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# Investigating the involvement of resistin/TLR4 signaling pathway in HFD-induced hypothalamic inflammation and reactive gliosis and whole body insulin resistance

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Obesity is linked to common metabolic diseases including low grade inflammation, insulin resistance (IR), and type 2 diabetes. Increasing evidence indicates that changes in adipose-secreted factors in obesity, dramatically affect insulin sensitivity. Among these adipokines, resistin is described as a key factor in obesity-mediated both inflammation and IR. However, little is known about the molecular mechanisms mediating resistin effects at the neuronal level. Recently, we have shown that central resistin acts by way of hypothalamic TLR4 receptors promoting whole-body IR. Here we aim to investigate the impact of resistin on hypothalamic inflammation, and to evaluate whether the blockade of resistin/TLR4 pathway using a long lasting resistin antagonist (RA) could prevent the HFD-induced hypothalamic inflammation, IR and related metabolic dysfunctions. Using C57BL6 mice, we show that central resistin infusion for 3 days markedly increases inflammatory markers in the hypothalamic arcuate nucleus and adjacent median eminence in association with reactive gliosis involving recruitment of both microglia and astrocytes. Interestingly, we report that the knockdown of TLR4 almost completely abolished resistin-dependent hypothalamic inflammation. Furthermore, we evaluate the impact of the blockade of resistin action, using (RA), on HFD-induced hypothalamic inflammation and whole body IR. For this purpose, C57BL/6 mice were fed with HFD for 6 weeks and then subjected, for 14 days, to daily injection of RA. We clearly show that RA leads to a significant decrease in body weight of HFD mice mainly due to loss of visceral fat. Importantly, RA treatment completely abrogates HFD-induced hypothalamic inflammation and ARC-reactive gliosis and restored both glucose tolerance and insulin responsiveness of HFD mice. Collectively, these findings indicate that Resistin/TLR4 signaling pathway constitute a crucial/key pathway promoting the onset of hypothalamic inflammation. Targeting this signaling pathway using RA may constitute a significant breakthrough to overcome obesity-induced hypothalamic inflammation, IR and their associated metabolic dysfunctions.

**Keywords:** Hypothalamus, inflammation, resistin, TLR4, Obesity, insulin, resistance

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# Dissociation between language- and math-responsive networks in the brain

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The relation between language and mathematics in human cognition is an essential issue of Cognitive Sciences. While it has been argued that mathematics emerges as an offshoot of human linguistic abilities, recent evidence tend to show that language and mathematics have evolved independently and even build upon dissociated neural substrates.

In a first experiment, we investigated the neural correlates of advanced mathematical reflection in professional mathematicians. During a high-resolution fMRI scanning session, subjects had to evaluate whether advanced mathematical and nonmathematical spoken statements were true, false or meaningless. Algebra, analysis, geometry and topology activated a reproducible set of bilateral frontal, intraparietal and ventrolateral temporal regions that completely spared areas related to language and to general-knowledge semantics, but rather coincided with sites activated by simple arithmetic in mathematicians and non-mathematicians alike.

In two control studies, led again in professional mathematicians, we interrogated the boundary between mathematical and general semantic processing. We first probed the influence of verbal memory, comparing rote mathematical facts, basic mathematical reflection, and basic general-knowledge facts about arts. Second, we tested the influence of minimal logical operators such as quantifiers and negation injected in very simple and syntactically identical math and nonmath statements. In both experiments, the dissociation between math- and language-responsive networks remained.

In conclusion, the math-responsive network we identified in these studies activates regardless of the domain or the difficulty and dissociates from language- and semantics-related brain circuits.

**Keywords:** fMRI, Mathematical cognition, Semantics

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\*Speaker

# Imaging neural correlates of learning in awake ferrets using functional UltraSound

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Large-scale functional imaging techniques are part of a fast growing field of neuroscience aiming at understanding whole brain activity. Functional Ultrasound Imaging (fUS) is a new technique giving access to changes in blood flow with a high spatial ( $\sim 100\mu\text{m}$ ) resolution and sampling rate (500Hz) for a typical imaged section of 1cm wide and 2cm deep, providing a more detailed image than fMRI. Using this technique in awake ferrets, we previously characterized 3D-tonotopic organization of several areas of the auditory cortex, and of deep and small structures like the inferior colliculus or the auditory thalamus. Here, we used fUS to monitor learning-related changes in sound encoding at the level of the primary auditory cortex (A1). A1 tonotopic map have been previously shown to be modified through experience in trained animals (Polley et al., 2006). However, characterizing the precise time-course of these changes across learning proved to be technically challenging and so far unresolved, despite its central role in cognition. We show that training ferrets on a fixed-frequency tone discrimination task elicited changes in A1 tonotopic map that were mainly present in the region coding for the reference sound. The size of these changes was correlated with the amount of water received during each session, a result reminiscent of previous studies on implicit perceptual learning in humans (Seitz et al, 2009). Overall, multi-voxel pattern analysis (MVPA) suggests that these changes improve the discrimination between target and reference sounds.

**Keywords:** perceptual learning, functional ultrasound, ferret

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\*Speaker

# Functional organization of the hippocampus during childhood and adolescence

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The hippocampus (HC) is a highly connected structure, critical for memory and spatial navigation. Several studies have shown that the HC is functionally organized along its anterior-posterior axis [1, 2]. However, developmental changes toward this anterior-posterior specialization remain unclear. Based on resting-state data of 30 healthy subjects (aged 7-17yo), we described the connectivity gradient of the HC using a new data analysis approach called ‘ConGrads’ [3, 4]. This approach aims to characterize the connectivity gradient in a brain area at the level of an individual participant. During the first step of the analysis, we estimated anterior-posterior gradients for each subject. ConGrads builds a gradient by establishing the brain connectivity map of each voxel in the HC and rearranging them by similarity using a non-linear manifold learning approach. During the second step, the gradients were segmented in two subparts using the median value as a threshold. These subparts were used in a seed-to-voxel analysis with age as a variable of interest. The main results showed, for all subjects, the presence of the anterior-posterior connectivity gradient in the HC, similarly to adults [4]. The segmentation of the gradient resulted in an anterior and a posterior subparts for each gradient. Seed-to-voxel analyses showed age-related connectivity changes of the hippocampal subparts with distinct brain regions. Overall, these results suggest a progressive specialization of hippocampal functional connectivity during childhood.

(1) Poppenk et al. (2013). Long-axis specialization of the human hippocampus. *Trends in Cognitive Sciences*, 17.

(2) Chauvin et al. (2016). Connectivity Maturation of the Temporo-mesial Memory Circuit from Childhood to Teenage Age. *OHBM Annual Meeting 2016*.

(3) Haak, Marquand & Beckmann (2016). Connectopic mapping with resting-state fMRI. [ArXiv:1602.07100](https://arxiv.org/abs/1602.07100)

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(4) Przezdziak et al. (2016). Mapping the cortico-hippocampal connectivity gradient in single subjects using resting-state fMRI. OHBM Annual Meeting 2016.

**Keywords:** hippocampus, development, functional connectivity, connectivity gradient



# Age-related changes in spatial learning of a real environment and gray matter integrity: a preliminary voxel-based morphometric study

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When bearings are lost, one must actively search for spatial cues to retrieve his position and orientation, and to infer the direction towards a goal. Although reorientation has been characterized in children and young adults, little is known about older adults' ability to reorient in space. We investigated how aging shapes the reorientation process in *a real environment* as well as the related cerebral atrophy of brain structures involved in spatial orientation. Twelve young ( $\mu=26$  y/o,  $\sigma=3.17$ ) and twelve old ( $\mu=70$  y/o,  $\sigma=2.83$ ) participants were requested to reorient themselves and navigate to an invisible goal fixed *in a real environment* (a 8.6x4.3 m street-like setup made of realistic relief sceneries) after being disoriented. The duration of the reorientation process (measured as the time needed prior to start navigating) was assessed during 8 trials. Behavioral results showed that older adults were significantly slower at reorienting compared to young subjects. Subsequently, participants underwent a MRI session including T1-weighted anatomical images and functional localizer acquisitions to map cerebral regions involved in spatial navigation. Whole-brain voxel-based morphometric analyses (VBM) and regions of interest (ROI) were calculated for: parahippocampal place area (PPA), retrosplenial cortex (RSC), occipital place area (OPA), entorhinal cortex (EC), medial prefrontal cortex (mPFC), and hippocampus (HC). Whole-brain VBM analyses showed a widespread gray-matter atrophy concentrated on frontal, temporal and parietal lobes of older adults. Interestingly, we found a significant positive correlation between reorientation duration and ROI atrophy in scene-selective regions (PPA, RSC, OPA), EC and mPFC but not HC. Because the reorientation process in our behavioral paradigm presumably involves active search of visual cues in the environment, our data suggest that scene selective areas (PPA, RSC, OPA) and high-level cognitive areas (mPFC) may play a more prominent role than memory-related areas (HC) in reorientation. Acknowledgments: Supported by ANR–Essilor SilverSight Chair ANR-14-CHIN-0001.

