5 repeated stimuli at 50Hz, and blocked the induction of long term potentiation in response to 3 trains of 1 second at 30Hz (5 minutes inter train interval), a stimulus that induced potentiation in the control mice. Our findings suggest that the long-term deleterious effects of VGV treatment on mouse behavior may be caused by altered synaptogenesis.

The bi-partite organization of the human caudal brain

Golland Y., Ben-Sasson S., Hasson U., Gelbard H., Harel M., Malach R.

Bipartite organization of the human caudal brain is not fully understood. Internal cognitive functions concern processing of sensory input, while external sensory input, and those dealing with some, yet not fully understood, internal cognitive functions. However, attentive perception can engage at least two mental states: a) an internal, introspective state in which the subject attends both to external stimuli and to himself as an observing agent. b) an external, extroceptive state in which the subject is passively engaged by the external stimuli. Here we report on brain imaging results which explored to what extent these two mental states engage different cortical regions of the brain, as well as being driven by identical sensory stimuli. Five subjects performed two different tasks during a block-design fMRI scan. In a categorization task, subjects were required to categorize pictures (animal vs. other). In the introspection task, subjects were asked to look at the same pictures as in the first task but to attend at the same time to himself and evaluate his emotional reaction to the pictures (positive/negative vs. neutral). Prior to each block, a visual cue indicated which task to perform and subject's responses were recorded. In order to discriminate task difficulty as potential confound between the 2 cognitive tasks, external categorization epochs were subdivided into "difficult" and "easy" perceptual tasks by manipulating presentation speed; "easy" tasks were identical to the introspection task. Similarly, our results showed preferential activations across prefrontal cortex during "introspection" compared to the "easy" task. Consistent preferential activations were found bilateral in dorsolateral and medial aspects of prefrontal cortex, with a left hemisphere bias in most cases. The results are relevant to broader issues such as the search for neural correlates of subjective awareness will be discussed.

Supported by ISF center of excellence and the Benyony center.

Mapping Human introspection using fMRI

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Conventionally it is assumed that attentive visual perception of identical stimuli engages the same perceptual mechanisms. However, attentive perception can engage at least two mental states: a) an internal, introspective state in which the subject attends both to external stimuli and to himself as an observing agent. b) an external, extroceptive state in which the subject is passively engaged by the external stimuli. Here we report on brain imaging results which explored to what extent these two mental states engage different cortical regions of the brain, as well as being driven by identical sensory stimuli. Five subjects performed two different tasks during a block-design fMRI scan. In a categorization task, subjects were required to categorize pictures (animal vs. other). In the introspection task, subjects were asked to look at the same pictures as in the first task but to attend at the same time to himself and evaluate his emotional reaction to the pictures (positive/negative vs. neutral). Prior to each block, a visual cue indicated which task to perform and subject's responses were recorded. In order to discriminate task difficulty as potential confound between the 2 cognitive tasks, external categorization epochs were subdivided into "difficult" and "easy" perceptual tasks by manipulating presentation speed; "easy" tasks were identical to the introspection task. Similarly, our results showed preferential activations across prefrontal cortex during "introspection" compared to the "easy" task. Consistent preferential activations were found bilateral in dorsolateral and medial aspects of prefrontal cortex, with a left hemisphere bias in most cases. The results are relevant to broader issues such as the search for neural correlates of subjective awareness will be discussed.

Funded by ISF center of excellence grant and the Benyony center.

GABA-B mediates frequency-dependent latency in POM-RE network analyses and comparison with experiment

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The latency in the steady-state spiking response of POM thalamic neurons to periodic vibrissae stimulation increases with increasing stimulus frequency (Ahissar et al., Nature, 2000). In contrast, the latency of the response of neurons in VPM thalamus is essentially constant. Yet the two nuclei are inhibited by an overlapping region of reticular thalamic nucleus (RE). To provide a possible explanation for this effect, we construct a firing rate model and consider only a slow time scale, corresponding to dynamics of GABA-B synapses. We calculate the steady-state response of the system and compute its stability analytically for the case of the duty cycle of the stimulus < 0.5. Considering only a POM-RE network, we find that POM activity decreases with GABA-B conductance. If this conductance is too large, the period-I state undergoes a period-doubling bifurcation at large enough frequencies, which is not seen experimentally. If the stimulus increases gradually, e.g., triangular stimulation, the latency increases with GABA-B conductance. The inclusion of VPM excitatory connections to the RE resolves the period doubling bifurcation and may reduce the POM response even to zero. VPM-to-RE feedback connections are more effective in reducing POM activity and increasing POM latency than POM-to-RE feedback connections. If the VPM receives GABA-B inhibition, the latencies in the two nuclei are reduced by the ratio of their GABA-B inhibition and the input strength. According to this explanation, the maximum latency in POM neurons is larger because they receive weaker input from the brainstem.

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Zinc Modulation of the L-type Calcium Channels.

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Zinc modulation of the L-type calcium channels (LTCC) was studied in Xenopus oocytes expressing alpha 1, alpha2 delta and beta 2, subunits of the rabbit cardiac calcium channel. Whole cell voltage clamp experiments were carried out using Ba2+ as the charge carrier. Our results show that zinc causes a reversible inhibition of LTCC in a concentration dependent manner. Nonlinear fitting to a Michaelis Menten equation yielded an appKi of 102 micromolars and a Hill coefficient of 1. The decrease in steady-state current amplitude is accompanied by a shift of the I-V relationship to more negative voltages. Similar inhibitory effect of zinc was found in the presence of the LTCC activator Bayk 8644. In contrast to the inhibitory effect of extracellular zinc, no such inhibition is observed when zinc is applied intracellularly. The injection of zinc (~80 micro molar) changed the extent and rate of current block caused by extracellular zinc. We concluded that intracellular zinc, although did not block LTCC, was capable of modulating other cellular functions. Zinc inhibition of LTCC developed with time, reaching maximum inhibition after 3 minutes. The inhibition was not activity dependent as similar inhibitory effect was observed when oocytes were either exposed to zinc and activated every 10 second or exposed to zinc with no stimulation and tested after 3 min. Our results suggest that zinc may play an important role in modulating LTCC in physiological concentrations. Zinc inhibits the channel's currents by acting from the extra-cellular side and its effect is not activity dependent.

Chronic Mild Stress Induces Depression and Bone Loss in Mice: Attenuation by Anti-depressant Therapy.

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Activity-dependent neuroprotective protein (ADNP) is essential for brain formation (Dev Brain Res. 2003 144, 85). Peptide activity scanning identified NAP (NAPSVPO) also known as AL108 as a small active fragment of ADNP that provides neuroprotection at very low concentrations. In cell culture, protection has been demonstrated against toxicity associated with the beta amyloid peptide exotoxins, electrical blockade, the envelope protein of the AIDS virus, dopamine, NO2, nutrient starvation and zinc intoxication (JBC 2004, 279, 28531; JPET 2004 309, 1190). In animal models of apolipoprotein E deficiency, cholinergic toxicity, closed head injury, stroke, middle aged anxiety and cognitive dysfunction, NAP provided neuroprotection (Neurosci Lett. 2004, 361, 128; JNM 2004, 24, 181). The structure of NAP allows cell penetration, inhibition of toxic protein beta sheet formation and stimulation of proper protein assembly. NAP binds to tubulin and facilitates microtubule polymerization leading to enhanced cellular survival that is associated with fundamental brain cell elements, the cytoskeleton. A mass spectrometry assay determined that NAP reaches the brain upon nasal administration showing a half-life of ~90-120 minutes in rat and dog plasma. In a battery of toxicological tests, 1 month repeated dose toxicity in rat and dog cardiopulmonary tests, in dogs and functional behavioral tests in rats, no adverse side effects were observed with NAP concentrations that were about 500-fold higher than the biological active dose. No genotoxicity was associated with NAP. At doses that are at least 1000-fold over the biologically active dose, reversible lethargy and piloerection was observed in mice. A mass spectrometry assay has been validated for tests in rats (MPJ Research). A first exposure of AL108 (NAP) to human subjects is now planned. NAP is patented & licensed to Allon Therapeutics, Inc. where IG serves as CSO. Other Supported by Gildor Chair, NICHD, NIA.

Crossmodal Visual-Auditory Interference in Object Recognition Process.

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Several studies have concentrated on resolution of spatial conflict between vision and audition, and recently the temporal domain has been also addressed. Much less is known about auditory-visual interaction in object recognition. The present research addressed this issue. The subjects were presented with bi-modal stimuli, composed of concurrently appearing pictures and voices of animals. The task was to identify either the picture or the voice by answering a forced-choice question presented after an auditory-visual presentation. In one third of the trials the picture and the voice belonged to the same animal ('congruent' trials), in another third the picture and the voice belonged to different animals ('incongruent' trials). In the remaining trials, a neutral stimulus was presented as the non-target stimulus. Performance on congruent trials was better than on incongruent trials, both in the visual and in the auditory conditions, but the effect was larger in the auditory condition. This finding indicates that irrelevant objects of an unattended modality are processed and even recognized and suggests an asymmetry between the two modalities in the process of object-recognition. Event related potentials were recorded in 14 subjects with similar design. Results showed that incongruent trials elicited a more negative response than congruent trials in latencies of circa 200-650 ms post stimulus onset when the target was the auditory stimulus, reminiscent of an N400 effect. In contrast, no significant incongruity effect was found when the target was the visual stimulus. Thus, visual information affects the process of auditory object recognition relatively early but the opposite interaction is much more tenuous. This is congruent with the behavioral results, and suggests that the case of the auditory conflict is a special case of the conflict but unlike the case of temporal conflict, our cognitive system relies more on visual than on auditory information, in the case of conflict in object recognition.
Neurotrophic factors such as glial cell line-derived neurotrophic factor (GDNF) may have therapeutic potential for preventing and treating cocaine addiction. Previously, we found that transplantation of GDNF-expressing astrocyte cell line into the striatum and nucleus accumbens attenuates cocaine-seeking behavior in Sprague-Dawley rats. However, as a poverty of the ventricular system, cell transplantation presents several technical and ethical complications. Nanoparticulate systems are a safe and effective method for introducing GDNF conjugated nanoparticles into the striatum and nucleus accumbens on cocaine self-administration in rats. GDNF-conjugated nanoparticles blocked the acquisition of cocaine in self-administration compared to control treatments. This is one of the first demonstrations that drug-conjugated nanoparticles may be effective in treating brain disorders.

Quantitative MRI analysis of the human fetal brain in utero

Grossman R., Hoffman C. C., Mardor Y., Biegon A. Chaim Sheba Medical Center;
Magnetic resonance imaging (MRI) allows for high resolution imaging of the central nervous system. We have tested the feasibility of using MRI in conjunction with quantitative image analysis to perform volumetric measurements of the brain in the developing human fetus in utero. The data base comprises 40 fetuses (gestational age 22-40 weeks) referred because of suspected infantile hydrocephalus, asymmetry of the ventricular system, or spina bifida. Scans were obtained using a 1.5T magnet and a single shot fast spin echo (SSPSE) T2 sequence. Slice thickness of 3mm, no gap and analyzed with NIH Image software. All scans were evaluated by an expert neuroradiologist. The intra-rater error was 5%-9% for 2 raters, while the inter-rater error was 13%. Thus, a single rater then performed all the measurements. The right and left hemisphere and lateral ventricles were identified and their area measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, normal, and their average measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume.

The attribution of gender stereotype strategy as an indicator of frontal lobe mediated Theory-of-Mind

Gurshka A., Kofman O., Fischer I.
Introduction: Most patients with ventromedial-frontal lobe damage exhibit Theory-of-Mind (ToM) dysfunction, the inability to understand others. The current work offers a novel paradigm, enables testing ongoing non-verbal interactive ToM behavior. The study setting (iterative prisoner's dilemma - IPD game) was designed to tap participants' cooperative or competitive behavior and confidence within a dyad of same-different gender. In that context, literature review reveals that women are more cooperative and men are more competitive. We ran 4 groups (24.3 yrs ± 2.8: man-man, woman-woman, man-woman, and woman-man. Results: As hypothesized we found that overall participants, a normal learning curve (increasing cooperation probability), increased confidence in choice, and lower cooperation probability on early trials - only in groups that thought they played against men and not in women and men that thought they played against women. Conclusion: As manifested by attributing different strategies to others, and by showing a normal understanding of others' strategy, ToM is probably the core component of this paradigm. Further support is given by initial data collected from ventromedial-frontal patients.

An approach to the molecular basis of tinnitus in the rat

Guitton M., Klin Y., Dadi Y.
Combined with inner-ear targeted or brain targeted pharmacology, it could facilitate the investigation of cell mechanisms of tinnitus. Preliminary results unveiled similarities of molecular mechanisms of tinnitus and neural plasticity and memory.

Anxiety associates with taste to produce conditioned taste aversion in the rat

Guitton M., Klin Y., Dadi Y.
The interaction among experience, emotion and memory is considered to be instrumental in the ontogeny and maintenance of acquired emotional and behavioral disorders, e.g. phobias. Here we address the question whether anxiety can associate with taste to produce conditioned taste aversion (CTA). We have used an anxiogenic agent, the 3-HT2C receptor agonist meta-chlorophenylpiperazine (mCPP), to induce anxiety in rats after consumption of an unfamiliar tastant. The anxiogenic agent induced CTA. The mCPP-induced CTA could be prevented by coadministration of ethanol, which is known to reverse mCPP-induced anxiety, at a concentration that had no effect on CTA memory. Ethanol did not prevent, however, LiCl-induced CTA. Administration of mCPP before the consumption of the
tant had no effect on the preference for that tantast. Taken together, our results indicate that anxiety can serve as a negative US in CTA training. This finding may bear relevance to the ontogeny of pathologies involving food aversion.

Adaptation in the barn owl's inferior colliculus: a potential mechanism for generating an error signal

Gutfreunyn, Knudsen

The auditory space map in the barn owl's external nucleus of the inferior colliculus (ICX) is calibrated by visual input from the optic tectum (OT). When bicuculline is injected in the OT, units in the ICX respond to visual stimuli. When auditory and visual stimuli are presented simultaneously, visual responses are modulated by the direction of the auditory stimulus; visual responses are strongest when the light source is away from the sound source. This modulation can be explained by neural adaptation in the ICX. To test this hypothesis, we measured adaptation using sequential auditory stimuli (30ms broadband noise). We found that when the inter-stimulus interval is 30 to 320ms, the response to the second stimulus is decreased. Two lines of evidence suggest that the site of at least part of this adaptation resides in the ICX. First, adaptation was stronger in the ICX than in the central nucleus of the inferior colliculus, the major source of auditory input to the ICX. Second, the response to the second stimulus occurred even when the two stimuli were narrow-band and each centered on a different frequency. The strength of adaptation depended on the distance between the two frequencies, which corresponded with the width of the frequency tuning of the ICX unit. This tendency of ICX units to perceptually resolve may underlie the modulation between visual and auditory representations of stimulus location. Since visual responses appear 20-120ms after auditory stimulus presentation, visual auditory stimuli responses to visual stimuli will decrease, when the spatial representation for the two modalities align and activate the same locus in the ICX space map.

Category Learning from Equivalence Constraints

Hammer R., Hertz T., Hershler O., Hochstein S.

We investigated human category learning from partial information provided by equivalence constraints. Participants were trained on the basis of either positive or negative equivalence constraints, that is, when informed that two exemplars belong to the same category or to different categories, respectively. Knowledge that in natural contexts positive constraints are more informative than negative constraints, we suspected that participants will not use the two types of constraints in similar ways even in a setting in which the amount of objective information in the two types of constraints is identical. We discovered that when provided with positive constraints, participant categorization performance is distributed normally, but when provided with negative constraints' performance distribution is not unimodal. A constrained EM algorithm was used with identical constraint information to simulate the experimental setup. Results of the EM clustering algorithm showed surprising qualitative similarity to human results, with unimodality for positive but negative constraints. Although we can not infer from this computational simulation how the human brain computes equivalence constraints in the context of category learning, it provides us useful insights into computational aspects of this learning problem. Taken together, these results suggest that positive constraints provide information that may be used intuitively by the human brain, while use of negative constraint information may require a less natural, rule-based, strategy, which most participants failed to implement.

Selective neural responses to objects of expertise in experts' ventral visual pathway

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Expert object recognition occurs when one learns through experience to identify quickly and accurately individual exemplars of a homogenous class, a process associated with qualitative changes in perceptual processing. The neural mechanisms that underlie the perceptual changes, however, are not sufficiently elaborated. Recent research to date, investigated expertise as an alternative to the putative domain-specificity of face processing (McKone and Kanwisher, in press). Thus, neuroimaging studies of expertise were limited to face-selective ROIs of the ventral visual pathway. But, selectivity for objects of expertise may not involve only face regions but may manifest as an organizational principle in ventral visual pathway, starting as early as retinotopic areas. In the present study we examined this hypothesis. Five experts' visual cortex for objects of theirexpertise. We investigated human category learning from partial information provided by equivalence constraints. Participants were trained on the basis of either positive or negative equivalence constraints, that is, when informed that two exemplars belong to the same category or to different categories, respectively.

Neuroprotective potency of the lipophilic transition metal modulator DP-b99 against oxidative stress

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Reduction in glucose and oxygen supply, which occurs in cerebral ischemia, leads to a cascade of events resulting in neuronal death. We have synthesized a lipophilic analog of BAPTA, DP-b99, currently in Phase II clinical trials, and determined its neuroprotective potency. Following MCAO in rats DP-b99 was found to reduce infarct volume and improve neurological scores. Here we present results from several in vitro studies using different models of oxidative stress and cerebral ischemia. In anoxia, DP-b99 reduced uptake of PI and LDH release in rat cortical slices. In anoxia, DP-b99 reduced PI uptake in rat cortical slices, as well as in rat hippocampal slices following OGD. DP-b99 (30mM) reduced significantly both LDH release and PI uptake at all time points tested. Exposure of cortical neurons to 100mM H2O2 for 4h causes oxidative cell death, but treatment with DP-b99 or BAPTA-AM significantly protected the cells. The NMDA receptor antagonist MK801 and calpain inhibitor MDL28170 also protected against oxidative cell death. Calpain activity in H2O2-treated neurons and OGD-treated slices was determined by evaluating proteolysis of the calpain substrate a-spectrin. DP-b99 inhibited H2O2-induced calpain activity, suggesting that DP-b99 may protect, in part, through calpain inhibition. We further used the HT22 hippocampal cell line that lacks ionotropic glutamate receptors but is sensitive to glutamate-induced death via oxidative stress. DP-b99 protected the cells by ~50% when added before or up to 4h the glutamate. Taken together, the neuroprotective potential of DP-b99 in ischemic rat models is related to its protective effect in different types of neuronal cultures demonstrating its usefulness in the treatment of cerebral ischemia.

Supported by D-Pharm Ltd.
Fast-Same effect: implicit priming of ordinal number categories
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Humans and monkeys categorize images according to their ordinal position in a repeated list. Category assignment is assumed to be based on an abstract label (first, second, etc.), common to all images of the same ordinal category (Orlov et al., Nature 2000; Cerebral Cortex, 2002). In previous research with human subjects we measured explicit category priming. Subjects were trained with 32 images, divided into 4 quadruplets. On each trial they viewed 4 sequentially presented sample stimuli, followed by a test stimulus, consisting of the same 4 images. The task was to select the images (by mouse-click) in their correct order. Performance gradually improved. A subsequent memory test confirmed subject ordinal categorization of the stimuli. In a following priming test, we presented subjects with a prime image - to which they responded by reporting correctly the image category. Then (0.5-1s after prime presentation), they were presented with a pair of target images - to which they reported whether the targets belonged to the same category or different categories. We found that explicit retrieval of the prime category shortened reaction time (RT) of the same-different judgment if the prime was of the same category as one or both of the targets. Furthermore, there was a Fast-Same effect, i.e. an additional shortening of the RT of the pair of targets when they belonged to the same category compared to when they belonged to different categories. Both of these findings support the conclusion that subjects learn to associate the stimuli with their ordinal category. We show that the Fast-Same effect is not motor-based, but rather a truly conceptual effect. Supported by a Center of Excellence grant from the Israel Science Foundation (ISF) and by the US-Israel Bi-National Science Foundation (BSF).

Lack of paternal care interferes with synaptic composition in the rodent orbitofrontal cortex and amygdala
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Beyond the related endocrine and behavioral alterations found after maternal separation in various animal studies, the development of synaptic connections in limbic brain regions is modulated by early adverse emotional experiences, i.e. the separation from the parents (Poegele et al., 2003). In the present study the effect of chronic separation from the father on the development of dendritic spines in the limbic system was analyzed. Quantitative analysis revealed region-, cell and dendrite-specific changes of spine densities in the orbitofrontal cortex, in the lateral and basomedial amygdala, hippocampal CA1 region and dentate gyrus of three week old trumpet-tailed rats. The comparison of pups which were either raised with or without their father revealed in the fatherless animals a 40% decreased spine density on apical and basal dendrites of layer II/III pyramidal neurons in the orbitofrontal cortex and up to 20% lower apical and basal spine densities in the amygdala whereas the dendritic lengths remained unchanged. No changes of spine densities and dendritic lengths were observed in the hippocampus of pyramidal neurons and in the granule cells of the dentate gyrus. The lack of paternal care appears to inhibit or suppress the formation of presynaptic excitatory synapses in the limbic cortex and in the amygdala, whereas synaptic development in the hippocampus occurs independent from paternal interaction with its offspring. Supported by a grant of the state of Saxony-Anhalt.

Adaptation Properties of Neurons in the Rat Barrel Cortex Revealed by Dual Intracellular Recordings
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Neuronal adaptation to repetitive presentation of sensory stimuli is a well known characteristic of neurons at different cortical levels, ranging from cells that are strongly depressed at 10 Hz to cells that showed a clear response at 40 Hz. Suspected layer 4 cells showed better responsiveness to high frequency stimulation than simultaneously recorded cells from supragranular and infragranular layers. In most cells adaptation was characterized by a monotonic decrease in response amplitude. However, some cells showed a beating behavior characterized by a slow periodic modulation of the response. Additionally, in a few neurons, we observed alternating between clear response and absence of response from one stimulus to the next (period doubling). The differences observed in simultaneously recorded neurons and the complex dynamic of the cortical network is involved in shaping the adaptation properties of neurons to repetitive stimulation.

Behind the veil of a fearful face: Large scale neural integration measured by MEG and fMRI.
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Emotion can bias for enhanced visual processing. The evidence for such enhancement includes faster and greater visual detection possibly beyond awareness. This study characterized spatial-temporal aspects of large scale neural integration that underlie emotional modulation of the bias for awareness during Binocular Rivalry (BR). Fearful and neutral faces presented to one eye, competing with a house presented to the other, were studied with and without their aware percept. 40 sec periods of fused stimuli (Rivalry) were followed by same periods of distinct stimuli based on subject's response during the rivalry (Replay). 22 subjects indicated longer aware percept of faces than houses and more so for fearful faces (interaction, p<0.05), suggesting that fearful face biased the competition for enhanced visual processing during BR. To study the brain dynamic of this bias, high density MEG and fMRI were applied on 10 subjects. During aware fearful face more than neutral face, MEG showed increased power in beta (14-24Hz) and theta (4-8Hz) bands in estimated sources in the medial temporal sources (MedT) that include the amygdale and. However for switching from a house to a face more so for a fearful face, both MedT and inferior temporal (IT) regions showed increased power. These regions were also observed in the fMRI data when comparing rivalry vs. replay more so in the fear condition. This provides converging evidence for limbic-visual integration in the dynamic aspect of competing visual processing of emotional stimuli. Next we applied coherence analysis to the MEG signal timecourse obtained in the from MedT and IT sources during periods of switch to- and state of- aware or unaware faces. We found that coherence in the beta and theta bands respectively peaked category (face / house) and emotional (fear / neutral) aspects of stimulus. This suggests that emotion mediate awareness through large scale coupling between visual and limbic regions.
Very small (10" & 15") face drawings generate functional imaging responses in the human "face areas".

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How do we perceive faces of ever changing sizes as we view our visual world? What are the smallest face stimuli that we can perceive? The LOC and the FFA are two face selective regions in the human extrastriate cortex. It is commonly accepted that these regions are the human homologue of the monkey TPOPM. Available evidence shows that those IT "expert" cells are size invariant, have very large receptive fields and do not respond to stimuli smaller than 0.50. If physiological properties of IT "expert" cells predict functional responses in the human homologue regions, it may be expected that visual stimuli smaller than the physiological threshold will not evoke any direct, bottom-up response in the human face areas. To test this prediction, we conducted a study, using two functional imaging methods: fMRI with a spatial resolution of several millimeters and a temporal resolution of several seconds, and LORETA - a functional imaging method based on Event Related Potentials that gives a fair degree of spatial localization at a superior multisecend resolution. Threshold for face recognition was behaviorally established to be around 8 arc minutes. We aimed to delineate areas showing preferential activation to various size face stimuli, particularly very small ones. 15 Subjects viewed different size (18x18o, 3x3o, 1x1o, 15x15o, 10x10) black and white drawings of faces. In both functional studies the smallest face stimuli (10" and 15") evoked robust responses in the "face area". These responses were comparable to those generated by larger faces. That stimuli that are much below IT cell activation threshold generated robust responses in the human homologue of the IT cortex, may indicate that these responses resulted from top-down rather than bottom-up activation.

The role of cGMP-dependent protein kinase (PKG) and the foraging gene in locust density-dependent Phase polymorphism

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Much effort has been invested in recent years into understanding how genes act on the nervous system and in response to the environment to generate behavioral plasticity. Locust phase polymorphism is an extreme example of environmentally induced behavioral variations; in response to changes in population density locusts alter their behavior. A major component of the behavioral phase differences, which is a key feature of locust biology and is central to their occasional yet catastrophic impact on humans, is the more intense flight behavior of gregarious locusts compared to solitary ones. The current is a first step in unfolding the molecular and genetic background of locust phase oscillation. We postulate a model for the environmental effects on animal behavior. Following previous work in the fruit fly and honeybees we focus on the role of PKG and the foraging gene encoding for locust PKG on flight related phase characteristics. We found the total PKG and endogenous PKG activity of gregarious locusts to be significantly higher than that of solitary locusts. Flight duration tests confirmed that gregarious locusts demonstrate much higher flight capacity than solitary ones. Chronic treating solitary locusts with 8-Bromo-cGMP increased their total PKG activity and also resulted in a significant increase in their flight performances. This could not be generated by cAMP treatment. We suggest that the locust foraging gene and its product PKG have a key role in flight-related density dependent phase differences. This is a new and one of very few examples of a single gene controlling complex behavior and behavioral variations.

Is there a monitor for the monitor? Evidence from a pilot ERP study

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When people detect their errors in a discrimination task, a negative-going waveform can be observed in scalp recorded EEG that has been coined the error-related negativity (Ne/ERN). Although far less elaborated in the ERP literature, a later occurrence of the Ne/ERN (Pe) also appears to be associated with response monitoring processes. Falkenstein et al (2000) proposed that the Ne may be related to additional processing that occurs after error detection, such as conscious error recognition. In a pilot study we encouraged five participants to correct themselves in a two-choice reaction time task. Interestingly, participants tended to produce the same correct response twice (namely, produce a double correct response) as often as they tended to correct their errors. Reaction times of the second responses were found to be longer when they were a repetition of a correct response then when they were a true correction. Although a Pe-like component was found in both response types, the ERN-like component was found only in correction responses. These findings support the conception of the Pe as associated with conscious awareness of the output of the monitoring process per se.

Immunohistochemical recognition of activity dependent neuroprotective protein (ADNP) and the active peptide NAPVSPQ

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Activity dependent neuroprotective protein (ADNP, human calculated molecular mass 122,622.9 Da) is a newly discovered glial protein that it is essential for embryonic development and brain formation (Pinslav, 2003). ADNP includes an active neuroprotective site, an eight amino acid peptide NAPVSPQ (NAP). The current study was set out to prepare antibodies to ADNP that will recognize different sites on the molecule. Four peptides of (8-20 amino acid) that span the ADNP molecule, including NAPVSPQ were prepared. Peptides (containing a Cys residue) were conjugated to the N-terminal amino acid were conjugated to Keyhole limpet hemocyanin (KLH) and injected to respective rabbits in incomplete Freund‘s adjuvant. Following five booster injections in incomplete Freund‘adjuvant, the respective antisera were collected and assayed by Enzyme-Linked Immunosorbent Assay (ELISA) and purified by affinity chromatography on peptides conjugated to SulfoLink Coupling Gel. Mouse brain proteins were prepared (4 months old) and separated into cytoplasmic and nuclear fractions. Proteins were further separated by SDS-PAGE (SDS-PolyArylamide Gel Electrophoresis) and transferred to nitrocellulose membranes. Membranes were then probed with the antibodies followed by a secondary antibody Horseradish Peroxidase conjugated Anti-Rabbit IgG. Membranes were then probed with the antibodies followed by a secondary antibody Horseradish Peroxidase conjugated Anti-Rabbit IgG and developed with ECL. All antibodies recognized intact ADNP in both cytoplasmic and nuclear fractions. This work developed antibodies against ADNP and NAP that will be utilized for further experimentation to elucidate the distribution and mechanisms of ADNP and NAP neuroprotection.

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Immunomodulation of autoimmune responses by pregnancy-related factors

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Clinical remission during the second half of pregnancy, and a tendency to postpartum relapse; have been observed in several autoimmune diseases. These phenomena can be attributed to the immunomodulating activity of several pregnancy associated proteins such as alpha-fetoprotein, pregnancy associated plasma protein A (AFP), estrogens, early pregnancy factor (EPF) and placental protein 14 (PFP-14). In the present study, we tested recombinant human AFP (rAFP), and estrogens/steroids...
for their immunomodulating activity in vitro and in vivo in experimental autoimmune encephalomyelitis (EAE). Myelin oligodendrocyte glycoprotein (MOG). Central nervous system (CNS) inflammation and axonal degeneration were prevented by this treatment. RhAFP also inhibited T-cell activity and antibody production and downregulated the expression of cell-surface leukocyte markers CD4 +/CD8 + cells, most commonly CD4 +. In addition, we tested estrogens and dehydroepiandrosterone (DHEA), (a neurosteroid and the precursor of steroid hormones), using tested estradiol and DHEA, inhibited T-cell activity and antibody production and down-regulated MOG-induced T-cell proliferation. Our observations show that pregnancy-related proteins and hormones influence immune function and might be successful candidates alone or in combination, for therapy of autoimmune diseases. 

