SYMPOSIUM I - PREDICTIVE NEURAL CODING IN AUDITORY AND VISUAL PERCEPTION

S1.01.

Prediction-based auditory responses to omissions of self-generated sounds

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Prediction affects the processing of incoming sensory information. Effects of prediction can be observed, e.g., in an attenuation of sensory responses to self-generated sounds or in the elicitation of the mismatch negativity to deviant stimuli. However we know very little about the form that the underlying prediction takes in the human brain or whether different effects of prediction are achieved through a common neurophysiologic substrate. We combined a self-generation and a regularity extraction paradigm in order to induce a strong, specific, prediction. We then isolated electrophysiological activity associated to the specific prediction, by randomly omitting the predicted stimulus. Participants pressed a button and a sound click was delivered. In separate blocks, self-generated sounds were omitted with a probability of p=.12 or p=.50. Omissions of self-generated sounds evoked a clear peak of activity that resembled responses to the actual sounds in timing and amplitude over temporal sites. The activity was localized to the auditory cortices by means of inverse source modelling. This auditory-like omission response was only elicited when omissions were rare; however, the auditory N1 response was attenuated relative to passive listening when sounds where delivered only in 50% of the button presses. Thus, predictive processes underlying self-generation effects and deviance detection appear to be independent.

S1.02.

Predictive models in auditory stream segregation

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Listeners usually experience sounds in terms of patterned sequences or streams, such as sentences, tunes, series of footsteps, etc. Since the emergence of the Gestalt school of psychology, the question of what makes the brain to group together certain elements of the sensory input while keeping others separate has been an important focus of perception research. Cumulating evidence led many psychologists, physiologists and computational modellers to suggest that sensory processes are inherently predictive. Taking this notion one step further, we will review evidence suggesting that auditory stream segregation is based on establishing predictive models for the regular aspects of the auditory environment and that these predictive regularity representations form the core of the representation of auditory streams. Based on behavioral and event‑related brain potential (MMN, ORN, P1/N1, P3a)

evidence, we will argue that minimizing prediction errors drives the competition between stream candidates and that regularity representations are evaluated on the basis of how well they predict future acoustic events within the actual environment. Finally an outline of a functional model of auditory stream segregation will be provided, which can account for a number of behavioral and ERP phenomena and may form the basis of a new computational model of auditory stream segregation.

S1.03.

Different cases for predictive modeling in audition

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Predictions are of outmost importance to make sense out of the world. This is quite obvious for many domains such as decision making (e.g. about investments in the stock market) or action planning (e.g. in dancing) but even holds for basic auditory processing. The establishment of predictive models of the acoustic environment enables a fast and effective processing of the acoustic input, that is needed – for example – to understand speech, to identify an instrument, or to locate a mosquito. In this talk, several approaches that tap into auditory predictive modeling will be introduced: Mismatch paradigms, Omission paradigms, Match paradigms, Self-generation paradigms. Several components of the event-related brain response (e.g. P1, N1, MMN, Incongruency Response, Repetition Positivity) and of oscillatory activity (Evoked Gamma Band Response) are indicative of predictive modeling. It will turn out that the effects can be found along different time scales (some starting as early as 30 milliseconds after sound onset), some even being anticipatory. Surprisingly, predictive modeling can result in an increase but also in an attenuation of the responses elicited by a predicted sound. It will be argued that predictive modeling is mandatory to keep track of the rapidly changing sound waves (i.e. alternation in pressure) arriving at our ears, which contain the information that we experience as auditory events. In fact, it seems that we listen to the auditory world via our predictive models.

SYMPOSIUM II - NEURAL BASES OF SPEECH PERCEPTION IN HUMAN INFANTS

S2.02.

Perceptual capabilities underlying music perception in newborns

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Music and also language are universally present in all cultures suggesting that both are deeply rooted in the perceptual and cognitive abilities of the human species. The basic building blocks necessary for perceiving music may be identified as general processes of audition which are possibly shared with language perception. Music perception is the product of interactions between innate predispositions, environmental constraints, and learning. Understanding the musically relevant abilities which are already functional at birth can help to disentangle these interactions. Further insights into processes underlying communication by sounds (including music and language) may be gained by identifying how acoustic information is processed by newborns. ERP measurements in newborns are well suited to gain information unavailable to classic behavioral methods. Discriminative responses, similar to the mismatch negativity found in adults, were used in auditory oddball paradigms to investigating neonatal abilities underlying the perception of musical pitch, timbre and rhythm. Based on these results it appears that babies are born well equipped for analyzing information necessary for music perception; their abilities are comparable to those of adults.

