# THE AGONY OF CHOICE

**Alex Pouget**
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Most of what we understand of the neural basis of perceptual and decision making is currently limited to binary choices based on a single source of evidence whose reliability is fixed over time. In contrast, real life decisions often involve multiples choices and multiple sources of evidence with unknown time varying reliability. I will present a pair of studies in which we have started to explore the neural basis of these realistic decisions. I will start by presenting a neural theory of optimal decision making for 3 or more choices which explains in particular why people agonize when choosing among equally good options. In the second half of the presentation, I'll present a model of optimal multisensory decision making based on the theory of probabilistic population codes. I'll show that this theory is consistent with the population response of parietal area LIP in monkeys trained to perform optimal multisensory integration.

# THE FUNCTIONAL CONSEQUENCES OF TRIPARTITE SYNAPSES ON CORTICAL CIRCUITS

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The brain consists of two major cell classes: neurons and glia. Traditionally, neurons have been considered to convey and process information, while glia have been thought to be support cells, helping maintain the balance of ions and provide nutrients but not participate directly in the brain's major function of information processing. Our research overturns this view, showing that astrocytes, the major glial cell type in the nervous system, contribute to the processing of synaptic information by neuronal networks.

Interneurons are involved in fundamental aspects of brain function playing a key role in the operation of neuronal networks. Thus, fast time course of GABAergic signaling controls the neuronal outputs. The GABAergic signaling to astrocytes has been previously shown, being able to activate intracellular $Ca^{2+}$ signaling. However, the impact of the interneuron-astrocyte signaling into neuronal network operation remains poorly defined. We will discuss evidence of how astrocytes sense and decode interneuron activity transforming inhibitory signals into an excitatory output, contributing to the emergence of novel network properties resulting from the interneuron-astrocyte interplay. These results will show the existence of new mechanisms to fine-tune the output of local synapses by astrocyte activity that might contribute to control the excitation-inhibition balance at the hippocampal circuits. Addtionally, we will discuss how new technical advances can help to unmask active roles of astrocytes in the information coding by neuronal networks

# DO ASTROCYTES CONDUCT THE NEURONAL SYMPHONY?

**László Héja**
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The function of astrocytes in the brain has been continuously evolving since the early days of neuroscience. Once considered to be merely ‘glue’, they were eventually recognized as supportive cells of neurons. In the last two decades a massive amount of evidence, showing that astrocytes significantly modulate synaptic activity, necessitated to leave this view behind andastrocytes have been acknowledged as important players in the tripartite synapse.In the last few years, experimental data extended even this notion and demonstrated that beyond the cellular level interactions, astrocytes also display network level activity that guides neuronal networks and plays a remarkable role in higher cognitive functions.

A unique feature of the astrocyte network is that cells are extensively interconnected by gap junctions. Due to the effortless transport of ions and small molecules through this pathway, the astrocytic syncytium can be quickly synchronized in large areas, making the astrocytes ideally positioned to introduce or extend neuronal synchronization. We explored the potential role of astrocytes in two distinct, characteristic synchronized neuronal activity, the physiologicalslow wave activity (SWA) and the pathophysiological, high frequency epileptiform activity. Importantly, themechanism by which synchronized neuronal firing emerges is not identified in either of these processes. To address the possibility of astrocytic involvement in SWA, we used a transgenic rat line expressing a calcium sensitive fluorescent protein in both astrocytes and interneurons and simultaneously imaged astrocytic and neuronal activity in vivo. We demonstrated, for the first time, that the astrocyte network display synchronized recurrent activity in vivo coupled to UP states measured by field recording and neuronal calcium imaging. Furthermore, we presented evidence that extensive synchronization of the astrocytic network precedes the spatial build-up of neuronal synchronization. Similarly, long-range astrocytic synchronization, spatiotemporally coupled to the synchronized neuronal activity was also observed in the low-[$Mg^{2+}$] in vitro epilepsy model.Since blockade of astrocytic gap junctional communication reduces the ratio of both astrocytes and neurons involved in SWA in vivo as well as prevents the appearance of seizure-like events in vitro, we concludethat the astrocytic syncytium plays a causal role in the generation of different types of neuronal oscillations.

