Thalamocortical Networks 2024

May 16th -17th, 2024

DONOSTIA-SAN SEBASTIAN

BASQUE COUNTRY, SPAIN

PROGRAM SUMMARY

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** For Social Event II Registrees ONLY

WELCOME

We are delighted to welcome you to the inaugural Thalamocortical Networks (ThalNet) conference in Donostia–San Sebastián, Spain. Thank you for joining us and for your valuable contribution to this event.

ThalNet aims to bridge the gap between cellular and cognitive neuroscience in our shared shared pursuit of deeper insights into thalamic function, structure, and thalamocortical networks. Recognizing the potential synergy between these two disciplines, ThalNet brings together experts from both fields to initiate, foster, and maintain interactions among researchers. Our goal is to advance and strengthen our understanding of thalamocortical and corticothalamic networks and their roles in perception, cognition, emotion, memory, and action.

With this objective in mind, we have organized ThalNet, and we hope that over the next few days, you will enjoy this scientific event, engage in fruitful interactions with colleagues, and explore the beauty of this Basque coastal city. We encourage you not only to indulge in excellent science but also to savor the unforgettable culinary experiences and the breathtaking sights along the bay of Donostia–San Sebastián.

The organizing and scientific committees would like to express our heartfelt gratitude for your presence here today. We also extend our sincere appreciation to the administration committee whose support and expertise have been instrumental in making this event possible. Special thanks go to Oihana Vadillo, Leire Arietaleanizbeascoa, and Ana Fernández for their invaluable assistance with multiple aspects of the conference.

Kepa Paz-Alonso, Francisco Clascá, Liu Mengxing and Amaia Carrión-Castillo
ThalNet scientific and organizing committee

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ABSTRACTS

[K-1]

Thalamocortical interactions in cognitive control and flexibility

Michael Halassa [1]

[1] School of Medicine, Tufts University, Boston, US

Interactions between the thalamus and cortex are critical for cognition but the exact contribution of the thalamus has been unclear. Classical theories depict thalamic relay of signals to or between cortical areas, but recent studies have highlighted the existence of bona fide thalamic computation and a diversity of thalamic output patterns capable of non-relay functions. In this talk, I will discuss findings that highlight the role of the mediodorsal (MD) thalamus in generating unique task-relevant variables and regulating prefrontal excitatory/inhibitory balance and effective connectivity during decision making. These findings indicate a role for the MD thalamus in hierarchical reasoning by engaging computations relevant to credit assignment. In addition to being central to many higher level cognitive processes, these computations are perturbed in schizophrenia. If time allows, I will present work that directly shows this link and our collaborative efforts to identify biomarkers and treatment targets.

[K-2]

Creating a visual prosthesis by interfacing with the visual thalamus

Pieter R. Roelfsema [1]

[1] Netherlands Institute for Neuroscience, Amsterdam; Institut de la Vision, Paris

A long-standing dream of scientists is to be able to directly project images from the outside world onto the visual brain, bypassing the eyes. This method could provide a solution for blind and visually impaired patients. It is the only possible solution for patients in whom the connection between eye and brain is lost so that a prosthesis in the eye is not an option.

I will first give an overview of the functioning of the LGN and visual cortex, where lower level brain regions analyze simple visual features and higher areas more complex properties such as object category and faces. I will then discuss the mechanisms that determine whether a visual stimulus will reach consciousness or not. It is well established that the electrical stimulation of electrodes in the visual brain leads to artificial percepts called "phosphenes". This method also works in patients who have been blind for decades. The goal of our own research is to bring a prosthesis for the visual brain closer. We implanted 1000 electrodes in the visual cortex to generate complex visual patterns. We demonstrated that this stimulation leads to interpretable images, in the same way that pixels form recognizable patterns on a screen. We are now looking into possibilities to interface with the LGN, which would facilitate clinical translation. These new neurotechnological developments take important steps in the direction of prostheses that can restore a rudimentary form of vision.

[K-3]

The tiny and the fast: The role of the sensory thalamus in speech recognition

Katharina von Kriegstein [1]

[1] TU Dresden, Germany

Human communication signals are complex and operate at rapid time scales across multiple modalities. For instance, speech must be processed in real-time, often in challenging conditions. My research aims to uncover the sensory mechanisms that allow us to perceive these complex signals and effectively communicate with one another. During my presentation, I will share studies demonstrating a role of modulated responses in the visual and auditory sensory thalami (lateral geniculate nucleus, LGN; medial geniculate body, MGB) in speech recognition. This modulation can be explained by a predictive coding framework, where predictions generated in the cerebral cortex optimize the processing of auditory and visual speech in MGB and LGN. Disruptions to these cortico-thalamic systems are linked to two neurodevelopmental disorders, namely developmental dyslexia and autism. Recent high-resolution magnetic resonance imaging indicates differences, particularly in the magnocellular subsections of the visual sensory thalamus, between individuals with dyslexia and autism compared to typically developed controls. Overall, these findings suggest that modulation of MGB and LGN is crucial for processing rapidly changing communication signals, and their dysfunction may contribute to symptoms observed in neurodevelopmental disorders.

[S-1]

Mutimodal function of the pulvinar in health and disease

Theme Speaker: **Melanie Wilke**

[S-1.1]

Contribution of the primate pulvinar to blindsight

Kristine Krug [1]

[1] Department of Sensory Physiology, Otto-von-Guericke-University & Leibniz-Institute for Neurobiology, Magdeburg, Germany

Visual perception in primates arises through processing of visual input in a large but increasingly well-defined network of cortical and subcortical areas. Lesions of human primary visual cortex (V1), a major gateway for visual input from thalamus to cortex, lead to Blindsight with a loss of conscious visual perception. In contrast, we have been able to identify more than two Rhesus monkeys (Macaca mulatta) with sizeable, naturally occurring lesions in primary visual cortex but with generally unremarkable behaviour. In these cases, bilaterally enlarged lateral ventricles occupied the area directly underneath central visual field representations of primary visual cortex, displacing white matter and the deep mushroom-like structure representing peripheral vision. Given the significant direct input from the pulvinar and the lateral geniculate nucleus to extrastriate visual cortex, the hypothesis has been put forward that these inputs are strengthened in Blindsight and mediate remaining visual functionality. We investigated structural, diffusion-weighted and functional MR images of the monkeys without V1. In comparison with typical monkeys, subcortical visual brain structures, like the pulvinar, connectivity and patterns of myelinations in recipient extrastriate visual cortex showed little differences. Based on these findings and other studies, I will examine the potential contribution of the pulvinar for visual perception.