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S2.03.

Mismatch negativity modulations reflect infants' processing of speech stress patterns

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Considering word stress processing the main theoretical question is the nature of representation. According to our theory, there exists a long-term pre-lexical template emerging in accordance of the actual stress cues of the mother tongue. Since this theory has strong statements for development of stress perception, we can test whether this template exists in different ages. In our experiment we examined the ERP components elicited by stress pattern violations of pseudo-words (PSW). Thirty-three 6 and 10 months old infants participated in the experiment where we used a passive odd-ball paradigm. Two pseudo-words were used as standard and deviant, constructed from two syllables identical for segmental features, but different for position of the stressed syllable. The PSW construct could have stress-related acoustic cues either on the first or on the second syllable. In the irregular condition we introduced a mirror condition by using the former standard as deviant and vice versa. In the regular condition we had a familiar pattern we could find in adults'

stress processing. However, when locating and analyzing further these components, we are able to show that infants detect stress as an acoustic cue but we can trace the matching to a long term representation only in case of 10 month-olds. In the irregular condition we could detect a simple mismatch response as was the case in the regular condition, and no further process of dissimilarity. Our results imply that we form our language-specific, long term templates and build up a well-functioning stress representation relatively slowly with growing experience and lexical knowledge at the second part of the first year.

SYMPOSIUM III - THE DYNAMIC PROPERTIES OF NEURONS AND THEIR NETWORKS: FROM SINGLE CELLS TO NETWORK OPERATION

S3.02.

Changes in the structure of cellular activity during transitions of hippocampal activity patterns in vitro

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We induced quick and reversible SPW to gamma state transition in the CA3 area of in vitro submerged hippocampal slices by cholinergic receptor activation. Both patterns can be considered as periodically recurring transient increases of activity in the recurrent network of CA3. We hypothesize that an active period is initiated in the CA3 recurrent excitatory network when a sufficiently high number of pyramidal cells is active at the same time. The model predicts that as network size decreases, networks will generate SPW-Rs with a lower frequency and higher inter-SPW-R interval variance. This prediction was successfully verified by decreasing functional network size with a pharmacological approach. Using electrophysiological and neuronal network modeling tools, we proved that the SPW-R to gamma state transition is the result of the concurrent increase of cellular excitability and decrease in the probability of synaptic transmission. During SPW-R state when the excitability of neurons is low, synchronous events are infrequently initiated, but activity builds up to a high level in the strongly connected network. In the gamma state, as a result of cholinergic activation, the excitability of the neurons is high, resulting in frequent and regularly timed synchronous events, but these spread only to a limited extent due to the weak connectivity of the network. The contribution of recurrent processing vs. initially active neurons is different in the two states, suggesting distinct information processing modes.

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S3.05.

Laminar analysis of slow wave activity in humans

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Brain electrical activity is composed of hierarchically organized oscillations at characteristic frequencies. The slow wave activity (SWA) is a fundamental cortical rhythm, in animals models it was shown to modulate higher frequency oscillations, orchestrating brain electrical rhythms in sleep. To elucidate the intracortical neuronal mechanisms of SWA in humans, laminar multichannel microelectrodes were chronically implanted into the cortex of patients with drug resistant focal epilepsy undergoing cortical mapping for seizure focus localization. Intracortical laminar local field potential gradient, multiple unit and single unit activities were recorded during slow wave sleep. We found that SWA in humans reflects a rhythmic

oscillation between widespread cortical activation and silence. Cortical activation was demonstrated as increased wideband power including virtually all bands of cortical oscillations, increased multiple and single unit activity, and powerful inward transmembrane currents. Neuronal firing in the active state was sparse, action potentials were tightly synchronized across all cortical layers. These findings provide strong direct experimental evidence that SWA in humans is characterized by hyperpolarizing currents associated with suppressed cell firing, alternating with high levels of oscillatory synaptic/trans-membrane activity associated with increased cell firing. Our results emphasize the major involvement of supragranular layers in the genesis of SWA.

SYMPOSIUM IV - SYSTEM FAILS: NETWORK DISTURBANCES IN EPILEPSY

S4.01.