**Keywords:** aging, spatial cognition, VBM

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# The R67C intellectual disability mutation of the *pak3* gene impairs adult hippocampal neurogenesis and cognitive functions

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Several gene mutations have been identified to cause Intellectual Disability (ID); however, the cellular bases and pathophysiological mechanisms that lead to ID remain largely unknown. Studies in models of ID have reported alterations in adult hippocampal neurogenesis, a form of plasticity known to play a crucial role in hippocampal-dependent cognitive functions. Here we investigated hippocampal-dependent memory and adult hippocampal neurogenesis in mutant mice bearing the missense R67C mutation of the *pak3* gene (*pak3*-KI) known to cause a severe form of ID in humans. We therefore studied basal adult hippocampal neurogenesis in *pak3*-KI mice, their cognitive abilities in behavioural tasks known to require hippocampal neurogenesis and the recruitment of adult-born neurons by learning.

Our results show *pak3*-KI mice have normal proliferation, differentiation and neuronal maturation in basal conditions. However, an accelerated death of adult-born neurons was observed during the critical period of 18-28 days after their birth, without consequences for later survival rate. Behaviourally, *pak3*-KI mice display deficits in a successive spatial delayed non-matching to sample task in a radial maze, characterized by impaired retention and high sensitivity to interference. They also display deficits in long-term spatial memory assessed in a water-maze task.

We investigated the recruitment of adult-born neurons after recall of spatial memory, using the expression of the transcription factor Zif268. We found normal post-recall activation of mature dentate gyrus neurons in *pak3*-KI mice, but a complete failure of recruitment of young DCX+ neurons. Together, these results suggest that new neurons may not be fully functional and consequently may not be able to be activated and recruited during the task. This incomplete maturation could be in part responsible for the accelerated neuronal death and for some of the cognitive deficits observed in this mouse model of ID. Supported by Jerome Lejeune Foundation and FRC.

**Keywords:** Intellectual disability, adult hippocampal neurogenesis, learning and memory

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# Interactions between numerosity and mean size perception in humans with and without dyscalculia

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Humans, as other species, have a number sense. However, number judgments can be influenced by other quantities, leading to suggestions that number is not extracted independently. In this study we generated sets of dots orthogonally varying in mean size and numerosity, to evaluate their reciprocal interference. In different sessions participants with and without dyscalculia were asked to compare sets on either their number or their mean item size, while the irrelevant dimension also varied, but could only take extreme values. Importantly, stimuli were chosen such that on average the size and number task were equated for difficulty. Despite the large change in the irrelevant dimension, control subjects showed no significant size interference when judging numerosity, suggesting that they could discard the competing size information. However, when judging size subjects showed a clear number interference, overestimating mean sizes when presented with higher numerosity. On the contrary, dyscalculic subjects showed strong size interference when judging number, but did not differ from control subjects in the degree of number interference when judging size, excluding a mere general inhibition deficit hypothesis. Overall, these results suggest that at least in some circumstances number can be perceived without interference from other visual cues, however these might become more salient in case of an impaired number sense.

**Keywords:** dyscalculia, number sense, average size, inhibition, task switching

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\*Speaker

# Sequence processing in a songbird secondary auditory area

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In the field of auditory neurophysiology, studies have investigated how basic acoustic features are mapped into brain, but it is still not clear how sequences of multiple sounds are encoded. Songbirds offer a unique opportunity to address this issue. Birdsongs resemble speech in that they consist of learned structured sequences of distinct vocal units, called ‘syllables’. Like speech, songs convey relevant information in their acoustic and sequence patterns. Songbirds also have a set of interconnected telencephalic auditory areas in which auditory responses reveal complex coding properties. In one of these areas, the nidopallium caudo-medial (NCM), neurons respond more robustly to conspecific than to heterospecific songs and habituate to repeated presentation of the same song.

Taking advantage of this property, we examined the sensitivity of NCM neurons to the temporal order of syllables within songs or short sequences. In anesthetized adult male zebra finches (*Taenopygia guttata*; n=14), using multi-electrodes, we recorded responses to 50 presentations of a given song (ABCDE where A, B, C, D and E are song syllables) followed by 10 additional presentations of the same song in which the order of syllables was altered (e.g.BCEAD). Using short sequences of song syllables (e.g.ABAB), we also assessed the impact of a change in the temporal order.

Analyses of the firing rate of n single units indicate that responses habituated rapidly when the stimulus, a song or a sequence was repeated. They continued to decrease when the same stimulus was presented while they showed an increase when the syllable order or the syllable identity was different.

Our study, therefore suggests that neurons in an auditory brain area, considered as being analogous of the secondary auditory cortex of mammals, encode the temporal structure of vocal sequences and could recognize them as a single object.

**Keywords:** auditory processing, songbird, secondary auditory area, electrophysiology

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\*Speaker

# Modeling Gamma Oscillations in Adaptive Exponential Integrate-and-Fire Neurons

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Gamma rhythms are observed in both waking and sleep states, in different species and in several brain regions. However, despite of the large number of studies about this phenomenon, the exact mechanism of their genesis and coexistence with other brain states is still largely unknown.

Recent findings in human data showed that, with respect to the oscillatory gamma cycle, during slow wave sleep and awake states, there is a higher proportion of inhibitory neurons spiking with higher frequency, in contrast to the excitatory population. Furthermore, the inhibitory neurons fire earlier than excitatory ones on average, suggesting that inhibitory cells play a key role in the generation of gamma rhythms in humans.

Here, we use modeling to attempt to reproduce some of these recent findings, with the aim to understand the genesis of gamma oscillations in humans, and ultimately, how such oscillations are involved in processing external stimuli. We first used a generator of gamma oscillations from interconnected inhibitory neurons. Next, we embedded this oscillator in a network of Adaptive Exponential (AdEx) neurons, displaying asynchronous states similar to in vivo recordings. We describe how the inclusion of gamma generator circuits allows the whole network to display synchronous irregular gamma oscillations with some features consistent with recordings in humans.

**Keywords:** Computational Model, AdEx, Gamma Rhythms

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\*Speaker

# Regional effects of radiotherapy on cognitive decline in children treated for posterior fossa tumors

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Pediatric posterior fossa tumors (PFT) survivors who have been treated with cranial radiation therapy often suffer from specific cognitive deficits that might relate to IQ decline. Radiotherapy distinctly affects brain regions involved in different cognitive functions. However, the relative contribution of regional irradiation on the different cognitive impairments still remains unclear. We explored, in thirty children treated for a PFT, the relationships between the changes in different cognitive scores and radiation dose distribution. The purpose of the study was to designate regions of the brain that should be preferentially avoided, whenever possible. To avoid biases linked to the spatial correlations between close irradiated regions, due to similar radiation therapy protocols across patients; our exploratory analysis was based on data-driven Principal Component Analysis. Our results suggest an association between working memory decline and high dose (Equivalent Uniform Dose, EUD) delivered to the orbitofrontal regions; whereas decline of processing speed appeared more related to EUD in the temporal lobes and posterior fossa. This original approach that identifies regional effects of radiotherapy on cognitive functions may help to adapt future radiotherapy protocols.

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\*Speaker

**Keywords:** Pediatric posterior fossa tumors, radiation therapy, specific cognitive deficits

# Closed-loop estimation of retinal network sensitivity reveals signature of efficient coding

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Understanding how sensory systems process information is an open challenge mostly because these systems are non-linear. Here we present a novel perturbative approach to understand the non-linear processing performed by sensory neurons, where we linearize locally their responses to a stimulus. Starting from a reference stimulus, we added small perturbations to the stimulus and tested if they triggered visible changes in the responses. We updated the perturbations according to the previous responses using closed-loop experiments. We then developed a local linear model that accurately predicts the sensitivity of the neural responses to these perturbations. Applying this approach to the retina, we could estimate the optimal performance of a neural decoder and show that the non-linear sensitivity of the retina is consistent with an efficient encoding of stimulus information. Our approach is general and can be used to characterize experimentally the sensitivity of neural systems to external stimuli, or relate their activity to behaviour.