[S-1.2]

Multisensory function of the pulvinar in primates

Suliann Ben Hamed [1]

[1] Institut des Sciences Cognitives Marc Jeannerod, CNRS

The pulvinar has been proposed to act as a functional hub of cortical processes due to its extensive reciprocal connectivity with the cortex. However, its role in cognition is not fully understood yet. I will present a series of functional imaging studies in humans and non-human primates aiming at elucidating the organization of the functional connectivity of the pulvinar with the brain at rest and during the processing of sensory information from different modalities. In a first part, I will describe the organization of visual, auditory and tactile information in the human and non-human primate pulvinar, during different tasks. I will show that how the different pulvinar sub-nuclei encode different sensory modalities is strongly dependent on the task and the context. In a second part, I will describe that, in addition to two global cortical functional connectivity gradients along the antero-posterior and ventro-dorsal pulvinar gradients, multiple local cortical pulvinar projection fields can be identified along the main cortical sulci. I will propose that these multiple pulvinar projection fields correspond to a fundamental principle of pulvino-cortical connectivity, supporting sensory processing and cognitive flexibility, and accounting its task and context dependent functional properties.

[S-1.3]

Visuomotor functions of the pulvinar nuclei: perturbation and electrophysiological studies in primates

Igor Kagan [1]

[1] Decision and Awareness Group, Cognitive Neuroscience Laboratory, German Primate Center, Goettingen, Germany

Flexible primate cognition and behavior depend on concerted activity across distributed brain circuits, including inter-hemispheric and thalamo-cortical interactions. I will present a series of causal perturbation, imaging and electrophysiological studies aimed at elucidating contributions of the pulvinar to bihemispheric visuomotor processing of eye and hand actions in space. To address pulvinar-cortical interactions, I will first describe pulvinar microstimulation-elicited brain-wide effective fMRI connectivity and time-specific effects on oculomotor choice behavior. Then, I will illustrate inactivation-induced spatial and hand-specific deficits and associated changes in the connected cortical regions at the level of single neurons and population activity, and discuss these effects in the context of inter-hemispheric competition and compensatory mechanisms. I will then summarize how pulvinar neurons encode visuomotor saccade and reach contingencies as well as postural variables such as gaze. Based on these results, I will argue that the role of dorsal pulvinar extends beyond purely visuospatial domain and active cortical state maintenance, to reference frame transformations, flexible selection and integration of visually-guided eye and hand actions.

[S-1.4]

Pulvinar contributions to reach and grasp behavior

Melanie Wilke [1 2]

[1] Department of Cognitive Neurology, University Medicine Goettingen
[2] Cognitive Neurology Group, German Primate Center, Goettingen, Germany

Most concepts of visually-guided limb movements in primates emphasize interactions across fronto-parietal and cerebellar networks. Those networks also connect through higher-order thalamus, opening the question what kind of information these loops contribute. With a focus on the pulvinar, I will present evidence from monkey inactivation and human lesion studies that the pulvinar is critical for reach-grasp behavior beyond spatial attention. In a larger population of patients with focal thalamic stroke, we show that reach-grasp deficits follow a posterior-anterior pulvinar gradient. While limb ataxia can be a consequence of pulvinar lesions, it does not seem to be critical for (implicit) visuomotor learning, which predominantly relies on the classical "cerebellar thalamus". We furthermore show that, despite its strong connectivity and electrophysiological effects on parietal cortex during reaching, pulvinar lesions do not lead to optic ataxia. Instead, optic ataxia was observed with lesions in the lateral part of the mediodorsal and centrolateral thalamus. In two patients with (chronic) bilateral pulvinar lesions, we show that the pulvinar critically contributes to trunk and limb coordination for standing and walking. Our results suggest that pulvinar function goes well beyond its subscribed role in visuospatial cognition and should be rather conceived as an integrator of multimodal sensorimotor activity including postural control.

[S-2]

Circuits for cognition: the higher-order nuclei of the primate thalamus

Theme Speakers: **Carmen Cavada/Francisco Clascá**

[S-2.1]

Thalamic inputs to the macaque superior parietal lobule: sensory-to-motor loop

Michela Gamberini [1]

[1] Dipartimento di Scienze Biomediche e Neuromotorie Università di Bologna

The medial route of the dorsal visual stream has been recently named “reach-to-grasp network” because of its involvement in the full sequence of prehension act. In macaque monkeys, this stream involves the areas of the superior parietal lobule, showing a caudorostral trend in their visuo-somatic properties, and is directly connected with the dorsal premotor cortex. We analyzed the thalamic inputs to the dorsomedial stream areas by injecting retrograde neuronal tracers separately into different superior parietal: areas V6, V6A, PEc, and PE. All these areas receive thalamic afferents from LP and pulvinar complex, with some peculiar specificity. Thalamic afferents bring ‘visual’, ‘bimodal’, ‘somatosensory’, ‘somatomotor’, and ‘oculomotor’ information, as well as information about direction of spatial attention. The distribution of these afferents helped us in understanding the functional properties of dorsomedial stream areas and suggested how it may guide limb interaction with objects, particularly in structured and dynamic environments. Grants: H2020-EIC-FETPROACT-2019-951910-MAIA; PRIN2020- 20208RB4N9.

[S-2.2]

Input-output motifs in the primate pulvinar complex

Francisco Clascá [1 2]

[1] Autonoma de Madrid Univeristy, Spain
[2] Federal University of Rio Grande do Norte, Natal, Brazil

The medial division of the thalamic pulvinar complex (MPul) is massive in higher primates, particularly in humans. Unlike the rest of the pulvinar, MPul is not directly involved in visual processing and, reportedly, it is connected to a variety frontal, parietal, cingulate, insular and temporal areas. The precise wiring of these multiple connections and their organization within MPul has not been investigated. We used microiontophoretic injections of biotinylated dextran (BDA) in MPul or retrograde tracer deposits in the cortex to map the area and lamina distributions of axons arising from small clusters of MPul neurons. We analyzed MPul axon trajectories throughout the cerebral white matter and quantified terminal varicosity number and size.