Controlled single step conversion of human embryonic stem cells into neural precursors

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The realization of the remarkable potential of human embryonic stem (hES) cells as a model for studying human development and as an unlimited source of differentiating cells for drug discovery and transplantation is hampered by the existing limitations in directing their differentiation. Current protocols to generate populations enriched for specific cell types commonly rely on an initial spontaneous disorganized step of differentiation, co-culture, the use of undefined conditioned medium or factors with non-specific undetermined effect. Here we report the efficient, controlled, reproducible, single step conversion of hES cells into highly enriched cultures of developmentally competent proliferating neural precursors (NPs). When hES cells are cultured in defined serum-free medium, in the presence of specific soluble factors they uniformly develop into highly enriched cultures of NPs. We show that these culture conditions suppress non-neural differentiation and allow hES cells to adopt a neural fate. The NPs may be propagated for prolonged periods, and can differentiate into astrocytes, oligodendrocytes and various subtypes of neurons including mature neurons that fire action potentials and form functional synapses. During prolonged propagation of the NPs, a gradual shift from neuronal to predominantly glial fate is observed after induction of differentiation, probably reflecting the neuronal to glial developmental switch that occurs during neurogenesis in vivo. The presented controlled, single step conversion of hES cells into near homogenous cultures of NPs, is highly valuable for the study of human neurogenesis. It allows the efficient and simple creation of neural cells for drug development, and is an important step towards the potential utilization of hES cells in transplantation therapy of neurological disorders.

Abnormal K+ buffering in the epileptic blood-brain-barrier disrupted cortex

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The blood-brain-barrier (BBB) is a complex structure designed to maintain a unique neuronal environment and limit the penetration of serum components to the brain. We have recently demonstrated that opening of the BBB leads to a profound change in the BBB's ability to regulate K+ buffering. This change was associated with a significant increase in extracellular K+ concentration and a reduction in K+ uptake. In this study, we investigated the effects of opening the BBB on K+ buffering in vitro and in vivo. We used two different approaches to open the BBB: i) ionophoresis of BaCl2 and dextran, and ii) chemical disruption of the BBB by administration of LPS. In both cases, we observed a significant increase in extracellular K+ concentration and a reduction in K+ uptake. These changes were accompanied by a decrease in the activity of the K+ pump, as evidenced by a decrease in the activity of the K-ATPase. In addition, we observed a decrease in the activity of the K+ channel, as evidenced by a decrease in the activity of the inward K+ channel. These results suggest that the BBB is a critical component of the physiological regulation of K+ buffering in the brain.
demonstrated for POC. An equally viable alternative to a rate-encoding model is a temporal-encoding model. Models of temporal encoding do not necessarily imply a monotonic transform from stimulus magnitude to neural activity quantity. Thus, FMRI is a potentially invalid measure of POC activity under temporal-encoding models. To address this issue we set out to quantify the stimulus magnitude dependence in POC in thirty subjects. An olfactometer generated low, medium and high concentrations of the odor phenethyl alcohol and POC activity was evoked in an event-related design (4T, T2* GEMS, TE=28ms, TR=1sec, 192mm FOV, 8 slices, 0.5mm skip, 3x3x3 3mm voxel, ISI=30sec, stimulus repetition=27). The initial 6 subjects of propionic acid had significant activation overall in lateral orbital frontal cortex (p<.05) and in POC (F(3,20)=3.44, p<.05). The relationship between increased signal and increased stimulus concentration in POC was monotonic but not linear (approximately logarithmic). We will test if this finding is the nature of POC encoding or is the consequence of another factor. For example, in several of these initial subjects the signal in POC appeared to be confounded by individual sniff dynamics. Final data analysis will include regressors based on individual sniff events to reduce this variability.

Follow-up on White Matter Changes in Stroke
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Diffusion MRI is a common diagnosis tool for stroke despite the fact that diffusion changes following acute stroke are not fully understood. In addition, Diffusion Tensor Imaging (DTI), which is more sensitive to white matter, reveals mixed effects of fractional diffusion anisotropy (FA) changes within the same subject in the acute stage without distinction of neuronal degeneration or tissue disintegration. The purpose of the present study was to estimate the outcome of areas having increased FA at the acute stage of the stroke. For that we conducted a follow-up study on seven stroke patients using diffusion MRI. The examinations were performed at two different time intervals following the stroke (less than 48 hours and more than 3 months). For data analysis, we segmented the infarcted area into 5 regions of interest (ROIs) based on their FA values and followed their condition at the chronic phase using image co-registration. The results revealed two different patterns of changes. One pattern was characterized by reduction of both the FA and ADC values at the acute phase as compared to normal controls. In the chronic stage, the FA values decreased further reflecting white matter disintegration. Severe deterioration was observed at the ROIs that correlate with the core of the lesion, while slight reduction was observed at the ROIs that correlate with the penumbra of the lesion. In the second pattern, at the acute stage, the ADC reduction, at the ROIs that correlate with the core of the lesion, was accompanied with increased FA (as compared to control values). At the chronic stage the FA values approached control values. These two different patterns of changes may reflect different mechanisms of pathology. This preliminary study suggests that higher FA values, at the acute phase following ischemic stroke, may predict poor tissue recovery, while reduction in FA values at the acute stage may predict further deterioration at the chronic phase.

The balance between production and continuous delamination of neural crest progenitors.
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We have previously found that delamination of premigratory neural crest (NC) cells from the dorsal neural tube contributes to both regeneration BMP/noggin signaling and successful transition from G1 to the S-phase of the cell cycle. These two mechanisms are hierarchically related as BMP is upstream of Wnt1, which in turn promotes G1/S transition and NC delamination. In light of the continuous departure of NC cells from the tube upon synchronization to the S phase, we investigated the mechanism by which the premigratory pool of NC cells is replenished. Two alternative models were analyzed. First, a stem cell model implying asymmetric cell divisions in the dorsal midline, as a consequence of which, one daughter cell delaminates while the other remains in the tube to generate another round of a delaminating cell+stem cell. The second model involves the existence of a dorsolateral source of NC cells, which translate dorsomedially into the BMP/Wnt domain and then delaminate (Source and sink model). Our data support the second mechanism. Results are highly significant for our understanding of NC ontogeny as well as of the histogenesis of the CNS midline.

Extracellular Regulated Kinase I/II (ERKl/II) as a coincident detector of neuromodulation and fast neurotransmission
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In order for a particular neural representation to become consolidated for longer periods, long lasting changes in the neural connectivity should take place, as well as other intrinsic neural changes. These changes depend upon molecular processes such as signal transduction; transcription and protein synthesis. We hypothesize that in order for an afferent isotropic "fast" experience (N-Methyl-D-Aspartate, NMDA) to be consolidated as a long-term memory, it should come in convergence with another metabotropic "slow" modulatory input (Dopamine). First, we set up to define time and dose curves of ERKII activation by Dopamine and NMDA in hippocampal slice preparation. We find that application of 10-100uM Dopamine creates a dose dependent rise in ERKII activation. When Dopamine is applied in 100uM it raises the ERKII activation in about 50% of basal level, in a time frame maximal at 5 minutes. We also find that when NMDA is applied in different doses ranging from 10uM to 100uM it creates a dose dependent rise in ERKII activation. 100uM NMDA raises the ERKII activation in about 50% in a time frame maximal at 5 minutes. The kinetics of ERKII activation by 10uM and 100uM NMDA is different. Mutual application of NMDA and Dopamine in the same temporal phase does not cause any augmentation in ERKII activation. The results do not dismiss the hypothesis of convergence in different temporal phases.

Neuronal Synthesis and Release of D-Serine to Activate NMDA Receptors
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High concentrations of D-serine occur in central nervous system where it may play an important role in excitatory neurotransmission. D-Serine levels in the brain are a third those of L-serine and it appears to be an endogenous co-agonist of a subtype of glutamate NMDA receptor. D-serine is synthesized from L-serine, an enzyme previously shown to be enriched in gila. We now investigated possible localization and synthesis of D-serine in neuronal cells using new antibodies for both serine raceame and D-serine. We observed significant synthesis of D-serine and expression of serine racemase in purified neuronal cultures of cortex, hippocampus, striatum and cerebellum. Levels of D-serine and serine racemase were comparable in purified astrocyte cultures and the synthesis of D-serine required the presence of L-serine in culture media. Immunohistochemistry experiments expressing of serine racemase in neurons in rat cerebral cortex and hippocampus. D-serine immunoreactivity was also detected in neurons of rat brain, indicating that neuronal cells play a role in synthesizing D-serine in vivo. We found the release of D-Serine from cultured neurons to be elicited by agonists of several glutamate receptor subtypes. Depiction of endogenous D-serine in cortical cultures by the enzyme D-serine dehydratase was neuroprotective against NMDA-elicted cell death. Our data indicate that regulation of D-serine level remains an important topic for research. D-serine plays a role in NMDA receptor activation, with implications for the regulation of glutamatergic neurotransmission.
Separating signal from noise in contrast perception
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A basic problem in psychophysics is the independent estimate of the mean internal response and the noise amplitudes evoked by the sensory stimulus. An analysis of the two-alternative force-choice method derived from the standard detection theory, frequently applied in studies of contrast discrimination, shows that this method is not suitable for the estimation of these unknown parameters (mean and variance). To overcome this problem we used the Thurstonian scaling method of successive intervals. Three observers were tested on a visual identification task, using Gabor signals at five contrast levels as targets. In each trial one of five targets was presented to the observer and he was asked to report which one he saw, pressing the numeric keyboard button to monotonically five. The model for each trial one of five targets was presented to the observer and he was asked to report which one he saw, pressing the numeric keyboard button from one to five. The model parameters, namely, mean internal responses (n=5), noise amplitudes (n=5) and category boundaries (4 criteria) were found using a best least square fit to the data. In all experiments the noise amplitudes were found to be independent on the contrast. The internal responses were found to be best described by a saturating function of contrast. Surprisingly, the obtained criteria were uniformly distributed and not optimally set. The confidence intervals found using Monte-Carlo simulations of the identification task. The reason was later found to be large increase of contrast discrimination thresholds with contrast is due to reduced sensory gain and not due to increasing internal noise.

Estimating the Portion of Shared inputs Activated by Different Sensory Pathways in the Rat Barrel Cortex
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Receptive fields of neurons in the barrel cortex are composed of several whiskers. Thalamic receptive fields however are not limited to a single whisker. Thus it is not clear if multi-whisker receptive field of cortical neurons is determined by convergence at the cortical level or by their thalamic afferents. To examine at what stage convergence occurs and to estimate the portion of common inputs arriving to a cortical neuron we used the known adapting behavior of cortical cells as a tool. Adaptation of cortical neurons is believed to result from depression of the thalamocortical and cortical synapses. Therefore reduction of response to stimulation of one whisker after adapting the cell to stimulation of another whisker is a possible evidence for cortical cross talk or shared inputs. Indeed we show, using several simultaneous extracellular recordings, that adaptation to repetitive stimulation is strong in cortical neurons and almost absent in thalamic neurons. Average membrane potential recorded from neurons of different cortical layers. To calculate the percentage of common inputs out of the total response of one of the whiskers we used a simple linear model. We assumed that the response after depressing one pathway is an algebraic sum of the non adapted, non shared inputs and of shared inputs that were adapted by the second pathway. On average ~40% of the inputs are shared, the remaining ~60% found large variability in the shared inputs across cell population. Examination of various parameters reveals that the portion of shared inputs is related to recording depth. Assumed layer IV cells showed the smallest portion of shared inputs while cells from other layers showed larger portions. Our results are in agreement with anatomical and electrophysiological studies suggesting that convergence of extrathalamic inputs occur at the stage of layer IV cells, while neurons in other layers are likely to receive inputs from different whiskers after convergence at layer IV.

VAMP-2 regulates the activity of the voltage-gated K+ channels Kv2.1 and Kv2.2
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Kv2.1 has been shown to interact physically and functionally with t-SNAREs, Syntaxin 1A and SNAP-25 (Michaeli et al., 2003). Also, Kv2.2, exhibiting high sequence identity with Kv2.1 throughout the N-terminus and the core transmembrane region, but has a pro- and sequence divergence at their C-terminus, interacts with Syntaxin 1A and SNAP-25 (in preparation). However, the interactions of both channels differ (in preparation). Recently, we have shown that the Kv2.1 interacts also with VAMP-2. The central conserved domain of VAMP-2 has binding sites for both syntaxin 1A and SNAP-25 and is required for SNARE complex formation and synaptic vesicle membrane fusion. In this study we characterize the interactions of Kv2.2 with VAMP-2 and compared with those of Kv2.1. A co-immunoprecipitation analysis, using antibody against Kv2.2 and Kv2.1, reveals physical interactions of both channel proteins with VAMP-2 in Xenopus oocytes injected with the corresponding mRNAs. The functional implications of these physical interactions are revealed using two-electrode voltage clamp analysis performed in Xenopus oocyte cells. Thus, VAMP affects in a concentration dependent manner both steady-state activation and inactivation of Kv2.1, i.e., shifting half-activation and half-inactivation potentials to more negative voltages without affecting the slope factor of both activation and inactivation. The same effects can be detected in Kv2.2, however, at lower VAMP-2 concentrations. Namely, Kv2.2 is more sensitive to VAMP-2. Additionally, VAMP co-expression with ether Kv2.1 or Kv2.2 decreases the channel conductance by a dose-dependent manner. The effect was further investigated in Kv2.2. Different temporal relationship between the injection of VAMP-2 and channel mRNAs were de-tected for the different effects of VAMP-2 on Kv2.2, indicating that the reduction of channel amplitudes is due to impaired trafficking to plasma membrane and/or synthesis.

Anti-P-ribosomal antibodies induce depression in mice
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There is indirect evidence that anti-P-ribosomal Abs is associated with CNS disease. Anti-P-ribosomal autoantibodies occur specifically in systemic lupus erythematous (SLE) patients and are associated with organ involvement. The aim of study was to examine the pathogenic role of anti-P-ribosomal in animal models by intracerebroventricular (i.e.v.) injection of polyclonal anti-P-ribosomal affinity purified Abs from patients with SLE. Naive female mice (C3H/Hej) were injected i.e.v. with 6 mg/ml anti-P-ribosomal Abs or with 6 mg/ml IVIg as control. The mice were examined for neurological dysfunction in a staircase test, cognitive swim T-maze, grip strength, Rota rod, elevated plus maze (EPM), forced swimming test (FST), and passive avoidance. Anti-P-ribosomal Abs injected mice had a significantly different behavior in the EPM and FST compared to controls. In the EPM, the mice injected with anti-P-ribosomal Abs had significantly less exploration and were less active compared to the controls. In the FST, the anti-P-ribosomal Abs injected mice were found significantly more depressed (a significantly prolonged immobility time) compared to the controls. No significant differences were found between the study and the control groups in the staircase, grip strength, Rota rod, and cognitive (swim T-maze and passive avoidance) tests. Conclusions: Anti-P-ribosomal Abs injected mice display highly significant behavioral changes compatible with depression. Motor or cognitive effects were found in this model. The anti-P-ribosomal Abs injected mice display highly significant behavioral changes compatible with depression. Motor or cognitive effects were found in this model. The anti-P-ribosomal Abs injected mice display highly significant behavioral changes compatible with depression. Motor or cognitive effects were found in this model. The anti-P-ribosomal Abs injected mice display highly significant behavioral changes compatible with depression. Motor or cognitive effects were found in this model.
Effects of controllable vs. uncontrollable stress on amygdalar neuronal activity and plasticity.

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We studied the effects of controllable versus uncontrollable stress on neuronal activity and synaptic plasticity in the amygdala, using the electrophysiological procedure of long-term potentiation (LTP) induction. Rats of the controllable stress group were presented with 100 trials of a tone followed by a foot shock in a two-way shuttle avoidance box. The uncontrollable stress group could avoid the shock by pressing a bar during the tone, or escape the shock by passing to the opposite side of the box during the shock. From this group two sub-groups emerged: rats that learned the task well and avoided more than 50 shocks (good learners) and those which avoided less than 50 shocks (bad learners). Rats of the uncontrollable stress group could not avoid or escape the shocks which were presented according to the average performance of the good learners. A naive group was left until the recording commenced. Immediately after the training rats were anesthetized and prepared for stimulating the entorhinal cortex and recording in the amygdala. The neuronal activity was not significantly affected by the training. The good learners did not differ from the naive, but the bad learners and uncontrollable stress groups showed less LTP than the naive and the good learners. There was no difference in LTP between the bad learners and the uncontrollable stress group. These results show that a strong stressor reduces amygdalar synaptic plasticity, and suggest that failure to learn the task might be emotionally perceived as uncontrollable situation.

Neuronal activity and plasticity in the amygdala, the dentate gyrus and the CA1, following controllable vs. uncontrollable stress.

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The level of controllability has been shown to modulate effects of stress on physiology and behavior. We studied the effects of controllable versus uncontrollable stress on neuronal activity and synaptic plasticity in the amygdala, the dentate gyrus (DG) and the hippocampal CA1, using the electrophysiological procedure of long-term potentiation (LTP) induction in the rat. Rats of the controllable stress group were trained in the Morris water maze to locate a hidden underwater platform, thus escaping the cold water, immediately before the recording. The uncontrollable stress group was exposed to the water for the averaged time of the controllable group, without the platform. A naive group was left until the recording commenced. The controllable stress group showed no difference from the naive in any of the measures in the dentate gyrus and in the amygdala. The uncontrollable stress increased baseline activity of the amygdala, and enhanced LTP in the dentate gyrus. In the CA1, both stressors impaired LTP, but the effect of the uncontrollable stress was more robust. These findings were further verified in a second experiment in which the effects of amygdalar activation on DG and CA1 activity and plasticity were assessed. Stimulation of the amygdala increased neuronal activity in DG, but not in the CA1. Further findings show differential effects of stress, controllability and amygdalar activation on different brain regions, and suggest that the amygdala mediates some of the effects of stress on hippocampal activity and plasticity.

Constraining compartmental models using multiple voltage-recordings and evolutionary algorithms

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In the last decade there has been a significant advancement in the use of recorded parameters and ion channels from dendrites. Compartmental models with many non-linearly dependent parameters are used to learn the physiology of such complex neurons. However, the number of compartment parameters makes it impossible to construct the desired model manually. Recently, progress has been made using automated parameter search methods, such as evolutionary algorithms. These stochastic algorithms enable to construct a compartmental model of a neuron, using recorded spike trains. However, these methods are limited to somatically recorded spikes using relatively simple target functions. We've used a new fitting method based on trajectory density in a phase plane to compute a robust fitness coefficient. We exclude the time parameter by plotting the membrane potential V(t) versus its first time-derivative V'(t), in which the periodicity of the signal is reflected by a closed loop that can be geometrically analyzed, and each point of the plane can count how many times it has been hit during the entire recording. This method prevents from the algorithm to ignore the steep spikes and thus converge into a straight line. We investigated the contribution of several recording locations (soma, dendrites and axon). At each location a set of 5 currents (2 passive + 3 spike trains) was measured. We combined least square sum function for the passive currents with the trajectory density for the spike ones. We concluded that convergence efficiency improves as more recording locations are used.

Proteolytic processing of F-spondin is required to elicit its affect on commissural axon fasciculation at the floor plate

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F-spondin, a gene expressed at the floor plate, encodes a secreted guidance protein that plays a role in patterning axonal trajectory in the spinal cord. The carboxyl half of F-spondin, which contains 6 thrombospondin type 1 repeats (TSR), is proteolytically processed. The cleaved products of F-spondin have different properties and activities: the 1-4 TSR fragment neither binds the ECM nor promotes axonal outgrowth, while the 5th and 6th TSRs bind ECM and promote outgrowth. To test the relevance of F-spondin processing in vivo, we applied genetic tools to the chick embryo. Cell-specific expression was achieved by electroporation of DNA utilizing a floor plate specific enhancer. The activity of the specific enhancer was further amplified by the use of DNA site-specific Cre recombinase and Plox conditional constructs. The ectopically expressed 1-4 TSR domain is deposited along the membrane of floor plate cells, while the 6th TSR is found in the basement membrane underlying the floor plate, reflecting its ECM binding properties. By utilizing protein tags at the amino and carboxyl ends of the protein, we demonstrate that F-spondin is processed in vivo. Mutating the putative cleavage sites generated a non-cleavable protein, comprising the two domains, that accumulated on the surface of floor plate cells. The re-routing of the neurite outgrowth-promoting domain of F-spondin to the membrane of the floor plate cells, rather than the basement membrane, resulted in the redirection of commissural axons growth dorsally into the floor plate cells. Thus the cleavage of F-spondin is required for the deposition of the adhesive motifs at the basement membrane, which can facilitate the fasciculation of commissural axons at the ECM below the floor plate.

Neurogenesis, long-term potentiation and learning and memory processes are impaired in immune deficient mice

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Autoimmune T cells have been shown to benefit neuronal survival after CNS injury, and hence to help maintain the equilibrium of motor and sensory functions of the brain under adverse conditions. In this study we found that T cells play a role in spatial learning and memory both under physiological and adverse conditions, e.g. neurodegeneration and demyelination. We found that mice with severe immune deficiency long-term potentiation (LTP) and learning and memory processes are impaired and adult neurogenesis is significantly reduced. Remarkably, immune deficient mice with T cells restored hippocampal plasticity. Under adverse conditions, caused by neurotransmitter imbalance, a T cell-based vaccination was
sufficient to overcome the behavioral malfunctioning. The beneficial effect is attributed in part to brain-derived neurotrophic factor (BDNF). These findings, by suggesting that a peripheral immune deficit or a local neurotransmitter imbalance or both can lead to cognitive impairment, highlight the role of the peripheral immune system in CNS maintenance.

**Trajectory control during rodent whisking**

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The relative simplicity of the rodent vibrissal system facilitates a systematic study of motor control and sensorimotor loop dynamics. Multiple anatomical loops contribute to active control of the vibrissal plant during explorative behavior. We have examined motor control during exploratory and task-related whisking in rate and responses using high-speed video, monitoring whisker trajectories and extracted various kinematic parameters from the whisker motion. We analyzed repetitive whisker movements with a forward (protraction) and a backward (retraction) phase. We found that, across tasks, the protraction phase during high-amplitude whisks is characterized by a pulsatile forward motion with relatively constant velocity. The amplitude of protraction is governed primarily by the duration of movement whereas retraction amplitude is governed primarily by speed. During protraction, object touch is followed by a rapid (~10 ms) active thrust of the ongoing movement, typically observed as an increase in whisker velocity. These observations are consistent with the notion that the protraction phase acts as the sensory acquisition stage during whisking and that rapid brain loops can process and adjust pre-planned movement trajectories in the behavior of rodents.

Transgenic mice overexpressing different variants of acetylcholinesterase are hyperalgesic but have opposite responses to the elevated plus maze.

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Mice that overexpress either the synaptic variant of acetylcholinesterase (ACHE-S) or the rare readthrough variant (ACHE-R) (developed by H. Sorocz, Hebrew University) that show sensitiv response to pain using the hot plate paradigm and for unconditioned and learned anxiety in the elevated plus maze (EPM). Acetylcholine mediates in fear-potentiation startle, and the response to anxiety. Furthermore, ACHE-R is elevated following exposure to stress or to the cholinesterase inhibitor disopropylfluorophosphate, suggesting that the two transgenic genotypes would show alterations in measures of reactivity to aversive stimuli. EPM was tested using a transparent maze with 2 open and 2 closed arms. Mice were placed in the middle of the open arms for 6 min in 2 sessions separated by 48 hours. Reactivity to pain was measured in the hot plate test at 470 and 500°C. The ACHE-S mice showed significantly less exploration than the ACHE-R and FVB/N control on the second, but not the first exposure (F = 14.5, p < 0.0005), whereas the ACHE-R showed significantly more exploration (F = 34, p < 0.01) on the second exposure. In addition, ACHE-R taking mice were more reactive on the first exposure whereas, ACHE-S females had more risk taking than males on the second exposure. Both ACHE-S and ACHE-R responses to paw lick on the hot plate test, suggesting hyper-reactivity to pain. These findings confirm the involvement of ACHE in anxiety behavior, and suggest that ACHE-R is related to a deficit in inhibitory behavior.

Locally uncaged calcium induces rearrangement of GluR1 receptor clusters in the heads of dendritic spines of hippocampal neurons in culture.

Korkojian E. and Segal M.

Department of Neurobiology, The Weizmann Institute, Rehovot; Previous investigations have demonstrated that dendritic spines are able to undergo remodeling and extend calcium concentrations (Ca2++) independently of the adjacent dendrite such that synaptic elevation of [Ca2+] is mainly restricted to the spine head. The spine neck is a critical regulator of communication between the dendrite and the spine head. In previous studies we have shown that spine length can affect [Ca2+] levels in the parent dendrite by controlling the diffusion of [Ca2+], released by local flash photolysis from caged NP-EGTA-[Ca2+] compound in the spine head. Diffusion of calcium is a function of spine size, so that only the fraction of shorter (<1.5 um) spines revealed significant calcium diffusion into the dendrite. We now extend these observations to examine the functional relevance of calcium reaching the dendrite after uncaging in the spine head by measuring changes in GluR1 receptor clusters. Cultured hippocampal neurons transfected with pDred and GluR1GFP were preincubated with APV during 2-3 days and imaged in a confocal microscope (Pascal, Zeiss). Caged EGTA AM (7μM, Molecular Probes) was loaded into cells over 1.5 hr of incubation at room temperature. Pulses of 4ns UV laser light were directed on a spine head through a 53x water immersion objective. About 80% of APV treated spines did not express GluR1 puncta whereas almost all of control spines contained GluR1. UV flashes released [Ca2+] transients which peaked at 1-2 ms and decayed exponentially with time constants of 10-12 ms. Sequences of about 30-60 pulses applied at 0.2Hz on spines without GluR1, induced in 60% of cases, its slow accumulation over 10 – 20 min. Single or infrequent UV pulses were not efficient. A clear correlation between the spine length and the appearance of GluR1 puncta was found, such that only shorter spines became GluR1-positive. These results indicate that spine length may play a pivotal role in dynamic modulation of GluR1 receptor localization.

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

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There is mounting evidence to support the concept of education producing a function reserve in the brain that is a process that provides some protection against the clinical manifestation of severe CNS illness. At the molecular level BDNF was suggested to mediate memory consolidation and synaptic plasticity produced by learning experience. This study aimed to examine whether pre-challenge learning prevents psychosis-like behavior in an animal model of schizophrenia, and to describe the learning-related cellular mechanisms which attenuate the course of schizophrenia. Rate were trained to distinguish between pairs of odors in an olfactory discrimination task. We examined whether such olfactory-learning induces protection against the effects of i.p. injections of MK801 in a series of behavioral tasks. The Morris water-maze, pre-pulse inhibition and elevated plus maze. Forty-eight hours after the behavioral tasks, rats were sacrificed and the frontal cortex, CA1, CA3 and dentate gyrus were dissected for BDNF measurements. MK801 caused sensory-motor disturbances, spatial learning acquisition deficit, and swimming strategy alterations in pseudo-trained and naive rats, to the point were they were unable to complete the task during the course of 4 days of training. Although MK801 strongly affected learning of rats from the olfactory-discrimination trained group, these rats performed better than the naive and pseudo-trained, and were able to complete the task. Moreover, administration of MK-801 significantly disrupted pre-pulse inhibition in the pseudo-trained and naive groups, but not in the trained rats. In learning rats, BDNF mRNA in the frontal cortex was significantly higher compared to naive and pseudo-learning rats. Our data support the notion that learning-induced protection against schizophrenic behavior is mediated by glutamatergic transmission and modifications in the frontal cortex, manifested as enhanced expression of BDNF mRNA levels.
Characterization of a novel brain protein – KIAA0863

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KIAA0863 belongs to a protein family, which includes activity – dependent neuroprotective protein (ADNP). Here we report a comprehensive expression analysis of ADNP and KIAA0863. ADNP is a protein that has protective effects on neurons (Regul Pep 2000 96, 39) and that is involved in neurodegeneration (Dev Brain Res 2003 141, 83). Computer analysis and sequence alignment with human ADNP identified a paralog protein, KIAA0863, with 33% identity and 46% similarity. KIAA0863 belongs to a proteinfamily, which includes KIAA0863 is abundantly expressed in month old mouse. KIAA0863 is composed of 5 introns, 4 exons, and encodes an 1131 amino acid protein with a molecular weight of 122832 Dalton. The protein structure contains 8 zinc finger motifs and a homobox domain, suggesting transcription factor activity and a nuclear localization. The protein is highly conserved in human, mouse, and rat (73% and 75% identity, respectively, to a human protein), and is mapped to chromosome 18 within these species. The mRNA expression of KIAA0863 was characterised using reverse transcription-polymerase chain reaction (RT-PCR) analysis in several tissues from a normal four month old mouse. KIAA0863 is abundantly expressed in distinct normal tissues. We showed increased expression of the mRNA in the heart, brain and kidney, similar to the findings on ADNP (J. Biol. Chem. 2001 276, 708). This study is the first description of KIAA0863 gene expression and the first step towards a better understanding of the activities and the relationship between the resembling proteins – ADNP and KIAA0863.

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Representation of tone in fluctuating maskers in the ascending auditory system

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Codulation masking release (CMR) is a phenomenon, within which the perception of low-level tones is facilitated by the increase in the bandpdf of accompanied slowly-fluctuating noise. We have shown that release is a neurological outcome of the phenomenon, the ability of low-level tones to suppress neuronal locking to the envelope of the fluctuating noise (locking suppression). Here, we study the neuronal responses to different paradigms, which were designed to evoke CMR, in a large body of the CMR, psychoacoustically. In addition, we studied the responses to one CMR paradigm in three successive auditory stations: inferior collicular, lateral geniculate body (MGB) and A1. While responses in IC were roughly isomorphic to the physical structure of the sounds, with only a small perturbation in their responses to the fluctuating noise following the addition of low-level tones, some neurons in MGB and all A1 neurons displayed striking suppressive effects. These neurons were hyperexcitable, showing suppression already with tone levels lower than the neurons threshold in silence, starting more than 75 ms after tone onset. Our findings demonstrate a qualitative change in the representation of tone in fluctuating noise along the IC-MGB-A1 axis suggesting the gradual segregation of signal from noise and the representation of the signal as a separate perceptual object in A1.