**Keywords:** Sensory systems, Retina, Efficient coding, Stimulus decoding, Information Theory, Fisher Information

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\*Speaker



# Neurofeedback therapy for tinnitus

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Background: Tinnitus is defined as the perception of sound in the absence of a corresponding external acoustic stimulus. It is a common problem that markedly impairs the quality of life of about 1% of the general population. Recent studies [1] [2] have explored the possibilities of neurofeedback as a long lasting relieving therapy for tinnitus sufferers. Ambition: our study aims to answer two questions: past works were elusive about the efficacy of neurofeedback therapy regarding the type of tinnitus of the sufferers (frequency of the tinnitus, origin of apparition). What category of patients benefits the most from a neurofeedback therapy? Secondly, in order to open the way for widespread clinical applications, the EEG headset used for the neurofeedback training should be as light as possible. What is the minimal number of electrodes such that an electrode placement to specifically target the information in the auditory cortex exists? Methods: To answer the first question, we gathered a set of labels characterizing tinnitus sufferers. We will select different arms of homogeneous populations of tinnitus sufferers and repeat the alpha training protocol of [2] and compare results between arms. To answer the second question, we will investigate theoretically what optimal placement of electrodes would achieve the desired outcome. We will then test its efficacy thanks to an alpha desynchronization protocol described in [2]. Current state: Test protocols are almost set and we expect to make the trials starting mid-May, we will be happy to present our preliminary results during the NeWs event.

**Keywords:** neurofeedback, tinnitus

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# Towards a fast brain-machine interface integrating sensory feedback

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Brain-machine interfaces use neuronal activity to control prostheses, with the long term goal of restoring motor abilities to impaired subjects. One of the successful strategies for implementing BMIs has been to operantly condition neuronal cortical activity. In recent work, we recorded multiple single-units in the motor cortex of head-fixed behaving rats. We demonstrated that firing rate modulations of a single conditioned neuron are sufficient to drive a one-dimensional robotic actuator controlling the position of an appetitive reward.

In the present work, we have adapted this BMI on the mouse. We use chronic extracellular recording in the whisker motor cortex (silicone probes) and optogenetical activation of the barrel cortex to feed back environmental information to the mouse. We patterned light activates the barrel cortex via a chronic window using a high-performance, high-frequency DLP projector (Vialux).

To ensure a reliable and fast information feedback, we have built a high-performance multi-threaded C++ software that reads the spiking activity (Blackrock NSP), computes a relevant feedback and generates the patterned light. Calibration experiments reveal a consistent 27 ms between the occurrence of a spike and a subsequent modulation of the photoactivation.

We aim to apply light stimulation patterns that are aligned on the barrel cortical map. Therefore, we integrated to our BMI setup an intrinsic imaging system that allows us to locate individual barrel at the surface of the cortex. We have validated this method and managed to generate light activations patterns that are registered on the barrel map topography.

Our next step is to train mice to compare the ability of mice to learn a sensori-motor task based on a topographic versus shuffled barrel cortex optogenetic feedback, in order to test if topographic feedback is in fact more efficient and/or easier to learn.

**Keywords:** Integrative neurosciences, sensory physiology, brain, machine interface

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# Specialization of coding properties in the rat primary and secondary whisker somatosensory cortices

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The vibrissal system in rodents plays a key role in the identification of objects in the environment. Such tactile recognition is likely to depend on controlled multi-whisker contacts with an object. The features of these multi-whisker contacts and their representations in the whisker somatosensory cortices are not well understood. To characterize the multi-whisker representations in the two largest somatosensory cortical regions, we applied three different types of stimuli to the caudal 24 macrovibrissae of anesthetized rats while recording the activity of single neurons in either primary or secondary whisker somatosensory cortex (wSI or wSII). A white noise analysis in which the same Gaussian stimulus was applied to all whiskers demonstrated that wSII neurons filter the stimulus in extended temporal windows when compared with wSI. By applying these region-specific temporal filters to whisker movements across time, it became feasible to study both wSI and wSII responses in a stimulation context where each whisker receives its own, independent Gaussian stimulus. This powerful approach allows the identification of whisker-pad scale spatio-temporal receptive fields during continuous, simultaneous multi-whisker stimulation for the first time. A feature analysis of the wSI and wSII responses in these two continuous stimulation contexts revealed that wSI and wSII contain specialized whisker representations. In wSII, many whiskers contribute equally to the firing of a single neuron, and these contributions occur over longer time scales than what is found in wSI. In wSI, the population encodes fine features of whisker movements on more precise spatial and temporal scales. These coding principles were then confirmed in a sparse noise stimulation context where each whisker was deflected independently but not simultaneously. In conclusion, the whisker system encodes both fine scale tactile features and broader tactile scene statistics and these representations are organized into specialized, complementary cortical regions.

**Keywords:** somatosensation, barrel cortex, sensory representations

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\*Speaker

# Anatomical and functional interrogation of the neuronal pathways underlying respiratory changes during exercise.

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When animals walk or run, respiration increases to match the augmented energetic demand and a temporal phasing of breaths and strides can be observed. A neuronal connectivity between respiratory and locomotor circuits has been suggested to mediate respiratory adjustments during, or in anticipation of, locomotor action. However the locations and identities, in both circuits, of the neuronal partners of such connectivity have remained uncharted. We here question the existence of a central drive from the locomotor central pattern generator (CPG) located in the spinal cord, to the respiratory CPG in the brainstem. An *in vitro* brainstem-spinal cord preparation was used to record, for the first time in the mouse, locomotor- and respiratory-like activities simultaneously by electrophysiological recording of specific motor roots. We show that pharmacological or optogenetic activation of the locomotor CPG, and thus of locomotor-like activity, is associated with a concomitant increase of the frequency of respiratory-like activity. We also show that the locomotor-associated respiratory response is abolished when a component of the respiratory circuit, the Retrotrapezoid Nucleus (or RTN) otherwise implicated in CO<sub>2</sub> chemosensibility, is genetically deleted. This indicates that the locomotor CPG circuit sends a neuronal ascending drive to the respiratory CPG, via the RTN, to upregulate respiratory frequency during ongoing locomotion. We are currently deploying trans-synaptic retrograde viral tracings targeted to the RTN on the one hand, and anterograde labelling from locomotor CPG neurons on the other to i) document anatomically the mono or poly-synaptic nature of the revealed pathway, ii) identify the CPG neurons that provide the ascending drive, and iii) identify putative RTN pre-synaptic neurons in supra-spinal, locomotor circuits. Altogether, our study unveils the existence of a locomotor-related ascending command onto the respiratory CPG that may participate to exercise hyperpnoea and for which the RTN is an obligatory component.

**Keywords:** Respiration, Locomotion, Brainstem, Spinal cord, Central pattern generator, Electrophysiology, Circuit tracings

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# A Forecasting Approach for Spontaneous Voluntary Actions Using Conditional Probabilities in Neural Data

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Identifying the neural origins of self-initiated movement is a long-standing problem, with major implications extending from neuroscience to philosophy of mind. The problem can also be described as the search for "intentions" in neural activity. Intentions can be operationally defined as neural states that reliably predict the onset of action with high fidelity. A common approach in identifying predictors of the onset of self-initiated actions is to use classifier models that are trained using segmented neural data time-locked to the onset of the action. However, this approach introduces a bias that can lead to artificially high classification accuracies even when there are no predictive signals. Here we offer a different approach based on conditional probabilities that can be used to forecast behavior based on brain activity. We tested this method using combined EEG and MEG data recorded while subjects performed a spontaneous button press task. We acquired a large set of data from each subject in order to generate robust conditional probability maps to estimate the probability of a movement at time  $t + \tau$  given the signal at time  $t$ , and tested its predictive accuracy on an independent data set using a leave-one-session out cross validation. As the method uses all samples in the data (time-unlocked), it provides a bias-free approach to evaluating predictors of movement onset. Forecasting performance on three subjects using correlation between consecutive samples, directional variance, and projection onto a virtual channel shows that EEG and MEG provide unique information in forecasting movements. Our approach reveals area under the receiver operating characteristic curve values well above chance level for forecasts of movement onset up to 200 ms in the future, and can be used as a general method to evaluate the forecasting performance of any given measure.