We show that, within MPul, several partially overlapping domains can be distinguished according to the targets of their axons in the cortex. Axons from one of these domains arborize in several heavy terminal foci. Neurons projecting to frontal, parietal, cingulate, or temporal areas form closely adjacent o intermingled clusters within MPul. In virtually all areas, MPul axons target mainly layers 3b-4 and layer 1. These features are consistent with the notion that PulM is a key neural hub in the neural networks that allow complex multisensory-guided social behaviors.

[S-2.3]

Neuromodulatory axons in the primate thalamus. Relevance for neurological disease.

Carmen Cavada [1]

[1] Department of Anatomy, Histology and Neuroscience. Universidad Autónoma de Madrid, Spain

Aminergic axons have widespread, but uneven and specific, distributions in the primate thalamic nuclei. The presentation will focus on dopaminergic (DA) and noradrenergic (NA) axons in the macaque and human thalamus. DA axons are densest in midline nuclei, and in the mediodorsal and lateral posterior association nuclei. These distributions suggest a role for thalamic DA in emotion, attention, cognition, and complex sensory processing. In parkinsonian macaque brains there is lower DA innervation in the mediodorsal and centromedianparafascicular nuclei. In the reticular nucleus, by contrast, DA innervation increases with the severity of parkinsonism. NA axons innervate mostly the midline nuclei, the intralaminar paracentral and parafascicular nuclei, and the medial sector of the mediodorsal nucleus. NA modulation of information in the thalamus may be mostly related to sensorimotor gating, cognition, and consciousness. NA loss is present in brains from Parkinson's disease patients, mostly in motor, limbic, association and intralaminar nuclei

[S-3]

Midline nuclei: a thalamic hub for sleep and affective behavior

Theme Speakers: **László Acsády / Ferenc Mátyás**

[S-3.1]

Paraventricular thalamic gating of hypothalamic feeding signals

Henning Fenselau [1]

[1] Max Planck Institute for Metabolism Research, Policlinic for Endocrinology, Diabetes, and Preventive Medicine (MF)

Feeding behavior is a complex process that requires the orchestration and organization of motivational and motor circuits, and this system has to precisely adapted to the energy state of the organism. The arcuate nucleus of the hypothalamus (ARC) is a core brain region for integrating hormonal and nutrient inputs signaling energy availability, and multiple ARC neuron populations have been shown to be necessary for the control of food intake. However, we are just beginning to understand the complex circuits these neurons form to actuate conscious sensations - such as satiety - which ultimately drive behavioural actions. I will present our findings demonstrating that the paraventricular thalamus (PVT), a nucleus of the dorsal midline thalamus, serves as a key relay station for ARC neuron-derived signals communicating systemic energy status to cortical and striatal circuits. I will then show our current data suggesting that this ARC◊PVT axis enables the precise, state-dependent adjustments of satiety signalling.

[S-3.2]

Cholinergic Modulation of Auditory Thalamus Mediates Associative Learning

Jan Gründemann [1]

[1] DZNE

Associative learning links predictive sensory stimuli from the environment with their outcomes. The accuracy of associative learning depends on reliable integration of sensory inputs that result in behavioral adaptations to ensure an animal's survival. Several cortical and limbic brain areas have been identified as sites for associative learning. However, the role of thalamic structures that relay sensory information is largely unknown. The medial geniculate body (MGB), or auditory thalamus, is a site of convergence for auditory as well as somatosensory information and at the core of the input drive to amygdala and the higher-level fear circuit. MGB has been shown to be crucial for associative fear learning and receives feedforward sensory as well as neuromodulatory inputs, e.g. acetylcholine – a key component in promoting learning. Prominent cholinergic fibres in MGB originate in the pontomesencephalic tegmentum (PMT) and form synapses on MGB neurons. However, the role of brainstem cholinergic inputs to MGB during associative learning remains elusive. Using a combination of deep brain imaging techniques such as fiber photometry and all-optical miniaturized microscopes in freely moving animals, we reveal the acetylcholine dynamics during associative fear conditioning and find that PMT inputs modulate the gain and adaptation rate of MGB neurons upon learning in a CS/US-dependent fashion. Furthermore, we find that optogenetic manipulation of cholinergic PMT inputs in MGB during fear acquisition affects learning bidirectionally. This study identifies the role of brainstem cholinergic inputs in multimodal sensory integration during fear conditioning in MGB, which broadens our view on how neuromodulators contribute to associative learning in thalamic areas.

[S-3.3]

The role of paraventricular thalamic nucleus in stress induced modification of behaviour

László Acsády [1]

[1] Institute of Experimental Medicine, Budapest, Hungary

The calretinin-positive neurons of the paraventricular thalamic nucleus (PVT/CR+ cells) form a critical hub in the brainstem-forebrain communication. We found that acute stress exposure triggers a prolonged increase in the firing activity of PVT/CR+ for several days. Attenuating PVT/CR+ neuronal activity for one only hour after the stress event rescued both the protracted increase in PVT/CR+ firing rate and the stress-induced behavioural alterations. Even when applied five days later, one-hour reduction of PVT/CR+ cell activity remained effective in ameliorating stress-induced changes in behaviour. These results demonstrate that enduring changes in the firing activity of PVT/CR+ neurons following a stress event is essential for behavioural changes associated with stress.

[S-3.4]

Thalamo-cortical principles define the complexity of information flow in the mouse and human amygdala

Ferenc Mátyás [1]

[1] Laboratory of Neuronal Network and Behavior, Institute of Experimental Medicine, Budapest, Hungary

Amygdala is a central element of emotional processing. This region can integrate incoming thalamic and cortical information providing environmental (multisensory) as well as salience signals and, in turn, control subcortical executive centers. Using classical and conditional anatomical and electrophysiological approaches, we further expand this knowledge by identifying two parallel thalamo-cortical pathways innervating the amygdala in a non-overlapping manner in mice. With Reproducible Tract Profiles 2 approach, we also demonstrate that similar dichotomy in the thalamo-cortico-amygdala network exists in human. We also show that these thalamo-cortical pathways drive different intra- and extra-amygdalar networks via the lateral (LA) and anterior basolateral amygdaloid nuclei (BLA) in mice. Our results challenge the well-accepted 'serial-type' intra-amygdalar wiring and introduce a complex connectivity pattern composed by parallel intra-amygdalar routes with distinct striatal outputs. This suggests that different aspects of emotional behavior are tailored by separate amygdalar routes.