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# CONTRIBUTION OF ASTROCYTE LARGE-CONDUCTANCE $CA^{2+}$-ACTIVATED POTASSIUM CHANNELSTOVASOCONSTRICTIONIN RESPONSE TO SPREADING DEPOLARIZATION

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Spreading depolarization (SD)-related potassium accumulation (>20 mM) isassumed to cause vasoconstriction and lesion progression in ischemic stroke. Astrocytesregulate cerebral vessel diameter by calcium dependent perivascular potassium release. Our aim was to investigate the role of astrocyte large-conductance $Ca^{2+}$-activated potassium channels (BK channels)in the SD-related vasoconstriction.

SDs were triggered by bipolar stimulation on rat coronal brain slices (350 µm) in vitro (n=8), or with 1M KCl in the cortex of anesthetized mice in vivo (n=18). Local field potential (LFP), extracellular $K^+$concentration ($[K^+]_e$) and CBF variations were assessed with glass capillary electrodes, $K^+$-sensitive microelectrodes and laser-Doppler flowmetry. Live fluorescent visualization of$[K^+]_e$(APG-2), vessel diameter changes (rhodamine dextrane), and calcium variations (Fluo-4 AM) in SR-101 labeled astrocyteswere performed using multiphoton microscopy. BK channels were blocked by paxilline (500 nM).

Arterial constriction (from 16.4±3.2 to 6.7±5.1 µm) in response to SD was coincident with the $[K^+]_e$ elevation(APG-2 fluorescence 0.14±0.03 $\Delta F/F$, corresponding to $[K^+]_e$ of 35.5±5.3 mM), and astrocyte calcium waves, but not tocalcium oscillations (percentage of active astrocytes; 92.73±5.71 vs. 25.6±8.51 %, waves vs. oscillations). Paxillinehampered the $[K^+]_e$ increase with SD (29.7±5.4 vs. 37.0±3.5 mM, paxilline vs. control) and diminished the related hypoperfusion (relative amplitude: 2.82±0.1 vs. 24.03±13.23 %, paxilline vs. control).

We propose that the activation of the astrocyte network and potassium efflux through BK channels are central to the cerebral blood flow response to SD. These data underscore the crucial role of astrocyte potassium release in cerebrovascular diseases in which SDs recur.

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# ASTROCYTE-DEPENDENTCHANGES OF NEURONALEXCITABILITY IN CELLULARMECHANISMS OF SLEEPHOMEOSTASIS

**Balázs Pál**

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**University of Debrecen, Faculty of Medicine, Department of Physiology, Debrecen**

Astrocytes are known contributors of sleep homeostasis via regulating neuronal functions by gliotransmitter release. Their roles were extensively demonstrated in cortical and diencephalic structures, but little is known about it in the reticular activating system (RAS). In the present project we aimed to observe the astrocytic component of different neuromodulatory actions on the pedunculopontine nucleus (PPN), a cholinergic nucleus of the RAS. We aimed to describe its actions on cellular and local network level.

It was found that cholinergic, serotonergic and cannabinoid actions elicit tonic inward and outward currents in a similar proportion and sometimes overlapping way. These actions were prevented by application of mGluR antagonists and preceded by increased astrocytic activity. Optogenetic activation of astrocytes led to similar actions on neurons. In parallel with tonic changes of excitability, NMDA receptor dependent slow inward currents (SICs) were also found on PPN neurons. If SICs had a low frequency in control, all neuromodulatory actions increased their frequency; and, in case of high original SIC activity, all actions inhibited them in a uniform way. The background of this phenomenon is the balance of NMDA receptor activation and desensitization. Neuromodulatory actions on SICs were independent from occurrence of tonic currents.

In summary, two independent astrocyte- and extrasynaptic glutamate-dependent actions were identified in the pedunculopontine nucleus. These actions seem to be uniformly participate in distinct neuromodulatory actions, probably serving as a homeostatic mechanism maintaining an intrinsic activity pattern of the PPN together with a certain low level of ’random’ neuronal activity.