**Keywords:** forecasting, self initiated actions, bias, EEG, MEG

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# A multilayer understanding of the auditory cortex

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Sensory processing and perception relies on non-linear operations to extract important features from the environment. In the auditory pathway, those operations are used to disentangle frequency, intensity and temporal information from the sound. Some non-linearities, like adaptation and divisive normalization, were already described in the auditory cortex to explain neuronal responses to simple and complex sounds [David et al., Wehr & Zador]. However, a simple auditory illusion based on intensity modulation challenges those models on behavioral responses and cortical activity. Recently Deneux et al. proposed a multilayer model, based only on the sound intensity, to explain this illusion. This kind of architecture is extensively used in artificial intelligence and machine learning as the current best models to perform perceptual tasks. In this study we aim to keep this architecture and to extend to model of Deneux et al. to the frequency domain.

We recorded more than 60000 neurons from the auditory cortex of awake mice with two-photon calcium imaging. With hierarchical clustering, we grouped neurons based on their activity and we identified the key auditory features extracted by the auditory cortex. Finally we constructed a data-based multilayer model to explain the cortical activity. The new model contains a frequency layer, an intensity layer and a temporal layer to take into account the multiple dimensions of the sounds. This work is part of a project that aims to describe the complete auditory pathway as a succession of layers for feature extraction.

Deneux, Thomas, et al. "Temporal asymmetries in auditory coding and perception reflect multi-layered nonlinearities." *Nature Communications* (2016).

David, Stephen V., et al. "Rapid synaptic depression explains nonlinear modulation of spectro-temporal tuning in primary auditory cortex by natural stimuli." *Journal of Neuroscience* (2009)  
Wehr, Michael, and Anthony M. Zador. "Synaptic mechanisms of forward suppression in rat auditory cortex." *Neuron* (2005)

**Keywords:** Auditory, multilayers, sensory processing

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\*Speaker

# Temporal metacognition as decoding self-generated brain dynamics

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Being aware of our own misjudgments is key to cognitive improvement. The ability to rate one's confidence in assessing external sensory inputs during decision-making tasks is well established. However, how does introspection work when the input is self-generated? Here, we asked human participants to produce a time interval and self-assess their duration on a continuous scale while being recorded with time-resolved neuroimaging. Both temporal production and metacognition relied on the synchronization of beta oscillations: while the strength in beta synchronization appeared to set the end point for the ballistic duration production trajectory, the distance in beta-state space provided the read-out for temporal metacognition. Performance monitoring subsystems and error awareness relied on alpha desynchronization following the production of duration. Altogether, our study provides novel insights on the role of neural oscillations in timing and crucially, how the human brain may decode self-generated internal dynamics for metacognition.

**Keywords:** Temporal judgments

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# Spectral Organization of Human Brain Activity

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The probabilistic nature of neural signals - thought to represent transiently communicating functional networks<sup>1-2</sup> - seems to occlude a deep understanding of brain activity. Between cognitive states and individual subjects, neural signals vary in magnitude, complexity, and spectral organization<sup>3,4</sup>. Here, defining the spectral energy and entropy of resonant modes in magnetoencephalography (MEG) signals recorded from 70 healthy adult human subjects while at rest and while performing a working memory task, we find conserved relationships between state variables consistent with thermodynamic definitions.

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**Keywords:** Magnetoencephalography (MEG), Human, Resting state, Working memory, Modes, Spectral organization

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\*Speaker



# A Bayesian Perspective on Accumulation in the Magnitude System

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Several theoretical and empirical work posit the existence of a common magnitude system in the brain. Walsh's A Theory Of Magnitude (ATOM) proposes that analog quantities are mapped in a generalized magnitude system which entails that space, time, and number may share a common neural code. Such a proposal implies that manipulating stimuli in one magnitude dimension (e.g. duration in time) should interfere with the subjective estimation of another magnitude dimension (e.g. size in space). Recent discussions in the field suggest that the combination and evaluation of quantities in a common representational system would be realized on the basis of Bayesian computations. Here, we asked whether a generalized Bayesian magnitude estimation system would sample sensory evidence using a common, amodal prior. In this study, participants were presented with clouds of dots which appeared dynamically on a computer screen. A cloud of dots was characterized by its duration, its numerosity and its surface. Two psychophysical experiments separately tested participants on their perception of duration, surface, and numerosity when the non-target magnitude dimensions and the rate of sensory evidence accumulation were manipulated. First, we found that duration estimation was resilient to changes in surface and numerosity, whereas lengthening (shortening) the duration yielded under- (over-) estimations of surface and numerosity. Second, the perception of surface and numerosity were affected by changes in the rate of sensory evidence accumulation, whereas duration was not. Our results suggest that a generalized magnitude system based on Bayesian computations would minimally necessitate multiple priors. Duration estimates were not only resilient to changes in numerosity or surface, but also to the rate of sensory evidence. These findings suggest that unlike surface and numerical estimates, duration may not rely on the accumulation of discretized sensory evidence.

**Keywords:** space, time, number, decision, making

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\*Speaker

# The involvement of YAP as a regulator of DNA replication timing.

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Replication timing (RT) is known as the temporal program that orchestrates the order in which segments of DNA along a chromosome duplicate. A strict control of the RT is essential to ensure faithful DNA replication and to sustain genomic stability. Recent studies have shown that stem cells share a specific RT profile that changes upon their differentiation. This is of utmost importance in the field of stem cells as these cells have the unique capacity of long-term self-renewal and as such may have developed specific mechanisms dedicated to maintain genomic integrity. The RT program could be a striking stemness feature, and is now proposed as a novel epigenetic signature of cell differentiation stages. Our previous data revealed that YAP, the downstream effector of the Hippo pathway, is required for proper RT in retinal stem cells from *Xenopus*. Indeed, we found that *Yap* knockdown leads to a shorter S-phase, alteration in the patterns of replication foci and consequent genomic instability. To dissect the function of YAP on DNA replication dynamics, we took advantage of *Xenopus* egg extract cell-free system. We showed that YAP is recruited to chromatin during replication and YAP depletion in egg extracts increases the speed of DNA replication. These preliminary data strengthen our *in vivo* observations and support a model in which YAP regulates DNA replication dynamics. This work provides novel avenues of research to understand the mechanisms involved in the control of the RT program.

**Keywords:** DNA replication, *Xenopus* egg extract, YAP

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# Impact of the temporal statistic of natural movies on the reliability of cortical dynamics in cat primary visual cortex.

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Efficient coding suggests that processing in the early visual system should be optimized and adapted to the environmental statistics. An intracellular study of the laboratory in the primary visual cortex (V1) showed that the reliability and the precision of the neural response are optimized for natural statistics.

Our aim is to compare the reliability and the precision of the mesoscopic signal (Local field potential (LFP) and single and multi-unit activity (SUA, MUA)) and to explore its laminar dependency. We want explore which statistics of the natural stimulation produce highly reliable responses, in particular if there is a role of the surround and of the temporal dynamics due to the simulated eye movement.

In order to answer these questions we used the same stimulus set as in the intracellular study: drifting Gratings, Gratings and natural images animated with simulated eye movements and dense noise, presented on the center of the receptive field only, in the surround only or both. We manipulated the statistics of the eye movement trajectory to explore its impact on the neuronal responses. We also created a bank of natural movies. These movies are presented with or without eye movements.

In response to these stimuli, we recorded with a 64 channel high-density linear silicon probe both SUA, MUA and LFP across the laminar profile of V1 in the anesthetized and paralyzed cat. Our results show that natural images induce a more reliable response than the other stimuli in the low frequency domain and that this reliability strength is layer-dependent for both SUA and LFP recordings. For all types of stimuli, reliability is stronger in the granular layer than in the other layers. Most strikingly, strong and reliable synchronizations of the LFP occur when we stimulate only the "silent surround" of the receptive field with the natural images.