[S-4]

Thalamic bases of adaptive behaviors

Theme Speaker: **Mathieu Wolff**

[S-4.1]

Thalamic contribution to fear memory consolidation

Gisella Vetere [1]

[1] ESPCI, Paris, France

Recently identified as pivotal hub nuclei in the brain's memory processing network, the thalamic subdivisions continue to captivate researchers seeking to unravel their role in fear memory consolidation. In this presentation, I will delve into recent findings elucidating the roles of the laterodorsal and anterodorsal nuclei of the thalamus in the consolidation of fear memories. Through novel data, I will demonstrate how these thalamic nuclei integrate inputs from both cortical and hippocampal pathways, shedding light on the intricate mechanisms underlying the recall of remote fear memories in murine models. Furthermore, I will examine the temporal evolution of head direction cell representation within these nuclei, offering insights into the dynamic nature of neural circuits associated with memory consolidation.

[S-4.2]

Global/local control of sleep oscillations by thalamic nuclei in mice

Audrey Hay [1]

[1] INSERM

Coordinated oscillations is a feature of sleep which could serve several purposes such as preventing awakening or promoting memory consolidation through local and global synchronisation of neuronal activity. These oscillations are the thalamocortical slow waves (0.5-2 Hz) and spindles (11-16 Hz) as well as the hippocampal ripples nested in sharp waves (SWR, 120-250 Hz). Correlative studies have highlighted the increased power of slow waves and spindles in specific cortical areas after learning, and an increase of sleep oscillation coordination across areas involved in the task. Moreover, locally promoting or impairing sleep oscillations coordination can promote or alter memory consolidation, respectively. However, how the oscillations are physiologically coordinated is still a matter of debate. Here, we suggest that the midline thalamic nuclei (MTN) might play a role in this coordination. We show that MTN neurons fire in burst at the beginning and end of the active phase of the slow wave. Moreover, their optogenetic stimulation promotes global Down states (inactive phase of the slow wave), while their silencing reduces the precision of Down states coordination. Last, using closed loop stimulation after detecting a SWR, we show that the optogenetic stimulation of MTN can promote memory consolidation of hippocampus dependent memory. Thus, MTN could play a critical role as sleep oscillation coordinator which is important for memory consolidation.

[S-4.3]

The role of thalamocortical circuits in adaptive behaviors and executive functions

Mathieu Wolff [1]

[1] Bordeaux Neurocampus, CNRS, France

In highly volatile environments, performing actions that address current needs and desires is an ongoing challenge for living organisms. For example, the predictive value of environmental signals needs to be updated when predicted and actual outcomes differ. Furthermore, organisms also need to gain control over the environment through actions that are expected to produce specific outcomes. The data to be presented will show that these processes are highly reliant on thalamocortical circuits and that thalamic nuclei make a critical contribution to adaptive decision-making. Over the past few years, our work has highlighted the specific contribution of multiple thalamic nuclei in the ability to update the predictive link between events or the causal link between actions and their outcomes via the combination of targeted thalamic interventions (lesion, chemogenetics, disconnections) with behavioral procedures rooted in experimental psychology. We argue that several features of thalamocortical architecture are consistent with a prominent role for thalamic nuclei in shaping mental representations. The mediodorsal thalamus in particular appears as crucial for executive functions.

[S-4.4]

Can we harness the thalamus to promote recovery of cognitive function for brain impairment?

John Dalrymple-Alford [1 2]

[1] School of Psychology, Speech and Hearing, University of Canterbury
[2] New Zealand Brain Research institute, Christchurch, New Zealand

The neuroscience community is fast becoming aware of the active roles of the thalamus in a wide array of brain functions. First, this relatively small but complex brain region is the source of recent theoretical developments to help explain how thalamic nuclei orchestrate cortico-subcortical function and normal cognitive processes. A complementary line of research is increasing attention to changes in thalamic integrity in the context of cognitive impairment in an array of neurological conditions. The current talk will address the third, but neglected side of this triangle, namely, potential contributions of thalamic manipulations to promote recovery of function to treat cognitive impairment. The currently limited evidence on this third perspective will be summarised. Reference is made to some recent animal neuroscience examples as well as human studies that begin to address this general question. New options will be proposed. Indeed, the very small size of thalamic nuclei may be advantageous to address impairments in a more tractable way than interventions focused on large structures such as the hippocampal system and the vast expanse of human cerebral cortex.

[S-5]

Thalamic contribution to conscious processing

Theme Speaker: **Mototaka Suzuki**

[S-5.1]

How deep is the brain? The shallow brain hypothesis

Mototaka Suzuki [1]

[1] University of Amsterdam

Deep learning and predictive coding architectures commonly assume that inference in neural networks is hierarchical. However, largely neglected in deep learning and predictive coding architectures is the neurobiological evidence that all hierarchical cortical areas, higher or lower, project to and receive signals directly from subcortical areas. Given these neuroanatomical facts, today's dominance of cortico-centric, hierarchical architectures in deep learning and predictive coding networks is highly questionable; such architectures are likely to be missing essential computational principles the brain uses. In this talk, I present the shallow brain hypothesis: hierarchical cortical processing is integrated with a massively parallel process to which subcortical areas substantially contribute. This shallow architecture exploits the computational capacity of cortical microcircuits and thalamo-cortical loops that are not included in typical hierarchical deep learning and predictive coding networks. We argue that the shallow brain architecture provides several critical benefits over deep hierarchical structures and a more complete depiction of how mammalian brains achieve fast and flexible computational capabilities. Lastly, I will briefly discuss what this shallow brain architecture implies about conscious processing.