# CONTRIBUTION OF INDIVIDUAL SYNAPSES ON DENDRITIC SPINES TO ELECTRICAL SIGNALING IN SINGLE NEURONS - A VOLTAGE IMAGING STUDY

**Dejan Zecevic**

**Yale University School of Medicine, New Haven, USA**

Electrical properties of neurons are extraordinarily complex, dynamic, and, in the general case, impossible to predict in the absence of detailed measurements. To obtain such a measurement one would, ideally, like to be able to monitor electrical subthreshold events as they travel from synapses on distal dendrites and summate at particular locations to initiate action potentials. It is now possible to carry out these recordingsusing voltage imaging. In these measurements, the voltage-sensitive probes can be thought of as transmembrane voltmeters with a linear scale, which directly monitor electrical signals. We combine voltage imaging and glutamate uncaging using computer-generated holography (CGH).The results demonstrated that patterned illumination, by reducing the areaof illuminated membrane, reduces photodynamic damage. Additionally, region-specific illumination practically eliminated the contamination of optical signals from individual spines by the scattered light from the parent dendrite. Finally, CGH allowsuncaging of glutamate on multiple spines to be carried out in parallel with voltage imaging from the parent dendrite and neighboring spines.Using this methodology, we showed, in several classes of principal cortical neurons, that synapses on spines are not electrically isolated from the parent dendrites. We next explored the temporal summation of evoked quantal EPSPs at single synapses. At high frequency of synaptic activation (100 to 200 Hz), both the electrical EPSC signal from the soma and the local optical EPSP signal from spines exhibit temporal summation. However, the summating signals saturated at a range of values from 15 - 80 pA for somatically recorded EPSCs and from 3 - 17 mv for optically recorded local EPSPs.This feature prevents synaptic saturation by maintaining the synaptic driving force approximately constant during repetitive activation of synapses.Our preliminary dataargue that AMPA-R desensitization is responsible for the saturation of EPSP response in spines during repetitive synaptic stimulation.

# GLIA-NEURON COMMUNICATION IN HEALTH AND ITS DISRUPTION IN HUMAN STEM CELL-DERIVED 2D/3D NEURODEGENERATIVE DISEASE PLATFORMS

**András Lakatos**

**John van Geest Centre for Brain Repair and Division of Stem Cell Neurobiology, Department of Clinical Neurosciences, University of Cambridge, UK &Wellcome Trust-MRC Cambridge Stem Cell Institute, UK**

Amyotrophic Lateral Sclerosis (ALS) is an untreatable and fatal disorder characterized by progressive loss of synapses and neurons in the spinal cord and in the brain, leading to muscle paralysis and to a variable degree of dementia. There is unmet need for treatments, but the precise causes are not understood. The emerging contribution to pathology by non-neuronal cells, such as astrocytes has opened up new avenues in pathomechanistic and therapeutic discoveries. However, the results from rodent disease models are not directly translatable in light of emerging differences and diversity of astrocytes between humans and other species. My talk will review our efforts in integrating the results obtained by using transgenic animals with findings from patient-specific 2D and 3D human induced pluripotent stem cell-based disease models. In particular, I will highlight our discovery of a novel neuroprotective pathway involving astrocytic ephrin-B1- and STAT3-mediated signalling and how it is lost in ALS.With its advantages and pitfalls human models are now emerging and are powerful tools in target development for devastating neurodegenerative diseases in combination with in vivo animal models systems.

# IN VIVO IMAGINGOF XENOGRAFTED ANDADULT-BORNNEURONS IN THE MOUSE BRAIN

**J. Tiago Gonçalves**
**Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA**

Recent advances suggest that neuronal repair through the generation of new neurons is a plausible future therapy for brain injury and neurodegenerative diseases. However, we do not understand the mechanisms underlying the correct wiring of new neurons in the adult brain. In our work, we combine cell labeling and transplantation with in vivo two-photon imaging, which has the unique advantage of allowing us to longitudinally follow the neuronal development of individual neurons as they integrate neuronal networks. In this talk will present data from xenografted human stem-cell derived neurons and endogenous, adult-born dentate granule cells.