**Keywords:** Primary Visual Cortex, Natural Images, Electrophysiology

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# Mapping cognitive concepts to brain activity with a high-resolution individual data and a cognitive ontology

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Recent developments on data-driven brain atlases are currently changing the way we analyze functional brain imaging data. Such developments have been particularly determined by functional connectivity and parcellation approaches. Meanwhile, the continuous growth of outcomes in brain functional specialization has only provided so far lists of brain locations, which are usually gathered and analyzed under the coordinate-based meta-analyses framework. One striking aspect concerns on how these two different approaches can be mutually exclusive and, thus, functional brain atlases do not truly represent the current state of knowledge about brain specialization. Moreover, both approaches are typically coarse, due to averaging issues inherent to multi-subject and multi-study methods. In the present work, we introduce a new paradigm of analysis relying on two main components: (1) a large collection of functional images acquired from individual subjects on the performance of distinct classes of behavioral stimuli, with millimeter-resolution of information; (2) the organization of functional contrasts, probed into a consistent ontology, by mapping different cognitive components, in replacement of study-specific experimental contrasts. The ongoing project will thus evolve in multiple directions. Releases of the Individual Brain Charting dataset are expected to include a wide range of stimuli tackling many cognitive skills, such as visualization plus interpretation of complex real-world setting scenes, mental time travel, decision-making, working memory during spatial enumeration, retinotopy and tonotopy. On the other hand, high-resolution anatomic (.7mm) and diffusion (1.3mm) images will be acquired, in order to clarify the anatomical nature of the functional territories extracted. Future analysis of the functional data include new types of alignment across subjects, since traditional anatomy-based methods typically lead to loss of information. Lastly, a major step accounts for a full revision of the cognitive encoding herein employed, as this study pertains to link fMRI data with the intrinsic relations among different mental concepts.

**Keywords:** functional brain atlas, cognitive ontology, fMRI, neuroimaging

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# The left occipito-temporal areas are implicated in colour naming, but not colour categorisation.

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Do we need language to categorise colours? We developed a task that aims at measuring colour categorisation without the need for colour naming. In one trial, two bipartite fields are presented, one with two colours from the same category (e.g. light and dark green), the other with two colours from a different category (e.g. orange and yellow). Observers indicate which of the bipartite fields contains colours from the same category. To control the involvement of verbal labelling, the task is performed under verbal(shadowing) and non-verbal(foot tapping) interference. We assessed this task with 30 non-clinical participants and used it to examine a patient with a left occipito-temporal damage. The patient suffered from colour anomia (impaired colour naming) while having non-clinical colour perception. If colour categorisation is independent from colour naming, verbal and non-verbal interference should similarly affect the performance in non-clinical observers. Also, the patient should be able to perform the task despite his problems with verbal naming. Preliminary results show that in non-clinical participants, verbal interference paradoxically improves categorisation, by reducing response times. Moreover, the patient's accuracy is well within the range of non-clinical participants. We conclude that colour categorisation and colour naming can be dissociated. The patient's ability to categorise without being able to name indicates that colour categorisation and colour naming are guided by different neural mechanisms, and that the left occipito-temporal brain region plays a crucial role in linking naming to categorisation. These findings provide a new approach to study the relationship between colour categorisation and language and allows for further investigation of the neural underpinnings of those two processes with neuroimaging.

**Keywords:** categorisation, naming, colour, perception, brain lesion

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\*Speaker

# Encoding variable cortical states with short-term spike patterns

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Neurons in the primary somatosensory cortex (S1) respond to peripheral stimulation with synchronised bursts of spikes, which lock to the macroscopic 600 Hz EEG wavelets. The mechanism of burst generation and synchronisation in S1 is not yet understood. We fitted unit recordings from macaque monkeys with a Poisson-like model including the refractory period (spike-train probability model, STPM). The model combines high-amplitude synaptic inputs with absolute and relative refractoriness. We show that these two properties can reproduce synchronised bursts observed in S1 neurons. The probabilistic nature of the model introduces trial-to-trial response variability. Similar to the experimental data, the variability can be decomposed into stereotypical spike patterns consisting of short bursts of spikes with variable number of spikes and length of within-burst intervals. Next, we extend the model to a population of uncoupled neurons, which receive common inputs fluctuating in amplitude across trials. We demonstrate that these fluctuations introduce correlations between neurons and between the single-neuron spike patterns and population activity (high-frequency EEG wavelets) as observed experimentally. To further study the biophysical mechanism behind S1 burst responses, we develop a single-compartment model (leaky integrate-and-fire, LIF) receiving intracortical and feedforward thalamic inputs. The intracortical inputs are assumed to be in a balanced state, where excitatory and inhibitory currents nearly cancel each other out yielding the neuron in the high-conductance state. This model can reproduce many features of experimental data, in particular the burst statistics and the presence of spike patterns. We conclude that neural systems could use refractoriness to encode variable cortical states into stereotypical short-term spike patterns amenable to processing at neuronal time scales (tens of milliseconds).

**Keywords:** somatosensory cortex, non, human primates, modelling, bursts

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\*Speaker

# The basis of sharp spike onset in standard biophysical models

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Hodgkin and Huxley (HH) described a model of action potential generation. They showed how voltage-dependent channels could interact to enable a positive current flow inside and back out of the cell. Currently, HH type models are widely accepted for modelling cell activity in the brain. However, the action potential shape is not precisely the same as in experimental recordings, namely action potential rises much faster in real neurons than predicted by HH model. Various, mutually exclusive hypothesis were proposed to explain this phenomenon [Naundorf et al., 2006 ,Yu et al., 2008 ,Brette, 2013], but final conclusion was never drawn. We have tackled this problem by computational modelling and theoretical analysis. We varied systematically the morphology of the neuron and distribution of the ionic channels along the cell, and tested how they contribute to the appearance of the kink. We asked three important questions: 1) How do sodium channels activate in the initiation site? 2) Is a big soma necessary? 3) Is back-propagation necessary?

Our analysis reveals that channels open abruptly in the axon initial segment causing discontinuity in the somatic I-V curve. We also show that big soma is necessary for the kink to be present while active backpropagation is not required.

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\*Speaker

**Keywords:** axon initial segment, action potential initiation



# Ethanol and Dopamine release: the role of neuronal synchronization

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Experimental data show that alcohol consumption produces an increase of dopamine (DA) release from dopaminergic neurons of the Ventral Tegmental Area (VTA). This brain region, and the computational processes it performs, are crucial for processing information about rewarding stimuli and reinforcement learning, and hence plays a central role in addiction. Consistent with this view, rewarding events and salient stimuli each increase DA release from DA neurons. Furthermore, dopamine concentration shows a transition from almost time constant (tonic) to oscillatory (phasic) release after ethanol assumption. The goal of the current study is to describe and explore how acute ethanol exposure alters the biophysical properties of VTA DA neurons through a computational model of the VTA circuit. By following experimental evidences of ethanol effects on DA proprieties, such a local circuitry model is able to predict the observed changes in dopamine release under ethanol assumption as a consequence of a different input/output processing from VTA. Furthermore, the model predicts a crucial role for the activity of cortical regions, e.g. prefrontal cortex, projecting to the VTA. We propose that the synchronization and average activity proprieties of such regions drive the dopamine response of the system after ethanol assumption. In particular, a certain level of synchronization in such structures is necessary for observing transient release of dopamine. Moreover, a high level of firing activity in these regions yields a complete opposite effect of ethanol, i.e. a monotonic decrease of dopamine release at any ethanol concentration intake.

**Keywords:** Reward, Dopamine, Addiction, Cortex, Synchronisation, Computational models

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# Parvalbumin expressing GABA-ergic neurons in primary motor cortex signal reaching

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The control of targeted reaching is thought to be shaped by distinct subtypes of local GABA-ergic inhibitory neurons in primary forelimb motor cortex (M1). However, little is known about their action potential firing dynamics during reaching. To address this, we recorded the activity of parvalbumin-expressing (PV+) GABA-ergic neurons, fast spiking units (FSUs) and regular spiking units (RSUs) in layer 5 of the mouse forelimb M1 during a sensory triggered reaching task. Injection of the GABA-agonist muscimol into forelimb M1 disrupted reaching. PV+ neurons showed short latency responses to the acoustic cue and vibrotactile trigger input, and an increase in firing at reaching onset that scaled with the amplitude of reaching. Unexpectedly, PV+ neurons fired before RSUs at reach onset and maintained proportionally higher firing rates until the end of the reach. Thus, increasing M1 PV+ firing rates may play a role in the initiation of voluntary reaching.