Improved spatial resolution to density estimation of voltage-gated potassium channel conductances in a non space clamped structure

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Currents yielded from voltage-clamp recordings performed in such structures, such as dendrites, are severely distorted due to voltage attenuation around the injecting electrode. Therefore, up till now it has been impossible to determine correctly the underlying ionic conductances of voltage-gated channels distributed in the membranes of such structures, and from them to accurately estimate channel densities. Recently, a numerical algorithm was developed by our lab, that has been shown to successfully correct such distortions in a number of simulated experiments using various neuronal structures inserted with a number of models of voltage-gated potassium channels, and correctly estimate channel kinetics and conductance densities when inserting a range of homogeneous densities and even non-homogeneous densities and slopes. However, one limitation of this correction algorithm is relatively poor spatial resolution, when estimating conductances in structures inserted with a number of voltage-gated potassium channel density, around the abrupt conductance step. This study shows an improvement in spatial resolution achieved by performing a sequence of voltage clamp simulations in locations progressively closer to the position of the conductance step, each time utilizing the conductances estimated in the farther positions. These improvements in kinetics and density estimations were successful with various potassium channel models and a series of increasingly larger conductance density steps.

Cation Binding at The Pore of Le-Type Ca2+ Channel Regulates Depolarization-Induced Exocytosis

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A unique coupling of voltage-gated Ca2+ channel (VGCC) with the release machinery suggests a role for the channel in depolarization-evoked exocytosis. To test this hypothesis, amperometry in chromaffin cells was used with trivalent ions that bind to VGCC but do not cross into the cytoplasm. We found that exocytosis is mediated by La3+ ions in divalent ion-free solution with no detectable change in intracellular Ca2+ concentrations. A stringent requirement of ionic radii for lanthanides activity and competition with nifedipine, verapamil and Ca2+ confirm La3+ binding to the VGCC. The time from fusion pore opening to dilation of single dense core vesicles ('foot signals') was significantly shorter in La3+ than in Ca2+, indicating different kinetics of the molecular structure that links vesicle and plasma membrane. The considerable effect of impermanent cations on foot dynamics implies that the channel participates in the fusion pore structure and controls exocytosis in a cation-dependent manner, upstream to intracellular proteins.

Quantification of synapses made by thalamocortical afferents reconstructed in 3-D serial thin sections.

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This study focuses on synapses made by reconstructed segments of thalamocortical afferents to layer IV of barrel cortex in the adult rat. A total of three cases were studied, and for LID and PHA-L labeled afferents. Preliminary results indicate that axonal varicosities form about 2 synapses each, a lower value than observed in preparations where lesion induced degeneration (LID) has been used to label synapses. It may be that during degeneration, the axonal varicosities complex and/or 'absorb' synapses situated in adjacent, non-varicose axonal segments. The ratio of axonospheres to axodendritic synapses was 1:1 and has been observed for BDA labeled afferents at 11 days postnatal, and for LID and PHA-L labeled afferents in adults (White, 1989).

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Induction of alpha-Synuclein aggregates in dopaminergic neuronal cell lines as an experimental model for Parkinson's disease

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Parkinson's disease (PD) is the most common neurodegenerative movement disorders. The pathologic hallmark of PD is the appearance of intracytoplasmic inclusion bodies, named Lewy bodies. Alpha-Synuclein is a major component of these inclusions and its mutated form causes autosomal dominant PD, implicating its central role in PD. Recent evidence suggests that failure of the ubiquitin-proteasome system leading to protein accumulation contributes to degeneration of dopaminergic neurons and Lewy body formation in the substantia nigra. The aim of this study is to characterize the conditions that induce protein aggregates formation in differentiated and undifferentiated dopaminergic cell lines. We established dopaminergic SH-SY5Y and PC12 cell lines overexpressing wild-type or mutant alpha-synuclein and exposed them to various ROS generators. Neuronally differentiated SH-SY5Y and PC12 cells were established by treating the cells with retinoic acid or nerve growth factor. The cell lines were also stably transfected with pDsRed-l-N1 plasmids containing WT or ubiquitinated-proteasome system leading to protein accumulation contributing to degeneration of dopaminergic neurons. Parkinson's disease (PD) is the most common neurodegenerative movement disorder. The pathologic hallmark of PD is the appearance of intracytoplasmic inclusion bodies, named Lewy bodies. Alpha-Synuclein is a major component of these inclusions and its mutated form causes autosomal dominant PD, implicating its central role in PD. Recent evidence suggests that failure of the ubiquitin-proteasome system leading to protein accumulation contributes to degeneration of dopaminergic neurons and Lewy body formation in the substantia nigra. The aim of this study is to characterize the conditions that induce protein aggregates formation in differentiated and undifferentiated dopaminergic cell lines. We established dopaminergic SH-SY5Y and PC12 cell lines overexpressing wild-type or mutant alpha-synuclein and exposed them to various ROS generators. Neuronally differentiated SH-SY5Y and PC12 cells were established by treating the cells with retinoic acid or nerve growth factor. The cell lines were also stably transfected with pDsRed-l-N1 plasmids containing WT or ubiquitinated-proteasome system leading to protein accumulation contributing to degeneration of dopaminergic neurons.

Perinatal enhancement of the GABA-ergic system modulates synaptogenesis

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Antiepileptic drugs acting through the potentiation of GABA-ergic pathways have adverse effects on brain development. Increased risk of impaired intellectual development was reported in children born to women treated for epilepsy during pregnancy. We have previously shown that vigabatrin (GVB) treatment during perinatal days (P) 4-14 delays reflex development and impair learning and memory in adult mice. Here we examined the possibility that enhancement of the GABAergic system at early postnatal age modulates synaptogenesis by evaluation of synaptic vesicle proteins. Perinatal GVB treatment significantly modulated the expression of synaptotagmin I (Syt I) and synaptobrevin/VAMP II but not Syt II. At the end of the GVB treatment period Synt I-immuno-reactivity (IR) was reduced in the hippocampus CA1 region (96.1% of control, P<0.01), secondary visual cortex, V2 (99.9%, P=0.01), and a trend of decrease was observed in the frontal association cortex, FrA (17.7%, P=0.07). A week later, at P21, Synt I-IR in CA1 and V2 was equal in both groups. However, at the age of 16 weeks the GVB group showed a significant increase in Synt I-IR in CA1 (164.8%, P=0.01). Thus, the short-term suppression of Synt I-IR switched into overall increase in Synt I in the hippocampus CA1 region. When VAMP II-IR was examined, the general trend resembled that of Synt I. However, the level of VAMP II treatment on VAMP II was significant mainly in the adult mice. An increase in VAMP II-IR was observed in CA1 (196.2% of control, P<0.01) and the cortical regions: FrA (204.3%, P<0.05), V2 (223.6%, P<0.01) and primary sensory cortex, S1 (218.5%, P<0.01). The association between perinatal GABA enhancement and modulation of synaptogenesis is reported here. Postnatal effects of GVB treatment on VAMP II was significant mainly in the adult mice. Increased risk of impaired intellectual development was reported in children born to women treated for epilepsy during pregnancy. We have previously shown that vigabatrin (GVB) treatment during perinatal days (P) 4-14 delays reflex development and impair learning and memory in adult mice. Here we examined the possibility that enhancement of the GABAergic system at early postnatal age modulates synaptogenesis by evaluation of synaptic vesicle proteins. Perinatal GVB treatment significantly modulated the expression of synaptotagmin I (Syt I) and synaptobrevin/VAMP II but not Syt II. At the end of the GVB treatment period Synt I-immuno-reactivity (IR) was reduced in the hippocampus CA1 region (96.1% of control, P<0.01), secondary visual cortex, V2 (99.9%, P=0.01), and a trend of decrease was observed in the frontal association cortex, FrA (17.7%, P=0.07). A week later, at P21, Synt I-IR in CA1 and V2 was equal in both groups. However, at the age of 16 weeks the GVB group showed a significant increase in Synt I-IR in CA1 (164.8%, P=0.01). Thus, the short-term suppression of Synt I-IR switched into overall increase in Synt I in the hippocampus CA1 region. When VAMP II-IR was examined, the general trend resembled that of Synt I. However, the level of VAMP II treatment on VAMP II was significant mainly in the adult mice. An increase in VAMP II-IR was observed in CA1 (196.2% of control, P<0.01) and the cortical regions: FrA (204.3%, P<0.05), V2 (223.6%, P<0.01) and primary sensory cortex, S1 (218.5%, P<0.01). The association between perinatal GABA enhancement and modulation of synaptogenesis is reported here.

Homocysteine Reducing Strategies Improve Symptoms in Chronic Schizophrenic Patients with Hyperhomocysteinemia

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Elevated homocysteine is reported to be a risk factor for several diseases including Alzheimer's and schizophrenia, and can be lowered by oral folie acid, B-12 and pyridoxine. Thirty seven schizophrenic patients with plasma homocysteine above 15 Micromolar were treated with these vitamins for three months and placebo for three months in a randomized double-blind placebo controlled crossover design. In all patients except for one non-compliant subject, homocysteine levels declined significantly. The therapy compared to placebo as did clinical symptoms of schizophrenia. A subgroup of schizophrenic patients with hyperhomocysteinemia may benefit from simple addition of B vitamins.

Effect of intraperitoneal Acetyl-L-carnitine (ALCAR) on anxiety-like behaviors in rats

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Acetyl-L-carnitine (ALCAR) is an acetyl derivative of carnitine, an endogenous molecule synthesized in vitamin and supplemented by diet mainly from meat and dairy products. Several parallel, double blind, placebo-controlled studies have demonstrated that ALCAR treatment produces beneficial effects in geriatric depression. Since most antidepressants also have anti-anxiety effects we examined whether ALCAR shows anti-anxiety effects in a rat model of anxiety. Compared with a control group, chronic administration of ALCAR at doses of 10 and 100 mg/kg (tested 24 hours after the last dose administration) showed no effects, whereas doses of 50 and 75 mg/kg significantly reduced anxiety-like behaviors in the elevated plus-maze. Acute ALCAR (100 mg/kg), on the other hand (tested 6 hours after administration), demonstrated anxiogenic effects. Our data suggest that chronic ALCAR administration may produce an inverted U-shape curve of dose dependent changes in anxiety-like behavior. The precise mechanism by which Acetyl-L-carnitine decreases anxiety-like behavior after peripheral administration remains to be determined.

Correlation between blood-free testosterone concentration and sleep duration in healthy young men

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Background: Healthy young men who underwent varicoceal chemical embolisation, required reduced sleep duration. Testosterone, an androgenic anabolic steroid, affects the central nervous system. We measured serum free testosterone in a group of these patients, to determine whether there is a correlation with decrease sleep duration. Methods: Thirty young men in general good health, underwent varicoceal chemical embolisation for infertility treatment. They were requested to complete a questionnaire regarding their sleep habits. They were asked to fill in the questionnaire before treatment and again 3 months after start of treatment. Serum free testosterone was measured at the same times. Results: In 40 young men (mean age 31 ± 7) serum free testosterone increased 3 months after the varicoceal procedure (6.5 ± 3.5 vs. 11 ± 3.1, P < 0.05). Sleep duration significantly decreased over time. We did not detect that the short and long term modifications in testosterone concentration, following varicoceal chemical embolisation, was associated with a decreased sleep duration.
Coupling TMS with EEG to “close the loop” between measurement and perturbation - first steps towards a closed loop system. 

We are using a novel, integrative approach that uses EEG and TMS (Transcranial Magnetic Stimulation) to “close the loop” between measurement and intervention. EEG is constantly being measured from the subject’s scalp, and the loop “between measurement and intervention.” EEG is discussed in these second paradigms. We apply the “closing the loop” in the experimental paradigm, we measured the effect of TMS on alpha wave oscillations, as TMS was applied at different phases and different locations relative to a reference EEG electrode. The ability to intervene, enhance and synchronize alpha oscillations will be discussed. In the second paradigm we applied the “closing the loop” system to the task of closing the loop where the brain response to the magnetic stimulation is constantly being measured from the subject’s scalp, and the loop “between measurement and intervention.” EEG is discussed in these second paradigms.

Probing synchronous internal processes by precisely controlled Transcranial Magnetic Stimulation

Levit-Binnun N., Peled A., Moses E.

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A central role for JNK pathway in antidepressant-induced weight gain and metabolic changes.

Levkovitz Y., Gil-Ad I., Shvartsman D., Elcon C., Ronnen D., Zick Y., Weizman A.

The development of drug addiction is associated with synaptic plasticity and neuronal adaptations including alterations in glutamatergic receptor such as NMDAR1 and p38 MAPK pathways. We determined a role of the p38 MAPK pathway in reward-related brain regions, mainly in the mesocumbens pathway. Intra-cranial self-stimulation of the medial forebrain bundle (MFB) induced an increase in glutamatergic transmission and receptor levels in these regions. We investigated the influence of repeated electrical stimulation of the MFB on the sensitized response and found that p38 MAPK activation is involved in the sensitized response.

Electrical Brain Stimulation of the Medial Forebrain Bundle Reduces the Effect of Cocaine Related-Cues on Locomotion and Craving

Levy D., Shaban-Simon M., Barnea-Yngel N., Zangen A.

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responses when neighboring whiskers are coactivated was revealed by blockade of inhibition using bicuculline (Kyriazi et al. 1996). However, the mechanism that leads to sublinear spatial integration remains unclear. Here we explored the mechanism of spatial integration by recording the membrane potential of neurons in the barrel cortex of the rat. We studied the integration of excitatory and inhibitory components arriving to the cell from two sensory pathways by stimulating two neighboring whiskers. Conductance measurements and intracellular blockade of inhibition demonstrated directly that excitatory components arriving from the pathways are summed almost linearly, suggesting that the output of the injury shows no significant amount of common inputs and are independent from one another. On the other hand, inhibitory components are summed supra-linearly: inhibition was on average 50% larger than predicted. These findings strongly suggest that sublinear spatial integration arises from nonlinear properties of the cortical network leading to activation of inhibitory inputs that are not activated by either stimulus alone.

Strain-related differences in response to neuroprotective therapy based on mucosal administration

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Ability to cope with ongoing neurodegeneration after optic nerve injury differs among animal strains and depends on the ability to manifest a T-cell-mediated protective response. In strains that show a higher neuronal survival following injury this ability also correlates with well-known parameters such as the number of thymocytes. We show that CD4+ T cells that infiltrate mechanically injured nerves in mice that vary in their ability to cope with the injury exhibited similar memory phenotypes, after 3 days the percentage of activated CD4+ T cells was significantly higher in mice with the higher neuronal survival. Such strains benefited from active immunization with myelin-related antigens. However, immune-based manipulations (via mucosal administration) evoking regulatory-cell generation and a shift in cytokine balance were neuroprotective only in mice with poor ability to cope with the insult and only when directed against certain epitopes. The results support a link between poor ability to cope with injury and susceptibility to development of experimental autoimmune encephalomyelitis, and suggest that immune regulation as neuroprotective therapy should be considered with caution.

Ubiquitylation of synphilin-1 and its role in Parkinson's disease

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Parkinson's disease (PD) is one of the most common neurodegenerative diseases and it is due to a progressive degeneration of dopaminergic neurons in substantia nigra. Mutations in the alpha-synuclein gene and its presence in Lewy bodies of PD patients indicate that alpha-synuclein plays an important role in the disease. We have found that alpha-synuclein interacts with a protein we have called synphilin-1. Synphilin-1 is enriched in brain, interacts with alpha-synuclein in vivo and is present in Lewy bodies of PD patients. Co-transfection of synphilin-1 with alpha-synuclein into mammalian cells leads to the formation of cosinophilic inclusions that resemble Lewy bodies, suggesting that synphilin-1 could modulate alpha-synuclein aggregation. We also found that synphilin-1 is a neuronal protein, widely expressed in brain and localized to presynaptic nerve terminals. Co-immunoprecipitation experiments show that synphilin-1 specifically associates with synaptic vesicles. More recently we found that synphilin-1 interacts with the ubiquitin-like domain called SIAH. SIAH promotes the ubiquitylation and degradation of synphilin-1 through the ubiquitin-proteasome system, and the formation of robust amount of inclusion bodies in the presence of proteasome inhibitors. Ubiquitylation is required for inclusion formation, since a catalytically inactive mutant of SIAH, which still binds to synphilin-1, fails to promote inclusions. SIAH is present in Lewy bodies of patients with PD, raising the possibility that synphilin-1/SIAH inclusions may be involved in neuronal death. We hypothesize that dysfunction of ubiquitin-proteasome pathway and accumulation of ubiquitylated synphilin-1 could be an early event in the pathogenesis of PD. We are currently extending our studies on synphilin-1/SIAH interaction and the role of ubiquitylated-synphilin-1 in cell death.

Hypoxia-sensitive, nonselective cation channels in layer 5 pyramidal neurons are activated by decreases in extracellular calcium

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We previously showed in nococortical neurons that when all voltage-dependent channels are blocked, a large, non-specific, outwardly rectifying, cationic current is revealed (Icat). The characteristics of Icat rapidly alter, as during an hypoxic episode, which elicits a significant increase in the inward Icat at negative voltages and a parallel decrease in the outward current at depolarization. Our data show that Icat is also activated by a drop in extracellular Ca2+ to nanomolar concentrations, such as may occur during hypoxia. Reduction of [Ca2+]o results in complete loss of Icat rectification, massive influx of cations at negative potentials and consequent membrane depolarization. Using cell-attached recordings from Ca2+-activated K+ channels, we monitored membrane potential and changes in [Ca2+]i. Hypoxia elicited a large, reversible depolarization which was accompanied by a 1000-fold increase in [Ca2+]i. These changes in Icat properties during hypoxia or during activity associated with seizures may contribute to neuronal vulnerability by providing a route for cation entrance and thereby depolarizing the neurons and increasing [Ca2+]i. It is noteworthy that many of the properties of Icat, including its partial blockade by La3+, are similar to those previously reported for TRP channel-mediated currents, which are also very sensitive to metabolic stress. It thus seems likely that in nococortex, as elsewhere, changes in the properties of TRP channels directly contribute to the neuronal pathogenic responses.

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Animal models for investigating the basis of the Thyroid hormone T3's activity in the treatment of depression

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T3 is long being used in the clinical setting for treating depressed patients, in two major paradigms: 1) monotherapy, in which T3 is given as a sole agent, augmentation and acceleration, - in which T3 is given as a supplementation to an antidepressant in order to induce a response to the drug or to accelerate an existent response to it, respectively. In order to investigate the basis of this clinical activity of T3, we first employed the in vivo microdialysis technique in order to measure the activity of presynaptic inhibitory serotonergic receptors and serotonin levels in selected brain areas. We hypothesized that significant changes in these parameters values may account for the clinical effects of T3. These changes, namely: the de-sensitization of the receptors, and the elevation of the serotonin levels) were found, in male rats, in a way that more indicates T3's value as a sole pharmacotherapeutical agent and less as an effective supplement to increase or to accelerate the activity of another antidepressant. In contrast, the measured parameters didn't change appreciably in female rats, either in the model mimicking T3 monotherapy or in the augmentation model. In order to create a link between the pharmacodynamical changes we've measured and the known activity of T3 in the clinical setting, and in
order to further elucidate the gender differences found in the microdialysis experiments, we've employed the behavioral paradigm of the modified forced swim test to rats of both genders. No consistent effect was found in this test to T3 and fluoxetine given in low doses for 2 weeks, but high T3 doses given for a week did generate an antidepressant effect, but only in female rats, and only in a delayed fashion (72 hours after the last injection), again constituting a marked gender difference.

Distribution of the pro-apoptotic protein ARTS in rat brain
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The distribution of the pro-apoptotic protein ARTS (Apoptosis Related protein in the TGF-beta Signalling pathway) has been examined by immuno-histochemical technique in normal rat (Sprag._e-Dawley) formalin-fixed brain tissue (cortex, striatum and cerebellum) by Western blot at apparent molecular weight of about 27 Kd, similar to that of human ARTS. ARTS was constitutively expressed in a proportion of neurons in most parts of the brain. In cortex part, a large number of ARTS-positive cells were seen in the external and internal pyramidal cell layers. The piriform cortex showed a high density of stained cells. In hippocampus, most neurons of the pyramidal cell layer were ARTS-positive. In striatum, medium spiny neurons were generally not ARTS-positive, but a small number of interneurons showed dense ARTS staining. In the substantia nigra, neurons of both pars compacta and pars reticulata showed ARTS-positive staining in cytoplasmic and nuclear components. Double fluorescent staining was performed to detect co-localisation of ARTS and tyrosine hydroxylase (TH) in the pars compacta. Most ARTS-positive neurons were not tyrosine hydroxylase-positive, but a small percentage of neurons were positive for both ARTS and tyrosine hydroxylase. In many, but not all neurons, ARTS occurs in nuclei as well as in the cytoplasmatic compartment. This contrasts with the picture seen following ARTS over-expression in peripheral cell lines such as COS, Hela, in which ARTS has a predominantly mitochondrial occurrence and enters nucleus at the onset of apoptosis. The significance of this finding is not currently clear.

Supported by a grant from the Chuttack Foundation, Technion Laiusch et al. (2000) ARTS, a novel mitochondrial septin-like protein, mediates apoptosis dependent on its F-actin motif. Nature Cell Biol., 2:915-21.

The Role of a Reference Tone in Auditory Discrimination Tasks
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Auditory discrimination tasks are often used in testing verbal working memory. Tasks are defined as easy or hard based on the memory resources necessary to achieve success. Previous work has found that the presence of a reference tone aids in the performance of difficult discrimination tasks. A simple discrimination task asks the subject to make a simple judgment about a tone pair, e.g. if two tones are the same or different. A difficult task requires a more detailed judgement, like identifying which tone in a pair is the higher tone. It has been found (K. Banai '04) that if one tone is a fixed reference, i.e. it is always the lower tone, then the difficult task becomes easy. To further investigate the efficacy of the reference tone, we devised a new task where the reference tone was always 1000 Hz., but sometimes it was higher and sometimes it was lower than the other tone in the pair. 23 teenage girls were tested in the six conditions - fixed reference, variable reference and no reference in the simple and difficult paradigms. In the simple paradigm, the just noticeable differences (JND) for the variable reference condition were the same as in the fixed reference condition (~7% vs. ~10%). In the difficult paradigm, on the other hand, JNDS in the variable reference condition were like those when no reference was present (~20%).

These results indicate that a reference is only useful when it can be given a label - in this case "low". Possibly, this ability to categorize is what changes a difficult task, using more memory resources, into a simpler, less demanding task.

DHEA and cocaine seeking behavior
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The aim of this study was to determine whether neurosteroids are involved in cocaine addiction and abuse. The effect of chronic DHEA injection on cocaine-seeking behavior was tested using the self-administration model. In addition rats were tested for brain neurosteroids levels following chronic exposure to cocaine. We also tested brain levels of different neurotransmitters (NT) known to be involved in the brain reward system, following chronic DHEA injection. Behavioral tests showed that DHEA attenuates cocaine-seeking behavior in rats. Biochemical tests revealed that DHEA elevates levels of relevant NT's (DA, 5-HT) in brain regions involved in the reward system. We also found that chronic exposure to cocaine increases the levels of neurosteroids in different brain areas. Conclusions: neurosteroids are involved in mood, motivation and reward. DHEA modulates the response to cocaine reward, selects the correct tone in a different DHEA brain levels following cocaine self-administration support a protective role for this neurosteroid by helping to maintain homeostasis of the reward systems and possibly protecting them from extreme conditions.

Expression of the pro-apoptotic protein ARTS in normal human brain and in Alzheimer’s and Parkinson’s diseases.
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The pro-apoptotic protein ARTS (Apoptosis Related protein in the TGF-beta Signalling pathway) is a broadly expressed 28 Kd septin-like protein found in a variety of tissues including CNS (Larisch et al. 2000). Following transfection of ARTS in COS, Hela and A549 cell lines, apoptosis induction by several different pro-apoptotic stimuli is enhanced. The occurrence of ARTS in normal and Parkinsonian (PD) brain has been studied by immunohistochemistry, and in PD and Alzheimer’s disease (AD) brain, in the substantia nigra, the globus pallidus, the hippocampus (hp), the cerebellum (cb), striatum (st) and mesencephalon (ms). In cx and hp, light ARTS-immunopositive staining was seen in a small proportion of neurons, mainly the large pyramidal cells. Cb and st were largely ARTS-immunonegative. In ms, ARTS-positive cells were seen in periaqueductal grey, pontine nuclei, red nucleus and substantia nigra. In the latter areas, the intensity of staining was markedly increased in PD brains. ARTS expression level was quantitated by Western blotting from deep-frozen tissue. Similar levels were seen in cx (inferior temporal cortex) of normal, PD and AD brain, and in st of normal and AD brain. Brain ARTS has a lower apparent molecular weight (about 28 Kd) than peripheral ARTS. Although ARTS levels do not markedly change in PD or AD brain, individual neurons may express high levels during the brief period of time that the apoptotic process is active.

Supported by a grant from the Chuttack Foundation, Technion Larisch et al. (2000) ARTS, a novel mitochondrial septin-like protein, mediates apoptosis dependent on its F-actin motif. Nature Cell Biol., 2:915-21.
SR141716A improves cognitive and neurological function in a model of secondary biliary cirrhosis in the rat.

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'Department of Human Nutrition and Metabolism, Brown's School of Public Health, Boston University; 'Department of Internal Medicine, Hadassah Hebrew University Medical Center, Mount Scopus, 'Department of Medical Chemistry and New Products, Medical Faculty, Jerusalem, Israel; Background/Aims: Hepatic encephalopathy (HE) is a major neuropsychiatric complication of both acute and chronic liver failure. However, the pathogenesis of this disease is still unknown. It has been suggested that the cognitive deficits characteristic of this state result from changes in some neurotransmitter systems in the brain, including the glutamatergic, cholinergic and monoaminergic systems. These changes may result from an ammonia accumulation in the circulation and in the brain due to an impaired metabolism of this substance by the liver.

Endocannabinoids function as neurotransmitters and immunomodulators in the CNS via specific receptors. Recently the endocannabinoid system was found to be involved in the vasodilated state associated with liver cirrhosis. Aims: We hypothesize that the endocannabinoid system might be involved also in Hepatic encephalopathy. Methods: Male, Sprague-Dawley rats were subjected to a ligature of the bile duct (BDL) under ketamine anesthesia. Sham operated animals were used as controls. 2 and 4 weeks post-surgery, animals receiving either vehicle or SR141716A, a CB1 receptor antagonist, were evaluated for cognitive and neurological function in the Morris Water Maze and in the Neurological Severity Score (NSS) tests, respectively. Results: Cognitive function in the Morris Water Maze was significantly impaired in the BDL rats 2 and 4 weeks post-surgery. SR141716A improved these deficits in the BDL animals compared to controls. NSS was significantly higher in the BDL group compared to the sham group and SR141716A returned this score to normal values in BDL animals. Conclusion: These results indicate an involvement of the endocannabinoid system in the pathogenesis of HE. Modulation of this system by CB1 cannabinoid receptor might have therapeutic potential.

A dual role for cAMP in regulating myelin phagocytosis by microglia/macrophages.

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Posttraumatic Stress Disorder (PTSD) does not develop in everyone exposed to a traumatic event. It is quite clear today that exposure to the stressor alone is not sufficient to trigger the disorders, and in fact a minority of those exposed will go on to develop the full-blown clinical conditions. Premorbid vulnerability and risk factors, are thus suggested to up-regulate myelin phagocytosis by inhibiting adenylyl cyclase, and consequently reducing cAMP levels. cAMP-dependent protein kinase (PKA) mediates many of the effects of cAMP. We thus expected PKA inhibition to augment phagocytosis. Surprisingly, PKA inhibition by 8-bromo-cAMP (mimics cAMP), forskolin (activates adenylyl cyclase to produce cAMP) and IBMX (inhibits phosphodiesterases that hydrolyze cAMP) increased phagocytosis of degenerating myelin in a dose dependent manner (PICA and as yet unidentified other target molecule(s).

In-context training prior to stress exposure reduces the after-effects of the stressor: The role of brain derived neurotrophic factor (BDNF).

Malka Y., Kozlovsky N., Kaplan Z., Matar M., Cohen H.
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Posttraumatic Stress Disorder (PTSD) does not develop in everyone exposed to a traumatic event. It is quite clear today that exposure to the stressor alone is not sufficient to trigger the disorders, and in fact a minority of those exposed will go on to develop the full-blown clinical conditions. Premorbid vulnerability and risk factors, are thus suggested to up-regulate myelin phagocytosis by inhibiting adenylyl cyclase, and consequently reducing cAMP levels. cAMP-dependent protein kinase (PKA) mediates many of the effects of cAMP. We thus expected PKA inhibition to augment phagocytosis. Surprisingly, PKA inhibition by 8-bromo-cAMP (mimics cAMP), forskolin (activates adenylyl cyclase to produce cAMP) and IBMX (inhibits phosphodiesterases that hydrolyze cAMP) increased phagocytosis of degenerating myelin in a dose dependent manner (PICA and as yet unidentified other target molecule(s).

In-context training prior to stress exposure reduces the after-effects of the stressor: The role of brain derived neurotrophic factor (BDNF).
Hypothalamic beta-endorphin and the HPA axis in two different genetic animal models of childhood depression

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A consistent finding in biological psychiatry is that hypothalamic-pituitary-adrenal (HPA) axis function is altered in adults and children with major depression. Recently, we found that juvenile rats from two different depressed lines— the Flinders Sensitive Line (FSL) and their controls, Sprague-Dawley (SD) rats, and the Wistar Kyoto (WKY) line and their controls, Wistar rats, show abnormality of the HPA axis. FSL juveniles demonstrated significantly lower plasma levels of corticosterone and ACTH compared to their controls, while WKY juveniles demonstrated significantly higher plasma levels of corticosterone and ACTH compared to their controls. Experiment 1 asked if these two different depressed lines have different basal levels in the hypothalamus of a neonpeptide which has behavioral effects diurnally opposite to those of ACTH – beta-endorphin. Experiment 2 examined HPA axis function of these two lines after chronic stress (-two weeks of social isolation). FSL juvenile rats demonstrated significantly higher basal levels of beta-endorphin and lower plasma levels of corticosterone and ACTH after chronic stress, compared to their controls, while WKY juveniles demonstrated similar basal levels of beta-endorphin, and similar plasma levels of corticosterone but lower plasma levels of ACTH after chronic stress, compared to their controls. Both depressed lines showed significantly lower levels of HPA hormones after chronic stress compared to basal levels, while the controls lines showed stable unaltered levels of these hormones compared to basal levels. These results suggest that both FSL and WKY are genetic models of depression in adolescent rats, exhibiting distinct abnormal patterns of the HPA axis function at basal and reactive states.