Seizure-induced endogenous anticonvulsive mechanisms

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Neuropeptides are co-transmitters of classical neurotransmitters such as GABA or glutamate. In animal models of epilepsy and in human TLE the expression of some neuropeptides is markedly altered. Thus, in rat models of temporal lobe epilepsy (TLE), expression of neuropeptide Y (NPY) becomes up-regulated and that of dynorphin down-regulated in mossy fibers of the dentate gyrus. In contrast, in human TLE, expression of NPY is unchanged in mossy fibers of the dentate gyrus, whereas that of dynorphin becomes markedly up-regulated in these neurons. In contrast, NPY-containing neurons sprout in the entire hippocampal formation, notably in the subiculum and in the dentate gyrus in human TLE. Both neuropeptides have anticonvulsive properties that are mediated by NPY-Y2 and kappa receptors, respectively and involve inhibition of glutamate release from principal neurons. These findings indicate that, although NPY has marked anticonvulsive actions in the rat, in humans it may exert a protective role only in chronic epilepsy, when it is released in excess from sprouted interneurons. In contrast, upregulation of dynorphin is fast and lasting in human TLE and related to acute seizure activity, indicating already an anticonvulsant action during acute seizures. On the other hand, since dynorphin expression is not up-regulated in animals models, endogenous dynorphin may have only a minor role on seizure activity.

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S4.02.

Helping NPY system to control seizures: Ligand-receptor combination gene therapy

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Neuropeptide Y (NPY) is considered as endogenous antiepileptic agent that can counteract seizures. In line with this notion, gene therapy using recombinant adeno-associated viral vectors overexpressing neuropeptide Y in the hippocampus has been shown to exert seizure-suppressant effects in animal models of epilepsy. Currently, this approach is being considered for clinical application in patients with intractable mesial temporal lobe epilepsy. NPY predominantly exerts its seizure suppression effect in the hippocampus by interacting with NPY Y2 receptors, which, together with NPY, are upregulated after seizures as a compensatory mechanism. We explored whether gene therapy-based overexpression of functional Y2 receptors using recombinant adeno-associated viral vectors was possible, and whether such upregulation of Y2 receptors could suppress seizures in the hippocampus. We

demonstrated that in two temporal lobe epilepsy models used, electrical kindling and kainate-induced seizures, the viral vector-based transduction of Y2 receptor cDNA in the hippocampus of adult rats was successful and exerted seizure-suppressant effects. Simultaneous overexpression of Y2 receptors and the ligand, NPY, had more widespread and powerfull seizure-suppressant effect. These results demonstrate that overexpression of Y2 receptors (alone or in combination with neuropeptide Y) using gene therapy approach is feasible and could be an alternative strategy for epilepsy treatment.

S4.03.

Functional reorganization of temporal lobe structures in epilepsy

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Both human and experimental temporal lobe epilepsies (TLE) are associated with network reorganizations. TLE is often characterized by a seizure-free – latent period following the initial insult. In experimental TLE, the initial insult (usually a status epilepticus) triggers considerable modifications (cell death, sprouting, channelopathies) in temporal lobe structures. These alterations are associated with cognitive deficits and a loss of theta rhythm, a rhythm central to many cognitive functions, well before the occurrence of the first spontaneous seizure. Using the HCN1 channelopathy as a model system of these reorganizations, we have identified one central mechanism of epileptogenesis (the process leading to epilepsy). The initial insult triggers the expression of the gene repressor NRST (REST), which is responsible for the downregulation of tens of genes. I shall discuss how interfering with this signaling pathway can restore network function and be disease-modifying.

S4.04.

Interictal activity in the epileptic human hippocampal formation

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Interictal spikes (ISs) detected in the EEG is a diagnostic key of human epilepsy. The characterization and localization of ISs observed between seizures are crucial to identify different epileptic syndromes. Here we describe the ISs recorded in the hippocampal formation of epileptic patients with temporal lobe epilepsy, in vivo, under anesthesia and in vitro, in postoperative tissue. In vivo, based on laminar field potential gradient, multiple unit activity (MUA) and current source density (CSD) analyses, the most frequently occurring spikes started with an excitatory current (CSD sink) in the pyramidal cell layer in all regions, usually associated with an increased MUA. In vitro, ISs were spontaneously generated in the subiculum and the CA2 region, also showing a CSD sink and an enhanced MUA in the cell layer. Two thirds of the intracellularly recorded CA2 pyramidal cells exhibited depolarizing

response, while most subicular cells (80%) showed hyperpolarizing response during ISs. Studies of K+-Cl- transporters indicated a perturbed chloride homeostasis associated with excitatory actions of GABA in the subiculum but not in the CA2 region. Morphological studies demonstrated the preservation of perisomatic inhibitory input and the presence of an extra excitatory input in the CA2 region, partly coming from sprouted mossy fibers. Overexcitation and an altered inhibitory network may account for the generation of ISs in the subiculum and the CA2 and CA3 regions of the human epileptic hippocampus.