[S-5.2]

Secondary Thalamus in Behavior

Randy Bruno [1]

[1] University of Oxford

Each sensory modality has its own primary and secondary thalamic nuclei. While the primary thalamic nuclei are well understood to relay sensory information from the periphery to the cortex, the role of secondary sensory nuclei is elusive. One hypothesis has been that secondary nuclei may support feature-based attention. If this is true, one would also expect the activity in different nuclei to reflect the degree to which modalities are or are not behaviorally relevant in a task. We trained head-fixed mice to attend to one sensory modality while ignoring a second modality and simultaneously recorded from secondary somatosensory and visual thalamus. Training could switch the modality that maximally activated a secondary thalamic nucleus. Movements do not account for this dramatic switch. Secondary nuclei appear to encode behaviorally relevant, reward-predicting stimuli regardless of stimulus modality.

[S-5.3]

Deep brain stimulation of the thalamus restores signatures of consciousness: how does it work?

Bechir Jarraya [1]

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Recently, research groups independently reported that the electrical stimulation of thalamic nuclei can awaken anesthetized non-human primates (NHPs). We could demonstrate that deep brain stimulation (DBS) of the central thalamus could restore consciousness signatures in deeply anesthetized NHPs by restoring behavioral responses, changes in resting-state fMRI dynamics, and the capability of hierarchical cortical error detection in auditory sequences ("local-global" paradigm). Using fMRI, we can document how DBS massively alter cortical activity by shifting spontaneous fluctuations of cortical activity from a rigid brain configuration similar to brain anatomy, to a flexible brain configuration with a rich functional repertoire of brain states, similar to the one observed in the wake state. fMRI clearly demonstrate that DBS achieves a double cortical input through cortico-thalamic axons stimulation (retrograde mechanism) and thalamo-cortical axons stimulation (anterograde mechanisms). Moreover, anesthesia-induced loss of consciousness is thought to be related to the suppression of cortical feedback while preserving feedforward cortical activity. A recent study demonstrated this decoupling at the cellular level using optogenetics. If this thalamic mechanism is fundamental to the loss of consciousness in anesthesia, then the observed wakefulness restoration by thalamic stimulation in anesthetized macaques would be associated with a restoration of feedback cortico-cortical activity. This has been demonstrated recently using layer-specific recordings in the macaque cortex.

[S-5.4]

Cortical computer modeling of facets of the neurobiology underlying psychiatric disorders: depression as an example

Mohamed Sherif [1]

[1] Brown University

There are multiple “levels” within the brain, including multi-region networks, microcircuits, individual neurons and interneurons, proteins and molecules, all the way down to genes. These different levels interact bi-directionally, making it complex to intuitively understand how manipulation at one level, e.g., through pharmacology or behavior, would result in changes at another level. Computer models have the advantage of connecting the different elements within one of these levels together in a way that makes all our assumptions explicit. Computer modeling also allows for different levels of abstraction to connect the different levels, again, with the assumptions about how one level affects others made explicit. Different frames of computer modeling exist to represent the different levels, including biophysical realistic microcircuit dynamical models and biologically constrained artificial neural networks. I will present work from my lab that illustrates some of these concepts, focusing on cortical models and depression as a case example.

[S-6]

Neuroimaging of the human thalamus and cognitive function

Theme Speaker: **Pedro M. (Kepa) Paz-Alonso**

[S-6.1]

Neuroimaging protocols to study the involvement of the human thalamus in cognitive function

Pedro M. (Kepa) Paz-Alonso [1 2]

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There is a strong need in the human neuroimaging field to implement reproducible research methods. Ideally, researchers should be able to replicate experimental data acquisition and reproduce the computational analyses presented in neuroimaging publications. Current scientific practices increasingly promote data sharing among researchers and labs. This facilitates colleagues in the scientific community and clinical practitioners to reproduce, verify, and further explore datasets and computational analyses. Moreover, these practices are evolving alongside continuous and substantial increases in algorithm complexity in functional and structural MRI methods. Over the last decade, our research team has developed MRI protocols for several purposes. These protocols include identifying and segmenting thalamic nuclei at the individual-subject level, obtaining and measuring first-order relay human thalamic white-matter tracts, investigating the white-matter pathways between the human mediodorsal thalamic nucleus, and understanding the relationship between thalamic nuclei and their white-matter projections across the lifespan. In the present talk I will provide an overview of these neuroimaging protocols and their results, as well as some of the findings we have recently obtained when applying them to understand the involvement of the thalamus in human language systems and working memory.

[S-6.2]

Perceptual inference involves corticothalamic computations

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Everything we sense is shaped by our prior knowledge of the world. Perceptual inference formalises this process as Bayesian believe updating: our previous experience generates prior believes on the sensory world that are updated with each observation. Although believe updating was for long assumed to be exclusively computed in the cerebral cortex, there is growing evidence that the sensory thalami are crucially involved in the process. In this talk I will present recent evidence supporting this view. We used abstract rules to manipulate the expectations of human participants on the presentation of auditory stimuli; we argue that, since the priors were derived from the rules, priors could only be generated in pre-frontal cortical areas. We then omitted the presentation of the tones and used fMRI to measure possible responses to the omissions in auditory thalamus; we argue that, in the absence of sensory input, these responses could only encode a believe update over the priors.

[S-6.3]

Segmentation of in vivo thalamic nuclei from joint structural and diffusion MRI

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Accurate identification of cytoarchitectonically designed histological nuclei is hampered on standard in vivo structural MRI by the lack of image contrast. Such contrast issues can present difficulty in differentiating both between thalamus and surrounding white matter or between in-dividual thalamic nuclei. However, diffusion weighted imaging provides complementary infor-mation for segmentation, highlighting both internal and external thalamic boundaries. In this talk I will present two recently developed tools for segmentation of thalamic nuclei from joint struc-tural and diffusion MRI. The first is a Bayesian method incorporating a probabilistic atlas con-structed from histology, to offer robust modelling of structural contrasts paired with high resolu-tion diffusion MRI. The second tool builds on Bayesian segmentations to train a convolutional neural network capable of rapidly segmenting 23 nuclei per hemisphere from T1 weighted imag-ing and diffusion tensor imaging acquired at a broader range of resolutions.