# AGE-EQUIVALENT AND ADULT-LIKE INDUCEDNEURONSTOMODEL HUMAN AGE-DEPENDENTCELLULARDEFECTS IN ALZHEIMER'SDISEASE

**Jerome Mertens**
**University of Innsbruck, Innsbruck, Austria**

Sporadic Alzheimer's Disease (AD) exclusively affects people at old age and represents the overwhelming majority of all AD cases, as genetically defined familial cases are the rare exception. Still, most research on AD has been performed on genetic causes and their directly related pathways, also because we were in lack of models that can reflect complex human genetics, physiology, and age in an appropriate human neuronal context. While patient-specifici PSC-based models represent an attractive solution, iPSC reprogramming results in cellular rejuvenation and thus yields phenotypically young neurons. By contrast, direct conversion of old patient fibroblasts into induced neurons (iNs) preserves endogenous signatures of aging. To control forthe involvement of aging in human neuronalmodels for AD, we took advantage of combining both technologies and generated age-equivalent fibroblast-derived iNs, as well as rejuvenated iPSC-derived neurons from a large cohort of AD patients and controls. In addition to their rejuvenated state, we found that iPSC neurons transcriptionally resemble prenatal developmental stages, while iNs reflect adult-like neuronalstages and show little correlation with the prenatalbrain. Thus not surprisingly, only age-equivalent adult-like iNs, but not rejuvenated prenatal-like iPSC neurons, revealed a strong AD patient-specific transcriptome signature, which shows high concordance with previous human post-mortem AD studies, and high lights functional gene categories known to be involved in neurodegeneration. Based on AD patient-specific transcriptional, functional, and epigenetic changes, we found that AD iNs display a more de-differentiated neuronal state than control iNs, which might underlie many of the here and previously observed changes in AD. These data show that iNs represent a unique tool for studying age-related neurodegeneration, and support a view where a partially de-differentiated state of aged cells might permit the loss of the specialized neuronal fitness in AD.

# CAN WE GET CLOSER TO SCHIZOPHRENIA BY MEANS OF INDUCED PLURIPOTENT STEM CELL BASED IN VITRO DISEASE MODELING?

**János Réthelyi**
**National Brain Research Project (NAP) Molecular Psychiatry Research Group, Hungarian Academy of Sciences and Semmelweis University, Budapest, Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest**

Schizophrenia is a chronic, debilitating neuropsychiatric disorder of complex, poorly understood etiology. Despite intense research efforts using clinical, brain imaging, genetic, transcriptomic, and animal model approaches, the exact molecular disease pathways underlying schizophrenia remain unclear. It has been shown that induced pluripotent stem cells (IPSCs) derived from diseased and healthy individuals represent an important research tool for modeling neuropsychiatric disorders. These self-renewable human cell lines can be used to generate various neuronal types in vitro and to study their morphological, electrophysiological and pharmacological properties.

In my lecture I will review recent studies that have shown the usefulness of the IPSC based approach to investigate schizophrenia. Results will be presented about our in vitro disease modeling studies investigating schizophrenia patients carrying de novo mutations. Using molecular, functional and pharmacological assays in conjunction with genome-editing methods we aim to link these mutations to specific molecular pathways.

This study was funded by the National Brain Research Program (NAP) of Hungary (Grant NAP-B KTIA_NAP_13-2014-0011.

# FROM PATIENTS TO BASIC NEUROBIOLOGY AND BACK

**Gaia Novarino**
**Institute of Science and Technology, Wien, Austria**

Neurodevelopmental disorders such as autism, intellectual disability and epilepsy affect millions of people, and are often refractory to treatments. Not infrequently autism spectrum disorder phenotypes, intellectual disability and epilepsy are coexisting, suggesting the existence of common molecular mechanisms underlying these syndromes. The causes of epilepsy and autism remain unknown for the majority of cases. Of these, a significant number have a genetic basis and many causative genes remain to be identified. With DNA sequencing being more accessible, the genomes of many patients can be analyzed and more disease-causing genes will be recognized. Even though we predict that each identified gene may represent only a tiny fraction of the total genes involved in these disorders, studying the mechanisms underlying rare inherited forms of neurodevelopmental disorders can be extremely helpful. In my talk I will describe some key discoveries we made in the last few years as well as outline possible future directions.