**Keywords:** motor cortex, behavior, gaba, ergic neuronal subtypes

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\*Speaker

# Dynamic conversion of sensory evidence to decision signal in ferret frontal cortex

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The frontal cortex is often associated with enhancement of relevant information for goal-directed behavior. In particular, frontal cortex (FC) neurons of the behaving ferret have been shown to respond selectively to target auditory stimuli during discrimination tasks (Fritz et al., 2010). However, in natural and cluttered environments, sounds are not necessarily presented in token-based sequences. Instead relevant events are embedded in continuous sound streams and their detection demands to dynamically update the representation of incoming stimuli (Lawlor et al., 2017). Here, we attempt at characterizing the extraction of relevant sensory information from complex continuous sounds performed at the level of frontal areas. To address this question, we trained ferrets on a change detection paradigm where animals have to constantly monitor a stochastic and continuous acoustic stream to detect subtle statistical changes. We then gathered electrophysiological data in the dorso-lateral FC of the behaving ferret. Because modulations in FC neurons’ firing rate can be correlated with a large variety of overlapping task-relevant and irrelevant events, we used a Linear Non-Linear Poisson model to disentangle the contribution of different predictors (sound onset, change in stimulus statistics, decision, motor activity...) to those modulations. Our model allows us to orthogonalize the responses to each predictor and quantify their specific contribution to the firing rate of individual neuron. Comparing the neurons’ responses for different types of changes and outcomes, we found that neurons encoded both stimulus changes in a stimulus-dependent manner and perceptual decisions in a categorical stimulus-independent fashion. A substantial fraction of the neurons (~25%) displayed a dual encoding of these two types of events, suggesting that conversion from sensory evidence towards a decision signal may take place in the FC.

**Keywords:** Decision making, Frontal cortex, GLM, Auditory perception

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\*Speaker

# Early asymmetric transfer of auditory information across hemispheres: Insights from infants with corpus callosum agenesis

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The left hemisphere specialization for language is a well-established property of the adult human brain. While this hemispheric asymmetry could be related to genetically determined differences<sup>1</sup>, some evidence suggests that lateralization could emerge due to the interaction of inter-hemispheric pathways (through callosal fibers conveying information from one hemisphere to another) on cerebral specialization<sup>2</sup>. The latter hypothesis on the emergence of language lateralization yet remains poorly investigated, requiring further studies on the role of callosal pathways in the development of the auditory network.

Using Electroencephalography (EEG), we investigated auditory processing for sound stimuli presented binaurally, monaurally (either left- or right-ear stimulations) and dichotically, in 18 typical infants (age:  $13.9 \pm 2$  weeks) and 13 infants with a developmental agenesis of the corpus callosum (labelled "AgCC", age:  $16.3 \pm 2.2$  weeks). We recorded auditory evoked potentials for different stimuli presented binaurally or monaurally, and compared their topography between the two groups. We further measured the amplitude and latency of P2 responses in the left and right hemispheres.

In terms of spatial distribution of responses, AgCC infants showed lower fronto-medial activity compared to typical infants, suggesting that callosal fibers contribute to the spatial distribution of auditory responses. When comparing responses in the hemisphere ipsilateral to monaural stimuli, we observed that responses to leftward stimuli (i.e. in the left hemisphere) had longer latency (delay  $\sim 80$  ms) than responses to rightward stimuli (in the left hemisphere), in typical infants but not AgCC infants.

We suggest that this delayed response may correspond to the transfer of contralateral responses from the right to the left hemisphere, and is mediated by callosal fibers. This asymmetric transfer of auditory information, facilitating right-to-left but not left-to-right transmissions, could be potentially related to the emergence of left lateralization for language processing.

1) Bishop et al.,2013 2) Jeeves & Temple.,1987

**Keywords:** EEG, agenesis of corpus callosum, auditory processing, development

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\*Speaker

# Necessity and sufficiency of auditory cortex representations for sound perception

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The Auditory Cortex (AC), represents simple (pure tone) and more complex features (e.g. temporal features) in precise spatial maps. While there is long standing evidence for these maps, causal links between particular activity patterns on these maps and a particular percept have not been yet established. To address this issue, we are currently performing optogenetic silencing and targeted activation experiments through chronic cranial windows in head-fixed mice performing an auditory Go/NoGo discrimination task. Using PV-Cre x flox-STOP-ChR2 mice and broad blue light illumination, we have already shown that strong bilateral inactivation of AC does not abolish discrimination of simple pure tones. However, bilateral AC silencing much more severely impairs discrimination of temporal features (e.g. amplitude or spectral modulations). These results suggest that auditory cortex is not always necessary to perform an action selectively on particular sounds. To better understand this result, we used Emx-Cre x flox-STOP-ChR2 mice and a novel digital micromirror device to activate neurons in the auditory cortex. We showed that mice can discriminate two distinct optogenetic patterns but interestingly the reaction time of the animal in these conditions was significantly larger than for pure tone discriminations and similar to the reaction time observed for spectral modulations discriminations. This suggests that AC influences behavior in a slower manner than other competing pathways and is bypassed by these faster pathways for simple discriminations. Finally, we also tested whether behavioural responses to discriminated sounds can be influenced by patterned cortical stimulation. We already observed that local activations have no effect on pure tone discriminations and can influence, although weakly, a discrimination of pure tone and a frequency ramp. Altogether these results demonstrate that auditory discriminations do not necessarily require AC but rather emerge through a network competing pathways which includes AC according to the perceptual demand.

**Keywords:** behavior, optogenetics, sounds, perception

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# Characterization of the diffusion process of different Gd-based nanoparticles within the brain tissue after ultrasound induced Blood-Brain Barrier permeabilization

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The *in vivo* characterization of Gd-based MRI Contrast Agents (MR-CA) diffusion within brain tissue is of interest for the understanding of drug transport in brain parenchyma. We present a new method to study the diffusion process of different MR-CAs after ultrasound-induced blood-brain barrier (BBB) permeabilization.

## Methods

Four Gd-chelates with different hydrodynamic diameters (dH) were tested. The MRI acquisitions were performed with a 7T/90 mm Pharmascan scanner (Bruker). The DFree of all the compounds were evaluated from in-vitro experiments. The diffusion was followed for 1 hour by acquiring T1-maps. MR-CA concentration maps were calculated from T1-maps [Marty, 2013]. On each CA-map, a 2D Gaussian function was fitted (Fig.a) and the DFree was calculated from the fit. Focused ultrasound induced BBB disruption was performed in the right striatum of 11 rats by using our motorized MR-guided FUS system [Magnin, 2015]. After the microbubble intravenous injection, pulsed ultrasound were shot at 1.2 MPa (3ms/100ms for 60s). Then MR-CA were injected intravenously and their diffusion starting from the BBB disruption site was followed by acquiring T1-maps for 1 hour. The Gaussian fit was applied on the MR-CA concentration maps and the ADC of all compounds were estimated as for the *in vitro* measurements (Fig.b).The tortuosity ( $\lambda$ ) was then calculated.

## Results and Conclusion

For all the MR-CAs the measured dH values were in accordance with the values obtained with DLS and both DFree and ADC decrease when dH increases. The values of  $\lambda$  are comprised between 1.7 and 1.5, the same range measured in healthy brain tissue using optical techniques [Nicholson, 1998]. This means that using ultrasound to deliver MR-CA enables to measure brain tortuosity as well as to predict spatial distribution of nanomedicines, but also confirms that the diffusion properties of the tissue are not altered by the ultrasound induced BBB permeabilization protocol[Marty, 2013].

**Keywords:** Focused ultrasound, Blood, brain barrier, Brain tissue tortuosity, Drug delivery

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# Neuropeptidergic and Environmental modulation of the Evening Oscillators in *Drosophila*

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Circadian clocks have evolved to enable organisms keep the time of the day. In *Drosophila*, around 150 neurons constitute a circuitry that regulates the daily bimodal activity-rest rhythm. Inter-neuron communications among these anatomically dispersed and functionally diverse neurons require several neuropeptides in this network. Pigment Dispersing Factor (PDF), a small neuropeptide, is produced by the lateral ‘morning’ neurons and modulates the phase of the evening (E) activity; through its receptor expressed in the ‘evening’ neurons. Ion Transport Peptide (ITP), another neuropeptide, is expressed in only 2 pairs of clock neurons, which have already been ascribed to be part of a broader subset of neurons required for the E activity. We establish here that the ITP neurons are not just sufficient for E activity but they are also hierarchically superior to the rest of the evening neurons. Interestingly, PDF seems to strengthen the output of ITP neurons; thereby possibly contributing to the establishment of the superiority of these neurons. Environmental conditions too, like PDF, structure the degree of contributions from ITP and non-ITP evening neurons on the E activity. While ITP neurons are crucial for the E activity in a short winter-like day, the non-ITP neurons play a vital role under long summer-like days, especially when the flies experience daily variations in temperature. In addition to this, PDF seems to be important for the proper phasing of E activity under long days. We show that, PDF and ITP decipher the day-length by modifying their levels in the clock neurons. We observe that the PDF and ITP neurons communicate and affect each other. Studying PDF and ITP levels across seasons, of several recently wild-caught strains, we are currently investigating the nature of interaction between ITP and PDF in adjusting the E activity to the seasonal variations.