[S-6.4]

Frontal thalamocortical networks in cognitive flexibility

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Cognitive flexibility, a vital aspect of brain function, is pivotal for adapting behaviors in uncertain environments. Evidence from non-human animals suggests that the interaction between the mediodorsal thalamus (MD) and the prefrontal cortex (PFC) plays a central role in cognitive flexibility. Specifically, when confronted with decisions involving multiple sources of uncertainty, such as that of sensory input and the mapping between sensory input and internal meaning, the MD can arbitrate errors from different sources. In response to changes in the external environment, the MD appropriately attributes accumulated errors to environment changes rather than internal misjudgment. This triggers PFC reconfiguration, ultimately leading to behavioral adjustments. However, the extent to which this neural mechanism can be generalized to human cognitive flexibility remains unclear. In this talk, I will discuss our recent findings regarding the involvement of human MD and PFC in a hierarchical decision task requiring context switching. Through multivariate analysis of human brain signals, we observed that MD activity can decode contextual representations. Furthermore, both MD and dorsomedial PFC signals are correlated with the probability of contextual switch. Subsequent analyses will investigate the interaction between these structures during contextual switch. These findings underscore the significance of frontal thalamocortical networks in facilitating flexible decision-making and adaptive behavior in humans.

[P-1.1]

A mouse lateral posterior nucleus parcellation based on thalamocortical projection motifs

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The higher-order thalamus is critically involved in cortical function, both as a combinatorial hub for integration of cortical and subcortical inputs and communication. The lateral posterior thalamic nucleus (LP) in rodents is thought to be homologous to the primate visual pulvinar. Like the pulvinar, mouse LP is reciprocally connected with all visual cortical areas and receives a strong projection from the superior colliculus. Previous studies have distinguished several subnuclei within LP based on cytoarchitecture and immunocytochemical markers, but it is unclear whether they reflect functionally distinct domains of LP.

We directly visualized the thalamocortical axons originated in different LP portions using microiontophoretic tracer injections (BDA or AAV2/1.hSyn.eGFP.WPRE.hGH) or single-cell electroporation (Sindbis-Pal-eGFP). Comparison of a large experiment dataset consistently revealed the existence of a number of distinct multiarea targeting patterns (“projection motifs”). Shared motifs across injection experiments delineate several domains within LP, which align only in part with subdivisions based on cyto- or chemoarchitecture. Moreover, the same motifs were observed in micropopulation or single-cell labeling experiments in any given LP domain. Individual LP neurons always target two or more cortical areas, often arborizing in different layers, and may also target the striatum and amygdala as well.

[P-1.2]

Development of EEG alpha rhythm is linked to thalamocortical white matter pathways and visual detection performance

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Alpha is the strongest electrophysiological rhythm in awake humans at rest. Despite its predominance in the EEG signal, large variations can be observed in alpha properties during development, with an increase of alpha frequency over childhood and adulthood. Here we tested the hypothesis that these changes of alpha rhythm are related to the maturation of thalamocortical white matter pathways (i.e., optic radiation). We capitalized on a large dMRI-EEG dataset (dMRI n=2,747, EEG n=2,561) of children and adolescents of either sex (age range: 5-21 years old) and showed that maturation of the optic radiation specifically accounts for developmental changes of alpha frequency. Behavioral analyses also confirmed that variations of alpha frequency are related to maturational changes in visual perception. The present findings demonstrate the close link between developmental variations in thalamocortical white matter tissue properties, electrophysiological responses, and behavior.

[P-1.3]

Exploring the impact of interthalamic adhesion on human cognition: insights from healthy subjects and thalamic stroke patients

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The interthalamic adhesion (IA) connects the median borders of both thalami, displaying anatomical variations and functions that are not well understood. This study investigates the IA's impact on cognition in 42 healthy subjects and 40 patients with chronic isolated thalamic strokes, incorporating neuroimaging and neuropsychological assessments. The presence, absence, type of anatomical variant, and lesion of an IA were assessed. Among participants, 76% possessed an IA, with a higher occurrence in women (92%) compared to men (61%). Neither the presence of the IA nor its variant types influenced neuropsychological outcomes in healthy individuals. However, patients lacking an IA (n=10) exhibited poorer cognitive performance compared to those with an IA (n=18), particularly in verbal memory and Stroop tasks, independently of age, infarct laterality, volume, or lesion location. Patients with a lesioned IA (n=12) showed a similar pattern to those without an IA, though this could be related to larger lesion volumes. Therefore, while the IA seems non-critical for cognition in healthy individuals, it may serve a compensatory role in patients with thalamic damage.

[P-1.4]

Exploring the Role of the Pulvinar in Multisensory Processing: Insights from Functional Connectivity in fMRI

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The pulvinar nucleus emerges as a critical hub that plays a pivotal role in coordinating sensory information and facilitating high cognitive functions. The involvement of the pulvinar, particularly in visual processing, has been extensively studied due to its strong reciprocal connections with the visual cortex. However less is known about its involvement in orchestrating multisensory processing in humans. In the present study, using functional magnetic resonance imaging (fMRI) technique, we investigate, in humans, the dynamic interplay between the different distinct subregions of the pulvinar and the cortex within multiple sensory modalities: Visual, Auditory and tactile. Twenty-five subjects participated in this study and were asked to perform during MRI scanning three different tasks: (i) Face Localizer task (ii) Voice localizer task and (iii) Tactile localizer task. Functional connectivity results reveal that the three sensory modalities are differentially organized across the main subdivisions of the pulvinar. These results show a dynamic modulation of pulvinar connectivity based on the sensory context and highlight the multisensory coordinating pulvinar role. Indeed, this nucleus, combines multiple sources of sensory information and changes its connectivity with the cortex depending on the sensory context. This gives a new understanding of how the pulvinar gates multisensory processing.