Activity-dependent neuroprotective protein regulates neurogenin1: A novel gene important for neurogenesis

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Activity-dependent neuroprotective protein (ADNP) was recently cloned in our laboratory (1 Neurochem 1999, 72, 1283; 2J Biol Chem 2001 276, 706). ADNP is a novel gene with sequence similarity to the homologous family of proteins (KIAA0319) involved in development and stress response. However, its specific biological function remains unknown. Previous studies have demonstrated that ADNP is expressed in the brain and spinal cord of the mouse and human embryos. In this study, we aimed to investigate the role of ADNP in neurogenesis and neuroprotection. We generated ADNP-knockout (KO) mice and subjected them to a series of developmental events, including embryonic and postnatal stress. Our results showed that ADNP KO mice displayed a dramatic down-regulation of several genes involved in neurogenesis, including NeuroD and NeuroG1. In contrast, normal levels of these genes were observed in control mice. These findings suggest that ADNP plays a critical role in neurogenesis and neuroprotection.
tested we found an elevation of GAD in M1 layers 4-6 (P<0.05) and the hippocampus (P<0.01), compared to control. In contrary, PV cell loss was observed in M1 layers 4-6 (P<0.01) and the hippocampus (P<0.01). Our data indicate that hypoxia induced loss of PV cells without affecting GAD. Lack of effect on GAD could suggest that hypoxia induced an increase in inhibitory synapses to compensate for the PV cell loss. Alternatively, differentiation of other types of inhibitory neurons may be facilitated.

Neuroprotective influence of plasminogen activator during CNS inflammation.
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Multiple sclerosis (MS), a demyelinating disease of the central nervous system (CNS), is characterized by perivascular infiltrates containing auto reactive T cells and macrophages. Extracellular proteases such as plasminogen activators (PA) and matrix metalloproteinase (MMP) play a role in tissue remodeling and response to injury. In the present study we tested the role of PA in axonal and myelin damage. Using CNS tissue from experimental autoimmune encephalomyelitis (EAE), the latter being the animal model used for MS studies. EAE was induced in mice lacking urokinase PA (uPA) receptor (uPAR) or MMP. In comparison to the wild type group, all knockout (ko) mice exhibited more severe neurological symptoms and PAR -/- mice displaying more severe clinical symptoms. The extent of demyelination and axonal loss correlated with aggravated clinical outcome. T-cell reactivity towards the encephalitogenic peptide MOG 35-55, was reduced in ko animals while macrophage responses were enhanced. The urokinase derived peptide, A6, that blocks the interaction between uPA and its receptor, markedly inhibited encephalitogenic T-cell reactivity. Our results indicate that the PAs system may be a potential target for treatment of CNS inflammatory and demyelinating disease.

The Posner Spatial Orientation Paradigm as an Examination of Lateralized Striatal Dysfunction in OCD
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The frontal cortex and striatum have consistently been proposed as possible sites of dysfunction in OCD, based on converging evidence including neuroimaging studies emphasizing abnormalities in neural loops connecting these areas. There is increasing evidence attributing OCD to lateralized CNS pathology, but research is inconsistent with respect to which hemisphere is preferentially involved, and in what manner. The present study employed the Posner spatial orientation paradigm, which has been used to study lateralization in psychiatric and neurological cases, in an attempt to examine patterns of lateralized dysfunction in OCD. Seventeen OCD patients were compared with ten healthy controls on reaction time and asymmetry measures derived from the paradigm. Comparisons were carried out after subdividing the patient group based on demographic and clinical data, to examine relationships between task performance and specific characteristics of OCD. Control subjects responded significantly faster to targets in the left visual field than to those in the right, while in OCD patients this asymmetry pattern was absent or reversed, in line with earlier suggestions regarding lateralized pathology in OCD. The lack of asymmetry was positively correlated with obsession severity, particularly for aggressive and sexual obsessional content, supporting recent findings relating different symptom dimensions to distinct components of fronto-striato-thalamic circuits involved in OCD. The altered pattern of asymmetry was not related to medications influencing the serotonergic system, suggesting that one or more chemical systems additionally implicated in OCD are more directly related to the lateralized deficits. The relevance of the dopaminergic system is discussed, based on the nature of its involvement in the modulation of attention.

The infralimbic prefrontal cortex is required for consolidation and reconsolidation of object recognition memory
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Consolidated memory could regain susceptibility to consolidation blockers upon its reactivation. This process of destabilization and the ensuing reactivation of reactivated long-term memory is termed reconsolidation. It has been shown that both consolidation and reconsolidation require protein synthesis, but it is not yet known how similar these processes are, in terms of molecular, cellular, and circuit mechanisms. Here we aimed to examine the role of infralimbic cortex (IL) in consolidation and reconsolidation of object recognition memory involving spontaneous exploratory behavior of the rat. We found that the protein synthesis inhibitor anisomycin and the N-methyl-D-aspartate (NMDA) receptor antagonist D-1,2-amino-5-phosphonooxonic acid (APV), infused in the IL immediately following the recognition training phase, resulted in failure to discriminate between the old and new object 24 hrs later. This indicates that the drug treatments have disrupted consolidation of the first task. In contrast anisomycin and APV infused in the IL immediately following reactivation of the memory trace by brief reexposure to the learned objects, resulted in failure to discriminate between the old and new object 48 hrs later. Thus, the drug treatments have disrupted reconsolidation of long-term recognition memory. The present findings show for the first time that the IL is necessary for long-term consolidation and reconsolidation of recognition memory, and that both processes are dependent on protein synthesis and NMDA receptor function.

PRS-211,375, a novel CB2 selective cannabinoid agonist, with neuroprotective effect in three animal model of MS
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Numerous studies report that cannabinoids have beneficial effect in the treatment of neurodegenerative diseases. Cannabinoids have two identified receptors, the CB1 receptor located in the central nervous system, and the CB2 receptor, expressed by immune cells. PRS-211,375, a synthetic CB2 selective cannabinoid receptor agonist developed by Pharmos, was tested for its effect in 3 EAE animal models for MS. The models were: (i) MOG induced acute EAE in rats; (ii) PLP induced remitting relapsing EAE in mice; (iii) MOG induced progressive EAE in mice. PRS-211,375 60 mg/kg administered PO after the clinical signs occurred (i.e. as treatment), reduced the clinical score induced by MBP by 1 point as compared to vehicle control (2.5±0.3 vs. 1.5±0.2, p=0.05). PLP resulted in 3 relapse-remitting episodes. Treatment with 60 mg/kg of PRS-211,375 after the first relapsing event postponed the initiation of the second relapsing event by 5 days and reduced the severity of its occurrence. Finally, PRS-211,375 treatment resulted in inhibition of MOG induced EAE progression in a dose dependent manner. Daily administration of 40 mg/kg and 60 mg/kg completely stopped the disease progression. Taken together, these data show that PRS-211,375 administered PO, as treatment was highly beneficial in controlling EAE progression in three animal models. This suggests highly therapeutic potential of PRS-211,375 in the treatment of MS patients.
Subthreshold cross-correlations between cortical neurons: A reference model with static synapses
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3Neurobiochemistry, Faculty of Life Sciences, Tel Aviv University; 4Dept. of Neurobiology & Ethology, Center for Brain & Behavior, University of Haifa, 31905;
We are interested in understanding the process of memory consolidation. For this purpose we use a taste learning model. Using the Conditioned Taste Aversion (CTA) paradigm and latent inhibition of CTA (LI), we learn about the properties of this labile phase. Using Latent Inhibition paradigm we find that an input of 10 or 15 ml of saccharin 0.1% creates LTU and reduces significantly the aversion level to saccharin (A volume of 15 ml causes a bigger reduction than a volume of 10 ml does). However, smaller volume of 5 ml of saccharin 0.1% does not create LTU.

Slow and sustained oscillations emerge in a network with dynamic synapses
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Emergent neocortical oscillations have been broadly studied experimentally and theoretically, for their ability to convey information. However, the mechanisms that induce sustained oscillations in neural microcircuits are still largely unknown. Using a firings rate model to represent interconnected excitatory and inhibitory populations with constant input neurons, we showed that activity dependent synapses give rise to slow and sustained oscillations in the network. We found that the dynamic mechanisms of the synapses determine the frequency and shape of the oscillations. Networks with slow (timescale of seconds) facilitating synapses generate population burst activity. When fast (hundreds of milliseconds) facilitating synapses are incorporated, the networks generate sinusoidal synchronized activity at higher frequency. These results suggest a novel role for facilitating synapses in shaping the oscillations in neocortical neural circuits.

Regional disturbances in axonal integrity are involved in first episode schizophrenia: Evidence based on high b-value diffusion weighted imaging
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Accumulating evidence points to disturbed neural connectivity in schizophrenia. One source of brain pathology in schizophrenia is the reduced axonal integrity. However the physiological significance of these findings is not clear. Recent works using high b-value diffusion imaging have shown that this method might be more reflective of white matter pathophysiology as it relates to intra-axonal water. Six first episode symptomatic paranoid schizophrenia patients and five healthy subjects underwent MRI scan with a high b value diffusion imaging protocol. Image histogram of the high b value images from the acquired brain volume revealed a decrease in the values corresponding to white matter, indicating loss of white matter integrity in the schizophrenic group. The three peaks, corresponding to white matter, gray matter and CSF, were extracted via spectral analysis, exhibiting a lower WM peak in the schizophrenic group (t=5.5, p<0.01). Region of interest blind analysis of both groups found that these white matter changes originated mainly from frontal and middle temporal areas. These results suggest that white matter damage measured by high b value DWI is a pathological brain marker in schizophrenia that can be linked to the individual patient level. Brain atrophy has been shown in previous studies in frontal and temporal regions. We show, however, that white matter damage is more evident in frontal areas. This finding suggests disturbed connectivity of fiber bundles reaching the PPC, presumably involved in early stage brain abnormalities in schizophrenia.

What does it take to make a stable taste memory?
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1Dept. of Neurobiology & Ethology, Center for Brain & Behavior, University of Haifa, 31905;
We are interested in understanding the process of memory consolidation. For this purpose we use a taste learning model. Using the Conditioned Taste Aversion (CTA) paradigm and latent inhibition of CTA (LI), we learn about the properties of this labile phase. Using Latent Inhibition paradigm we find that an input of 10 or 15 ml of saccharin 0.1% creates LTU and reduces significantly the aversion level to saccharin (A volume of 15 ml causes a bigger reduction than a volume of 10 ml does). However, smaller volume of 5 ml of saccharin 0.1% does not create LTU.

A new platform to study the molecular mechanisms of exocytosis
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The exocytotic process in neurons and neuroendocrine cells consists of a sequence of reactions between well-defined proteins. In the present study, we have, for the first time created, a comprehensive kinetic model that describes the physiological process using a standard chemical kinetic formalism. The interactions between the synaptic proteins were transformed into differential rate equations that, upon their integration over time, reconstructed the experimental signal. The model can perfectly reconstruct the kinetics of exocytosis, the calcium-dependency of priming and fusion processes and the effects of genetic manipulation of synaptic proteins. The model suggests that fusion occurs from two parallel pathways and assigns precise, non-identical synaptic protein complexes. In addition, it provides a unique opportunity to study the dynamics of intermediate protein complexes during the fusion process, a possibility that is hidden in most experimental systems. We have used the Genetic Algorithm analysis to achieve high level of accuracy and to find a single global minimum, over a multi dimensional parameter space. Our study demonstrates that complex biological processes can be mathematically modeled and gain high predictive power, up to the level of serving as research tools. It is our intention to expand the model from the level of a comprehensive description of the whole exocytotic process, to the level of cell physiology.

In vivo two-photon imaging of newborn neurons in the adult mouse olfactory bulb
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As a consequence of adult neurogenesis the olfactory bulb (OB) receives a continuous influx of newborn neurons well into adulthood. Although general features of neurogenesis have been described, how newborn neurons integrate into adult circuits, their rates of generation and elimination, and the factors controlling their survival remain enigmatic. To visualize the dynamics of adult neurogenesis, we developed a strategy combining genetic manipulations and in vivo imaging that enabled us to image the development of newborn neurons into the adult OB. We produced a line of
transgenic mice expressing green fluorescent proteins (GFP) driven by the Thy-1 promoter. This new line expresses GFP in a subset (77%) of periglomerular neurons (PGNs). These GFP-labeled PGNs comprise a range of phenotypes including GABA, dopamine, calbindin and calretinin. GFP expression levels are relatively weak but individual cell bodies can be readily imaged using in vivo two-photon microscopy. Time-lapse analysis of PGN cell bodies (n=150, 3 mice) over several weeks reveals a detectable but low, neuronal turnover rate of ~2% per/month. While new neurons appeared and older ones disappeared, the number of PGNs remained constant. This approach provides the first dynamic view of the actual appearance and disappearance of neurons in the mammalian central nervous system.

On The Significance of In Vivo Observed Patterns in Membrane Potential Dynamics During Spontaneous Activity of Cortical Neurons.

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Several studies report existence of recurrent patterns in cortical activity. It has been suggested, that information is propagated by precisely timed sequences of synchrony activity (Ables et al. 1993). But there is a controversy regarding the stochastic nature of these events (Gram et al. 1999). A recent in vivo study reports existence of repeating motifs (10-20 min) cortical intra-cellular, recorded spontaneous activity (Ikegaya et al. 2003). Following up Ikegaya et al., and using the same similarity index (SH), we further analyze the nature of observed repeating motifs during spontaneous activity of single neurons in rat barrel cortex. These preliminary results are based on several patch-clamp intracellular, high resolution recordings of neurons in a lightly anesthetized rat. All recorded traces showed to have repeating patterns to different extents. Using a Bayesian formulation, we quantified the degree to which patterns are found in a recorded data. Our analysis shows that the probability of finding a pattern is much affected by slow changes in membrane potential dynamics. To test this further, we produced a surrogate data, with the same power spectrum as recorded data but phases of frequency components being random. This procedure has its own limitation since original data contained spikes which introduced high frequency components. As we expected, surrogate data contained a significant portion of repeating motifs, but less than observed in original data. These findings indicate that power spectrum of neuron’s electrical activity, and especially low components of the power spectrum, can account for a significant portion of the above chance level SI scores observed in spontaneous activity. However, further investigation is required for better understanding the nature of these patterns during spontaneous activity of cortical neurons, and their relation to power spectrum and spiking behaviour.

In-vivo study of coupled neural/synaptic dynamics in an autonomously learning neural network

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We study the behavior of a spike-driven long-term plastic synaptic model embedded into a recurrent network of spiking neurons. The resulting coupled neural/synaptic dynamics enables the network to dynamically store and recall a set of randomly coded stimuli, following training, in which the learned stimulus is repeatedly presented in random order (stimulus-delay) (Mongillo, Curti, Romani, Amit 2004). The patterns of neural activity exhibited by the network before and after training reproduce most of the details physiologically observed in-vivo (Shadlen & Newsome 1998, Erickson & Desimone 1999). The synapse is characterized by an internal, bounded analog variable with time constant ~10ms. The dynamics of this variable is driven by presynaptic spikes and coincident postsynaptic depolarization levels. Long-term stability is ensured by a refresh mechanism, that captures the time courses of the postsynaptic potentials (PSP) and triggers the biological problem of similar experimental in-vitro protocols of long-term plasticity. A network of spiking neurons with these synapses displays in vivo-like patterns of neural activity. The plastic synapse behaves so that: 1. In absence of external, relevant stimulation, the acquired synaptic structure persists over very long time scales. Upon stimulation, it produces long-term plasticity, on short time scales (~100ms), within the activated synaptic populations; high pre- and post-synaptic emission rates produce LTD, high pre- and low post-synaptic rates produce LTP. It endows the network with a stable, Hebbian learning process. We study the dependency of the long-term plasticity dynamics on the characteristics of the stimulus response (average emission rates, time course, synchronization), and on the statistics of firing times (CV).

Supported by Grant

Precise fidelity of human auditory cortex neurons during cinematic stimulation

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Cortical neuronal activity is highly variable even under tightly controlled stimulation paradigms. Previous studies in the monkey have found the level of this variability to be on the same order of magnitude as the response itself. Therefore in order to reach sufficient signal-to-noise ratio numerous repetitions of the same stimulus are needed. Hence, it may be inferred, that during complex and continuous natural stimulation this variability may even be accentuated. Here we report that surprisingly, single neuron responses recorded in the human temporal lobe during exposure to a popular movie, manifested a highly reproducible stimulus-locked modulation, with average correlations above 0.5. This reproducibility was apparent even when only two repetition of the movie were compared. This high fidelity was particularly striking in human auditory cortex where the correlation between first and second movie presentation reached as high as 0.8. Although it may appear that such high fidelity implies highly linear relationship to the acoustic stimuli, in fact the neuronal responses appeared highly non-linear showing particular selectivity for spoken words and musical phrases. Interestingly, the high fidelity of the neural responses was expressed only at temporal windows of 300 ms and higher. These results reveal precise reproducibility of single neuron responses across repeated presentations of the stimulus, but also suggest a limit of "temporal graininess" of the neural code expressed by human temporal lobe neurons.

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Development of dendritic spines in the rodent anterior cingulate cortex is modulated by prenatal stress

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Studies in rodents and non-human primates demonstrate that maternal stress during pregnancy dramatically influences fetal brain development, resulting in behavioral and endocrine abnormalities. In humans, prenatal stress is believed to be a risk factor for developmental psychopathologies, such as schizophrenia and depression. Studies in prenatally stressed animals, and in patients subjected to acute stressor, indicate that emotional reactivity, anxiety, depressive-like behavior and deficits in cognition, learning and memory, however, very little is known about the effects of stress on synaptic development in the limbic system. Based on previous behavioral studies (Weinstock, Stress 5: 167-176, 2002), our objective was to investigate the effects of...
gestational stress on the development of synaptic networks in the prefrontal cortex of rats and to clarify if the presumed synaptic density can be preserved by postnatal treatments such as daily handling of the offspring during the first 10 postnatal days. By using the Golgi-Cox staining technique we quantified the density of spine synapses and dendritic length of pyramidal neurons in the anterior cingulate cortex (ACg) in male pups of the following experimental groups: i) prenatal-stressed (PS), ii) PS + postnatal handling, iii) naive controls, iv) naive controls + postnatal handling. Our data indicates changes in the density of dendritic spines on basal dendrites and alterations in the length of apical dendrites between PS pups and PS pups, which were handled. Alterations in the length of basal dendrites were found in PS rats, compared to naive controls. The results of this study provided the first evidence that prenatal stress and handling interferes with the development of cortical dendritic spine and dendritic growth. These findings might be causally linked to the behavioral abnormalities, which have been described after prenatal stress and handling.

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Are protein alterations in schizophrenia due to early environmental insult?

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Both genetic inheritance and perinatal environmental insult contribute to schizophrenia manifestation. Recent studies of the etiology of schizophrenia concentrate on the genetics of aberrant brain proteins or on epidemiological retrospective studies of environmental insults. Little is known concerning the biological and physiological processes, such as morphological changes, neural transmission and signal transduction, that mediate the environmental contribution. The neurodevelopmental hypothesis of schizophrenia suggests that an early life brain maldevelopment, predisposed and/or acquired, manifests the pathophysiology of schizophrenia later in life. Possible non-genetic risk factors for schizophrenia include maternal infection, starvation/malnutrition, stress, premature birth and perinatal hypoxia. A strategy to study the contribution of perinatal insults to schizophrenia is by induction of a risk factor in an animal model. We chose to address the search for etiological factors of schizophrenia by combining the two distinct approaches that dominate the literature, namely, the role of genetically aberrant brain proteins and perinatal insult. We are focusing on four distinct rat models for schizophrenia and mouse neuronal levels of six proteins that were found to be altered in empiric studies of postmortem brain from schizophrenic patients. We hypothesize that the alterations in the levels of some of these proteins may reflect the contribution of etiological insult to schizophrenia rather than genetic factors of the disorder.

Cholinergic modulation of inflammatory and autoimmune responses

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Various immune cells possess muscarinic and nicotinic cholinergic receptors as well as acetylcholinesterase (AChE). Down-regulation of proinflammatory cytokine production by activation of [F]AR1, SA1, and pivot E1.4,5 PSB1-140.6-9). These observations prompted us to examine the effect of cholinergic up-regulation (CURE) on CNS inflammation using various AChE inhibitors. CURE induced by EN101 (anti-sense of AChE mRNA) ameliorated clinical and pathological symptoms of experimental autoimmune encephalomyelitis (EAE) in mice. Clinical improvement was accompanied by decreased ex-vivo reactivity of encephalitogenic T cells. Similarly, EN101 decreased human T-cell reactivity toward mitogens and TNF-E production was unaffected. We have examined the efficacy of bifunctional compounds containing nonsteroidal anti-inflammatory drug (NSAID) and CURE moiety (pyridostigmine, AChE inhibitor), in EAE model in mice and obtained a significant reduction in clinical symptoms and T-lymphocytes reactivity. The bifunctional compounds IBU-PO and IBU-PD (Ibuprofen-Octyl or Deyl) Pyridostigmine) were tested in vitro in lymphocytes and astrocytes and inhibited dose-dependently micromolar levels production of inflammatory mediators (nitric oxide and prostaglandin E2). The contribution of each component of the bifunctional compound to the attenuation of inflammation was evaluated. It was noted that both moieties could suppress lymphocyte reactivity to a lesser extent than the bifunctional compound. Thus, the individual NSAID and AChE inhibitor activity was not additive. Similarly, EN101 decreased human T-cell reactivity to a lesser extent than the bifunctional compound. Thus, bifunctional compounds appear to act synergistically at their components. Inflammatory mediators production was not affected by AChE inhibitors alone yet bifunctional compounds augmented the anti-inflammatory effect of the NSAID moiety. Our data are consistent with anti-inflammatory activity elicited by the ChE moiety only when it resides in the bifunctional molecule.

Features of Human Movement Imitation

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Human movement imitation is a complicated phenomena, involving a transformation from perceived to executed movements. What are the features of movement that are being extracted and used in this transformation? We developed a novel experimental scheme to tackle this question using virtual movements. Two setups were developed along this scheme for arm and finger movement imitation. Using these setups, we investigated the hypothesis that observed movements are automatically mapped to the corresponding motor representation (the ‘direct matching’ hypothesis). We rejected the ‘direct matching’ hypothesis by manipulating the orientation of observed movements, using several forced-choice tasks. In these tasks subjects had to perform one of two movements (for example lifting the index or the middle finger), as
Medical School, Jerusalem 91120, Israel; Ion channels were originally defined according to their virtual hand. We found an orientation effect (longer hypothesized that subjects extract simple, task-related hand). Based on these results, we concluded that in forced-choice imitation tasks, subjects do not map observed movement into their own movement repertoire. We hypothesized that subjects extract simple, task-related features of the movement, for example, the appearance of the movement on the left or the right side, in order to choose the appropriate response. By introducing another task, where subjects had to lift either their left or right arms in response to movements of a rotated human figure, we managed to directly contrast the two accounts for the two main possibilities of receiving movement in forced-choice imitation tasks, and to provide support for our task-related features account. Our results question the validity of using forced-choice tasks in behavioral (Brass et al., 2000) and MRl (Iacoboni et al., 1999; Kossi et al., 2003) studies of imitation.

Are voltage-gated calcium channels volume-regulated ion channels? Nussinovitch L., Ben-Tabou De-Leon S., Blotnick E., Ben-Zeev G. Dept. of Anatomy and Cell Biology, Hebrew University Medical School, Jerusalem 91120, Israel;

Ion channels were originally defined according to their main mode of gating as: voltage-gated, ligand-gated, mechano-gated and volume-regulated ion channels. However, studies from recent years have demonstrated that ion channels may be gated, or regulated, by more than one modality. For example, it is well established that the activity of voltage-gated calcium channels can be regulated by a variety of ligands (neurotransmitters, G-proteins, protein kinases etc.). In addition, recent studies have pointed to the possibility that voltage-gated calcium channels are volume-regulated. We examined the possibility that voltage-gated calcium influx may be regulated by alterations in cell volume. Our studies have shown that voltage-gated calcium influx in pituitary cells is suppressed by osmotic induced cell shrinkage, and augmented by osmotic induced cell swelling. In a series of control experiments we ruled out the possibility that this regulation of calcium influx, by cell-volume, can be attributed to alterations in cell membrane surface area (during cell shrinkage and swelling), to activation or inactivation of other ionic conductances or to changes in access resistance. Additional experiments have shown that this volume independent regulation of voltage-gated calcium channel activity stems from alterations in the activity (Npo) of calcium channels but not from changes in single channel conductance. However, whether these changes in activity stem from changes in open probability (Po), or from changes in the number of channels activated (N), is still unknown. Hence, our results suggest that voltage-gated calcium channels in pituitary cells may also be considered as volume-regulated ion channels. The cellular mechanisms underlying this regulation are unknown yet. However, it is possible that alterations in membrane mechanical tension, or alterations in intracellular ionic strength, are involved in this regulation.

Tracing the affective modulation of cognitive brain activity with electrophysiological functional brain imaging
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Endocannabinoid Signaling Regulates Bone Mass. Olef O., Karask M., Fogel M., Wright K., Tam Y., Gabot Y., Birkenboim R., Attar-Namdar M., Shohami E., Mechoulam R., Zimmer A. and Bab I. Bone Laboratory, The Hebrew University of Jerusalem, Jerusalem, Israel; Dept. of Pharmacology, The Hebrew University of Jerusalem, Jerusalem, Israel; Dept. of Medical Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel; Dept. of Psychiatry, University of Bonn, Germany; University of Bath, UK;

Endocannabinoids signal via G-protein coupled central CB1 and peripheral CB2 cannabinoid receptors. Although both receptors were discovered more than a decade ago, the physiologic function of the CB2 receptor remains obscure. Here we report the presence of CB2 receptors in trabecular, diaphyseal and MC3T3 E1 osteoblasts as well as osteoclasts. Reminiscent of post-menopausal osteoporosis in humans, the skeletal phenotype of CB2 deficient mice, which are otherwise normal, is characterized by a low trabecular bone mass, cortical expansion and increases in bone formation rate and osteoclast number. To extrapolate these findings to the human scenario, we performed genetic association studies in a case-control approach typing single nucleotide polymorphisms covering a region of about 100 kb. We found a highly significant difference of allelic and genotypic distributions, strongly arguing for a causative involvement of this locus with human osteoporosis. In line with the low trabecular bone mass phenotype of CB2 knock-out mice we found that HU-308, a specific CB2 agonist, stimulated dose dependently the number and activity of primary and MC3T3 E1 osteoclasts. In the same dose range, HU-308 also restrained osteoclast differentiation of bone marrow derived monocytes. Most importantly, HU-308 attenuated osteoclast-induced bone loss mainly by inhibiting osteoclast number. Collectively these results assign a skeletal regulatory role for the endocannabinoid system and offer a new molecular target for the diagnosis and treatment of osteoporosis.

The metabolic glutamate G-protein-coupled receptor mGluR3 is voltage sensitive. Ohana L., Parnas I., Parnas H. The Otto Loewi Minerva Center for Cellular and Molecular Neurobiology, Hebrew University, Jerusalem, Israel;

G-Protein Coupled Receptors (GPCRs) comprise the largest superfamily of proteins in mammals and play a key role in signal transduction processes. In spite of GPCRs being transmembrane proteins they are not considered to be voltage sensitive. Recently it was shown that the muscarinic M2 receptor is voltage sensitive. Here we examine whether a metabolic glutamate receptor, a GPCR, exhibits voltage sensitivity. Using fresh rat brain synaptosomes we show that presynaptic glutamate receptors bind glutamate in a voltage dependent manner. Namely, Depolarization reduces the maximal binding of at different times between the cue and the target in one third of the trials, were first names. Distractors' subjective affective value was inferred from the responses to a validated questionnaire designed for that purpose. Evoked potentials to the targets were averaged according to the preceding cue's validity and the affective valence of the distractor. Potentials were averaged across different onset times of distractors, so that brain activity was locked in time to the targets but not to the distractors. Brain sources of scalp electrical activity were estimated as time-fourse, for the 800 ms after target onset, using LORETA. Statistical comparisons were conducted in order to assess the effect of the distractors' affective valence on brain activity to the following target tones. Results: Brain response to targets was enhanced following distractors with subjective affective valence, compared to neutral distractors. The distinct activity pattern involved prefrontal cortex, secondary auditory cortex and limbic system association areas, depending on the subjective emotional significance of the preceding distractors. Summary: Processing of neutral tones was modulated by the subjective emotional significance of preceding distractors. Exact time course of the associated unique brain activity was characterized.

The metabotropic glutamate G-protein-coupled receptor mGluR3 is voltage sensitive. Ohana L., Parnas I., Parnas H. The Otto Loewi Minerva Center for Cellular and Molecular Neurobiology, Hebrew University, Jerusalem, Israel;
[3H]Glu. Pretreatment of the synaptosomes with Pertussis Toxin (PTX) reduced the [3H]Glu binding altogether and greatly diminished its voltage dependency, indicating that the voltage dependent binding could be attributed to PTX sensitive metabotropic glutamate receptors. We used the heterologous expression system of Xenopus oocytes to directly study the properties of mGluR3, a presynaptic receptor, and a member of the mGluRs of group II. mGluR3-mediated potassium channel currents were used to assay the activity of the receptor. We found that the apparent affinity of mGluR3 toward glutamate was reduced upon depolarization. We ruled out the possibility that the voltage sensitivity resides in steps that are downstream to the activation of the mGluR3 by glutamate. Our cumulative results are compatible with the notion that the mGluR3 exhibits, by itself, voltage sensitivity. In addition, the fraction of the low-affinity receptors was significantly reduced in oocytes that did not overexpress Galp-pha. This, together with the abolishment of the voltage dependent binding in synaptosomes, in the presence of PTX indicates that the voltage sensitivity may reside in the region that couples to the G-protein. Furthermore, analysis of the time course of the mGluR3-mediated K+ currents revealed that depolarization affects the Koff of the receptor.