# MOLECULAR MECHANISM OF AXON DEGENERATION

**Robert Adalbert[1,2], Jonathan Gilley[1], Richard J. Piercy[2] and Michael P. Coleman[1]**

**[1]John van Geest Centre for Brain Repair, University of Cambridge, Cambridge, United Kingdom**

**[2]Royal Veterinary College, University of London, London, United Kingdom**

Axon pathology is a common feature of many neurodegenerative diseases in humans and animals. It renders neurons functionally inactive, or less active if axons are lost, in a manner that is often irreversible. When axons are severed, the portion of the axon distal to the injury site undergoes extensive fragmentation, a process termed Wallerian degeneration. Our group and others have shown that a pathway, which involves NMNAT2, SARM1, PHR1, and Axed, regulates Wallerian degeneration of injured axons. This pathway is largely conserved between mammals, *Drosophila* and fish. Beside physical injury, apoptotic death of the soma, protein synthesis inhibition, knockdown or deletion of NMNAT2 and axonal transport impairment can also activate the Wallerian pathway.
Many of the challenges axons face relate to their extreme length. Longer axons have a higher risk of focal transport blocks (e.g. injury, inflammation), present a larger target for diffuse transport impairment (e.g. in poorly oxygenated tissue or genetic disorders) and require longer to deliver cargoes to their terminals. Our findings that NMNAT2 is a short-lived protein whose loss limits the survival of axons make this protein an excellent candidate to explain ‘dyingback’ axon loss in long nerves. To test the hypothesis that length-dependent nerve loss is related to deficits in the NMNAT2, we are using an equine disease model with recurrent laryngeal neuropathy. A better understanding of this survival pathway could be the key to uncovering novel therapeutic targets in length-dependent human peripheral neuropathies.

# NEUROMUSCULAR FUNCTION AND SYNAPTIC DEGENERATION IMAGED BY CONFOCAL ENDOMICROSCOPY

**Richard R Ribchester**
**Cornelia Roesl, Ross A Jones, Kosala N Dissanayake, Leire Ledahawsky, Thomas H Gillingwater, Paul A Skehel**

**Centre for Discovery Brain Sciences and the Euan MacDonald Centre for Motor Neurone Disease Research, University of Edinburgh, Edinburgh UK**

Neuromuscular junctions (NMJs) are among the first components of motor neurones that degenerate in amyotrophic lateral sclerosis (ALS) but diagnosis still depends mainly on clinical judgement supplementedby electromyography (EMG). We have shown previously that EMG combined with fibre-optic confocal endomicroscopy (CEM) can be used to trackdegeneration ofNMJs in transgenic mouse models expressing green fluorescent protein (GFP) variants in motor neurones. An obstacle to the translationof this technique to wild-type animals or human NMJs is the requirement for vital stains that can safely be administeredand that bind selectively to motor nerve terminals and axons. Using In-Fusion cloning and bacterial expression wemadetruncated variantsof the tetanus toxin heavy chain (TetHc) conjugated with either emerald-GFP or Alexa488. Several of these produced bright, high-contrast staining of rodent and human NMJs without affecting neuromuscular function. Binding to intact and degenerating motor nerve terminals was also readily visible in preparations from presymptomatic*G93ASOD1* mice and 4-6d axotomized $Wld^S$ mice. However, although NMJs could reliably be identified using CEM in rodent preparations, high background staining together with their small sizehave thus far limited our ability to locate human NMJs using this technique. Further investigations are ongoing in our lab to identify a complementary vital stain for axons. Nonetheless, we have shown that vital staining and CEM of NMJs when combined with electrophysiology provides opportunities for further investigation into mechanisms of synaptic degeneration and its mitigation by gene mutations or pharmacological treatments.Supported by MNDA Research Grant 838-791