[P-1.5]

Functional and anatomical evidence suggesting the existence of an auditory subcortical route for fast threat detection in humans

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Rapid threat detection is key for survival. In vision, a direct neural route from the pulvinar of thalamus to amygdala is thought to serve this purpose. This route consists of fast and coarse visual inputs, conveyed predominantly by magnocellular neurons. In audition, non-human animal evidence suggests the existence of a homologous subcortical magnocellular route, but it remains uncertain in humans. In Study 1, we analyzed electroencephalography data from healthy subjects during fear conditioning. Conditioned (threatening) sounds delivered at high temporal modulations (to which magnocellular auditory neurons seem particularly sensitive), elicited earlier auditory and pupillary responses than those at low modulations (presumably activating a parvocellular, slower route). In Study 2, we anatomically reconstructed candidate auditory subcortical pathways to amygdala in 200 human subjects, analyzing tractography of diffusion-weighted images from the Human Connectome Project. We identified white matter tracts directly projecting to amygdala from medial geniculate body of the thalamus and from inferior colliculus, with fiber density in these tracts correlating with individual scores of fearfulness. Together, these findings are compatible with fast neural responses to threat when encoded through magnocellular inputs to amygdala, and provide human anatomical evidence for subcortical auditory pathways to this structure, homologous to those described in vision.

[P-1.6]

Involvement of human anterior and mediodorsal thalamus in episodic memory recollection and familiarity across the lifespan

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[2] IKERBASQUE Basque Foundation for Science

Human episodic memory relies on binding individual elements to create contexts, attending to associative, spatial and temporal dimensions of events. These relational memory dimensions have rarely been examined together and their neural substrates remain to be ascertained. Higher-order thalamic nuclei may be critical in modulating the interplay between the medial temporal lobe (MTL), critical in binding processes, and the PFC which supports mnemonic control during memory retrieval. Moreover, anterior and mediodorsal thalamic nuclei might be differentially involved in recollective- and in familiarity-related processes. Here, we investigated the involvement of these thalamic nuclei in episodic memory and in their interactions with MTL and PFC across the lifespan. Forty-two children, thirty-seven young adults and forty-four older adults underwent MRI scanning during a memory retrieval task comprising item memory, and associative, spatial and temporal relational memory for semantic and non-semantic materials. Results revealed strong impact of semantic memory on episodic memory, especially with age. Stronger involvement of anterior thalamus in recollection-related and of mediodorsal in familiarity-related retrieval processes was observed in children and young adults, but not in older adults. Anterior thalamus exhibited significant functional coupling with PFC and MTL regions. Results are discussed in line with Aggleton and Brown's episodic memory model.

[P-1.7]

Microcircuit ultrastructure comparison of first and higher order thalamocortical projections into layer-specific somatosensory cortices

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Thalamocortical synapses are key cellular links in sensory, motor and cognitive information processing. In rodents, ventral posteromedial thalamic nucleus (VPM) axons innervate both layer 4 of primary and secondary somatosensory cortex (S1, S2). Posterior nucleus (Po) projects to the same somatosensory areas as a "higher order" nucleus. Despite "primary" and "secondary" functional characterization, substantial information is lacking on VPM and Po axon synapse structure and their postsynaptic targets. Here, we try to elucidate the ultrastructure of VPM and Po synapses on these two areas and compare them.

We microinjected adult mice with an anterograde tracer (BDA) to selectively label thalamocortical axon arborizations. Following a 5-day survival, mice were perfused, and their brains sectioned into two parallel series. BDA-labeled cortical arborizations were located on a light-microscopy series. Adjacent sections were stained for BDA and included for electron microscopy. Area and layer-specific serial images samples were obtained with ssTEM or FIB/SEM, 3D reconstructed and measured. Our results are consistent with previous evidence that VPM axon synapses are mostly located (83-85%) on spiny cell dendrites, while remaining dendrite shafts probably correspond to interneurons. VPMc-S2L4 synaptic boutons are significantly smaller than VPMr-S1L4. Surprisingly, Po-S2L4 boutons show the highest synaptic vesicle count among all datasets.

[P-1.8]

Multisensory integration at single cell and local field potential levels in the medial pulvinar

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Based on its connectivity, the medial pulvinar is proposed to play an important role in sensory processing and multisensory integration. However, its contribution to multisensory integration has rarely been directly investigated. To fill this knowledge gap, two macaque monkeys were trained on a fixation task, during which auditory, visual and audiovisual stimuli were presented. We recently showed multisensory integration in the medial pulvinar at single cell level (Vittek et al., 2023). Here, we characterize local field potentials of the medial pulvinar associated with unisensory and multisensory stimuli. In the temporal domain, we describe an early and a late period showing multisensory integration, both dominated by sub-additive processes (audiovisual response inferior to the sum of the unisensory responses) and highly correlated between both epochs. In the frequency domain, multisensory integration is predominant in the 4.5-8.5Hz and 8.5-20Hz frequency bands and less dominant in the 35-60Hz and 60-120Hz frequency bands. Thus multisensory integrative processes vary across frequency bands. Similarly to what is observed in the temporal domain, they are mostly sub-additive. These findings strongly suggest that the medial pulvinar is a multisensory hub, integrating visual and auditory information in different frequency bands and that it contributes to cortico-pulvino-cortical multisensory computational loops.

[P-1.9]

Nucleus-specific axonal architectures and thalamocortical arborization patterns of the mouse ventral motor nuclei

Carmen Alonso-Martinez [1], Mario Rubio-Teves [1], Rembrandt Bakker [2], Nestor Timonidis [2], Paul Tiesinga [2], Cesar Porrero [1] & Francisco Clascá [1]

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The thalamus is a central link between cortical and subcortical brain motor systems. Axons from the deep cerebellar nuclei and the output nuclei of the basal ganglia innervate prominently the ventral motor thalamus, defining three main nuclei: the pallidal ventral anterior (VAp), the ventrolateral (VL) and the ventromedial (VM). In turn, axons from these ventral nuclei innervate the motor and premotor areas of the cortex, where their input is critical for planning, execution and learning of rapid and precise movements.

To investigate thalamic input sources to different motor cortex regions, we use anterograde micropopulation and single-cell labelling, to examine and compare the branching patterns and distribution across the cerebral hemisphere of the thalamocortical axons originated in the various mouse ventral motor thalamic nuclei. Our preliminary data of micropopulation-level axon tracing experiments reveals that VAp, VL and VM have unique laminar and tangential patterns of cortical arborization. We have also explored high-resolution single-cell axonal morphologies of these three thalamic nuclei from the MouseLight dataset, where whole mouse brains are imaged with two-photon microscopy at submicron resolution, allowing reconstruction of complete axonal arborization of individual neurons. These single-cell morphologies align with the patterns observed at the population level. Funding: MINECO/FEDER BFU2017-88549.