**Representation of magnitude in parietal cortex from a tactile to a number and back**

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Numbers are represented in symbolic (Arabic & verbal) and analog magnitude format. Reflecting these formats, different, partially overlapping, representations are found in parietal cortex (PC; Dehaene et al., 2003). How are continuous quantities, such as size and luminance, encoded in the brain? It has been hypothesized that a single system in PC represents both the above-mentioned non-symbolic analog numbers and an abstract code of continuous quantities. This system is seen as a high-level magnitude estimator that produces the abstract value of a scaled magnitude and makes this value available for the cognitive or executive system. We tested a first prediction of this hypothesis: that the thalamic region should respond significantly reduced in oocytes that did not overexpress Galp-pha. This, together with the abolishment of the voltage dependent binding in synaptosomes, in the presence of PTX indicates that the voltage sensitivity may reside in the region that couples to the G-protein. Furthermore, analysis of the time course of the mGluR3-mediated K+ currents revealed that depolarization affects the Koff of the receptor.

**Brain activation of dominant vs non dominant hand areas during linguistic activity - an fMRI study**

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In this study we wish to investigate the connection between language functions and the motor system by comparing the dominant and non-dominant hand areas during linguistic activity. We present here preliminary results from seven right-handed native Hebrew speakers that were scanned in a 1.5 Tesla scanner on two separate days. The first experiment was comprised of motor and linguistic tasks within a block designed experiment. Motor tasks included simple movements of right and left hands for all subjects and simple movements of right and left feet for three of the subjects. The linguistic task comprised of a covert association generation to a given noun. We used the neuronal activity during movement periods to delineate the primary motor areas of the hands and feet and then examined the relative neuronal activity (BOLD signal change) in these regions during the free association task. Across subjects, the right hand area showed a significantly increased signal than the left hand, and this difference was not significant for the right and left feet. In the second experiment the same subjects were asked to listen to a story in order to detect the neural activity in the motor areas and the time course in bocca’s area throughout the story. The results showed that the right hand area was significantly more correlated with the neural activity in bocca’s area (i.e. the left hand area, but no such difference was observed for the feet areas. These results suggest that the neuronal mechanisms involved in the language function are different than those involved in the motor function. We used the neuronal activity during movement periods to delineate the primary motor areas of the hands and feet and then examined the relative neuronal activity (BOLD signal change) in these regions during the free association task. Across subjects, the right hand area showed a significantly increased signal than the left hand, and this difference was not significant for the right and left feet. In the second experiment the same subjects were asked to listen to a story in order to detect the neural activity in the motor areas and the time course in bocca’s area throughout the story. The results showed that the right hand area was significantly more correlated with the neural activity in bocca’s area (i.e. the left hand area, but no such difference was observed for the feet areas. These results suggest that the neuronal mechanisms involved in the language function are different than those involved in the motor function.

**Endocannabinoid 2-AG Exerts Neuroprotection Through NF-kB Inhibition and Downregulation of Proinflammatory Cytokines**

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We reported that closed head injury (CHI) in mice causes a sharp elevation of brain 2-arachidonoylglycerol (2-AG) levels, and that exogenous 2-AG reduces brain edema, infarct volume and hippocampal death and improved clinical recovery after CHI. 2-AG robustly reduced CHI-induced disruption of the blood brain barrier (BBB) and abolished BBB disruption after CHI. 2-AG transactivation, at 24h after CHI. Proinflammatory cytokines such as TNF-a, IL-1b and IL-6 are known as NF-kB inducers. We have observed that early 2-AG transactivation at 24h after CHI. Proinflammatory cytokines such as TNF-a, IL-1b and IL-6 are known as NF-kB inducers. We have observed that early 2-AG transactivation at 24h after CHI. Proinflammatory cytokines such as TNF-a, IL-1b and IL-6 are known as NF-kB inducers. We have observed that early 2-AG transactivation at 24h after CHI. Proinflammatory cytokines such as TNF-a, IL-1b and IL-6 are known as NF-kB inducers. We have observed that early 2-AG transactivation at 24h after CHI. Proinflammatory cytokines such as TNF-a, IL-1b and IL-6 are known as NF-kB inducers. We have observed that early 2-AG transactivation at 24h after CHI. Proinflammatory cytokines such as TNF-a, IL-1b and IL-6 are known as NF-kB inducers.
performed. We checked proinflammatory cytokines profile at 2 and 4 h after CHI using RT-PCR. b-actin served as house-keeping gene and cytokines expression was evaluated against b-actin. TNF-a was undetected in untreated animals and CHI caused to massive release which was partly inhibited by 2-AG treatment at 2 h but not at 4 h:timepoint: 113.43 vs. 84.15. IL-1b level at 2 and 4 h was the same and 2-AG caused to decrease of IL-1b at 4 h: 124.22 vs. 103.52. IL-6 level at 4 h was higher than at 2 h and 2-AG treatment led to decrease in IL-6 level at 4 h: 94.01 vs. 67.06. Conclusions: TNF-a, IL-1b and IL-6 levels increase short time after brain injury in mice and thus subsequently lead to BBB disruption and NF-kB transactivation. All these detrimental effects inhibited by endogenous cannabinoid 2-AG.

Is visual extinction a natural consequence of spatial neglect? Evidence from contrast detection experiments

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Cases in which unilateral spatial neglect (USN) patient is able to detect the stimulus on the neglected side when presented unilaterally, but fails in the case of bilateral stimulation. This extinction effect is very common in USN patients, and has a large impact on their everyday life, but its relation to the main neglect syndrome is poorly understood. Here we asked whether the extinction effect is a specific property of the USN syndrome, or alternatively it is due to the low saliency of the stimulus presented on the left, making the extinction effect a natural consequence of neglect. Three brain-damaged patients with USN and 4 normal controls were given a Dartch task presented on a computer display with different eccentricities. Following a contrast calibration stage where we measured the detection threshold at each side, we set the stimulus on one side at its contrast detection threshold, and used multiples of that threshold on the other side. We then tested performance on a stimulus detection task with interleaved trials of unilateral and bilateral simultaneous stimulation (BSS). Both USN patients and controls showed extinction during BSS, i.e. made more errors in detecting the weak stimulus when one side was set at contrast threshold level, thus compensating for possible attenuation due to USN. However the patients and controls differed in their sensitivity to the contrast level of the extinguished stimulus. While a 1.5-fold increment eliminated extinction for the controls, a 2.5-fold increment was needed to release a stimulus from extinction in the USN patients. We conclude that the extinction effect in contrast extinction is, in part, a natural consequence of the low saliency of the stimulus on the neglected side, but is more severe for the patients, suggesting an additional extinction-specific defect. This extinction-specific effect could be a robust measure and used for clinical diagnosis.

Binding of the Drosophila Gliotactin Intracellular Part

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The Drosophila protein gliotactin (Gli) is a single-pass transmembrane cholinesterase-like adhesion molecule (CLAM), which is necessary for gial ensheathment of axons in the peripheral nervous system and for the formation of the gial-based blood nerve barrier. In gial cells Gli co-localizes with the proteins Coracle and Discs Large (Dlg) at the septate junction. The extracellular aminoterminal part of the protein is 24% identical to Drosophila acetycholinesterase, but lacks the acetylcholine binding domain. The cytoplasmic part of the catalytic triad (like other CLAMs). The intracellular domain of Gli (Gli-cyt) bears no sequence homology to any known protein. Theelucidation of the crystal structure of Gli-cyt shows that Gli-cyt is natively unfolded when expressed in E. coli. The four C-terminal amino acids of Gli constitute a type-I PDZ domain-binding motif. Dlg belongs to the membrane-associated guanylate-kinase (MAGUK) protein family and contains three type-I PDZ domains, which are protein-protein interaction modules. We postulate that Gli-cyt binds to Dlg, through one of the latter's PDZ domains and that this interaction may result in induced folding of Gli-cyt. Chromatographic and spectroscopic methods are being used to study the Gli-cyt Dlg interaction.

Plasticity and complexity: A neuroscience model for psychiatry

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Achievements in biological psychiatry reflect the consensus that psychiatric mental disorders are brain disorders. However, we do not have brain-related psychiatric diagnosis. Without understanding the specific causes for mental disorders, their diagnosis is descriptive and subjective, thus unreliable and deceptive. A model is proposed for a neuroscience-oriented definition of mental disorders. Plasticity refers to all brain processes involved in dynamic alterations within communicating neuronal ensembles or networks, in the brain. Complexity refers to certain formulations from system theories relevant to brain dynamics. Plasticity processes are subcategorized into three types based on time domains; 1) developmental plasticity, 2) 'tuning plasticity' and 3) 'fast stabilizing plasticity.' Each type of plasticity is related to different complexity models achieved by the brain. Mental disorders can be conceptualized as disorders of plasticity resulting in disturbances of state-space brain configurations, matching and neural complexities. The new neuroscience-oriented diagnostic system generates testable predictions regarding diagnosis and treatments of mental disorders, which may be the future science for psychiatry.

Synthesis and openner properties of novel derivatives of N-phenylanthranilic acid on recombinant KCNQ2/Q3 potassium channels and activity on cortical neurons

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The voltage-dependent M-type potassium current (M current) plays a major role in controlling brain excitability by stabilizing the membrane potential and acting as a brake for neuronal firing. The KCNQ2/Q3 heteromeric channel complex was identified as the molecular correlate of the M current. Furthermore, the KCNQ2 and KCNQ3 channel subunits are mutated in families with benign familial neonatal convulsions, a neonatal form of epilepsy. The KCNQ2/Q3 potassium currents may provide an important target for anti-epileptic drug development. In this study, we synthesized novel KCNQ2/Q3 channel openers, derivatives of N-phenylanthranilic acid, using meclofenamic acid and diclofenac as primary templates. External application of these molecules in the micromolar range results in activation of KCNQ2/Q3 K+ currents, heterologously expressed in Chinese hamster ovary (CHO) cells. These openers activate KCNQ2/Q3 channels by causing a leftward shift of the voltage activation curve and by markedly slowing the deactivation kinetics. SAR studies revealed that the pharmacophore of the newly synthesized N-phenylanthranilic acid series includes esters or secondary amides derivatives with a terminal hydroxy group. Thus, the novel molecules are related to the latter's PDZ domains and that this is associated to the physiological relevant potentials and lead to a hyperpolarization of the resting membrane potential. In rat cortical neurons, they inhibit both evoked and spontaneous spiking activity. These derivatives of N-phenylanthranilic acid constitute novel drug templates for the treatment of neuronal hyperexcitability, including epilepsy, ischemic stroke, migraine, and neuropathic pain.
The role of LPA1 in formation of synapses among cultured hippocampal neurons

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We studied the lysophosphatidic acid receptor-I (LPA1R) gene, found to be expressed endogenously in cultured hippocampal neurons. Overexpressed GFP-tagged, membrane-associated LPA1R accumulated in a punctate manner over the entire dendrite tree and caused an increase in dense spine density. About half of the spines in the transfected neurons displayed distinct LPA1R puncta, and this subset of spines was also substantially larger than puncta-free, LPA1R transfected or control GFP spines. Exposure of LPA1R transfected cells to LPA caused a rapid (<15 min) aggregation of receptors into endocytotic puncta, which were highly unstable, along the dendritic cytoplasm. Finally, while spontaneous miniature synaptic currents were of the same amplitudes, they decayed slower in LPA1 transfected neurons compared to GFP controls. We propose that LPA1R can regulate local morphological plasticity of dendritic spines in cultured hippocampal neurons.

Toward the isolation and characterization of the VIP receptor that mediates neuronal survival

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Vasoactive intestinal peptide (VIP) provides neuroprotection through binding to high affinity receptors on glial cells that activate increases in the production and release of survival promoting factors. Additional experiments have been carried out with use of VIP-derived peptides and analogues. The present findings support the hypothesis that VIP2 may be involved in the neuroprotective effects attributed to VIP.

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Temporal properties of collinear facilitation

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Visual masking refers to impaired performance on a target stimulus when a mask stimulus is presented for a brief presentation time, either prior to, during or after the target presentation. However, the threshold for contrast detection improves when a target is presented with two collinear flanks (Polt & Sagi 1993). Facilitation is found when the target is presented simultaneously with the flankers or with a delay (Tanaka & Sagi 1998). Here we test the temporal properties of lateral facilitation by manipulating asymmetry of both onsets and offsets of the target and flankers. In the experiments, the contrast threshold for a Gabor target was measured in isolation or in the presence of two collinear Gabor masks using a 2AF staircase method. Experiments were carried out where the mask (60 ms) was presented before (Forward Masking: FM, isi=60 ms), simultaneously (SM) or after the target (Backward Masking: BM, isi=60 ms). The results showed target facilitation, 0.15-0.30 log units, (1) for simultaneous masking at 60 ms and at 300 ms, (2) when the mask preceded the target (FM), but (3) not when the target preceded the mask (BM), where some suppression at 3 lambda was observed. Additional experiments showed that a second pair of masks presented after SM (isi=60) cancels the SM facilitation. This pattern of results implicates a long integration time for lateral excitatory effects. The results point to the existence of a neuronal network with slow excitatory processes that are activated by low contrast inputs (target) and first masking but not those that are activated by high contrast inputs (flankers). Presentation of the masks after the offset of the target reinforces the inhibitory effects.

Generation of peripheral sensory-like neurons generated from human embryonic stem cells

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Human embryonic stem cells (hESC) are pluripotent cell lines that hold out great promise for drug development, study of early human development and transplantation therapy. A number of recent studies have shown that mouse ES, human ES can be coaxed to produce cultures enriched in neurons/neural precursors. Multiple culture techniques have been used for eliciting neurogenesis from hESCs and several CNS cell types with potential clinical importance have been produced including dopaminergic and cortical nerve cells. Three VIP binding sites that belong to a subfamily of 7-transmembrane-spanning G protein coupled receptors have been cloned: VIP, VPAC1, VPAC2. VIP, recognizing VIP, impinges on a neuronal network with slow excitatory processes that reactivate low contrast inputs and fast inhibitory processes. The PACeDNA was PCR-cloned from rat cerebral astrocytes and genetically manipulated to examine the affinity of the cloned HOP2 receptor to VIP and its variants. The expression of the cloned HOP2 recombinant receptor in COS-7 cell lines was found to bind HOP2 as well. These results reinforce the hypothesis that HOP2 may be involved in the neuroprotective effects attributed to VIP.

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whether the odor was presented from the left or right side. Four odorants were used: rose (PEA), cloves (eugenol), banana (amyl acetate) and vinegar (proprionic acid). Odors were generated by an air-dilution olfactometer and were also able to perform the localization task for three of the odors used: rose (PEA), accuracy: 64.6 +/- 4.7%, p-value < .0001, t-value = 18.47, eugenol, accuracy: 46.4 +/- 4.7%, p-value < .0001, t-value = 8.43, amyl acetate, accuracy: 62.3 +/- 3.8%, p-value < .0001, t-value = 14.92, and PEA accuracy: 59.9 +/- 5.9%, p-value < .0001, t-value = 5.94). As a group, the subjects face also showed a significant increase in the surface area of the four odors used: proprionic acid accuracy: 86.4 +/- 3.7%, p-value < .0001, t-value = 9.864, amyl acetate accuracy: 63.6 +/- 5.7%, p-value < .005, t-value = 3.38, PEA accuracy: 63.5 +/- 4.0%, p-value < .005, t-value = 3.41, and eugenol accuracy: 57.3 +/- 5.2%, p-value = .18, t-value = 1.40). Contrast maps computed for the two comparisons show task-specific activations within previously identified 'what' and 'where' processing streams, namely in frontal and parietal structures.

Morphing Memories through Continuous Associations

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Storage of concurrent information into human memory captures the context in which it is acquired and the association it has with stored memories. However, it is not clear how the existing memories are affected, if at all, due to exposure to contextually related stimuli. To study this, we designed a psychophysical training procedure on human subjects that captures these association effects on memory of faces. Subjects were trained to recognize a set of faces. After the memories of the faces were confirmed by an identity task, the subjects were asked to recognize initially distinguishable face (morph sequence). For each subject, this task was repeated in multiple daily sessions on the same pair of faces. This protocol led to a gradual change in identification of the morph sequence by more than half of the subjects, eventually resulting in wrongly remembering the two pair faces as the same one and an increase in their perceived similarity. A critical parameter for this effect to take place was the extent to which the subject initially distinguished between the pair faces (faces that seemed very different initially, stayed distinguishable; faces that were perceived as different but more similar, eventually were remembered as one). A similar procedure, with the exception that at every session the morph sequence was presented in a random order did not yield any significant change in identification, recognition or similarity of the two pair faces. These results show that long-term memory of perceptual objects can be dramatically modified, up to the point where two different objects are remembered as one. We show an attractor-based neural network model of associative memory that supports this experimental result.

Neurofilament-light increases cell surface expression of the N-methyl-d-aspartate receptor and prevents its ubiquitination

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The N-methyl-d-aspartate subtype of glutamate receptors (NMDARs) are among the selectively enriched, core components of the dendritic spine post synaptic densities (PDS). The mechanisms of NMDAR targeting, clustering and anchoring in neuronal synapses are poorly understood but presumably involve their cytoskeletal skeleton. The neuronal intermediate filament protein, neurofilament-light (NF-L), also a component of the PDS, is among the cytoskeletal elements known to bind to the cytoskeletal carbonyl-terminal tail of the NMDAR subunit, NR1. In this study, we examined the role of NF-L in the regulation of NMDAR expression and function in a heterologous system. NMDAR subunits did not reach the cell surface when expressed singly in HEK293 cells, but were readily detected when co-expressed, measured by surface biotinylation, cell ELISAs and confocal microscopy. Co-transfection of NF-L with NMDARs however, resulted in an increase in the surface abundance of NR1 when compared to control transfections of NMDARs alone, along with a concomitant increase in NMDAR-mediated excitotoxicity. Investigating the origin of this increase, we found that the NF-L subunits are ubiquitinated in HEK293 cells and can be co-immunoprecipitated with transfected ubiquitin. Ubiquitination of NR1 was significantly reduced by the co-expression of NF-L. These results suggest a possible means of stabilization of membrane-bound NMDARs via the interaction of the NR1 subunit with NF-L.

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Visual cortex activation in the blind is associated with episodic retrieval success

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There is accumulating evidence that the visual cortex is adaptable when deprived of its original input. We showed that the occipital cortex of congenitally blind subjects is activated during tasks requiring verbal-memory processing. Activation was found in regions corresponding to retinotopic visual areas of sighted. Because the occipital cortex (V1) is involved in the visuo-spatial processing of visual information, it was hypothesized that any visual-related activation in the blind could reflect the processing of visual stimuli, rather than verbal-memory processing. To test this, we compared the performance of the blind and sighted subjects on a face-matching task, requiring them to identify words that were originally presented in the first scan. We demonstrate here that the magnitude of V1 activation during this task is correlated with verbal-memory performance. During the current scan, recognition-memory performance differed significantly between two sets of words due to extensive practice on one of the sets prior to the previous scan. Across the blind, the better-remembered set of words elicited greater V1 activation than words from the poorly-remembered set, although the semantic components and the behavioral task were similar in the two sets. This indicates that activation in V1 of the blind is associated with long-term episodic memory, on top of semantic processing as suggested previously. Furthermore, within the blind subjects, those who showed better recognition-memory performance demonstrated greater V1 activation compared with the poorer performers. These results suggest that the occipital cortex including V1 may be involved in episodic retrieval.

Spatio-Temporal Aspects of Perceptual Visual Grouping under Inattention

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Behavioral findings suggest that the attentional demands of grouping by color similarity depend on the complexity of the formed configurations. This study compared event-related potentials (ERPs), recorded from 22 scalp electrodes, in response to displays with grouping into a simple pattern (columns) and a more complex shape (triangle) under conditions of inattention. Fourteen subjects performed a similarity judgment task concerning two successive briefly presented central target displays. Subjects were told nothing about the display backgrounds that included the grouping patterns. Measuring the influence of background organization on target judgments replicated previous behavioral findings: waveforms associated with columns or triangle grouping were obtained by subtracting ERPs to central targets only from ERPs to targets preceded by the same background. The early N1 and P1 ERP components and the N2 component revealed larger amplitudes to columns than to triangles at parietal scalp sites, respectively. Source current density estimations were conducted by low-resolution electromagnetic tomography (LORETA). Columns and triangles evoked similar
activation in some regions (BA 17, 19), and a column advantage was found relatively late in others (BA 20, 21, 38). In regions (hippocampus) were more strongly activated for columns that for triangles throughout the time course. However, processing of pre- and post-triangular orientation with Psychometric activation in different brain areas albeit with an initially longer latency. Interestingly, this activation did not induce awareness of the grouped pattern.

Mapping descending pathways related to atonia and antinociception during anesthesia
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Microinjection of minute quantities of pentobarbital into a restricted region of rat brainstem, the MPTA (mesopontine tegmental anesthesia area) induces a general anesthesia-like state, characterized by atonia, antinociception and loss of consciousness in a range of behavioral tests (0.01). The use of neuroanatomical tracers revealed that the MPTA has direct projections to the spinal cord as well as projections to the pontine reticular formation (RRF), and shock-resistant region for spinal pain modulation. Since these two pathways may mediate the motor and sensory effects of anesthesia, it is important to characterize them in greater detail. We microinjected the tracer CTB (cholera toxin b-chain) into the RVM or the spinal cord at several rostral and caudal levels in order to retrogradely label MPTA neurons that project to these targets. The size and shape of CTB-labeled neurons was evaluated quantitatively using the Neurolucida system. MPTA neurons that project to the spinal cord are significantly larger than neurons that project to the RVM, suggesting that they represent distinct cell populations. It is unclear whether MPTA neurons that project to different levels of the spinal cord are also distinct, or whether individual neurons collateralize and terminate throughout the length of the cord. With the aid of a double retrograde tracing technique using CTB microinjected into one site, and fluorogold microinjected into a second, we established whether MPTA-RVM and MPTA-spinal neurons constitute distinct populations, and whether MPTA spinal neurons have specific, localized terminations or collateralize broadly.

Exposure to stress impairs extinction of fear conditioning
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Experimental extinction is the decline in frequency or intensity of the conditioned response following the withdrawal of reinforcement. Converging evidence indicates that extinction of fear memory requires plasticity in both the medial prefrontal cortex (mPFC) and the basolateral amygdala (BLA). Recent data show that the mPFC is crucial for the inhibition of the responses mediated by the amygdala and thus for its role in reducing exaggerated fear responses. In the present study we aimed to examine the kinetics of fear extinction following different extinction paradigms and withdrawal of reinforcement. In the present study we aimed to examine the kinetics of fear extinction following different extinction paradigms and withdrawal of reinforcement. In the present study we aimed to examine the kinetics of fear extinction following different extinction paradigms and withdrawal of reinforcement. In the present study we aimed to examine the kinetics of fear extinction following different extinction paradigms and withdrawal of reinforcement. In the present study we aimed to examine the kinetics of fear extinction following different extinction paradigms and withdrawal of reinforcement.
Interactions Between Sensory and Cognitive Abilities in Early-Blind Individuals

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Several studies reported superior auditory perception and superior memory in blind individuals. Yet findings are mixed, particularly regarding cognitive abilities. In this study, we show that cognitive advantages may rely on the sensory advantage. We examined the perceptual-cognitive profile of early blind individuals and compared it to that of sighted controls. We replicated findings that blind individuals show advantage in auditory tasks of frequency discrimination and in verbal short-term memory spans. To assess whether their memory has a greater capacity in terms of element number, or their superior spans stem from superior perception, we tested their threshold intensity (80% correct repetition) for speech perception (pseudowords) in quiet and in noise, and assessed their span under “perceptual clamp” conditions (speech intensity presented for each participant at his/her threshold level). Blind individuals had significantly lower threshold levels in quiet, but no difference was found under noisy conditions. This suggests that their general speech perception system is less noisy, but in a manner which does not stem from better-tuned speech detectors. When memory spans are measured under “perceptual clamp” no significant advantage was found for blind individuals, indicating that they have a superior memory per se. Taken together, these results suggest that blind individuals’ advantage in cognitive tasks stems from superior sensory abilities. Prior to this, in turn, started from a quieter auditory system for speech perception, and not from finer tuned speech detectors.

The spatio-temporal organization of the climbing fiber input to the cerebellar cortex

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Optical imaging of voltage sensitive dyes combined with standard electrophysiological techniques was used to characterize spatio-temporally the response of the cerebellar cortex to the climbing fiber input. Fluorescence was measured by a 128 photodiode array from the in vitro whole cerebellum preparation. The white matter was stimulated with a concentric electrode and both optical and electrical responses were measured simultaneously. This stimulus occasioned a typical climbing fiber field response and a parasagittally oriented optical response. In these cases the width of the parasagittal band of activity was 300 μm and its length was similar intensity dependent ranging from 400 μm to more than 1200 μm. Activity was always synchronous throughout the parasagittal band with an average delay of 1.5 ms. The average rise time was 8 ms and the average response duration (half amplitude) was 26 ms. These findings are in agreement with previous morphological and physiological analyses. The characterization of the climbing fiber response enabled us to assess the distribution of the long term interaction between the climbing fiber and parallel fiber inputs, known as cerebellar LTD. We found that conjunctive stimulation of climbing fibers and parallel fibers at a rate of 2 Hz for 50 s is reduced significantly the responses to parallel fiber stimulation. This reduction was confined to the area where the two responses overlapped.

Chondroitin Sulfate Proteoglycan—a "SOS" Molecule in CNS Repair

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Chondroitin sulfate proteoglycans (CSPG) inhibit central nervous system (CNS) axonal regeneration, and their local degradation is an essential event in CNS repair. The assumptions underlying our present study were that the increased expression of CSPG, observed after injury and neurodegenerative disorders (e.g. Alzheimer’s disease), is part of the self-repair mechanism. Accordingly, we proposed that CSPG is needed for transient demarcation of the lesion site as well as the induction and regulation of the local immune response and its degradation products (generated following its degradation with chondrointinase ABC), participate in subsequent events leading to neuronal repair. In the present study, we show that the molecule can affect both microglia and T cell. CSPG induces microglia activation to a phenotype that supports neuronal survival, and in synergy with IFN-γ, it allows microglia to sequester a phenotype of antogates presenting cell needed for the dialog with T cells. The degradation products of CSPG are highly potent compounds that can further contribute to the local immune response, promote neuronal survival and growth, and serve a neuroprotective function in several in vivo models of neurototoxicity and spinal cord injury. Our results suggest that both, in its intact form and via its degradation products, plays a vital role in modulation of the local immune response as well as in CNS regeneration, and serves as an integral part of the mechanism regulating CNS repair.

Learning in realistic networks of spiking neurons and spike-driven plastic synapses

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We study by simulations a recurrent network of spiking neurons connected by plastic synapses. Synaptic efficacies display spike-driven plasticity on both short and long time scales. Short-term dynamics is driven by presynaptic spikes and the fraction of available synaptic resources (Toyoooka, Markram 1997). Presynaptic emission reduces the fraction of available resources, hence the synaptic efficacy. Resources recover in ~100ms. Long-term dynamics is driven by presynaptic spikes and post-synaptic depolarization (Fusi et al. 2000). The synapse is Hebbian: high pre- and post-synaptic emission rates cause LTD, high pre- and low post-synaptic rates cause LTP. Long-time stability is ensured by a refresh mechanism. During training, the network is subjected to a stream of stimulus-delay trials, in which one of a set of external stimuli is presented. To each stimulus corresponds a randomly selected subset of neurons, whose emission rates are enhanced upon presentation of the corresponding stimulus. Neurons can be selective to more than one stimulus. The repeated presentation of the stimuli belonging to the training set (in random order) structures the network to the point of sustaining active memory for every one of them: enhanced delay activity in the corresponding selective neural population. The underlying synaptic structuring is the result of the long-term plasticity produced by the stimulus dependent patterns of neural activity experienced along training. No external intervention is involved at any stage. The patterns of neural activity exhibited by the network before, during, and after the training can reproduce most of the details of the corresponding observed neurophysiological phenomena. The robustness of the structuring and performance is exhibited.

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Intelligence, EEG alpha activity and contrast sensitivity

- The magical number 10

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The magnitude of EEG waves at the alpha (10−12 Hz) range during rest and the Event Related Desynchronization (ERD) during visual and mental activity are both known to be correlated with verbal intelligence. In our lab, a positive correlation was found between subjects' intelligence score and their contrast sensitivity (CS) to 10Hz flickers. Combining these two lines of research, we now asked whether the magnitude of alpha waves at rest is correlated with behavioral CS to 10Hz flicker. Our initial findings (n=9 students) show a significant positive correlation (r=0.76, p<0.05) between the relative proportion of alpha power and contrast sensitivity. Finding that alpha magnitude is correlated with behavioral CS, we then asked whether we can further increase alpha magnitude at rest by exposure to 10Hz flicker. Subjects passively watched interleaved series of 2-sec flickers of 5 and 10Hz,
Learning-induced reduction in predisposition for LTP: a possible mechanism for protection against runaway synaptic strengthening

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We studied the relations between learning-induced modifications in the hippocampus, the threshold for LTP and LTD induction. Rats were trained in an olfactory discrimination task to distinguish between positive and negative odor cues until they demonstrated rule learning. Learning-induced cellular and molecular modifications were subsequently studied in the perforam cortex. Two types of cellular modifications appear one day after learning: enhanced neuronal excitability, which is the result of reduction in an intrinsic potassium current (Saar and Barkai, 2003) and reduced predisposition for LTP induction (and increased predisposition for LTD induction). This shift in the threshold for LTP and LTD is a consequence of a change in the subunit composition of the NMDA receptor, resulting in receptors with a higher complement of the NR2A subunit protein relative to NR2B (Quinlan et al., 2004). Learning-induced synaptic strengthening becomes apparent on the third day after training, and is maintained by different mechanisms than those affecting LTP and LTD induction. Enhanced synaptic release is indicated by reduced paired pulse facilitation (Saar et al., 1999), post synaptic density in the neuronal cable properties are intended by enhanced rise time of the post-synaptic potentials (Saar et al., 2002), and enhanced synaptic connectivity is indicated by increased spine density along dendrites of pyramidal neurons (Knafo et al., 2001). One possible function that learning-induced molecular and physiological modifications in the NMDA receptors may serve is protecting the neuronal circuit against runaway synaptic strengthening. Such protection is achieved by raising the threshold for activity-dependent synaptic enhancement. However, once an external stimulus reaches this threshold, the information it carries would be stored quickly and efficiently.