**Keywords:** Circadian clocks, Pigment Dispersing Factor (PDF), Ion Transport Peptide (ITP), E activity, Photoperiod

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# Towards a better predictive model of rest fMRI: benchmarks across multiple phenotypes

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Psychiatry and psychology are based on assessing individuals traits, characterized through behavioral testing and questionnaires. Imaging of brain activity raises the hope of measuring the physiological differences that underlie these psychological variations [1,2]. In [4], we have introduced an automated pipeline capable of learning this link across individuals using large cohorts of functional magnetic resonance images acquired during rest (Rest fMRI). We present an openly available implementation of this pipeline and how we used it to draw best practices from its application on various problems. Rest fMRI is a promising universal marker of brain function [3], as it can easily be acquired on many different individuals and is applicable to disease populations. It is used to capture functional-connectivity information, i.e. interaction patterns in brain activity. The challenge is then to relate it to behavior and pathology. Our pipeline successively defines regions from rest fMRI, build connectomes from time series signals extracted upon on these regions of interests, and compares connectomes across subjects using machine learning. We applied it on five datasets to i) determine the steps to obtain the best prediction, and ii) predict phenotypic information with good accuracy. Through systematic comparisons, we outline dominant choices for each pipeline step. Our results show that this analysis pipeline can be adapted to various psychological questions for instance in epidemiological studies [2], moving imaging closer to a diagnosis tools in clinical settings.

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**Keywords:** Psychiatry, human brain imaging, rest fMRI, Predictive modeling, Classification

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\*Speaker



# Parametric Models of Phase-Amplitude Coupling in Neural Time Series

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In neuroscience, phase-amplitude coupling (PAC) refers to the interaction between the phase of a slow neural oscillation and the amplitude of high frequencies within the same signal or at a distinct brain location.

To model PAC, we use new parametric generative driven auto-regressive (DAR) models. These statistical models provide a non-linear and non-stationary spectral estimation of the signal,

and are able to capture the time-varying behavior of PAC.

As the model is probabilistic, it also provides a score of the “goodness of fit” for the likelihood of the model,

enabling easy and legitimate model selection and parameter comparison; this data-driven feature is unique to our model-based approach.

Using three datasets obtained with invasive electrophysiological recordings in humans and rodents, we demonstrate that these models are able to replicate previous results obtained with other metrics, but also reveal new insights such as the influence of the amplitude of the slow oscillation.

Using simulations we demonstrate that our parametric method can reveal neural couplings with shorter signals than non-parametric methods.

We also show how the likelihood can be used to find optimal filtering parameters, suggesting new properties on the spectrum of the driving signal, but also offers a principled way to estimate the optimal delay between the coupled signals, enabling a directionality estimation in the coupling.

**Keywords:** phase, amplitude, coupling, cross, frequency, auto, regressive, model

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\*Speaker

# Rapid anxiolytic effects of a 5-HT4 receptor agonist involves prefrontal cortex/brainstem neural circuit recruitment

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Anxiety disorders are one of the most prevalent mental health conditions. Although benzodiazepines (BZD) are very effective in reducing acute anxiety, their adverse effects limit their use chronically. Selective serotonin reuptake inhibitors (SSRIs), usually prescribed in depression, are considered to be the first line of therapy for anxiety disorders, even they display a delayed onset of action. Therefore, the development of new anxiolytics is of considerable importance, and understanding the mechanisms underlying this delayed onset should offer insights into new approaches. Recent studies indicate that serotonin type 4 receptor (5-HT4) agonists are faster acting than SSRIs to treat anxiety-like behavior(1).

Here, we explored the neural circuit recruitment in acute 5-HT4 receptor stimulation-induced fast anxiolytic-like effects in anxious male BALB/cJRj mice. Unlike fluoxetine (SSRI), but similar to diazepam (BZD), acute 5-HT4 receptor agonist (RS67333) induced fast anxiolytic-like effect in anxiety-related behavioral tests (OF, EPM, NSF). Since the 5-HT4 receptor is expressed in the medial prefrontal cortex (mPFC)(2) and these cells project to the dorsal raphe nucleus (DRN)(3), a serotonergic nucleus implicated in emotional behavior, we evaluated the recruitment of this neural circuit in 5-HT4 receptor stimulation-induced fast anxiolytic-like activity. Interestingly, acute intra-cortical injection of RS 67333, which led to fast anxiolytic-like effect in the EPM and NSF, was abolished in serotonin-depleted mice, pointing out the critical role of serotonin release in these effects. By inhibiting optogenetic mPFC projection-targeting to the DRN with a AAV5-CaMKII-ArchT-GFP virus, simultaneously to behavioral testing, we confirmed this neural circuit recruitment in cortical 5-HT4 receptor stimulation in the anxiolytic-like effects of RS67333. In summary, 5-HT4 receptor stimulation via the mPFC-DRN neural circuit recruitment could represent an innovative and rapid onset therapeutic approach to treat anxiety disorders.

(1)Mendez-David et al., 2014, Neuropsychopharmacology ; (2)Vilaro et al., 2005, J. Comp. Neurol. ; (3)Lucas et al., 2005, Biol Psychiatry.

**Keywords:** anxiety, 5, HT4, RS67333, diazepam, mice, behavior, optogenetic, prefrontal cortex, dorsal raphe nucleus

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\*Speaker

# Correlation processing by neurons with active dendrites

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We investigate the processing of correlated synaptic input in neurons equipped with active dendrite. We discovered that these neurons can process correlation in the very different way than the single-compartmental neurons and the neurons with passive dendrite. We use three types of models in our study: biophysical FitzHugh-Nagumo model, multi-compartmental AdEx model and discrete state model.

**Keywords:** dendritic integration, dendrites, correlation processing, dendritic spikes

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\*Speaker

# Cortical and subcortical neuromodulation using focused ultrasound

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Noninvasive focused ultrasound (FUS) has been proven capable of modulating neuronal activity. The activation of cortical and subcortical brain structures have demonstrated the higher target specificity and superior depth of penetration of FUS in comparison with techniques such as transcranial magnetic stimulation. However, the underlying mechanisms of activation rely on hypothesis based on intramembrane cavitation and mechanical stress of ion channels yet to be experimentally confirmed. Inconsistent lateralization of motor elicited responses demonstrates, for example, that FUS drives excitatory and inhibitory control of the neuronal network. Pupillary responses have also demonstrated indication of modulation of brain structures associated with light reflex and cognition. In this study, we aim at mapping neural network activity using functional magnetic resonance imaging (fMRI). We first validated our setup by demonstrating tail and limb elicitation of anesthetized rats, as observed in other studies. Subsequently, preliminary results demonstrate correlation of hemodynamic response in fMRI when sonication was active. BOLD signal were observed in the cerebellum, which may explain elicited trunk movements outside the magnet. Currently, we are developing a setup to record inside the magnet videos of motor elicitation and pupil dilation, as well as animal’s vital signs to correlate with cortical and subcortical activation. We will target regions in the sensorimotor cortex and in the limbic system, with the later supporting functions such as adrenaline flow, emotion and behavior. With the modulation of the limbic system, we aim to confirm hemodynamic responses synchronized with pupillary response. Once the setup is validated, studies involving complex tasks may confirm cognitive responses with ultrasound neuromodulation.

**Keywords:** ultrasound neuromodulation, fMRI

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# Adaptive stimulation in a delayed Wilson-Cowan model for disruption of pathological oscillations

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Abnormal beta oscillations observed in the subthalamic nucleus (STN) and globus pallidus (GP) are positively correlated with increased symptoms of parkinsonism, especially bradykinesia. Deep brain stimulation (DBS) within STN successfully reduces those symptoms and leads to a decrease of these pathological oscillations (Hammond et al., 2007).

The current DBS practice uses permanent open-loop stimulation, regardless of the patient’s present condition. Most closed-loop stimulation strategies tested experimentally are on-demand, meaning that a prescribed stimulation signal is delivered whenever a pathological behavior is detected (Little et al. 2015).