# EQUINE RECURRENT LARYNGEAL NEUROPATHY – A HIGHLY PREVALENT DISEASE OF DOMESTICATION?

**Richard J Piercy**

**Comparative Neuromuscular Diseases Laboratory, Royal Veterinary College, London, United Kingdom**

Descriptions of equine recurrent laryngeal neuropathy (RLN) were first made by Bouley and Dupuy in the 1820s. Atrophy of laryngeal intrinsic muscles was commonly identified at necropsy in horses that ‘roared’ during exercise. The pathophysiology remains enigmatic as does the aetiology: genetic, acquired and environmental factors have each been proposed.The diseaseis described as a distal axonopathy of the longest motor nerve in the horse (2.5m) - the left recurrent laryngeal nerve - with secondary neurogenic muscle atrophy of intrinsic laryngeal muscles. The consequence is a reduced size of the rima glottis which becomesrelevantat exercise due to reduced PaO2.Certain crucial issues currently remain unresolved – (1) actual disease prevalence; (2) whether this is a polyneuropathy or a bilateral mononeuropathy and (3) aetiology and pathophysiology.

Estimates of RLN prevalence in horses vary widely. Indeed, advanced techniques, in particular exercising laryngoscopy, laryngeal computed tomographyand histology reveal it is hard to find a normal horse. This has profound implications for the search for the genetic cause.Histopathological changes within the distal nerves of horses with RLN reveal changes indicative of demyelination and remyelination, and accumulation of axoplasmic organelles and margination of microtubules. Such defects are seen in human neuropathies with suspected axonal transport defects. However, a combination of both a genetic and acquired component would seem to be necessary, since similar axonopathies are not known to be present in other athletic quadrupeds.Current data suggest that horses represent a valuable model for study of length-dependent neuropathies in humans.

# FOSTERING REGENERATION IN THE INJURED PERIPHERAL NERVE: IS MECHANOTRANSDUCTION THE KEY SOLUTION?

**Antal Nógrádi**

**Antal Nógrádi[1], David Hercher[2], László Gál[1], Krisztián Pajer[1], Thomas Hausner[2]**

**[1]Department of Anatomy, Histology and Embryology, Faculty of Medicine, University of Szeged, Szeged, Hungary**

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Low-energy extracorporeal shock wave treatment (ESWT) is a relatively new therapeutic tool that is widely used for the treatment of some chronic inflammatory conditions and to foster bone and wound healing. Shock waves, sonic pulses with high energy impact, are thought to induce biochemical changes within the targeted tissues through mechanotransduction. The biological effects of ESWT are manifested in improved vascularization, the local release of growth factors, and local anti-inflammatory effects, but the target cells too are influenced.
ESWT appears to have differential effects on peripheral nerves and has been proved to promote axonal regeneration in its early phase after axotomy. Already at 6 to 8 weeks of survival the ESWT-treated animals exhibit a significantly improved functional recovery relative to the controls. Electrophysiological observations at 3 weeks after axotomy reveal marked values of amplitude in the ESWT group. This finding is accompanied by significantly greater numbers of my elinated nerve fibres in the peripheral nerves relative to the controls 3 weeks after surgery. Three months after surgery, no significant differences are observed in the functional and electrophysiological data. It has also been shown that the most important pathways along which mechanotransduction induces the improvement of conditions for accelerated peripheral nerve regeneration are the augmented clearance by microglia cells, altered phenotype and activation of Schwann cells and better axon-Schwann cell contacts. Here we discuss the various morphological and molecular events occuring after ESWT treatment on injured peripheral nerves which suggest a multiple mechanism of action.