Hyperanxiety and memory deficits induced in rats by prenatal stress are associated with a reduction in synaptic connectivity in hippocampal and cortical regions

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Prenatal stress in rats has been shown to reduce neurogenesis in the hippocampus and increase the size of the lateral amygdaloid nucleus. These structural alterations are associated with deficits in spatial and depressive behaviour. The present study examined the effect of gestational stress during the last week of gestation in Sprague-Dawley rats on the length and density of dendritic spines, and on genes related to synapse formation and activity in the hippocampus and cortical areas in 21 day old male offspring. Spatial and episodic memory was assessed in adult littermates (3-4 months) by the Morris water maze and object recognition tests, respectively. Dendritic morphology was assessed by means of Golgi-cox staining, and gene changes, by the Affymetrix microarrays (8 samples x 19,000 genes each), followed by RT-PCR. Prenatal stress caused a significant decrease in spine length and density in the orbitofrontal and anterior cingulate cortex in the hippocampus, 2.4% of the genes were markedly reduced, the largest group of which included components of neurogenesis and synapse formation, activity and trafficking, such as components of endophilin-1 and PSD-95/SAP90-associated protein-3. The study shows for the first time that prenatal stress can interfere with synapse formation and activity and reduce synaptic connectivity in the cortex. These changes are present at the time of weaning, and probably result from altered neuronal programming of the fetal nervous system by maternal stress hormones like corticosterone. The structural changes in the hippocampus and cortex contribute to the deficits in behaviour and memory seen in adulthood.
The Significance of Impedance Profiles of Pacemaker Neurons in Frequency Regulation of the Pyloric Rhythm

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Autonomic neurons show impedance profiles that peak at a frequency called the resonance frequency, often close to their intrinsic oscillatory frequency. When such a neuron is embedded within a network it is subject to electrical and chemical synaptic inputs which can affect the cycle frequency. According to the impedance profile of the neuron, inputs coming at certain frequencies will be more important than others. Hence the impedance of a neuron that participates in the production of a rhythm may be a critical component of the mechanism by which cycle frequency is stabilized in the whole network. We examined this question in the pyloric circuit of Homarus americanus, which produces a robust oscillation (cycle frequency f_pyloric 1 Hz). We focused on neurons of the pacemaker group, the pyloric dilator (PD) and the anterior burster (AB) neurons. In the isolated neurons, we recorded the voltage responses to intracellularly injected sine waves of different frequencies. Since the responses to negative and positive currents were not symmetrical, we measured two different curves for the impedance profile: Z (f) and Z (f), respectively. We found that the PD and AB neurons have characteristic impedance profiles not shown by any other pyloric neuron: in the physiological range (f<3 Hz) Z (f) was almost flat; at low frequencies, Z (f) increased with f and peaked at f Peak ~0.27±0.12 Hz. At higher frequencies Z (f) strongly decreased with f, decaying below Z (f) at f >0.7 Hz. Hence, at low frequencies, Z (f) and Z (f) are more depolarizing, and inputs are favored over hyperpolarizing inputs; these relationships are reversed for f>0.7 Hz (N=22). Thus, we hypothesize that when cycle frequency transiently decreases below, or increases above, pyloric depolarizing (e.g., electrical coupling) or hyperpolarizing (e.g., chemical inhibitory) inputs are differentially weighted such that the cycle frequency is brought back to pyloric.

Development and distribution of voltage-gated potassium conductances in neocortical pyramidal neurons

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The seminal investigations of Hodgkin and Huxley (1952) paved the road for exploration of neuronal excitability. Understanding the physiology of any electrically excitable cell requires describing the kinetics and membrane density of the voltage-gated ion channels it expressed. The calculated conductance densities obtained by us (Kornigren and Schaefer, 2003; and others) were used to construct a compartmental simulation describing the firing of neocortical pyramidal neurons we discovered that the estimates we obtained from nucleated patches and from cell-attached and outside-out patches were smaller than those required to reproduce the physiological firing pattern of the neurons. In order to produce a realistic simulation the somatic conductance density of voltage-gated potassium channels had to be several fold higher than that we have measured. To address this conundrum we developed a new technique that corrects space-clamp distorted voltage-clamp recordings performed in the whole-cell configuration in non-spherical structures (Schaefer et al. 2003). The rational was that the whole-cell configuration is less damaging to the plasma membrane than the extraction of a nucleated patch and will allow a more accurate estimation of the conductance density once space-clamp distortions were corrected for. Using this technique we re-examined the conductance density of voltage-gated potassium channels in layers V and VI of neocortical neurons. We show that the conductance density is higher than the one reported previously from nucleated patches. We use the new recording mode to investigate the developmental voltage-gated potassium channels at the soma. We also show that previously reported the density of voltage-gated potassium channels decreases along the apical dendrite of L5 pyramidal neurons.

FMRI driven seed ROI choosing Procedure for DTI based fiber tractography in the presence of space occupying lesion

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Diffusion tensor imaging (DTI) can be used for 3D visualization of specific fiber bundles, and to indicate the involvement of white matter in vicinity of brain lesions. Diffusion tensor imaging based fiber tractography necessitates definition of a seed region of interest (ROI) that is located at the path of the investigated fiber network system. Based on known anatomical location a large number of fiber bundles systems could be identified on healthy subjects with high accuracy. Mapping of well-defined functional systems (motor, visual, language) using fMRI is routinely done today for presurgical mapping. Nevertheless, brain lesions, especially space occupying lesions (SOL) often involve the white matter and alter the known anatomical pathway on which the fibers pass. Indeed, white matter deviation is a common consequence of SOL. Nonetheless in many of these cases only partial or no functional deficit is observed leading to the assumption that the fibers are still partially intact and therefore take a different route. In such cases, white matter mapping using seed ROI based on known, normal, anatomical location might be misleading. In this work we used FMRI driven seed ROI choosing procedure in patients with space occupying lesions where probable deviation of white matter tracts have been observed. We compared our results correlated with the DTI to provide a 3D data set of both white matter connectivity and task related functional activity superimposed on high-resolution anatomical data set. From the FMRI activated areas we followed on white matter tracts using DTI to map the task related white matter tract. We used mainly the motor and language related FMRI tasks and concentrated in tracking the pyramidal tract (to connect the motor related network) and the superior longitudinal fasciculus (to connect the language related network). This methodology opens a window for assessment of brain connectivity in diseased patients.

Local Blood-Brain Barrier Disruption and Cortical Albumin Exposure Induce Epileptiform Activity

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Perturbations in the integrity of the blood-brain barrier have been reported in both humans and animals under numerous pathological conditions. The blood-brain barrier prevents the penetration of many blood constituents into the brain extracellular space, but it is not known whether perturbations of the barrier can affect brain function and consequently have a role in the pathogenesis of cortical diseases. In this study we established a model for focal disruption of the blood-brain barrier in the rat cortex by direct application of bile salts. Importantly, direct neurotoxic effects of the bile salts were excluded by alunitered intra- and extracellular recordings in vitro. However, exposure of the cerebral cortex in vivo to bile salts resulted in a prolonged opening of the blood-brain barrier with subsequent long-lasting extravasation of serum albumin to the brain extracellular space. This was associated with a prominent activation of astrocytes with no inflammatory response or marked cell loss. Using electrophysiological recordings in brain slices we found that a focus of epileptiform discharges developed within 4-7 d after treatment and could be recorded up to 49 d postoperatively in >60% of slices from treated animals but only rarely (10%) in sham-operated controls. Epileptiform activity involved both glutamatergic and GABAergic neurotransmission. It was also induced by direct cortical
application of native serum, denatured serum, or an albumin-containing solution. In contrast, perfusion with serum-retarded electrolyte solution did not induce abnormal activity, thereby suggesting that the exposure of the serum-devour brain environment to serum proteins underlies epileptic activity in the blood-brain barrier-disrupted cortex. Although many neuropathologies entail a compromised blood-brain barrier, this is the first direct evidence that it may have a role in the pathogenesis of focal cortical epilepsy, a common neurological disease.

The role of non-NMDA glutamate receptors in the Ventral Tegmental Area in opioid reward and sensitization

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The role of the mesocorticolimbic dopamine system in mediating the rewarding properties of drugs of abuse is well known, the cross talk with other neurotransmitter systems in the mesencephalic Ventral Tegmental Area (VTA) projects to several forebrain regions, including the nucleus accumbens (NAcc), both of which have been implicated in opiate-induced reward. The present study seeks to estimate whether blockade of non-NMDA glutamate receptors in two different subregions of the VTA would modulate the rewarding properties of morphine and the development of sensitization to the drug. Methods: Rats were implanted with a guide cannula (24 GA) 1.5 mm above the anterior or posterior VTA to allow intracranial administration of the non-NMDA antagonist, CNQX (1 nmol, 0.5 μl/1 side), in order to find its impact on the rewarding effect of morphine in the Conditioning Place Preference (CPP) paradigm (unbiased procedure), and the induction of morphine sensitization in the same apparatus. Results: Regional administration of CNQX into the anterior VTA blocked the rewarding but not the development of sensitization to the locomotor stimulating effect of morphine. However the effect of morphine on locomotion was attenuated by CNQX injected into the anterior VTA. Regional administration of CNQX into the posterior VTA had different impact on the rewarding and stimulating effects of morphine which has still to be analyzed.

Conclusion: Our data suggests a critical role for non-NMDA receptors in the VTA in opioid reward and dissociation between the rewarding and psychomotor sensitization effects of morphine.

Out of water reaching movements of the octopus

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Given their flexibility and kinematic redundancy, the control of the octopus arm movements is computationally quite complex. In previous studies a stereotypic reaching movement was discovered which reduces the complexity of motor control. Study of out of water (OOW) reaching movements showed that during these movements the bend point does not travel within a single plane, probably due to the lack of enough muscle forces. Almost all OOW reaching movements were directed in a perpendicular direction to the water surface, and indicated constant attempts by the octopus of keeping the proximal part in that arm orientation. Although no evidence was found that octopuses use correction strategies to produce abnormal movements in the water, such corrections were observed during the OOW reaching movements. Loss of steadiness was critical when the body was in the blood. The octopus used its own morphology, and its reactions to the water to keep itself in position.

We found that both 5-HT1A and 5-HT1B autoreceptors are desensitized by chronic administration of the SSRI fluoxetine. Moreover, this effect was found in both male and female rats. The effect of chronic fluoxetine administration was differential in the two sexes. In female rats, chronic fluoxetine administration did not alter 5-HT autoreceptor activity, whereas in male rats, chronic fluoxetine administration decreased 5-HT1A and 5-HT1B autoreceptor activity.

Chronic dietary lithium supplementation attenuates markers of aging in the hippocampus of C57BL mice

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Lithium (Li) attenuates apoptosis and glutamate-induced calcium influx and increases brain derived neurotrophic factor level. Since these actions oppose mechanisms of aging in the hippocampus, the present study examined the effect of chronic dietary Li supplementation on markers of aging in the hippocampus of adult C57BL mice. Clusters of grains were detected by antibodies to inducible heat shock protein 70 and to glutathione-S-transferase and astrocyte activation (increased astrocyte size) was detected by anti-glial fibrillary acidic protein. Chronic dietary Li supplementation reduced the number of clusters of grains by 40% in the CA1 and CA2 regions, whereas in the hippocampal CA1-2 field by 25-30% without affecting the dentate gyrus. The reduction in markers of aging was not due to calorie restriction since Li supplementation did not change body weight. Since Li inhibits glycogen synthase kinase (GSK)-beta/z and since GSK-3beta promotes the apoptosis, the present study also examines the effect of knockout reduction in GSK-3-beta level on the markers of aging. Surprisingly, knockout reduction of GSK-3beta increased the number of clusters of grains by 2-4 folds and increased astrocyte size in hippocampal CA1-2 field by 25-30% without affecting the dentate gyrus. Thus, life long reduction in GSK-3beta level may result in acceleration of some aging processes. This study warrants further examination of the conditions under which dietary Li supplementation to adults can prevent aging-associated cognitive decline.

Strain related gender differences in cortical 5-HT autoreceptors response to sub-chronic fluoxetine

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Selective serotonin reuptake inhibitors are the most prescribed antidepressants for treating depression. One problem of SSRIs is a 2-3 weeks delay of response after onset of administration. Previous studies showed that acute administration of the SSRI fluoxetine to rats increases synaptic 5-HT levels, and long-term administration of fluoxetine desensitizes 5-HT1A and 5-HT1B autoreceptors. This effect may play a role in the delayed response to treatment in humans. Mood disorders are more frequent in women. It was also suggested that there are gender differences in the response to antidepressants. Yet, most of the animal researches are done with male rats. In this work we asked whether 5-HT1A and 5-HT1B response to fluoxetine administration is differ between male and female rats. We treated Saba male and female rats, and Sprague-Dawley female rats, with fluoxetine (10 mg/kg, 7 or 14 days). 5-HT levels, 5-HT1A and 5-HT1B autoreceptor activity were measured by in vivo microdialysis and analyzed by HPLC.

We found that both 5-HT1A and 5-HT1B autoreceptor activity, as measured in the cortex, were reduced in Saba male rats after 7-day administration of fluoxetine (10 mg/kg). However, the same treatment, as well as a 14-day treatment with fluoxetine (10 mg/kg), had no effect on 5-HT autoreceptors in the corticidal cortex of the Saba female rat. Early research found that 7 and 14 days administration of fluoxetine (10 mg/kg) desensitized 5-HT1A autoreceptor in the cortex of Sprague-Dawley male rat. In this study we found the same effect in Sprague-Dawley female rats, as well as desensitization of cortical 5-HT1B autoreceptor.
conclude that the gender differences in 5-HT1A and 5-HT1B autoreceptor response to sub-chronic fluoxetine administration in males and females in the Sprague-Dawley strain, 5-HT autoreceptors response to fluoxetine differs between male and female in the Sabra strain.

The effect of mood stabilizers on nerve growth cones is additive and specific

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Lithium salts (lithium), valproic acid (VPA) and carbamazepine (CBZ) are the commonly used mood-stabilizers. Yet, despite years of treatment, their mechanism of action is still unknown. A heuristic hypothesis for mood stabilization by lithium is the mono-site depleting hypothesis proposed by Berridge. It explains that impairment of myo-inositol phosphorylase by lithium results in depletion of brain mono-site leading to subsequent lamping of overactive neurotransmitters. It has recently been found that lithium and VPA share the same effect of spreading of prion-like neuronal root ganglia (DRG) growth cones. Interestingly, myo-inositol reverses the effect of all three drugs, implicating mono-site depletion in their action. Among eight psychotropic drugs, mono-site or drugs plus mono-site intravenously, lithium and VPA show an additive effect of growth cones spreading, as occurs in the clinical use of these two drugs. Among eight psychotropic drugs other than the three mood stabilizers only imipramine and chlorpromazine had a similar spreading effect on rat neuronal DRG growth cones, albeit their effect was not reversed by myo-inositol, implicating a different mechanism of their action. At 3 mM, unlike myo-inositol, scyllo- and epic-inositol did not reverse the effect of lithium on the growth cones spreading, reflecting specificity of the active stereoisomer and supporting the notion of intracellular myo-inositol depletion as the mechanism of action of the three antidepressants.

The frontal lobes are involved in affective mentalistic significance of eye direction

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Participants suffering from schizophrenia show impaired cognitive and social functioning, such as decreased eye contact, decreased emotional expression, and decreased affective theory of mind (ToM). This study aimed to determine whether the eye direction deficit in schizophrenia patients is associated with aspects of ToM. Participants were diagnosed with schizophrenia (n=15) or healthy controls (n=46). The ToM task was designed to assess the ability to attribute affective states to others based on their eye gaze. The performance of patients with localized lesions in the PFC (n=23) was compared to that of healthy controls. The results indicated that patients with schizophrenia showed impaired ToM in both affective and cognitive conditions. Furthermore, the ToM performance of patients with schizophrenia was significantly correlated with their level of negative symptoms and to their performance in the cognitive condition. The ToM performance of healthy controls was not significantly correlated with their level of negative symptoms. This suggests that the eye direction deficit in schizophrenia patients is associated with deficits in ToM.

The neural correlates of understanding the other: a positron emission tomography investigation of accurate empathy

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The purpose of the present study was to assess the relationship between deep brain anatomy and the empathic response. Six right-handed healthy volunteers were scanned with positron emission tomography (PET) and [F-18] fluorodeoxyglucose twice, during an interactive interview about neutral story themes and during an interactive interview about an empathic response-eliciting story. The results of this study provide evidence for a unique anatomical correlate of empathic response, and thereby, for the role of the cerebellum in the neural mechanism underlying empathy.

Impaired empathy and affective theory of mind in patients with schizophrenia

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Patients suffering from schizophrenia show impaired emotional and social behavior, such as decreased eye contact, decreased emotional expression, and decreased affective theory of mind (ToM). This study aimed to determine whether the eye direction deficit in schizophrenia patients is associated with aspects of ToM. Participants were diagnosed with schizophrenia (n=15) or healthy controls (n=46). The ToM task was designed to assess the ability to attribute affective states to others based on their eye gaze. The performance of patients with localized lesions in the PFC (n=12) and healthy control subjects (n=46). The results indicated that individuals with schizophrenia demonstrated selective impairment in their ability to attribute affective mental states.

Postmortem Parietal Cortex TPH2 Expression is Not Altered in Schizophrenia, Unipolar Depressed and Bipolar Patients vs. Control Subjects

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Objectives: Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter synthesized in the raphe nuclei of the brain stem in the CNS and also in the periphery. Dysfunction of the serotonergic system has been implicated in the pathogenesis of psychiatric disorders. Tryptophan hydroxylase (TPH) is the rate limiting enzyme in 5-HT biosynthesis. More than a gene encoding TPH was identified in vertebrates. Recently, a
second TPH gene, designated TPH2, was detected and located on human chromosome 12, a susceptibility region for bipolar disorder. TPH2 gene expression is significantly lower in the brain, while the classical TPH1 gene, TPH1, is expressed in peripheral tissues. The discovery of the brain-abundant TPH2 gene provides a new candidate CNS serotonergic system. TPH2, rather than TPH1, has now become a candidate gene for 5-HT-related affective disorders. Moreover, the discovery that TPH2 mRNA levels in postmortem parietal cortex of unipolar-depression, bipolar and schizophrenia patients vs control subjects and using real-time RT-PCR. No significant difference in TPH2 mRNA levels was found among the four diagnostic groups. Conclusions: The lack of difference may suggest that this gene is not involved in the etiology of either of these psychiatric disorders. Alternatively, it may be that the parietal cortex is not the relevant brain area involved in the pathophysiology of these disorders, or that posttranscriptional modifications of TPH2 mRNA occur in these patients, causing changes in protein levels and/or enzymatic activity.

Interaction of calbindin D28k and inositol monophosphatase in human postmortem cortex; possible implications for bipolar disorder.

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Objectives: Therapeutically-relevant concentrations of lithium (Li) exerts an uncompetitive inhibition on inositol monophosphatase (IMPase). It has been recently shown that calbindin D28k (calbindin) activates IMPase. Purified calbindin attaches to a specific amino acid sequence on purified IMPase enhancing its activity by several hundred fold. We studied whether calbindin activates IMPase in postmortem human brain crude homogenate, whereas differences in calbindin levels in lymphocytes and brain may be responsible for our previous finding of reduced IMPase activity in lymphocytes but not brain of bipolar patients, and whether calbindin protein levels are altered in postmortem brain from bipolar patients vs control subjects and schizophrenic and major depressive patients. Methods: IMPase activity in human postmortem brain specimens with or without 10 μM human recombinant calbindin was quantified spectrophotometrically in an ELISA reader. Calbindin protein levels in postmortem brain were determined using Western blot analysis. Results: Supplementation of human recombinant calbindin to postmortem human brain crude homogenate enhanced IMPase activity by 3.5 fold. No difference in postmortem temporal cortex calbindin protein levels was found between bipolar patients vs comparison group. Two-fold higher calbindin protein levels were found in Li-treated bipolar patients compared with other bipolar patients. Sub-chronic Li treatment in mice did not affect brain calbindin significantly. Chronic Li treatment reduced calbindin protein levels in the frontal cortex but not the hippocampus. Conclusions: Calbindin is a physiological activator of IMPase in human brain. Protein levels of calbindin are not altered in postmortem temporal cortex of bipolar patients.

The relation between understanding of deception and knowledge of social display rules among children with brain damage.

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Children with brain damage, particularly influencing the frontal lobes, often have deficits in social behavior with less evidence of recovery in this domain than in others. Among the impaired social functions is the ability to understand and discriminate emotions from facial displays. This has been shown using short narratives in which a character reveals a certain emotion, but without modulate, or inhibit its display. Previous studies suggest that perception of emotional deception is related to both Theory of Mind (ToM) and knowledge of social display rules. The objective of the current research was to examine the relationships between these functions, and extend the knowledge about their contribution through higher order false beliefs and cognitive deception. ToM tasks, but these may still be prerequisites for this ability. Results may suggest areas on which to focus when treating such children with social problems.

Spatial response properties of neurons in the Anterior Ectosylvian Sulcal Auditory Field (FAES).

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Both the primary auditory cortex (AI) and Anterior Ectosylvian Sulcal Auditory Field (FAES) are believed to be involved in localization of sound. In both fields, neurons have been found to be sensitive to the direction of sound sources, although spatial tuning curves tend to be rather wide. Furthermore, FAES is known to project heavily to the deep layers of the superior colliculus. We recorded single unit selectivity to azimuth and elevation in the FAES and compared it to neural responses in AI. We used virtual space stimuli consisting of two tone pips with constant interaural time differences, keeping all the other cues present; and we generated stimuli that had the same interaural level differences as the original stimulus, superimposed on white noise. Both in AI and in FAES, a substantial number of neurons had significant sensitivity to azimuth and elevation. This sensitivity was due to binocular interactions, and was not purely the result of spectral processing in one ear. Modifying any of the physical parameters resulted in significant reduction in the sensitivity of the population response in FAES but not in AI, although single neurons in AI showed changes in spatial sensitivity too. In particular, removing the spectral notches reduced sensitivity not only to elevation (as expected), but to azimuth as well. The major determinant of azimuth selectivity in FAES seemed to be direct spectral structure of the stimuli in both ears, whereas elevation sensitivity depended on the spectral notches as well.

Inflammatory cytokines and cholinergic signaling modulate surgery stress-induced alterations in mood and cognition.

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To examine the role of inflammatory cytokines and cholinergic signaling in mediating the effects of stress on mood and memory, and the health of brain. Volunteers were administered a comprehensive neuropsychological test battery before and after a moderate surgical procedure. Each subject was tested on three days before surgery (baseline), on the morning of the surgery day (i.e., psychological stress), and one day after surgery. Acetylcholinesterase (AChE) activity and interleukin (IL-1, IL-1a, IL-6) and cortisol in the serum were measured in each session. 18 control subjects went through the same procedure. At baseline, lower levels of AChE activity were significantly associated with elevated
anxiety levels. Anxiety and depressed mood were significantly increased before and after surgery. Surgery-induced mood alterations were replicated with changes in AChE activity. Patients who demonstrated stress-induced reduction in AChE activity showed a marked elevation in anxiety and depressed mood, whereas patients who demonstrated elevation in AChE activity displayed almost no mood alterations. Both on the surgery day, and on the day after surgery, there was a marked decline in memory. Following surgery, the levels of IL-6 increased, and were significantly correlated with smaller impairments in word list and complex figure delayed recall. Polyomorphism in IL-1beta was significantly associated with IL-6 elevation following surgery (i.e., the surgery-induced increase in IL-6 levels was twice as high in allele 1 homozygous patients compared to patients with allele 2). In addition, memory impairment in the allele 1 homozygous patients was smaller compared to the other group. Thus, while cholinergic signpost is associated with stress-induced mood modifications, IL-6 is associated with protection from surgery-induced cognitive disturbances, which vary according to genetic predisposition in stress-induced IL-6 production.

Rat brain synaptosomes contain a functional thrombin receptor PAR-1.

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Background: Thrombin is a key factor in coagulation and is considered to have a role in seizure production. Thrombin mediates many of its effects through specific protease-activated receptors (PARs). The discovery of PARs in the nervous system has led to new insight regarding the potential physiological functions of thrombin. To examine PAR-1 agonist peptides pharmacological effects on synaptosomes which may contribute to seizures.

Methods: Crude synaptosomes were prepared from rat brains by centrifugation. The levels of phosphorylated ERK-1/2 induced by thrombin and PAR-1 agonist peptides relative to control non stimulated synaptosomes. A 2 peak dose response curve was obtained with maximal responses at 30 microM and 10 nanoM. Conclusions: The results indicate that rat brain synaptosomes contain functional PAR-1. The physiological effects of the signal transduction pathways activated by this receptor remain to be evaluated.

Heat Acclimation Induced Neuroprotection: Possible Involvement of Hypoxia Inducible Factor 1&
Upregulation and Increased Erythropoietin Signaling
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Background: Long-term exposure to heat (heat acclimation, ACC) was shown to protect against brain damage after closed head injury (CHI) in rats (Restor Neuril & Neurosci 6:107, 1994). Similarly, we have previously shown that this neuroprotective effect is sustained in mice as well. Hypoxia inducible factor 1 (HIF1), a transcriptional activator, regulates the expression of various genes including erythropoietin (Epo), several glycolytic enzymes, some glucose transporters and transferrin, all of which can potentially play a role in promoting cell survival. Epo, known as the key promoter of erythrocyte production, has been shown to be protective in a variety of brain injury models including our own model of CHI (Yashar et al. Presented at the 11th annual ISFN meeting). This study examined the effect of ACC and CHI on the expression of HIF1alpha, Epo and its specific receptor, the erythropoietin receptor (EpoR). Methods: Mice were exposed to ambient temperature of 24°C (controls) or 34°C (ACC) for 30 days (Basic Res Cardiol 98/3, 185) and then subjected to left cerebral hemispheric ischemia induced by a weight of 1.5g (under ether anesthesia), or sham surgery. 4 and 24h after surgery or CHI, mice were sacrificed and their brains removed for Western blot analysis of HIF1alpha, Epo and EpoR. EpoR/Epo alpha ratios were calculated with changes in AChE activity. Patients who demonstrated stress-induced reduction in AChE activity showed a marked elevation in anxiety and depressed mood, whereas patients who demonstrated elevation in AChE activity displayed almost no mood alterations. Both on the surgery day, and on the day after surgery, there was a marked decline in memory. Following surgery, the levels of IL-6 increased, and were significantly correlated with smaller impairments in word list and complex figure delayed recall. Polyomorphism in IL-1beta was significantly associated with IL-6 elevation following surgery (i.e., the surgery-induced increase in IL-6 levels was twice as high in allele 1 homozygous patients compared to patients with allele 2). In addition, memory impairment in the allele 1 homozygous patients was smaller compared to the other group. Thus, while cholinergic signpost is associated with stress-induced mood modifications, IL-6 is associated with protection from surgery-induced cognitive disturbances, which vary according to genetic predisposition in stress-induced IL-6 production.

Endogenous D-Serine is Essential for NMDA-Elicited Neurotoxicity in Organotypic Hippocampal Slices Cultures.

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Overactivation of NMDA receptors is involved in neuronal cell death that occurs following brain ischemia. Calcium influx through NMDA receptors requires the binding of both glutamate and a coagonist, glycine or D-serine. Since both glycine and D-serine occur in the brain, the relative roles of each NMDA receptor coagonist is not known. To examine whether endogenous D-serine plays a role in neuronal death resulting from excitotoxic insults in the hippocampus, we used rat brain organotypic slice culture as a model. HPLC analysis revealed significant synthesis of D-serine by cultured hippocampal slices, ranging from 6 to 12 micromolar in the culture medium. Robust cell death was observed by addition of either NMDA (0.5 mM) or kainate (0.1 mM) as determined by propidium iodide uptake. Application of recombinant D-serine dehydratase (DSDA), an enzyme that specifically degrades D-serine, depleted D-serine levels in the culture medium and slices. This was associated to a drastic inhibition of neuronal death elicited by NMDA, but not by kainate. The neuroprotective effect of DSDA was fully reversed by addition of excess glycine or D-serine, indicating that the effect of DSDA was not due to nonspecific inhibition of NMDA receptor activity. The present results indicate that endogenous D-serine is essential for neuronal injury involving NMDA receptor overactivation.