Control theory provides means to go beyond on-demand stimulation by continuously shaping the signal as a function of real-time brain measurements (Haidar et al. 2016). This study explores such a strategy in a Wilson-Cowan model representing the STN-GP dynamics and taking into account axonal propagation delays. We propose a closed-loop stimulation signal on the STN, depending on STN measurements only, and consisting in a proportional feedback with a dynamical gain that increases with the strength of pathological oscillations. We mathematically show that the proposed strategy successfully disrupts pathological oscillations with limited effects at other frequencies. Through numerical simulations, we also show that a variant of this stimulation strategy allows to disrupt targeted oscillations, with a control gain that decreases when targeted oscillations vanish. We also outline a framework to extend this work to allow for more complex models.

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**Keywords:** closed loop stimulation, Wilson Cowan model, parkinsonism

# Bipolar disorder and white matter microstructure: enigma bipolar disorder fractional anisotropy dti results

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Introduction: Using diffusion tensor imaging (DTI), connectivity differences between patients with bipolar disorder (BD) and healthy controls can be explored by looking at white matter microstructure. The mega-analytic methods used in this study increase the power of the analysis, to help harmonize the heterogeneity of results seen across previous studies. Methods: We analyzed data from 18 sites part of the ENIGMA BD DTI consortium, gathering 2804 (1501 female, 1303 males) adult subjects (1345 patients, 1459 controls), ages 18 to 65 (M= 37.25, SD= 12.40). All subjects underwent a DTI acquisition, and data was processed according to the ENIGMA DTI pipeline utilizing TBSS within FSL. This harmonizes data processing across sites. For each subject we calculated average FA values across 42 regions of interest (ROI). Using a linear mixed model, we compared FA between patients and controls, including age and sex as fixed factors and site as a random effect. Results: Using a likelihood ratio test, Bonferonni corrected for multiple comparisons, we saw statistically decreased FA in patients compared to controls within 29 of the 42 ROI: Anterior corona radiata right/left, Body of corpus callosum, Cingulum (cingulate gyrus) left/right, Corona Radiata left/right, External capsule left/right, Genu of corpus callosum, Posterior thalamic radiation left/right, Splenium of corpus callosum, Superior fronto-occipital fasciculus left/right, Sagittal stratum left/right, Uncinate fasciculus left/right (for all proceeding,  $p < .001$ ), Anterior limb of internal capsule left/right ( $p=.004$ ,  $p=.012$ ), Fornix (cres)/Stria terminalis right ( $p=.013$ ), Inferior fronto-occipital fasciculus left/right ( $p=.019$ ,  $p < .001$ ), Posterior corona radiata left/right ( $p=.045$ ,  $p=.005$ ), Superior longitudinal fasciculus left ( $p= 0.007$ ), Superior corona radiata right ( $p=.004$ ), Average FA ( $p=.004$ ). We did not find any significant increase in FA. Conclusions: Our results confirm and extend previous results from smaller studies. They highlight the importance of fronto-limbic dysconnectivity but also point towards the implication of other networks.

**Keywords:** Bipolar disorder, Neuroanatomy, Brain imaging, DTI

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# Age-related changes in functional connectivity and gray matter integrity on scene-processing and spatial navigation networks

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Spatial navigation involves multiple cognitive processes including the integration of perceptual information, visuo-spatial abilities, spatial memory, executive functions and decision-making. This integration process is mediated by numerous cerebral structures that can be separated into a posterior network (dedicated to visual and spatial navigation processing) and an anterior network (dedicated to memory and navigation planning). These brain networks are known to be most sensitive to the effect of aging. However, the relation between age-related deficits in visual information processing and in spatial navigation remains to be elucidated. We addressed this issue by combining voxel-based morphometry (VBM) and functional connectivity analysis based on regions of interest (ROI). Twelve young ( $\mu=26$  y/o,  $\sigma=3.17$ ) and twelve old ( $\mu=70$  y/o,  $\sigma=2.83$ ) participants performed a structural and functional magnetic resonance imaging study including T1-weighted anatomical images, resting state scans and two functional localizers to map cerebral regions involved in both visual scene processing and spatial navigation. These regions included the parahippocampal place area (PPA), the retrosplenial cortex (RSC), the occipital place area (OPA), and the projection of central and peripheral visual fields. In addition, from anatomical images, we segmented for each participant the entorhinal cortex (EC) and the hippocampus (HC). Our VBM results showed a widespread gray-matter atrophy across the older adults' brain, mainly involving frontal and temporal lobes. Concerning the functional connectivity, ROI-to-ROI analyses revealed an increase of connectivity between OPA, RSC and HC in old participants. Critically, the RSC, which is involved in the translation between egocentric (supported by OPA) and allocentric (supported by HC) spatial representations, showed the highest degree of gray matter atrophy with aging. These results highlight the central role of the RSC, at the junction of posterior and anterior navigation network, in both visual and spatial navigation deficits related to normal aging. Acknowledgments: Supported by ANR–Essilor SilverSight Chair ANR-14-CHIN-0001.

**Keywords:** Normal Aging, Functional Connectivity, Voxel Based Morphometry

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# Implication of an amygdalo-prefronto-dorsostriatal network in implicit timing of associative learning

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In Pavlovian aversive conditioning, the animal not only learns an association between a neutral conditioned stimulus (CS) and an aversive unconditioned stimulus (US), but also that the CS predicts the time of arrival of the US. Furthermore, while precise temporal behavioral output requires more than 200 trials of training, we know that the CS-US time interval is learned in as few as one trial (Diaz-Mataix et al., 2013). In search of neural correlates of CS-US interval timing, we recorded local field potentials in an amygdalo-prefronto-striatal network, as those structures are involved in either time processing or associative learning. We used a modified Pavlovian discriminative fear conditioning paradigm in which a 60-s auditory CS+ predicted the arrival of a US (footshock) at either 30 s or 10s, while another 60-s tone CS- was never associated with the US in behaving rats. Time-frequency analyses during trials without shock, before and after a single 12-trial session of conditioning, show area-specific dynamic changes in oscillations related to the temporal expectation of the US, with increased theta and gamma power in the prelimbic cortex, as well as decreased beta power in the striatum. Coherence in the theta range between the three structures of our network was also increased in a relation to the CS-US interval. Our results suggest an involvement of the amygdalo-prefronto-striatal circuit, as a functional network, in processing the CS-US interval early in training during Pavlovian aversive conditioning.

**Keywords:** Timing, local field potentials, aversive conditioning, rats

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# Low intensity rTMS induces neural circuit repair but depends critically on stimulation pattern and the presence of magnetoreceptors

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Focal high-intensity (rTMS) and diffuse low-intensity repetitive transcranial magnetic stimulation are used to increase neural circuit plasticity and show promise in treating neurological disorders through ill-defined mechanisms (DiLazzaro et al, Brain Stim 2013). We combined these approaches to create focal low-intensity stimulation (LI-rTMS, 10mT), which modifies neural circuit function without directly inducing firing of the stimulated neurons (Rodger et al, FASEB J 2012). It is important to determine whether this LI-rTMS, such as would occur in human brain tissue surrounding the central high-intensity focus, alters normal neurons and/or engenders negative outcomes.

To assess this, we applied LI-rTMS at a Biomimetic High Frequency (BHFS) to the mouse cerebellum to examine the cellular and behavioral sequelae. Three days BHFS increases Purkinje cell (PC) dendritic spine density. Four weeks stimulation increases PC dendritic arborisation in association with improved spatial memory. We also used our reproducible *ex vivo* explant model of post-lesion olivocerebellar climbing fiber (CF)-PC neosynaptogenesis (Letellier et al, PNAS 2009) to evaluate whether different LI-rTMS patterns induce CF-PC reinnervation. Only two complex patterns of stimulation, BHFS and intermittent Theta Burst Stimulation (iTBS), induced significant levels of reinnervation compared to sham.

Moreover, LI-rTMS changed the expression of genes involved in axonal plasticity in concert with the observed reinnervation. Thus the pattern/frequency of LI-rTMS are fundamental to its effects on neural circuits.

Given that LI-rMS does not directly induce firing in stimulated neurons, we tested a role for the magnetic field itself, by analysing reinnervation in explants knockout for potential magnetoreceptors, cryptochrome1&2. The absence of reinnervation following LI-rTMS in these explants suggests that activity-dependent plasticity is not essential for magnetic field stimulation-induced neuroplasticity; rather that magnetic fields can modulate neural circuits.

In conclusion, LI-rTMS alters the cerebellum at molecular, cellular and circuit levels and it affects cerebellar related functions.

**Keywords:** LI, rTMS, olivocerebellar pathway, reinnervation, pattern, cryptochromes

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