# **BETA**: **B**iological and **E**xperience-based **T**rajectories in **A**dolescent brain development

**Ilona Kovács (Hungarian Academy of Sciences – Pázmány Péter Catholic University Adolescent Development Research Group, Budapest**)

There is an emerging belief that adolescence is an exceptionally relevant period of human brain development where the maturation of brain networks is complemented by the specification of skills and behavioural changes. The adolescent brain continues to mature well into the 20s, with neural circuitry underlying executive functions among the last to mature. On the other hand, there is no consensus with respect to the developmental pace of other different cognitive functions. A usual pitfall of adolescent studies is that individual differences in puberty onset times are difficult to take into consideration against chronological age. The variability between individuals in the timing of the onset and in the pace of progression of puberty is very large, and the onset age can vary by as much as 6 years in typical development. There is a great uncertainty in both cross-sectional and longitudinal studies about the sheer contribution of genetically preprogrammed maturation versus experience.

The **BETA** (**B**iological and **E**xperience-based **T**rajectories in **A**dolescent brain development) projectaims to dissociate biological and chronological age for the first time, and to investigate their role independently in adolescent cognitive functioning and in the development of large-scale functional cortical networks. We assess biological maturity of a large sample of children and adolescents by a computerized estimation of their bone age, and then we select two cohorts of subjects for further investigations. Subjects are at the same biological maturity level, however different in chronological agein the “experience” cohort. In the “maturation” cohort, subjects are the same age, but they are different in maturity (or bone-age). We show that biological maturation as estimated by bone age and life-time experience related to chronological age are dissociable factors in adolescent brain development, and that their exact role is different depending on the studied developmental event.


# REGULATION AND DYSREGULATION OF THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL AXIS: THE IMPORTANCE OF STRESS COPING

**Antonio Armario**

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When facing stressors, subjects can use either passive or active strategies that are influenced by the possibility of control over the situation. The activation of the HPA axis is the most studied and well-characterized response to systemic and emotional stressors, but the extent to which particular behavioral traits (e.g. coping) or qualitative aspects of stressors (e.g. controllability) can affect the HPA axis is not well-known. We have then studied this relationship in rats using forced swim or foot-shocks as the stressors. No evidence for a relationship between individual differences in coping and HPA response to stress was found, supporting data obtained when comparing genetically selected strain/lines. In further work, we studied the impact of control over stress, using foot-shock exposure and a shuttle-box, by including a **master** group that could stop ongoing foot-shocks (escape) or prevent its occurrence (avoidance) moving from one compartment to another, and a **yoked** group whose behavior was irrelevant. In the escape task, activation of the HPA axis was similar in master and yoked rats even after repeated experience with the situation. However, in the avoidance task, master rats showed lower HPA response than yoked rats, but only after repeated experience. Master and yoked rats showed no differences in coping behavior during the FST and showed similar levels of HPA sensitization to this novel stressor as compared with rats not exposed to shocks. In conclusion, stress-induced HPA activation shows low sensitivity to particular quality of stressors, but might be sensitive to controllability under some circumstances

# THE SIGNIFICANCE OF EARLY LIFE FACTORS IN THE DEVELOPMENT OF DISORDERS

**Balázs Gaszner**
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A wide spectrum of animal models for depression were developed in the last decades. Environmental chronic stress paradigms are used in mice and rats to study how stress (mal)adaptation develops. In the last 30 years several lines of genetically modified animalsgenerated. In these mice, genes of important players of the stress adaptation response were manipulated in order to test their physiological significance in normal adaptation and disease. In the last decades it also became evident, that the expression of a particular gene does not depend exclusively on the base sequence of the DNA, but, long-term chemical modifications affecting gene transcription may also occur. These epigenetic changes are induced by environmental factors also. Long-term epigenetic changes caused by early life experience are believed to contribute to life-long changes in adaptation ability at gene transcription level.

In order to circumvent the limitations of „simple" environmental, genetic and early life stress models for depression, by applying the three-hit model of depression we combined genetic predisposition, early life stress and environmental chronic mild stress in mice to induce a depression-like phenotype.

Behavioral, neuroendocrinological and functional-morphological tools show that mice carrying a mutated allele of PACAP gene (genetic factor) with a history of maternal deprivation (epigenetic alteration) show disturbed chronic stress (environmental challenge) adaptation response and depression-like phenotype. Examination of patterns of epigenetic and neuronal activity markers in multiple stress centers revealed that the early life factors affect not only the stress adaptation response, but also the efficacy of antidepressant treatment.