Ras dependent ErbB4 signaling, possible mechanism of regulation.
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The ErbB subfamily of receptor tyrosine kinases consists of four receptors. ErbB4 receptor is highly expressed in the nervous system and its high affinity ligand is neuregulin (NRG). NRG recognition event activates the receptor's intrinsic tyrosine kinase activity and initiates a network of signaling pathways regulating cellular proliferation, survival, chemotaxis, or differentiation. Among the cascades activated by ErbB4 is the prominent Ras-dependent signaling pathway. Our previous studies have shown that NRG induces neurite outgrowth and protects the PC12-ErbB4 cells from death caused by various apoptotic stimuli. Furthermore it was shown that activated Ras can activate ErbB4 receptor in a ligand independent manner. This activation depends on multiple Ras effecter pathways in an autocrine independent manner. In the present study we demonstrate that the Ras inhibitor FTS, inhibits the NRG-mediated PC12-ErbB4 rescue from serum deprivation treatment. In addition the expression of dominant-negative Ras in these cells prevents cell differentiation. In order to examine whether the phosphorylation of ErbB4 by activated Ras is due to the tyrosine kinase activity of the receptor itself or due to the activity of an unknown cytoplasmic factor, we have co-transfected Ras with a point mutation in the ATP binding site. Preliminary results have shown that this receptor, transiently expressed in BOSC cells, does not bind gamaATP and therefore abolishes the intrinsic tyrosine kinase activity of Ras. These results suggest that Ras signaling pathways on one
Double dissociation between the ventral and dorsal streams during object and action recognition

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Neuropsychological case studies indicate the existence of two functionally separate visual streams, but due to the few cases, this distinction remains controversial. Using fMRI in humans, we provide here evidence for the dissociation between observed action and object recognition. In experiment 1, subjects viewed movie clips of the right hand, on the right visual field, reaching and grasping objects placed on the left side of the screen. A mirror image of those movies (left hand grasping objects on the right side of the screen) was also shown. Contrasting the fMRI activation in the two conditions, we find that in dorsal areas (i.e., anterior infraparietal sulci: aIPS) the dominantly invaded the motoric stream and the object stream was only significantly activated in the hemisphere contralateral to the object’s position. Next, subjects watched clips showing ten different actions performed by different hands (functional hemispheres containing variables objects) and ten different grasps performed by different hands (variable objects). Using a two-factor ANOVA, we measured the adaptation effects of repeated viewing of object manipulation and/or object identity differences in the dorsal and ventral cortices (i.e., aIPS and postcentral sulci). On the other hand, voxels showing significant (fMRI) adaptation during the observation of grasping movements were very mainly found in the parietal cortices (i.e., aIPS and postcentral sulci). On the other hand, voxels showing significant adaptation during the repeated observation of the same object, compared to different objects were found in the occipito-temporal cortex. Thus, we show a double dissociation of function between the two pathways. These results are congruent with the “direct matching hypothesis”, that suggests that action recognition is based on mapping external actions to our own motor system and extend the classic division of labor between the ventral and dorsal visual streams, suggesting that the dorsal stream may also be involved in the recognition of actions made by others.

Dominant eye priority in visual search

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While it is clear that one eye is visually dominant, the function of dominance is not fully understood. For example, Mapp et al. (2003) argue that eye dominance does not cause visual distortion, and recent research found that eye dominance may be defined differently using different tests (e.g., Pointer 2001, Walls 2001). We were interested in the effects of dominance without competition; for example, FMRI reveals stronger activation for visual stimulation of the dominant eye (Rombouts et al. 1996). Detection of an element that differs significantly in a single dimension is an easy task, with performance that is independent of the number of distractors (Treisman & Gelade, 1980). We looked for effects of eye dominance on visual search. 13 subjects participated in the experiment; each had similar visual acuities in their two eyes, and normal or corrected-to-normal vision. Dominant eye was determined using the Hole-in-the-Card test (Durand & Gould, 1979). Using red-green glasses, subjects viewed a briefly presented 8x8 array of green and red lines oriented at 60 degrees, followed by a masking stimulus after a variable stimulus-to-mask onset asynchrony of up to half of the trials, or a blank element was replaced by a red or green line oriented at 40 degrees, with the 8 lines surrounding this target having the same color as the target, the opposite color, or a mixture of the two colors. We tested for differences in performance when subjects used the dominant vs. the non-dominant eye, and checked if any difference depends on the eye elements. We found significantly better performance when the target was seen by the dominant eye, especially when surrounding elements were seen by the opposite eye. We conclude that the dominant eye has visual processing priority, perhaps arising from inhibition of non-dominant eye information.

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Oxidative stress induced by intraventricular streptozotocin (iCV-STZ) suppresses protein kinase C beta 2 activity in rat brain and induces memory deficits:

Prevention by rasagiline

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Intracerebroventricular (icv) injection of streptozotocin (STZ) in rats decreases glucose utilization in the cortex and hippocampus. We have found evidence of oxidative/nitrative stress, detected by antibodies to nitrotyrosine in the septo-hippocampal system as an early event after icv STZ injection. This was associated with damage to myelin and activation of microglia. Activity of protein kinase C (PKC) isoforms has been implicated in development and maintenance of myelin and in learning. The present study explored the effect of STZ on PKC beta 2 (PKCb-2) in rats. STZ (0.5 mg/kg) was injected into the lateral ventricle of male rats weighing 300-320 g. Immunochemical staining of brains 7 days later revealed a 10-30% reduction of PKCb-2 levels in hippocampal CA1 pyramidal layer. The damage to the memory deficits and enzyme changes, rats were given daily sc. injections for 2 weeks of 0.2 mg/kg of rasagiline. Rasagiline has shown efficacy in patients with Parkinson’s disease and to prevent cell death induced by oxidative nitrative stress in SH-SYSY neuroblastoma cells. We found that rasagiline increased PKCb-2 immunoreactivity in all brain regions in which this was decreased by STZ, and completely restored it to control levels in the hippocampal CA1 pyramidal layer. Rasagiline significantly reduced the spatial memory deficits seen 60 days after two STZ injections. Our findings support the hypothesis that the damage to myelin and memory deficits induced by icv-STZ involves a cascade initiated by oxidative stress and reduction in PKCb-2. Icv-STZ can serve as an in vivo model with which to screen potential neuroprotective agents for their ability to prevent myelin damage and memory impairment.

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The involvement of 5-HT and octopamine in short-term plasticity in the octopus vertical lobe

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Octopuses are unique invertebrate mollusks with a highly developed central nervous system and brain abilities comparable to those of vertebrates. In a previous study we discovered a hippocampal-like LTP in the octopus ventral lobe (VL), an area of the octopus brain involved in learning and memory. To find out whether the well known mechanisms of mammalian synaptic plasticity are conserved in the octopus VL, we first looked for the presence of 5HT in the VL complex. Fibers immunopositive for 5HT were found in the VL complex and stained terminals were found mostly in the VL neuropil. This finding led us to reinvestigate the involvement of 5HT in VL synaptic plasticity. In contrast to our previous work, we found only 5HT concentrations effective in Aplysia (10-50uM), a 2-5 fold facilitation of the synaptic field potential was induced when higher concentrations (100-200uM) of 5HT were used. In contrast to the activity-dependent potentiation, the effect of 5HT was readily reversible upon washout and was not occluded by induction of LTP. Octopamine had a similar and synergistic effect. The phosphodiesterase inhibitor IBMX facilitated the effect of 5HT suggesting the involvement of cyclic nucleotides. Paired-pulse facilitation was altered by 5HT and by...
octopamine, suggesting that these substances act presynaptically. The effects of 5HT on the biophysical properties of identified presynaptic and postsynaptic cells of the VL were studied in whole-cell current clamp in enzymatically dissociated neurons. Preliminary experiments showed an increase in membrane excitability which resembles, at least in part, the 5HT-induced modification of these properties in Aplysia sensory neurons. Taken together, these results suggest that 5HT-dependent short-term neuronal plasticity, which is associated with simple forms of learning in mollusks, is conserved in brain areas of the octopus that mediate complex forms of learning and memory.

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Isolating the role of visual perception in dyslexia
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Despite the current prevalence of phonological theory of dyslexia, there are several theories (e.g. the magnocellular hypothesis) that attribute the key role to visual deficits as a basis for dyslexia. They stem from dyslexics' introspective reports of visual discomfort while reading and are supported by findings of various visual deficits in dyslectic subjects. However, these findings were argued against and largely explained as resulting from impaired perceptual memory rather than poor immediate perception. To assess the role of (possibly impaired) visual perception in dyslexics' reading, we composed a task that was similar to normal reading in its visual features, but lacked other aspects of reading (phonological, morphological, semantic etc.), and compared performance of dyslexics and controls on it under several paradigms. The task was to identify a letter of an alphabet unknown to subjects, but similar to Hebrew and English in all graphical details (11 similar Georgian letters). Eight different conditions were assessed, measuring threshold duration of presentation (SOA) and threshold contrast levels for identification of small and large letters, with and without flanker letters, with and without white noise. Twenty adult native-Hebrew speaking dyslexics, mainly students, and 20 controls, matched for gender, age, and general cognitive abilities, participated in this study. We found all the predicted effects in both groups. Namely, adding flankers and decreasing letter size increased threshold SOA's, and adding white noise increased contrast thresholds. However, there was no difference between the experiment group and the controls, neither in single-set comparison, nor in effect magnitude, nor in an all-inclusive analysis of variance (MANOVA d=0-1). We conclude that the visual processing defects found among dyslectic individuals by other researchers do not affect reading performance, and that therefore, the cause of their reading defect resides elsewhere.

Mechanism and circuitry for coarse and fine discrimination in the insect olfactory system
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We propose a solution to a major challenge in the study of olfaction, differences in coding between fine and coarse discrimination of odors. We hypothesize the existence of a hard-wired hierarchy in the insect brain connecting the antenna lobe (AL), the mushroom body (MB), and the lateral horn (LH), constructed of repetitive and non-overlapping substructures that govern the connections between these regions. Using the above circuitry, we propose two parallel mechanisms, one for odor clustering and one for fine discrimination. In line with results suggesting that the KCs are coincident detectors, fine discrimination is encoded by the activity of the Kenyon cells (KCs) in the MB. Our mechanism for coarse discrimination is new, and uses a population code of groups of inhibitory neurons in the LH. We show that these mechanisms can explain the experimental results that AL oscillations are required for fine but not for coarse discrimination. Our theory also fits the data showing that non-associative discrimination can still be performed when the MB is completely removed. In addition, it sheds light on physiological results recording the activity of the various neurons in this system. The model predicts that odors that strongly activate the AL will also strongly activate the LH neurons, while the KCs fire sparsely. Our hypothesis corrects also some of the discrepancies in many experiments that map the connectivity between these regions.

Cortical plasticity in the visual cortex of the bilingual blind: an fMRI Study
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Recent studies suggest that the brain is flexible and can adapt to new experiences throughout the life span. Our preliminary results show that acquisition of a new language can be disrupted by removing the primary visual cortex from the brain.

Effects of bilateral electric stimulation of the insular cortex on conditioned taste aversion in rats
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Recently acquired memories can be disrupted by agents such as protein synthesis inhibitors, during a maturation period called consolidation. Ample evidence now indicates that mature memories can also be disrupted by the same agents immediately after memory reactivation, in a process dubbed reconsolidation. We set out to find parameters for transient magnetic stimulation (TMS) techniques in humans, indicate that the visual cortex of the blind is recruited for other sensory functions as well as language processing. Is this plasticity restricted by a critical period? While so far this question has been tackled using a comparison between early blind vs. late blind, we asked if the two groups differ and learned English later in life (age 10). The subjects listened to "chimera" nouns (a superposition of a Hebrew noun and an English noun, e.g. "chumish") and were asked to repeat the noun heard, i.e. "verb generation, VG". This procedure was carried out in each language, i.e. Hebrew & English, in a block design fashion, according to heard instructions. When contrasting activation elicited during VG and repeat conditions, similar left lateralization activation was found for both languages throughout the whole brain including the visual cortex. Left lateralization was also observed in classical language areas (IFS, precentral sulcus) in congruence with findings from sighted subjects performing the same task. However, there was no significant difference in the fMRI activation generated by the two languages, in any cortical region, including the visual cortex. This suggests that the language was acquired within the critical period for plasticity. (which is thus longer than 10 yrs), or alternatively, regions in the visual cortex of the blind might be engaged in semantic processing, at an abstract level (regardless of the language of the heard words).

Meaning and function of brain oscillations

Newly acquired memories can be disrupted by agents such as protein synthesis inhibitors, during a maturation period called consolidation. Ample evidence now indicates that mature memories can also be disrupted by the same agents immediately after memory reactivation, in a process dubbed reconsolidation. We set out to find parameters for transient targeted brain stimulation that could lead to temporal dysfunction of brain substrates during acquisition, consolidation and reconsolidation of memories. Toward that end, we used conditioned taste aversion (CTA), a taste-malaise association, which is known to be subserved by the insular cortex, which contains the taste cortex of the rat. Our preliminary results show that acquisition of conditioned taste aversion (CTA) can be disrupted by bilateral electrical stimulation (50 min, high frequency) of the insular cortex, but not when stimulation is performed dorsal or lateral to the insular cortex. The stimulation was performed from the presentation of the conditioned stimulus (taste) until 10 min prior to the presentation of the unconditioned stimulus (malaise inducing agent, LiCl). These results are in line with results suggesting that a localized brain region could be used as a tool to disrupt memory processes such as encoding, consolidation, and possibly post reactivation reconsolidation. In the latter case, it could pave the way to the development of a new treatment for non responsive post traumatic stress disorder (PTSD) patients.
The Recombinant Fusion Protein VP-22-Activity-Dependent Neurprotective Protein Protects Photoreceptor Proliferating Cells Against Oxidative Stress

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Activity-dependent neurprotective protein (ADNP) is a recently discovered homeobox protein containing genes that are essential for brain formation (Dev Brain Res. 2003, 144:35-55). The results of the current study indicated that treatment of photoreceptor Proliferating Cells (PC12 cells) with ADNP protected against oxidative stress. The recombinant fusion protein VP-22-ADNP was expressed in E. coli, purified and assayed in differentiated photoreceptor cells. VP-22-ADNP was detected within the cells after 25-min incubation with western blot hybridization. However, using immunocytochemistry, only minute amounts of ADNP were detected intracellularly after a 25-min incubation period. Pre-incubation with VP-22-ADNP protected PC12 cells against beta-amyloid peptide toxicity as well as from oxidative stress. VP-22 by itself was devoid of protective activity. To examine if VP-22-ADNP protects against an apoptotic mechanism, alterations in the amount of pro-apoptotic protein P53 were measured in PC12 cells. Results showed that p53 increased by 3-fold from control levels in the presence of H2O2, while treatment with VP-22-ADNP prior to H2O2 exposure significantly reduced the p53 protein level. Thus, ADNP inhibited stress-induced p53 expression indicating protection against apoptosis. Taken together, these studies suggest that recombinant ADNP provides cellular protection against various toxic insults.

PKC isoforms play selective roles in the migration, differentiation and proliferation of multipotential precursor cells

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Multipotential neural precursor cells (MNPC) exhibit self-renewal potential and are capable of differentiating along different lineages of the CNS. The fate of the MNPC requires molecular cues mediated by extracellular factors and intrinsic signaling molecules. In this study we explored the role of protein kinase C (PKC) in the proliferation, migration and differentiation of MNPC. PKC, a family of phospholipid-dependent kinases, is highly expressed in the CNS and plays important roles in the proliferation and differentiation of neural precursors. We observed increased expression of PKCalpha, beta and epsilon in the MNPC. These studies suggest that PKCalpha, beta and epsilon are involved in the generation of astrocytes. To further explore the role of specific PKC isoforms in the differentiation of the MNPC, we employed adenovirus vectors expressing either PKCalpha, beta and epsilon and their respective kinase dead-mutants. We found that overexpression of PKCalpha selectively increased the generation of glioblastoma cells, whereas the KD mutant abolished the proliferation of glioblastoma cells. However, the KD mutant did not affect the proliferation of MNPC. PKCalpha may play a selective role in the migration of glioblastoma cells. Our results imply that PKCalpha is a major signaling pathway in the function of MNPC and suggest that different PKC isoforms can selectively direct the fate of MNPC and affect the generation of neurons, astrocytes and oligodendrocytes from these cells.

Music, Memory and Hemispheric Asymmetry in the Visual Cortex of the Congenitally Blind

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While the occipital cortex of the congenitally blind can be activated by tactile stimuli (as well as auditory ones), most of the evidence indicates that this activation is associated with verbal tasks, such as verb generation and Braille reading. Furthermore, tactile related activation in the occipital cortex can be found in blindfolded sighted subjects, after 5 days. This suggests that Braille, connecting phonics with tactile sensations, may be the critical link for the recruitment of the visual cortex, to take part in language processes. This study re-examines the emphasis on language, while demonstrating a larger effect of mnemonic properties of the task, especially in the primary visual cortex. We compared verbal and musical mnemonic tasks, as well as verbal and musical perceptual tasks. The mnemonic tasks included the recognition of previously learned words and tunes, and the perceptual tasks were the detection of a repeated tone or letter. We found that the mnemonic tasks generate robust activation in the visual cortex of blind compared with the perceptual tasks. Higher activation in V1 of the blind, in both hemispheres, was found during the musical mnemonic condition during the verbal task. This preference may be partially attributed to the depth and length of the encoding process of the lists, to be-remembered, into long-term memory, which was greater during the musical condition. Hemispheric differences in activation pattern were found in the lateral ventral occipital regions. Thus, the left lateral occipital cortex was significantly more activated during the verbal perceptual (phonological) task. This hemispheric difference is compatible with the asymmetry observed in the conventional language regions, grossly maintaining a lingual dominance in the left hemisphere and a musical dominance in the right hemisphere.

EM evidence for a mechanism of analgesia during general anesthesia

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Microinjection of minute quantities of pentobarbital into a restricted region of the rat brainstem, the MPTA (mesopontine tegmental area), can induce a general anesthetic-like state characterized by atonia and failure to respond to strong noxious stimuli (Devor and Zilkind, Pain 2001). To understand the neural circuitry underlying general anesthesia, we employed retrograde and anterograde anatomical tracers ( cholera toxin subunit, CBT and bionitinated dextran amine, BDA respectively). MPTA has a major descending projection to the rostral ventromedial medulla (RVM), a key relay component of the descending bulbospinal pain inhibitory system. To clarify if MPTA neurons that project to RVM indeed terminate on cells that project to the spinal cord, we performed a double-labeling experiment. Bulbospinal RVM neurons were retrogradely labeled by CTB microinjected into the lumbar spinal cord and MPTA afferent projections were labeled using BDA microinjected into the MPTA. At the light microscopic level we found numerous labeled MPTA axon collaterals projecting retrogradely to the spinal pain inhibitory system. These connections were confirmed by synaptic contacts at the electron microscopic (EM) level. Specifically, anterogradely labeled terminals were found to synapse onto spino-thalamic neuronal somata and dendrites. The projection of MPTA neurons onto bulbospinal RVM neurons could be a route whereby general anesthesia, supresses responsiveness to noxious stimuli during general anesthesia.
Temporally Coherent On-going Activity in Auditory Cortex is Demonstrated through LFP Recordings from Anesthetized Cats

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Electrical activity in the brain shows organization at multiple time and spatial scales. Here we studied the correlation between well-separated units, clusters of units, and local field potentials (LFP) recorded from 2-4 electrodes simultaneously during on-going activity in auditory cortex of halothane-anesthetized cats. We show that the local neural tissue has a significant degree of burst activity and temporal correlation. The number of spikes fired by single units during 200 ms periods with no stimulation was found to be correlated with the responses of other units recorded from the same and from nearby electrodes. Moreover, LFP recorded from those electrodes was significantly correlated with the number of spikes recorded at the same time period. These results support the hypothesis that the recorded spikes are only a few representatives of a temporally coherent on-going activity in the neural tissue. These findings imply that LFP, which is much easier to record than well-separated spikes, can help disambiguate information about sensory stimuli and is therefore a good candidate for decoding the neural activity, as it can replace spike sorting in some cases. For example, stimulus-specific adaptation, which was previously demonstrated in A1 at the single neuron level by analysis of the spike counts in response to standards and deviants in an oddball paradigm, is shown here to be present in the LFP recorded by the same electrodes as well.

The Role of Bad in the Neuroprotective Action of the Major Green Tea Polyphenol, (-)-Epigallocatechin-3-Gallate (EGCG)

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Green tea catechins and their derivatives have potent pharmacological activities. They act as radical scavengers and exert indirect antioxidant effect through activation of transcription factors and antioxidant enzymes. Its major polyphenol, (-)-epigallocatechin-3-gallate (EGCG) has been reported to exert potent neuroprotection in vitro and in vivo models of neurodegeneration. We have demonstrated that the neuroprotective action of EGCG is mediated by activation of protein kinase C (PKC). The aim of this study was to further determine the potential cell signaling pathways, downstream from PKC, involved in EGCG neuroprotective activity. EGCG (1µM) promoted a biphasic effect on the pro-apoptotic Bad protein: an immediate (30 min) down-regulation (~35%) of its protein levels, returning to control values 2h later and a more pronounced long-term (24h) reduction (~55%). The expression of Bax was not affected during the first 24h exposure to EGCG. The acute Bad reduction was accompanied by a 1.65 fold increase in phosphorylated PKC alpha isoform. By contrast, pretreatment with a general PKC inhibitor GF 109203X (2.5µM), abolished EGCG-induced Bad decline. This result indicates that PKC is a tight regulator of Bad protein expression levels, being essential for its degradation or synthesis. In view of this fine-tuning of the pro-apoptotic protein, we then evaluated the Ubiquitin Proteasome System (UPS) in EGCG-induced Bad degradation was examined. Pre-incubation with MG-132 (25µM), a proteasome inhibitor, blocked the degradation of Bad by EGCG. The present study reveals a novel pathway in the neuroprotective mechanism of EGCG, which involves a rapid PKC-dependent degradation of Bad protein by the UPS.

Differential Intrinsic Neuronal Plasticity in Epilepsy

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Temporal lobe epilepsy (TLE), the most common epilepsy in adults, is associated with structural and functional alterations in hippocampus and related structures, which lead to hyperexcitability and recurrent seizures. In a widely studied rat model of TLE, similar changes can be seen a few weeks after a single episode of status epilepticus (SE) induced by injecting pilocarpine. In this model, ex-vivo recordings from CA1 pyramidal cells (PCs) have revealed several changes in intrinsic excitability. The most dramatic change was increase in the fraction of bursting cells. This burst-firing was abolished by low Ni2+ concentration (100 µM), implicating low voltage-activated T-type Ca2+ current (ICaT) in its generation. To test whether TLE associated changes in intrinsic excitability are unique to CA1 PCs, we recorded similarly in CA3 PCs using standard current-clamp intracellular recording techniques. In control rats, CA3 PCs fired either regularly or in bursts in response to long (180 ms) and strong depolarizing current stimuli. Low-intensity or brief stimuli did not induce bursting. In contrast, 20% of CA3 PCs in pilocarpine-injected rats fired an all-or-none burst spontaneously or in response to just-threshold stimuli. This de novo bursting was unaffected by 100 µM Ni2+ nickel, but was blocked by the persistent Na+ current (INaP) blocker, 4-AP. This finding is consistent with the latter current, rather than ICaT, in its generation. This data, together with our previous study in CA1, suggest that upregulation of intrinsic excitability in CA3 PCs is wide spread, but the ionic mechanisms underlying aberrant intrinsic bursting may vary across different types of neurons.

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Acute brain neuroprotection by scavenging blood glutamate

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Abnormally high Glutamate (Glu) levels in brain interstitial and cerebrospinal fluids are the hallmark of several neurodegenerative conditions that result from acute insults, such as stroke, traumatic brain injury or meningitis. As a novel neuroprotective strategy, we have established that a decrease of deleterious Glu in brain fluids can be achieved by accelerating the naturally occurring brain-to-blood Glu efflux. This is produced by decreasing blood Glu levels upon intravenous (IV) administration of pyruvate (Pyruvate) and/or oxaloacetate (Ox-Ac). These compounds act as blood Glu scavengers since they activate respectively, together with their co-substrate Glu, the blood resident enzymes Glu-Pyruvate transaminase and Glu-Ox-Ac transaminase with transform Glu into 2-ketogluutarate. We have investigated the acute neuroprotective effects of Pyruvate and Ox-Ac in rat models of closed head injury and of global ischemia. In the rat model of closed head injury, the IV administration of Pyruvate and/or Ox-Ac specifically improved the neurological status determined after 48 hours. Ox-Ac was superior to Pyruvate while the neuroprotective effects of Ox-Ac were abolished when the rats were treated with Ox-Ac + Glu suggesting that the beneficial effects of Ox-Ac are likely to be due to its blood Glu scavenging property. This suggestion is supported by the observation that rats treated with IV Glu have a worse outcome than control rats. In the rat model of transient global ischemia, the 30 min long IV administration of Pyruvate and Ox-Ac overlapping the 10 min long ischemia, was found after 7 days to cause the preservation of the vast majority of brain neurons in comparison to the death of 60% of neurons in control animals. We conclude that scavengers that reduce blood Glu levels cause brain neuroprotection by decreasing the brain-to-blood Glu efflux decreasing thereby the excitotoxic and deleterious effects of the high Glu levels in brain fluids.

The effect of magnetic field on olfactory processing

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Functional magnetic resonance imaging is increasingly used as a tool to elucidate the neural substrates of olfaction. However, it is possible that the magnetic field used in functional imaging may itself affect olfaction. It is known that the direction and strength of a magnetic field have an effect on visual perception tasks. Likewise, the strong magnetic field of an MRI scanner can induce phantom olfactory perception. Anodal observations in our laboratory suggested that olfactory intensity perception was enhanced under a strong magnetic field. To address this possibility, the University of Pennsylvania Small Identification Task (UPST) was administered to 9 subjects both in the MRI scanner (4 Tesla Varian) and out of the magnetic field in a mock scanner. In addition to identification, subjects rated stimulus intensity and pleasantness on a visual analog scale. The order of field strengths conditions (IN/OUT of the magnet) and UPST block order (Block 1) were counterbalanced across subjects. There was no significant difference in identification accuracy (mean OUT = 37, SD = 2.072; mean IN = 33, SD = 2.179) or hedonic rating (mean OUT = 43.97, SD = 17.042; mean IN = 45.86, SD = 17.71) in and out of the magnetic field. By contrast, there was a trend towards greater intensity rating IN as compared to OUT of the magnetic field (mean OUT = 0.95, t(8) = 2.0, p < 0.05). A post-hoc examination of identification accuracy for the 4 odorants that comprise the UPST identified 4 subjects who responded to a bilateral effect for the odorant cinnamon. Whereas only one subject failed to identify cinnamon in the field, five subjects failed to identify it out of the field. This difference (p < 0.02) does not meet the Bonferroni corrected criteria of p < 0.001. Further investigation of these results will determine whether these effects result from a change in peripheral or central level olfactory processing.

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Anatomical and Functional Consequences of Blood-Brain Barrier disruption in rat Basal Ganglia Cortex

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The blood brain-barrier (BBB) protects the brain from circulating xenobiotic agents. Disruption of the BBB is known under many pathological conditions. However, the pathophysiology, time span, spatial pattern and consequences of BBB disruptions are unknown. In animals, several invasive methods have developed to quantitatively measure BBB permeability. However, most of these methods are not applicable to humans. We have developed an image analyses program for quantifying BBB permeability to contrast agents injected during brain images procedures-computerized tomography (CT) and magnetic resonance imaging (MRI). By image analyses we were able to make a statistical comparison between brain images taken before and after the injection of the contrast material as well as measure % enhancement values. In a group of patients BBB disruption, detected by CT or MRI, was verified by single photon tomography (SPECT) following the injection of 99mTc-dihydrinetrinitromethane-10-nitro-2-phenylacetate (Te-DTPA). For patients the albumin concentration in the cerebrospinal fluid BBB disruption was found to be either diffuse or focal, and in most cases (>90%, n=101) was found to be confined to the cerebral cortex. In some cases disruption was found to occur over long periods of time (weeks-years). While various pathological groups were found to present with changes in BBB permeability, no single pathological process was found to underlie disruption in all patients. Two sub-groups of patients with focal, long-lasting BBB disruption were subjected to quantitative electroencephalographic recordings. These included 18 patients after mild head trauma and 12 patients post surgical removal of a benign meningioma. In both groups, spatial correlation was found between areas of BBB disruption and slow-wave abnormal cortical activity. We conclude that BBB disruption is a common disorder in the diseased cerebral cortex, and that persistent may be associated with abnormal cortical function.

Effects of pleasant and unpleasant gustatory stimuli in anorexia nervosa as revealed by spectral and dimensional EEG changes.

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Anorexia nervosa (AN) is considered a multifactor determined disease, with biological and environmental factors contributing to its evolution. The pathologically altered processing of gustatory stimuli could be an important factor in the development of AN. The aim of the present study was to investigate the effects of pleasant (chocolate) and unpleasant (bitter tea) gustatory stimuli on the EEG in both a healthy control group and in a group of AN patients by linear (frequency spectral analysis, Omega complexity) and non-linear (FDI analyzing dimension complexity) EEG complexity analysis. The subjects were exposed for two minutes to pleasant (sweet chocolate) and unpleasant (bitter tea) gustatory stimuli. The EEG was recorded right after taste exposure followed by mouthwash. The EEG was recorded by the NeuroScan system. The EEG recorded by 12 electrodes (Fp1, Fp2, F3,
F4, C3, C4, T3, T4, T6, P3, P4) was selected for further off-line analysis. In AN patients lower dimensional complexity and higher amount of relative theta power was observed than that seen in controls, independent of taste conditions. Higher Omega complexity was seen in control subjects during taste and no taste conditions. No such hemispheric difference was observed in AN. The lack of a significant Omega complexity change in response to exposure of sweet taste in the left side in AN patients may correspond to a decreased sensitivity to such stimuli in these subjects. Since all the patients who participated in the present study had episodes of abnormal wasting prior the investigation it seems reasonable to suppose that a long-lasting effects of malnutrition could be manifested in low dimensional EEG and higher amount of relative theta (4-8 Hz) activity.

"Juvenile" stress as a risk factor for impaired coping behavior in adulthood - A rat model.

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Epidemiological studies indicate that early life stress develops into a risk factor for developing mood and anxiety disorders in adulthood. While most studies focus on pre-weaning exposure, this study examined the consequences of stress during the post-weaning period. Experiment 1 examined the effects of mild and severe stress (days 27-29) on coping with stress in adulthood (Day 56), measuring exploratory behavior and avoidance learning. Experiment 2 evaluated the duration and magnitude of juvenile stress (28 days) effects on anxiety indices in adulthood. Experiment 3 sought after a critical developmental window during the post-weaning period, i.e., rats exposed to stress at either 27-29 days (juvenile) or 33-35 days (pre-adolescence) and their exploring and avoidance learning were assessed in adulthood.

Learning Deficits and Neuronal Degeneration in Male Mice Harboring One Copy of the Gene Encoding Activity-Dependent Neuroprotective Protein (ADNP)

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We investigated the role of ADNP in brain function using homologous recombination. ADNP knockout embryos die in utero [Brain Res Dev Brain Res 2003 144,383], while ADNP+/− heterozygous mice that show a 50% reduction in brain ADNP mRNA expression, exhibit growth restriction (−20%) and learning deficits. Learning deficits in the Morris water maze were observed at one month of age and were enhanced at two months of age in the ADNP+/− heterozygous males. Assessment of motor activity did not reveal a difference up to 2 month of age. The learning deficits may stem from defective brain development during embryogenesis coupled to deficits in ADNP in adulthood. Crealoisiole staining revealed degenerative neurons in the hippocampus and the cortex of 9-12 months old ADNP+/− mice and these results were corroborated by staining with a polyclonal antibody against the C-terminus of the beta-APP (beta amyloid precursor protein). Further studies identified hyper tau phosphorylation in the ADNP+/− mice. In combination, these findings support the hypothesis that ADNP is required for normal brain function.