S4.05.

Adaptive changes of the hippocampal network in epilepsy

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Inhibition is a crucial mechanisms in epilepsy. Beside the interneuronal network other factors also contribute in the regulation of GABAergic synaptic transmission. The endocannabinoid system plays a central role in retrograde synaptic communication, and controls both glutamatergic and GABAergic transmission via type 1 cannabinoid receptors (CB1). Both in sclerotic human hippocampi and in the chronic phase of pilocarpine-induced epilepsy in mice with sclerosis, CB1 receptor-positive interneuron somata were preserved both in the dentate gyrus and in the CA1 area, and the density of CB1 immunostained fibers increased considerably in the dentate molecular layer. This suggests that, while CB1 receptors are known to be reduced in density on glutamatergic axons, the CB1 receptor-expressing GABAergic axons sprout, and/or there is an increase of CB1 receptor levels on these fibers. The changes of CB1 immunostaining in association with the GABAergic inhibitory system appears to correlate with the severity of pyramidal cell loss in the CA1 subfield. These results confirm the involvement of the endocannabinoid system associated with GABAergic transmission in human TLE, as well as in the chronic phase of the pilocarpine model in mice. Pharmacotherapy aimed at the modulation of endocannabinoid-signaling should take into account the opposite change in CB1 receptor expression observed on glutamatergic versus GABAergic axon terminals.

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SYMPOSIUM V - TOWARDS AN INTEGRATIVE NEUROSCIENCE: FROM GENES TO BEHAVIOUR

S5.01.

Phylogenetic library for endogenous opioid peptides: an update

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Endogenous opioid peptides are processed from large molecular mass precursor polypeptides encoded by distinct genes. Proopiomelanocortin (POMC), Proenkephalin (PENK), Prodynorphin (PDYN) and Pronociceptin (PNOC) are the four ubiquitous precursors in mammals, and their respective genes are located in different chromosomes. In lower vertebrates, mainly in fish species, additional copies of such precursor propeptide genes exist as a result of gene or full genome duplications that occurred during the evolution of vertebrate animals. Matured endogenous opioids are processed from their precursors by sequential endopeptidase cleavages. Our systematic database survey reveals that individual peptides identified in genomic or cDNA data of various species exhibit remarkable polymorphism due to mutational changes. The entire set of opioid peptides from different taxa represents a natural- (NPL) or phylogenetic- (PPL) peptide library. The analysis of such libraries led to the identification of numerous unknown opioid peptide sequences, including Ile-enkephalin, xendorphins, Tyr1-nociceptins and many others. NPL for endogenous opioids seems to be important for phylogenetic, comparative bioactivity and systems biology studies. The formation of NPLs is driven by genetic and evolutionary mechanisms. The dynamically increasing content of NPLs represents amazing structural variegation, herewith it is a component of the chemical biodiversity.

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S5.03.

Anandamide attenuates neuropathic pain symptoms by spinal TRPV1 and CB1 receptor activation

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The endocannabinoid anandamide (AEA) binds to several receptors including the transient receptor potential vanilloid 1 (TRPV1) and cannabinoid receptor 1 (CB1) which are frequently co-expressed in neuronal cells. Still no data are published on the potential role of spinal TRPV1 activation by AEA in neuropathic pain. Rats chronically implanted with intrathecal (i.t.) catheters underwent sciatic nerve ligation (CCI), seven days after CCI mechanical allodynia and thermal hyperalgesia were measured. AEA (50 μg i.t.) displayed an antiallodynic and antihyperlagesic effect. The analgesic action of AEA was abolished by I-

RTX but not AM251, suggesting the involvement of spinal TRPV1 receptors. Depending on the administered dose, URB597 (10-200ug/rat) reduced thermal and tactile nociception via CB1 or TRPV1 receptors. URB597 (10-100ug) dose-dependently enhanced spinal AEA levels. Surprisingly those were reduced by 200ug of URB597 suggesting an indirect effect of an endovanilloid/endocannabinoid AEA action at TRPV1. Data on alterations in lipoxygenases (LOX) mRNA support the idea of alternative ways of AEA metabolism. We suggest that i.t. AEA reduces neuropathic pain by acting as an endovanilloid, on the he spinal cord TRPV1/CB1 neurons. When endogenously up-regulated dependent on efficiency of FAAH a secondary route of AEA metabolism plays a role in CCI model, indicating LOX pathway as a novel target for neuropathic pain.

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