[P-1.10]

Population and single-neuron mapping of anterior thalamic nuclei projections in the mouse.

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In addition to sensory relay, the thalamus plays a key role in selective attention, memory, and cognitive functions. The anterior nuclei (ATN) are a central hub of the brain's "limbic system", a network long known to be involved in emotion, attention, and memory. Recent studies have shown that ATN are also involved in head direction and spatial navigation.

We analyzed thalamocortical ATN neurons projections to isocortical and parahipocampal areas at micropopulation and single-cell levels. To map and compare the ATN output pathways, we generated an unfolded map of the parahipocampal areas. We plotted onto this map the ATN arborizations labeled by population adenoviral vector injections (Allen mouse connectome) or single-cell morphologies (Janelia Mouselight). Neurons in each of the three main ATN (anterodorsal, AD; anteroventral AV; anteromedial, AM) show each a specific projection motif. AM neurons innervate the frontal, cingulate, transitional subiculum, and perirhinal areas. AV neurons target the retrosplenial, dorsal subiculum and medial entorrinal areas. AD neurons innervate the retrosplenial, postsubiculum and medial entorhinal areas. Individual ATN neurons always innervate two or more cortical areas and the thalamic reticular nucleus. Support: MICINN PID2020-115780GB-I00.

[P-1.11]

Structural dynamics of human thalamocortical projections across the lifespan

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Thalamocortical projections undergo dynamic maturation and refining during postnatal development, sculpting the neural circuits supporting brain function. Despite their relevance, a characterization of changes in human thalamocortical and corticothalamic bundle structure across the lifespan is still lacking. Here, we employed validated diffusion MRI protocols to reconstruct and quantify first order (FO) relay thalamocortical white-matter projections and mediodorsal (MD) nucleus-prefrontal cortex (PFC) thalamocortical/corticothalamic projections in a healthy cross-sectional cohort (N = 259), spanning ages 6 to 81 years. We examined differences across lifespan periods in the bundles' microstructure, particularly fractional anisotropy (FA), and its relationship to the volume of the thalamic nuclei they originate from. Our results unveil distinct developmental profiles, with FO bundles showing anatomically-dependent variations in FA between age groups, similar to MD bundles albeit to a lesser extent. Associations between thalamic volumes and FA across the lifespan were only found in MD-PFC bundles, and with different associations along the tract: closer to the thalamus, larger MD volumes corresponded to lower FA of the bundles; closer to the cortex, larger MD volumes corresponded to higher FA of the bundles. These results are discussed in line with current hypotheses on signaling dynamics between higher-order relay thalamic nuclei and cortical areas.

[PS-.12]

TCF7L2 deficiency in the thalamus leads to alterations in social behavior profile

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TCF7L2 is a transcriptional effector of the Wnt/β-catenin signaling pathway and a risk gene for autism spectrum disorder (ASD). TCF7L2 is expressed in the thalamus, where it regulates the establishment of thalamocortical connections and electrophysiological maturation of neurons. The role of TCF7L2 in regulating behavioral profiles has not been fully investigated. We hypothesized that postnatal thalamus-specific deficiency of TCF7L2 impairs thalamocortical circuits and leads to autism-like behaviors. Using mice with Tcf7l2 knockout in thalamic neurons, we analyzed the behavioral profile of the conditional Tcf7l2 knockout (Tcf7l2 cKO) mice to assess anxiety, repetitive behaviors, and social performance. Tcf7l2 cKO mice showed no difference in the repetitive behavior. Still, they presented a decrease in social interest, not interacting with other mice during the chamber exploration, and spending less time near the social scent, demonstrating that the deletion of Tcf7l2 affects conspecific social cue recognition. They seemed less anxious with a significant decrease in grooming behavior and a tendency to spend more time in an open and brighter arena. These results corroborate a hypothesis that thalamic dysfunctions originating from perinatal development can be a primary cause of social deficits, and impairments in thalamocortical circuits play a role in the pathogenesis of ASD.

[P-1.13]

Thalamic contributions to working memory manipulation

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The cortical substrates of working memory (WM) have been extensively investigated. However, less research has investigated the role of the thalamus and thalamocortical pathways in WM in humans. This could be due to the lack of detailed probabilistic atlases of the human thalamus or the small size of the thalamic nuclei as compared to regular voxel sizes. In the present MRI study, twenty-six participants performed a variation of a standard WM task with maintenance and manipulation components. In this task, participants were presented with a sequence of three images and were asked to remember them either in 'forward' or in 'backward' order. We investigated the involvement of thalamic nuclei and to what extent thalamocortical functional and structural connections were related to WM abilities. Our results revealed that the mediodorsal thalamus is involved in WM manipulation during the delay period, whereas the anterior nucleus and frontoparietal cortical regions are involved in WM manipulation during both the delay and retrieval periods. These findings highlight the relevance of the thalamus and thalamocortical connectivity in models of human WM.

[P-1.14]

Unique features of layer 5 frontal cortical axons in the thalamus.

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Top-down corticothalamic layer 5 afferents (L5) has profound impact on their thalamic targets in sensory corticothalamic circuits. In this project we asked whether L5 corticothalamic inputs from frontal cortical regions show similar anatomical and electrophysiological characteristics. We found that in contrast to the giant sensory L5 terminals, frontal cortical L5 axons establish small boutons, their size distribution closer to that of the L6 boutons. Small L5 terminals were as effective in driving thalamic spiking as large L5 terminals in vivo and displayed less short-term depression in vitro and in vivo. Despite their similar size, the ultrastructural properties of small L5 terminals were distinct from that of L6 terminals. Frontal L5 boutons targeted dendritic spines. In vitro two photon glutamate uncaging demonstrated that glutamate evoked Ca2+ transients in thalamic spines were compartmentalized similarly to CA1 hippocampal pyramidal cell spines. Optogenetic inhibition of small L5 terminals from the secondary motor cortex in the thalamic ventromedial nucleus negatively affected motor performance of mice in a horizontal wheel running learning experiment. We conclude that the presence of functional spines on thalamic dendrites with a specialized cortical input can potentially endow thalamocortical cells with the ability of scaling and plastic regulation of incoming cortical inputs.

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