# STRESS, SLEEP AND DEPRESSION NEW FACTORS IN AN OLD CIRCUIT

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Sleep deprivation actsas a stressor, and in long term influences stress responsiveness of the HPA axis. Sleepproblems are alsoamong the leading symptomsin patients with major depressive disorder (MDD). Furthermore, sleepproblemsfrequently precede the onset of recurrent episode of MDD, thereforeabnormal sleepis now regarded as an independent risk factor of MDD. Similarly to the relationship between mood disorders, sleep and stress, an association can be found between stress, stress-related disorders and metabolic disease.The functional interaction of the above systems is supported morphologically.Energy balance, stress and circadian rhythm regulation are all mediated by largely overlapping neural circuitslocated mainly in the hypothalamus, and many neuropetides possess multiple functions participating in several aspects of homeostatic regulation. Since theseinterrelationships may have significant therapeutic implications, systematic investigation of divergent roles of neuropeptides is vital. The present work focuses on two anorexigenic neuropeptides nesfatin-1 and prolactin-releasing peptide.They are coexpressed in the brainstem noradrenaline cell groups providing the main input about stress–related information toward the hypothalamus. Nesfatin-1 is also expressed in the lateral hypothalamus, a well-recognized area in regulation of sleep, appetite and mood. Functional significance of both peptides in stress and sleep was investigated. Data show that both nesfatin-1 and prolactin-releasing peptide participate in HPA axis regulation and influence the vigilance.The latter is moderatedby actingprobably onlateral hypothalamic MCH neuronsthat arecritical in the generation and maintenance of sleep, and hyperactivity of which underlies the pathophysiology of depression.

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# STRESS ADAPTATION IN THE BRAIN

**Dóra Zelena[1], Péter Csikota[1], Anna Fodor[1,2], Diána Balázsfi[1,2], Szilamér Ferenczi[3], Kornél Demeter[1], Zsuzsanna E. Tóth[4], Katalin Könczöl[4], Judith Camats Perna[5], Imre Farkas[6], Krisztina J. Kovács[3], Hiroaki Mizukami[7], József Haller[1], and Mario Engelmann[5,8]**

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According to Hans Selye the hypothalamic-pituitary-adrenocortical(HPA) axis is the main component of endocrine stress adaptation.Originating in the hypothalamic nucleus paraventricularis the corticotropin-releasing hormone colocalized with arginine vasopressin (AVP) are released from the parvocellular cells to regulatethis axis. The contribution of AVP of magnocellular origin on HPA-axis regulation is still under discussion.
We used anAVP-containing adeno-associated virus (AVP-AAV) vector, injected into the supraoptic nucleus (SON) of AVP-deficient Brattleboro rats (KO) and compared wild-type, KO and AVP-AAV treated KO male rats.
AVP-AAV treatment functionally rescued AVP synthesis. It also rescued peak levels of adrenocorticotropin triggered by immune and metabolic challenges without affecting the corticosterone response. The elevated corticotropin-releasing hormone receptor 1 mRNA levels in the anterior pituitary of KOs were diminished by the AVP-AAV-treatment. Altered c-Fos synthesis of KOs in response to application of a metabolic stressor was normalized by AVP-AAV in both the SON and medial amygdala (MeA), but not in the central and basolateral amygdala, or lateral hypothalamus. Although KOs did not show an altered social investigation and aggressive behavior, SON AVP-AAV treatment resulted in an enhancement and reduction, respectively, of these social behaviors. In vitro electrophysiological recordings showed an AVP-induced inhibition of MeA neurons.
In conclusion, AVP released from the magnocellular SON neurones may contribute to HPA-axis regulation by stimulating adrenocorticotropin secretion in response to defined stressors and controls the activity of MeA cells. Moreover, our data indicate the importance of AVP signalling in the MeA in the fine-tuning of social circuitry.