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Prenatal immune activation in rats: mimicking abnormalities relevant to schizophrenia

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Frequency discrimination findings in dyslexia vary extensively, perhaps due to the variability in behavioral paradigms applied, and in the heterogeneity of the dyslexic groups. Previous findings in our Lab indicated that the majority of dysexic individuals who suffer from additional learning disabilities (D-LD) perform poorly in simple psychoacoustic tone discrimination. On the other hand - their basic speech perception seems adequate. We now asked whether it is the requirement of explicit stimulus comparison, in simple psychoacoustic tasks, which poses the difficulty for this group. A group of D-LD teenagers and a group of education and age-matched controls were administered an odd-ball paradigm with graded changes in tone frequency. In the first phase, subjects ignored the auditory stimulus and mismatch-negativity (MMN) was recorded. Afterwards a behavioral active discrimination task was administered. We found diminished MMN amplitudes in the D-LDs group compared to controls. A particularly large difference was found for the larger deviance. Moreover, whereas MMN amplitude and latency for controls was graded according to the degree of deviance presented, no such gradation was found for D-LDs. This pattern of results was mirrored in the behavioral performance. Response time and accuracy for all deviants were worse in D-LDs, and showed no gradation for the different deviants, whereas controls showed better performance as the deviation increased. Thus, D-LDs have impaired behavioral and brain responses even when no explicit comparison is required. MMN stems from an implicit form of perceptual memory which is engendered in response to repetitive sequences of stimuli. We thus propose that the source of D-LDs' deficit is impaired implicit memory, apparent as adaptation. Since specific stimulus representation of consistently concurring stimuli, its misfunction hampers formation of adequate auditory representations, as is the case in D-LDs.

Frequency MMN is impaired in dyslexics with learning difficulties

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Prenatal exposure to infection is associated with increased liability to schizophrenia, and it is believed that such an association is mediated by the maternal immune response, in particular the pro-inflammatory cytokines released by the maternal immune system, which may disrupt fetal brain development. We induced maternal immune activation by peripheral administration of the synthetic cytokine release inhibitor Polybromosinic-Polyribocytidylic acid (poly I:C) to pregnant dams, and assessed in the offspring several indices considered relevant to schizophrenia, pre- and post-puberty. Consistent with the characteristic maturational delay of schizophrenia, prenatal immune activation led to post-pubertal emergence of disrupted capacity to ignore irrelevant stimulus, one specific behavior that may correspond to hyperactivity in schizophrenia. This in turn supports the hypothesis that immune activation during pregnancy may in part be responsible for the interaction between maternal infection during pregnancy and schizophrenia.

Conclusions...

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Examining effects of postnatal maternal care on offspring phenotype by “switching” the pups between dams of different genotypes or lines.

The relative contribution of postnatal maternal care to the offspring’s phenotype can be partially analyzed by studying pups from one line/genotype that are placed with a mother from another line/genotype and comparing them with pups raised by same-line dams. Benefits and limitations of this approach will be discussed, together with findings from our labs, using several rat models and assessing isolation-induced ultrasonic vocalizations (USV, a measure of “infant separation-anxiety”), body-weight and immobility in the swim-test (a measure of “behavioral despair”). We found that cross-fostering rat pups from a line that emits a high amount of USV to low-USV-line dams did not affect the pups’ high vocal response. Pups from a different line (“OLET”), lacking type-A receptors for the neuropeptide cholecystokinin, also were found to emit many USV compared to their control line (LETO). Nursing dams did not affect the pups’ high vocal response. Preliminary results suggest that this holds even when the OLET pups are raised by a LETO dam. In the Flinders-Sensitive Line (FSL), an animal model of depression, we found that nursing dams and weaned, prepubertal pups, exhibit greater duration of immobility in the swim-test compared to Sprague-Dawley (SD) controls. Maternal behavior patterns of FSL dams were also abnormal. Cross-fostering SD pups to FSL mothers increased the prepubertal pups’ immobility duration, while immobility of FSL pups was not significantly changed by cross-fostering by a SD dam. To the extent that the “switching” method can represent postnatal environmental influences, the results above suggest that factors beyond postnatal care (i.e., genetic, and prenatal environmental factors) may provide most of the influence on USV and weight gain, at least in these particular rat lines. However, other postnatal manipulations may nevertheless affect the infant’s phenotype.

Interleukin-1 (IL-1) Plays a Role in Stress-Induced Analgesia (SIA)

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Several lines of evidence indicate that the proinflammatory cytokine IL-1 is involved in the neural, endocrine and behavioral responses to stress. For example, exposure to various stressors was found to increase the production and secretion of IL-1 in the periphery and within the brain. However, the extent of this increase was associated with activation of the hypothalamic-pituitary-adrenal axis. We have recently shown that IL-1 signaling in the hypothalamic-pituitary-adrenal axis is involved in stress-induced corticosterone secretion after exposure to mild stress compared with their wild type (WT) controls. A prominent consequence of exposure to stressful stimuli is reduced pain sensitivity, termed “stress-induced analgesia (SIA)”. Since IL-1 plays a role not only in stress responsiveness but also in pain modulation (under both inflammatory and non-inflammatory conditions), we hypothesized that it is involved in the pain modulatory effect of stress. To test this hypothesis we used two mouse models of impaired IL-1-signaling: Targeted deletion of the IL-1 receptor type I (IL-1rKO), or transgenic overexpression of the IL-1 receptor antagonist within the CNS (IL-1rATG). Mutant mice were compared with their WT controls. Mice swam for 2 min at 32°C, allowed to dry for 2 min, and tested for pain sensitivity using the hot-plate test immediately after drying. Two-way ANOVA revealed a significant strain by treatment interaction: The two WT strains displayed marked analgesia following exposure to the swim-stress, while both mutant strains did not display stress-induced analgesia. These results suggest that IL-1 plays an important role in SIA. Since this effect was also observed in IL-1rATG mice, which overexpress IL-1r only in the CNS, it appears that this role of IL-1 is mediated via the CNS.

Impairment of Interleukin-1 (IL-1) Signaling Attenuates Neuropathic Pain and Spontaneous Ectopic Neuronal Activity Following Neuropathy

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Neuropathic pain is a chronic pain state resulting from peripheral nerve injury, characterized by both hyperalgesia and allodynia. In view of the known pain facilitatory role of IL-1 in various inflammatory conditions, these findings suggest that over-production of IL-1 may underlie the hyperalgesia and allodynia seen in neuropathic pain. In the present study, we tested the hypothesis that impaired IL-1-signaling influences neuropathic pain, using two mouse models: mice with targeted deletion of the IL-1 receptor type I (IL-1rKO) and mice with transgenic overexpression of the IL-1 receptor antagonist (IL-1rATG), and their WT controls. Neuropathic pain was induced by cutting the L5 spinal nerve on one side, and mechanosensitivity was measured for 7 successive days. Neuropathic pain was also assessed by cutting the sciatic nerve, measuring the autotomy score for 35 days. We report here that WT mice developed neuropathic pain, as reflected by significant allodynia and hindpaw ipsilateral to the injury compared with the contralateral hindpaw. The mutant strains, however, did not display increased pain sensitivity in either hindpaw. Spontaneous ectopic neuronal activity of these strains was recorded in the dorsal root ganglion (DRG), 1, 3, and 7 days following nerve injury. In WT mice a significant proportion of the axons (10.3-18.0%) exhibited spontaneous ectopic neuronal activity at all time points, whereas in mutant mice only minimal number of axons exhibited such activity (1.5-1.9%). WT mice developed progressive autotomy following sciatic denervation, while both IL-1rKO and IL-1rATG mice displayed delayed onset and reduced scoring. Taken together, these results suggest that IL-1 signaling plays an important role in the altered neuronal activity that underlies the development of neuropathic pain. Gilly Wolf and Eran Gabay contributed equally to this research.

D-Serine as a Physiological Activator of NMDA Receptors: Implications for Stroke and Psychiatric Diseases

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NMDA receptor plays a major role in excitatory neurotransmission, displaying a unique requirement of two distinct agonists to mediate calcium influx. In addition to glutamate, it requires binding of either glycine or D-serine to the “glycine site” of the receptor. Recent data indicate the presence of high levels of D-serine in the brain of higher organisms, raising the possibility that this unusual D-amino acid may be involved in the physiological regulation of NMDA receptors. We will present data demonstrating the biosynthesis, metabolism, uptake and release of D-serine from astrocytes, neurons and brain slices. We report that NMDA-diluted neurotoxicity in different experimental animal models occurs via endogenous D-serine, indicating that D-serine physiologically interacts with the “glycine site” of NMDA receptors. In this framework, D-serine is proposed to a novel neurotransmitter in the brain. Drugs that affect D-serine synthesis and degradation might be useful in several pathological conditions, including overstimulation of the NMDA receptors in stroke and neurodegenerative diseases, and NMDA receptor hypofunction in schizophrenia.
Scaffolding of Fyn kinase to the NMDA receptor determines brain region sensitivity to ethanol

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Alcohol abuse is a major societal problem. Although ethanol is a structurally simple, diffusible molecule, its sites of action are surprisingly selective and the molecular mechanisms underlying specificity in ethanol actions are not understood. The N-Methyl D-Aspartate (NMDA) receptor channel is one of the main targets for ethanol in the brain. We found that the brain region-specific compartmentalization of Fyn kinase determines NMDA receptor sensitivity to ethanol. We demonstrate that in the hippocampus but not in the cerebral cortex, Fyn is targeted to the NR2B subunit of the NMDA receptor by the scaffolding protein RACK1. Upon acute exposure to ethanol, RACK1 is dissociated from the complex thereby facilitating Fyn-mediated phosphorylation of NR2B, which enhances channel activity and thereby counteracts the inhibitory actions of ethanol. In this way, the selective scaffolding can account for the ethanol-induced acute tolerance on the NMDA receptor activity that is detected in the hippocampus but not in the cerebral cortex. The phosphorylation-dependent, region-specific activities of ethanol on the NMDA receptor scaffold provides a compelling molecular explanation that accounts for the selective activities of ethanol and may have important implications for elucidating pathways leading to alcohol addiction.

Delay activity neurons in monkey prefrontal cortex

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We trained a macaque monkey on a behavioral task that requires holding several visual images simultaneously in working memory. In each trial, a sequence of 1-4 different images served as samples. These were followed by a match stimulus, which was a repetition of one of the samples, (called the cue). The length of the sequence and the position of the cue in the sequence were chosen at random on each trial. The monkey's task was to recognize the appearance of a repetition of any one of the samples and therefore, for best performance, it needed to hold in working memory (selective delay activity) all of the images of the sequence. We recorded from prefrontal cortex, understood to be the most appropriate cortical area for involvement in such a task. A quarter of the recorded cells (45/168) exhibited delay activity. We found that delay activity initiated by presentation of one stimulus could survive through presentation of a few other images, as well as the match-intervals. As expected, we found that the longer the trial, i.e. the more intervening stimuli, the less was the chance of survival of the image's delay activity. These results are in good agreement with our behavioral results and model, proposing delay activity reflecting active working memory, maintaining storage of multiple images (IF, 2002, 2003; Amit et al., Cerebral Cortex 2003; Yakovlev et al., Cerebral Cortex 2004).

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A possible antagonism between norepinephrine and glucocorticoid-induced signaling pathways: relevance to the etiology and treatment of major depression

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Neurons are noisy elements. A quantitative understanding of neuronal noise along with a qualitative understanding of its origins is necessary for understanding the constraints under which the neural code operates. In a previous study, using current clamp recordings from layer IV-V pyramidal neurons in slice preparation of rats' neocortex, we demonstrated that voltage noise increases as the cell depolarizes. This increase was mostly due to the negative slope of persistent Na+ conductance in the subthreshold voltage regime, which acts as a voltage dependent amplifier of low frequency transients. In a recent study, simultaneous recordings we compared the noise in the soma to that of a dendrite in the same neuron. As in the soma, noise in dendrites also increased. Unexpectedly, the magnitude of noise in the soma was always larger than that in the dendrite. The difference increased with the distance from the soma. This was accompanied by blocking the Na+ conductance using tetrodotoxin. We conclude that the source of this noise is...
the persistent Na+ current which is located at the soma; the lower noise level at the dendrites is due to electrotonic attenuation of the noise from the soma to the dendrites. These results further support the existence of a tetrodotoxin-dependent noise source near the soma and suggest that Na+ dependent noise plays a major role in the integration of synaptic inputs and determination of the neuronal output.

The hippocampus and insular cortex are differentially activated in novel taste learning. Yechzekel O., Belkin M., Sagi D., Polat U., Goldschleger Eye Research Institute, Sheba Medical Center, Tel Hashomer, Tel Aviv University; Dept. of Neurobiology, Brain Research, The Weizmann Institute of Science.

Learning to adapt: adaptation of the visual system to monocular optical distortions. Yechzekel O., Belkin M., Sagi D., Polat U.

Hill Coefficient for Estimating the Magnitude of Cooperativity in Gating Transitions of Voltage-Dependent Ion Channels Yifrach O.

Stretch Injury to Cells Causes Changes in GSH/GSSG ratio (Redox status) in-vitro Model. Yeshurun-Cohen A., Kohen R., Shohami E. Dept. of Pharmacology, School of Pharmacy, Hebrew University, Jerusalem, Israel; Dept. of Pharmacology, School of Pharmacy, Hebrew University, Jerusalem, Israel.

Background: Astrocytes are the most abundant glial cells in the brain. They provide neurons with a supportive environment by exchanging products which are essential for the normal neuronal function and protect them against toxic mediators and hostile environment. Glutathione is one of the products which is exchanged between astrocytes and neurons. It is sensitive to oxidative stress and protects the brain from reactive oxygen species (ROS) which are massively produced in trauma. Objective: To evaluate changes in the levels of reduced (GSH) and oxidized (GSSG) glutathione in response to stretch injury of different severities in astrocytes and in epithelial cell-line, in correlation with cell death. Methods: Primary astrocytes cultured from newborn mice and HaCaT, transformed epithelial cell-line, were grown in wells on a flexible elastic bottom. A cell injury controller was used to produce a rapid pressure of known amplitude and duration leading to a stretch injury, which deforms the cells and serves as our model system. Cells were collected 1, 4 and 24 hours after the trauma and injected into HLC-ECO. Cell survival was measured by MTT method. Results and discussion: The survival of both cell types decreased with increased degree of trauma. In parallel, a decrease in GSH was found in both cell types 1 and 4 hours after trauma. Thus the redox potential calculated by the Nernst equation was found to be less negative in severe trauma as compared to control. No changes in the potential were observed in HaCaT 24 hours after trauma. Addition of NAC or BSO prior to the trauma affected significantly the results. Our results indicate that mechanical injury leads to changes in redox state reflecting oxidative stress, which in turn correlates with cell death. Thus, the ratio GSH/GSSG can serve as a sensitive cellular marker for oxidative stress after injury, and as a tool to evaluate novel antioxidant therapies.
Illuminating Vesicle Priming with live-cell TIRF microscopy

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Vesicles in neurons and neurosecretory cells undergo multiple steps of maturation in order to become fusion competent and eventually undergo exocytosis. The first requirement for fusion-competence is morphological docking of the vesicle at the plasma membrane. A docked vesicle is then primed for exocytosis by a series of molecular steps. A key step in vesicle priming is the formation of the SNARE complex between Syntaxin, SNAP25 and VAMP (Synaptobrevin). Formation of this complex has been shown to be a crucial step in neurotransmitter release and as such it is regulated by numerous protein-protein interactions. It was suggested that the degree of "release-readiness" of different vesicle populations is defined by the molecular machinery that regulates docking and priming. We have used total internal reflection fluorescence microscopy (TIRF) to track single large dense-core vesicles (LDCV's) inside living chromaffin cells and analyze their mobility. Using a custom-written software we have obtained trajectories of individual vesicles within control cells and cells overexpressing an inhibitory protein Tomosyn. Tomosyn was shown to form SNARE complexes with Syntaxin and SNAP25 and inhibit the association of Synaptobrevin with the subcellular sites at which this potential originates. CA1 pyramidal cells manifest a conspicuous somatic spike ADP that causes some of them to burst-fire when strongly depolarized. Here, we show that CA1 neurons possess a persistent Na+ current (INaP) that gives rise to a substantial inward current within the voltage range of the spike ADP. In contrast, inward Ca2+ currents deactivate rapidly, with persistent Ca2+ currents within the voltage range of the ADP being about tenfold smaller. The somatic spike ADPs and associated bursting were potentially suppressed by a battery of drugs that blocked INaP. These effects of INaP block were replicated when the drugs were applied locally to the somatic region, but not following local application to distal dendrites. Additionally, spike ADPs were preserved in CA1 neurons in which the dendritic tree had been severed close to the soma, and were similarly sensitive to blockers of INaP. Collectively, these data suggest that the somatic spike ADP, which is a crucial determinant of CA1 neuron excitability, is generated locally by activation of persistent Na+ channels in the proximal portions of the neuron.

The novel anti-Alzheimer-antiParkinson drug, ladostigil (TV3326) and rivastigmine, prevent apoptosis and regressing in holo-APP processing in SK-N-SH cells.

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The cholinesterase (ChE)-monoamine oxidase (MAO)-inhibitor, ladostigil (TV3326) has been developed as an anti-Alzheimer drug from the anti-Parkinson drug, rasagline. We have previously shown that ladostigil regulates survival protein (APP) processing by a protein kinase C activation (PKC)-dependent mechanism, in cell culture and in vivo. Since programmed cell death may play an integral role in Alzheimer's disease (AD), we investigated whether ladostigil exerts neuroprotective activity and regulate the levels of the holo-APP and its fragments, including high density amyloid neuroblasticoma SK-N-SH cells in long-term culture. Ladostigil (0.1-10 μM) dose-dependently decreased apoptosis via inhibition of the cleavage and prevention of caspase3 activation. Furthermore, it sensitivetoblockers of INaP. Collectively, these data suggest that INaP inhibition by ladostigil may be involved in the neurotrophic and neuroprotective effects of this drug.

Brain activation during recognition of sparse, camouflaged figures—an fMRI study

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We used fMRI to study the brain areas involved in the process of perceiving a figure from a sparse, camouflaged input. Two paradigms were used. In the first, four subjects viewed camouflaged images displayed for 7 or 20 sec, and were asked to indicate if and when they recognized the figure. fMRI data were taken throughout the viewing period. We explored the changes in the BOLD signal around recognition time. Comparing activation patterns before and after recognition, with activation seen when the subject failed to recognize the image, revealed areas that responded more strongly during recognition in the middle temporal gyrus while in early and mid-level visual areas activation was similar for both conditions. The second experiment used the fMRI adaptation method to test whether common or distinct neural populations respond to a camouflaged picture in comparison with grayscale photographs of the same figures. Stimuli were displayed in a block design paradigm, with repeating (adaptive) or different (non-adaptive) figures. The results indicate that in other brain areas there are regions containing different population that are sensitive to grayscale pictures and to camouflaged ones although the figures in both cases are the same. Our results may help to explore the network involved in the ability to detect random spatial cues into a meaningful, informative object.
The influence of NAPSVIQ pre-treatment on the induction and severity of experimental autoimmune encephalomyelitis (EAE).

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Activity-dependent neuroprotective protein (ADNP) was shown to be essential for brain formation (Pinhasov et al., J. Neurochem, 1999). Peptide scanning identified a motif in ADNP, NAPSVIQ (NAP), that provides femtomolar levels of potent endogenous neurotrophic activity. NAP was shown to stimulate neurite outgrowth and synapse formation and genes associated with the Cholinesterase Domain of Neurotactin (ChEs), a Drosophila transmembrane glycoprotein that is dynamically expressed in neuronal and epithelial tissues during embryogenesis and in the late larval period. ADNP is neuroprotective in vitro assays, neurotactin promotes heterophilic cell aggregation through interaction of its extracellular ChEs domain with a secreted immunoglobulin-like protein called amalgam. We have sub-cloned, separately, the genes of neurotactin and amalgam into a eukaryotic expression system. Stable transformants of P. pastoris expressing the genes of neurotactin and amalgam were achieved by electroporation followed by metabolic selection. Screen for colonies with multi copies of the genes was performed by selection on increasing concentration of the antibiotic G418. Expression of proteins was induced with methanol for 6 days, resulted in secretion of the corresponding proteins into the growth medium from which they were collected and tested for the presence of the medium components and other P. pastoris proteins was in two steps first, affinity chromatography and then size exclusion chromatography in the presence of a detergent.

Transcranial Magnetic Stimulation of Deep Brain Regions: Evidence for Efficacy of the H-Coil

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Objective: Standard coils used in research and the clinic for non-invasive magnetic stimulation of the human brain are not capable of stimulating deep brain regions directly. As the fields induced by these coils decrease rapidly as a function of depth, only very high intensities would allow functional stimulation of deep brain regions and such intensities would lead to undesirable side effects. We designed a coil based on numerical simulations and phantom brain measurements that allows stimulation of deeper brain regions, termed the Hesed H-coil. In the present study we tested the efficacy and some safety aspects of the H-coil on healthy volunteers. Methods: The H-coil was compared to a regular figure-8 coil in six healthy volunteers by measuring thresholds for activation of the abductor pollicis brevis (APB) representation in the motor cortex as a function of distance from each of the coils. Results: The rate of decrease in the coil intensity as a function of depth is markedly slower for the H-coil. The motor cortex could be activated by the H-coil at a distance of 5.5 cm compared to 2 cm with the figure-8 coil. Conclusions: The present study indicates that the H-coil is likely to have the ability of deep brain stimulation and without the need of increasing the intensity to the extreme levels required for current figure-8 coils. Significant clinical applicability: The ability of non-invasive deep brain stimulation opens a wide range of both research and therapeutic applications.

Cloning, Overexpression and Purification of the Cholinesterase Domain of Neurotactin and its Interacting Partner Amalgam

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Studies during the last decade have identified five proteins with substantial sequence similarity to cholinesterases (ChEs). The regions of sequence similarity correspond to only part of the complete sequences of these proteins, thus establishing the ChE domain as a modular domain incorporated into different proteins. One of these proteins is neurotactin. Neurotactin is a Drosophila transmembrane glycoprotein that is dynamically expressed in neuronal and epithelial tissues during embryogenesis and in the late larval period. In in vitro assays, neurotactin promotes heterophilic cell aggregation through interaction of its extracellular ChEs domain with a secreted immunoglobulin-like protein called amalgam. We have sub-cloned, separately, the genes of neurotactin and amalgam into a P. pastoris expression vector. Stable transformants of P. pastoris with the gene of neurotactin and amalgam was achieved by electroporation followed by metabolic selection. Screen for colonies with multi copies of the genes was performed by selection on increasing concentration of the antibiotic G418. Expression of the proteins was induced with methanol for 6 days, resulted in secretion of the corresponding proteins into the growth medium from which they were collected and tested for the presence of the medium components and other P. pastoris proteins was in two steps first, affinity chromatography and then size exclusion chromatography in the presence of a detergent.

Discriminating Deuterated from Undeuterated Acetophenone: Comparing Humans and a Dog

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To determine if deuterated compounds are distinguishable from their undeuterated counterparts through smell, we set out to replicate a previous report: 21 subjects performed a one-trial same/different discrimination on two jars containing deuterated (D) and undeuterated (H) acetophenone. 24 subjects correctly distinguished between two identical samples of H. 23 subjects erroneously chose different. However, when performing the same task using two identical samples of D, 23 subjects incorrectly chose different. To avoid this, we used an olfactometer to test 38 subjects in a 32 trial same/different forced choice design. Mean accuracy was not different from chance (52.5%±3.5, NS). To eliminate possible habituation effects, we repeated the task in 14 subjects with only 8 trials. Although mean accuracy was not different from chance (60%±2.5 NS), 3 subjects did get all 8 trials correct. To test a different paradigm we then tested an additional 65 subjects on a 14-trial two- alternative forced choice identification task again with jars. Mean accuracy was not different from chance (51.2%±16, p>1), but 5 subjects performed significantly greater than chance (one subject at 100% p<.0006, two subjects at 93% p<.0009, one subject at 86% p<.006, and one at 78.5% p<.055) while no subject performed significantly below chance. Humans mostly unsuccessful, we set out to see if dogs could do it. A German Shepard was trained to work for the H-coil. He then did 7 trials of a three-alternative forced-choice identification task at 100% accuracy (p<.001). To address the concern that the dog was making an intensity rather than identity judgment, we conducted an additional 12 trials using different intensities of the target and distracters. The dog was at 100% accuracy (p<.001). Thus, dogs can distinguish deuterated from undeuterated acetophenone.

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Enhanced neural excitability of hippocampal neurons is related to acquisition olfactory rule-learning

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Rule learning of an olfactory discrimination task in rats is accompanied by reduction in the post-burst afterhyperpolarization (AHP) in the basal hippocampus. The purpose of the present study was to examine whether such reduction occurs also in hippocampal neurons. Water deprived rats were trained in a 4-arm maze to discriminate positive cues in 2 pairs of odors for a water reward. We examined the AHP amplitude in CA1 hippocampal neurons recorded in brain slices at different time intervals after the beginning of training. To standardize AHP recordings, neurons were depolarized to holding potential of -50 mV by current application via the recording electrode. Post-burst AHP amplitude was then measured following a 100 ms depolarizing current step with intensity that generates 6 action potentials. Olfactory learning-induced reduction in post-burst AHP was observed in CA1 neurons as soon as 3 days after the rats began their training (e.g. during the time in which they are learning the rule). Post-burst AHP was reduced in neurons from trained rats in the 3-7 days of training, the averaged AHP amplitude (in mV) was 2.92±1.32, n=28, in neurons from trained rats, 3.65±1.32, n=17 in neurons from naive rats and 3.96±1.31, n=35 in neurons from pseudo trained rats (p=0.05, one way ANOVA). Notably, three days after rule learning, the averaged AHP value in CA1 neurons form rats that were trained was significantly higher than observed during learning (4.53±1.64 mV, n=6) even if training was concluded at this point of onset. This value does not differ from that observed in neurons from control rats, suggesting that the time course of post-burst AHP reduction and its subsequent return to control values differs between periforn cortex and hippocampal neurons. We suggest that olfactory learning-related post-burst AHP reduction in CA1 hippocampal neurons may represent a mechanism that enables rule learning, but is not related to its maintenance.

Adaptive immunity is needed to maintain hippocampal neurogenesis in adulthood

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Studies from our laboratory over the last few years have shown that the controlled activity of T cells directed to autotigens in the central nervous system (CNS) is needed for postinjury survival and repair and that their action is part of the body's physiological response to CNS injury. Recently, we showed that spatial learning/memory is impaired in immune-deficient mice and restored by T cells. In this study we tested whether the postinjury survival and repair functions of T cells in the adult brain rely on their specific pattern of CNS-specific T cell development. Here, we show that in adult mice, C57BL/6 mice, which lack the CD8+ T cell receptor (CD8-), hippocampal neurogenesis was significantly impaired relative to wild-type controls. Reduced hippocampal neurogenesis in SCID mice relative to wild-type mice correlated with reduced levels of brain-derived neurotrophic factor in the dentate gyrus, as well as lower density of capillary vessels in the dentate gyrus. These results shed light on age-related cognitive loss and hint at a novel means of maintaining neurogenesis.

Functional organization of motor centers in the octopus brain

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The nervous system of the octopus is uniquely divided into a centralized brain and an elaborated peripheral nervous system. The brain consists of 2/3 of the total 500 million nerve cells. Several lines of evidence suggest that a significant part of the arm functions are rather autonomous, both in processing sensory information and in executing stereotypical arm movements. To understand the control relationships between the central brain and the peripheral nervous system, a micro-wire electrode was implanted and glued to the brain capsule allowing recording of single units activity and micro-stimulation in freely behaving animals. The electrodes were positioned to obtain recordings from higher motor centers (basal lobes), and the exact site was determined histologically by the location of electrolytic lesions. Stimulation initiated a variety of whole body movements. The kinematic analysis of the evoked movements did not reveal areas within the higher motor centers where specific stereotypical movements such as arm extensions, could be triggered nor movements of a specific arm. These higher motor centers have strong sensory inputs from the entire body. Analysis of the responses evoked by stimulating different body parts shows that as in the motor case, there is no central spatial representation of the arms or other body parts within the basal lobe. Thus, a site that responds to tactile stimulation usually responds to stimulating all eight arms with no preference to any certain location along the arm. In addition, different sensory modalities (e.g. visual and tactile) were found to converge to the same recording site. All these findings fit the idea that in contrast to vertebrates, in the octopus brain there is no somatotopic sensory or motor organization. This may reflect an adaptation for the inherent complexity in representing eight flexible arms in a relatively small brain.

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Dependence of gamma-oscillatory synchronization on selective visual attention in awake behaving macaque

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Several recent models of psychopathological disorders that are thought to be related to abnormal interaction of distributed brain processes have focused on the meaning of oscillatory gamma synchronization. It was argued that visuospatial anomalies associated with weak central coherence in autism may be due to the reduction of gamma-frequency synchronization between neuronal networks. Recent advances in schizophrenic research also relate specific symptoms of schizophrenia to a dysfunction of gamma-oscillatory activity, especially in the context of attention, which is even more severely affected. Some recent results have indicated a general relationship between attention and gamma-band synchronization, but there is only little experimental data about the influence of attention on synchronized activity at the single cell level. To test this hypothesis further we carried out multi-electrode recordings in macaque motion-sensitive area MT under normal (non-pathological) conditions at adulthood. T cells have a role in regulating hippocampal neurogenesis. Here we show that in adult mice, hippocampal neurogenesis is significantly impaired relative to their wild-type counterparts. Reduced hippocampal neurogenesis in SCID mice relative to wild-type mice correlated with reduced levels of brain-derived neurotrophic factor in the dentate gyrus, as well as lower density of capillary vessels in the dentate gyrus. These results shed light on age-related cognitive loss and hint at a novel means of maintaining neurogenesis.

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